ABSTRACTS
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Bioengineering Abstracts .............................................................. Pages 1-40
Cardiac Abstracts ........................................................................ Pages 41-87
Pediatric Abstracts ....................................................................... Pages 88-96
Pulmonary Abstracts ............................................................... Pages 97-106
Renal Abstracts ........................................................................ Pages 107-116
Author Index Page .................................................................... Pages 117-125
10
Quantitative Evaluation of the Relationship Between Shunt Murmur Characteristics and Fluid Parameters

Study: A time-frequency analysis of shunt murmurs obtained in clinical trials was performed to find a method to quantitatively evaluate vascular access (VA) function. Parameters such as the shunt murmur frequency components and duration time that show the state of the shunt vessel may be affected by vortices and turbulence arising from changes in blood flow. Previous studies have been conducted on the relationships with fluid parameters such as vorticity and turbulent energy obtained from simulated shunt murmur measurements in artificial angiostenosis models made of vinyl chloride. In this study, the material of the artificial angiostenosis model was changed to one that is more flexible and realistic in order to reproduce a state that is more similar to living tissue.

Methods: The artificial angiostenosis model was a silicon tube with an inner diameter of 6 mm in which silicon tubes with an inner diameter ranging from 1–5 mm and outer diameter of 6 mm were inserted for different stenosis severities. To simulate living tissue, the stenotic lesion of the models was enclosed in a water bag to which acceleration sensors were attached to the surface. A pulsatile flow that simulated the pulse in a hemodialysis patient was circulated through the vessel, and a Bio Sound Analyzer was used to measure the simulated shunt murmur. The shunt murmur without stenosis was used as reference data, and the shunt murmur with incremental changes in stenosis severity was used as comparison data. The normalized cross-correlation coefficient $R$ was calculated for the two images to quantitatively evaluate changes in the shunt murmur caused by differences in stenosis severity.

Results: Stenosis severity of greater than 50% was found to cause a drastic decrease in the flow rate in the circuit that was accompanied by large changes in the shunt murmur. This led to a major drop in $R$. This trend is similar to that seen in clinical trials and indicates the ability to monitor changes in shunt flow rate due to stenosis.

11
Artificial Liver MARS Application in ACLF Patients: A New Concept.
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Study: The aim of this study is to show the evolution of MARS application and the real detoxification of single substances following the engineering model indications in different periods.

Methods: Two hundred-thirty ACLF patients treated with MARS in waiting list for transplant, were enrolled in this study. The patients were divided in two groups following the MELD score. In the first groups, patients with a MELD range 20–27 (Group A), in the second one, patients with MELD range 28–36 (Group B). The parameters were inserted in an engineering model to evaluate detoxification efficiency ($\eta$), defined as the fractional reduction of the toxin concentration respect to volume blood pump, volume albumin circuit, membrane pressure, type of dialysis machine and ratio between patient albumin and circuit albumin.

Results: The MARS application was analyzed in three different periods from 1999 to 2013. The application of engineering model determined an improvement of Responder to treatments and survival in the second and third period. In particular, following the model, we highlighted an improvement of detoxification efficiency ($\eta$), an increase of Responders and survival at 3 months of Group B in the third period thanks to the change of adsorbents after three hours only. In patients with high level of toxin, the “fast adsorption regime” is observed, characterized by a typical breakthrough curve, and the toxin absorption in the columns is nearly zero with complete saturation of the adsorbents. The model has to be adapted to each treatment and each patient. MARS like a “personal therapy”. The correct application of flows, membrane pressure, albumin concentration and type of dialysis machine are essential aspects to obtain the optimal detoxification. A change of carbon and resin adsorbents after few hours can improve the detoxification in patients with high MELD score.
Quantitative Evaluation of Improvement of Swallowing Function by Swallowing Viscosity Adjusted Foods and Carbonated Beverages

Study: Thickening agents are added to meals for patients with dysphagia, to adjust to the appropriate viscosity, and this prevents food and beverages from passing too quickly into the throat, enabling safer ingestion of food. In other words, adjusting food to an appropriate viscosity is extremely important. However, the relationship between viscosity and changes in swallowing sounds has not been clarified. At the same time, it has been said that with carbonated beverages, the stimulation caused by the fizziness of the carbonation promotes the swallowing reflex, but, as with viscosity, there are almost no reports of experimental studies on the effects of the properties of foods and beverages on swallowing sounds.

Methods: As a preliminary experiment on healthy subjects, the authors herein measured the swallowing sounds made when subjects swallowed water, viscosity-adjusted test samples, and carbonated beverages by using an acceleration sensor attached to the neck of subjects. Time-frequency analysis of the recorded sounds was then done using wavelet transform. In order to quantitatively express the degree of thickening when a thickening agent was added to water and the amount of thickening agent was varied in units of 1 g, we used the Line Spread Test (LST) method with a simplified thickness measurement plate to measure the viscosity.

Results: With the viscosity-adjusted samples, the viscosity increased with the amount of thickening agent added, and a tendency was seen for the sound II position to approach the sound I position in relation to the overall swallowing sound in response to this change. We also found that when carbonated beverages were swallowed, the sound II position moved closer to the sound I position compared to when water was swallowed. As a result, we were able to quantitatively demonstrate the possibility that addition of an appropriate amount of thickening agent and stimulation caused by carbonated beverages can reduce the risk of aspiration.

Performance Characteristics of a Novel Collapsible Percutaneous Heart Pump for Acute Left Ventricular Support
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Study: There is growing clinical need for a ventricular assist device which provides rapid acute hemodynamic support. HeartMate PHP™ (Percutaneous Heart Pump) is a catheter-based axial blood pump designed to provide left ventricular hemodynamic support of over 4.0 lpm and is delivered percutaneously via typical femoral insertion. The 12F catheter contains a distal collapsible covered nitinol cannula with an integrated impeller that expands to 24F when deployed across the aortic valve. Computational and in vitro studies were conducted for pump development.

Methods: In order to maximize pump efficiency, CFD and FSI studies were conducted in designing the polymer based flexible impeller. Impeller blade attacking angle, leading and trailing edge shape, cannula inlet and outlet, and tip gap were modified to improve hydraulic performance, minimize secondary flow, reduce shear stress on blood and ensure collapsibility. Blades and cannula coating deformation was studied with FSI simulation to understand the loaded configuration of flexible impeller blades and cannula wall. In vitro flow loops were constructed to test the hydraulic characteristics of pump design iterations.

Results: Results show the larger cannula diameter and optimized impeller design generates higher performance and reduces the shear stress on the blood. (Fig.1). In vitro flow tests demonstrate PHP is able to sustain average flows of 5.2 lpm with minimal shear stress at an impeller speed of 20K rpm. Flows up to 6.5 lpm were observed by varying pressure differentials to approximate different disease models. The comprehensive computational study and in vitro tests of PHP show its excellent hydraulic performance at relatively low pump speeds. The successful development of this heart pump may provide clinicians with a superior solution for acute hemodynamic support.
30
Experimental Investigation of The Effects of Pressure Guide Wire Thickness on Fractional Flow Reserve Using Coronary Stenosis Models
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Study: The outer diameter of pressure guide wires is very small, at only 0.014 inches (0.36 mm), and the thickness of the guide wire is said to have a minimal effect on fractional flow reserve (FFR). However, in stenotic lesions with an inner diameter of about 1 mm, the lesion will be partially blocked by the insertion of the pressure guide wire. Despite the potential effects this may have on the measured pressure values before and after the stenosis, there have been few reports on experimental or theoretical studies of these effects. In order to experimentally investigate the effects of guide wire thickness on FFR calculations, acrylic coronary stenosis models with varying stenosis severity and lengths were produced, and FFR was calculated from pressure gradient measurements before and after the stenosis using a pressure guide wire.

Methods: Four types of acrylic coronary stenosis models were made, with stenosis severity of 50% (2-mm inner diameter of the stenotic lesion) or 75% (1-mm inner diameter) and stenosis length of 10 mm or 20 mm. Water was circulated through the model, and the flow rate was increased by 100 mL/min between 100 and 500 mL/min. The pressure gradient before and after the stenosis was measured using a pressure guide wire, and the FFR was calculated. Next, FFR was then calculated from the flow rate with and without stenosis and compared to the FFR obtained from the pressure gradient measurement with a pressure guide wire to identify the effects of pressure guide wire thickness.

Results: No effects from the pressure guide wire were seen in the coronary stenosis model with stenosis severity of 50% when comparing measured pressure gradients with theoretical values and with values obtained from the flow rate. However, in the stenosis model with stenosis severity of 75%, simply inserting the pressure guide wire caused elevation of the pressure in the areas proximal to the stenosis, which may affect FFR.

31
Evaluation of Vascular Access Function Based on the Normalized Duration Time of Shunt Murmurs
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Study: In this study, a shunt murmur signal measured over time in the same maintenance dialysis patient was approximated by a cubic spline function, and the duration time of the shunt murmur signal was defined as the time needed for the amplitude to attenuate to a threshold value determined from the peak amplitude value on the approximated curve. The possibility of a new screening test method capable of numerically quantifying shunt murmur changes in the time-frequency domain, in order to complement the deficiencies of each method.

32
Flow Analysis of the Tip of a Hemodialysis Puncture Needle Based on Computational Fluid Dynamics

Study: Generally, in hemodialysis, two puncture needles are placed in the arteriovenous fistula: one for blood removal and one for returning. Jet flow or turbulent flow can be created at the needle tip, particularly on the returning side. This jet flow or turbulent flow could potentially damage the vascular shunt, and poses a risk of stenosis of the blood vessel and associated coagulation of the blood. We therefore took a number of puncture needles already commercially available and used computational fluid dynamics (CFD) to analyze flow in the vicinity of the tip of the needle. We also used particle image velocimetry (PIV) to visualize flow, and compared the results with the analysis results.

Methods: In this experiment, we placed two types of puncture needles in the simulated blood vessel: one with side holes and one without. We inserted these puncture needles into a simulated blood vessel comprising a tube made of polyvinyl chloride with an inner diameter of 12 mm, and used a roller pump for a heart-lung machine to circulate water inside the simulated blood vessel at a flow rate of 700 ml/min. We connected the puncture needle to the connector on the vein side of the hemodialysis circuit, and placed the connector on the artery side in a bucket containing water in which microparticles had been mixed to make it visible. The simulated blood vessel was irradiated with a laser light sheet from below, and a high-speed camera was used to photograph flow in the vicinity of the needle tip, from the side of the simulated blood vessel.

Results: Pooling was observed in the vicinity of the needle tip when the water was removed. When the water was returned, it was seen to move vigorously from the tip of the puncture needle into the tube. These results correspond relatively strongly with those obtained from flow analysis using CFD, and suggest that the inner walls of blood vessels could thicken as a result of blood coming in vigorous contact with the inner walls over a long period of time, or that blood could coagulate as a result of pooling.
Hemodynamic Monitoring of Large Animal Chronic Studies after Median Sternotomy: Experiences with Different Telemetric Physiological Devices

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Study: Telemetric physiological monitoring systems (TPMS) have enabled accurate continuous measurement of animal physiologic variables including blood pressure. Recent innovation has also enabled blood flow monitoring telemetrically. There is a paucity of literature about approaches to accurately monitor blood pressure and flow continuously in large vessels, especially inside the heart using telemetry. We describe our initial experience using two types of TPMSs and discuss their merits.

Methods: Twelve lambs (20-37kg) underwent sternotomy and implantation of either standard (cabled) pressure-monitoring catheter and perivascular flow probe for acute monitoring (C&F group; n=3) or wireless intravascular pressure-, and 3 types of vascular flow-sensors (TPMS group, n=7). The TPMSs used were EG1-V3S2T-M2 (EG1; n=5; Endogear, Transonic Inc.) and Physio-Tel Digital L21 (PTD; n=2; Data Sciences Inc.). The EG1 can measure 2 or more blood pressures as well as up to 3 blood flows. The PTD can measure up to 2 blood pressures but cannot measure blood flow.

Results: Two deaths due to respiratory problems occurred in lambs with EG1. The problems were attributed to lung compression by the battery pack. After moving the battery pack to the subcutaneous space, no respiratory problem occurred. No death was observed in other groups. Aberrant data were easily recognized in TPMS group, thus clear consistent trends of blood pressures and flows were recorded Vs. C&F group. Management of animals was easier and less labor-intensive in TPMS group. Comparing the two different TPMSs, the Initiation cost was ca. $28K (PTD) vs. $20K (EG1) and the renewal cost was $1,700 (PTD sensor exchange) vs. no additional cost (EG1 in-lab reprocessing), for each case. Implantation of TPMS was feasible via median sternotomy in lambs. TPMS significantly improves reliability of hemodynamic monitoring in chronic survival animal study. EG1 was less costly than PTD.

Control System to Diagnosis and Treatment of Failures for Ventricular Assist Devices
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Study: This work proposes applying mechatronic concepts to the develop a safety control system for a Ventricular Assist Device (VAD), a novel control architecture which considers interactions between the VAD and the patient must be proposed. This architecture should: (i) examine events based on the patient behavior; (ii) observe events based on the VAD; (iii) consider fault diagnosis and treatment according to the occurrence of global events. Therefore, a modeling tool which is based on Discrete Event Dynamic Systems theory (DEDS) is used. The safety control system presents indeterminism related to time: events may occur without a correlation with time, but they have a causality relationship between themselves.

Methods: This study used the Hazard and Operability (HAZOP) method to develop this safety control system. Bayesian Network (BN) was used to model Faults Diagnosis Functions. Each Functions is modeled using Petri Nets (PN) for verification and validation. When modeling the faults treatment, PN is also applied. For each fault, a Filter module based on PN is applied for treatment of spurious failures. The set of these models were used in the design the architecture of the Safety Cardiovascular System (SCS), shown in figure below.

Results: This approach allows diagnosis and treatment of failures in VAD systems which can degenerate or regenerate the system to a safe condition depending on the criticality of failure. In vitro and in vivo tests using this architecture are being performed at the Dante Pazzanese Institute of Cardiology.
Six-Year In-Vitro Reliability Results of the HeartWare HVAD® Pump
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Study: The ability of ventricular assist devices (VADs) to provide long-term support will become increasingly important as the destination therapy population expands. The purpose of this experiment was to demonstrate reliability of the HVAD Pump (HeartWare Inc., Miami Lakes, FL) in an in vitro Life Cycle Test (LCT) System.

Methods: Reliability testing was conducted using the LCT System, a custom, pulsatile mock-loop created to produce physiologic pressures and flows. A 35% glycerol borate buffered saline solution was used to simulate the viscosity (2.6 cP), acidity (7.2 pH), salinity (0.9%), and temperature (37°C) of whole blood. A sample size of eight pumps (n = 8) was selected using the Weibull reliability model. The aim was to prove the device was 80% reliable with an 80% confidence interval, considering a 2-year test period. Should no device failures occur within this 2-year test period, the experiment would continue until a device failure was observed. Each of the eight pumps underwent daily speed changes representing low, nominal, and high operating conditions for 6 hours, 17 hours, and 1 hour, respectively. The three operating conditions were achieved by either increasing or decreasing the following simulated physiologic parameters: heart rate, pump speed, pump flow, left ventricular pressure (preload), and aortic pressure (afterload). Pump parameters (voltage, current, speed, estimated flow) and system parameters (system flow, VAD flow, LAP, LVP, AoP, temperature) were recorded every hour.

Results: Eight HVAD Pumps operated for over six years. No device failures of any type occurred during the test period, surpassing the stated experiment goals. Conclusions: Pump testing is currently ongoing and will continue until a device failure is observed. The results of this experiment validate the long-term reliability and durability of the HVAD Pump.

Improved Homocompatibility of Extracorporeal Circuits coated with a Combined Direct Thrombin Inhibitor and Nitric Oxide Releasing Polymer.

Study: Nitric oxide (NO) releasing (NORel) materials have been extensively investigated to create localized increases in NO concentration by the proton driven diazeniumdiolate-containing polymer coatings and demonstrated to improve extracorporeal circulation (ECC) hemocompatibility. In this work, the NORel polymeric coating composed of a diazeniumdiol-dibutylhexanediame (DBH0-N2O2)-containing hydrophobic Elast-eonTM (E2As) polyurethane was combined with a direct thrombin inhibitor, argatroban (AG).

Methods: The AG and control ECCs were evaluated in a 4 h rabbit thrombogenicity model without systemic anticoagulation.

Results: The combined polymer film was coated on the inner walls of ECC circuits to yield significantly reduced ECC thrombus formation compared to argatroban alone. ECC control after 4 h blood exposure exposed to 0.6 + 0.1 AG/HMDI/NORel vs 1.7 + 0.2 pixels/cm2 AG/HMDI control. Platelet count (2.8 ± 0.3 AG/HMDI/NORel vs 1.9 ± 0.1 x 108/ml AG/HMDI control) and plasma fibrinogen levels were preserved after 4 h blood exposure with both the NORel/argatroban combination and the AG/HMDI control group compared to baseline. Platelet function as measured by aggregometry remained near normal in both the AG/HMDI/NORel (63 ± 5%) and AG/HMDI control (58 ± 7%) groups after 3 h compared to baseline (77 ± 1%). Platelet Selectin mean fluorescence intensity (MFI) as measured by flow cytometry also remained near baseline levels after 4 h on ECC to ex vivo collagen stimulation (16 ± 3 AG/HMDI/NORel vs 11 ± 2 MFI baseline). These results suggest that the combined AG/HMDI/NORel polymer coating preserves platelets in blood exposure to ECCs to a better degree than NORel or AG alone. These combined antithrombin, NO-mediated effects were shown to improve thromboresistance of the AG/HMDI/NORel polymer-coated ECCs and move closer to mimicking vascular endothelium.

Leakage of Central Venous Catheter Locking Fluid by Hemodynamic Transport
P. McGah1, K. Gow1, A. Aliseda1. 1Mechanical Engineering, University of Washington, Seattle, WA, 2Seattle Children’s Hospital, Seattle, WA.

Study: Central venous catheters are often filled when not in use with an anti-coagulating fluid, usually heparinized saline, known as the locking fluid. However, the use of heparin locking fluid is associated with known risks, such as bleeding events, due to “leakage” of the lock. Previously, the physical mechanism of the leakage has been hypothesized, based on in vitro experiments, to be fluid motion driven by buoyancy forces between the heavier blood and the lighter locking fluid. However, previous experiments may not be physiologically realistic as these experiments placed heavier fluids inside the catheter which is the opposite of what occurs in vivo. A new hypothesis is proposed here to explain the lock fluid leakage; that the leakage is due to advective and diffusive mass transfer by blood flow around the catheter tip in situ.

Methods: The current hypothesis is justified by mathematical models of a catheter placed inside an idealized model of the superior vena cava. Three-dimension computational hemodynamic simulations are performed to assess the leakage by advective-diffusive mass transfer on time scales associated with the venous pulse (1 second). A one-dimensional mass transfer model is used to assess the leakage on longer time intervals (24–48 hours).

Results: The 3D model predict an initial, fast (<10 s) advection-dominated phase, which depletes most of the initial lock near the catheter tip representing about 10% of the total initial lock amount. The initial phase is followed by a slow diffusion-limited phase whereby an additional 1–2% of locking fluid leaks during a 48 hour period as predicted by the 1D model. The current results predict leakage rates which are closer to published in vivo data (which report about 10% leak over 48 hours) when compared to the buoyancy hypothesis predictions, which tend to grossly over-estimate leakage rates (about 70–80% over 1 hour). The leakage by advection-diffusion predicted by our model also occurs independently of buoyancy effects or lock fluid instillation effects.

Development of Novel Treatment With an Artificial Esophageal Wall for Benign Esophageal Stricture
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Study: Using a large animal model, we examined whether circumferential stricture after esophageal endoscopic submucosal dissection (ESD) can be corrected by grafting a bioabsorbable esophageal patch.

Methods: Circumferential ESD was performed on the thoracic esophagus in pigs (n=6) to create a stricture, for which one of the following interventions was performed: (1) the stricture site was longitudinally incised, and an artificial esophageal wall (AEW) was grafted after placing a bioabsorbable stent (AEW patch group, n=3); (2) endoscopic balloon dilatation (EBD) was performed every other week after stricture development (EBD group, n=3). In both groups, esophageal fluoroscopy was performed 8 weeks after the interventions, and the esophagus was excised for histological examination of the patched site.

Results: (1) In the AEW patch group, esophageal fluoroscopy revealed favorable passage through the patched site. Histologically, the mucosal epithelium and lamina propria had regenerated as in the normal area. (2) In the EBD group, the circumferential stricture site showed marked thickening, and there were hypertrophic scars associated with epithelial defects on the luminal surface. Histologically, defects of the mucosal epithelium and full-thickness proliferation of connective tissue were observed. Esophageal patch grafting was suggested to be a potentially novel treatment strategy for post-ESD esophageal circumferential stricture.

Leakage of Central Venous Catheter Locking Fluid by Hemodynamic Transport
P. McGah1, K. Gow1, A. Aliseda1. 1Mechanical Engineering, University of Washington, Seattle, WA, 2Seattle Children’s Hospital, Seattle, WA.

Study: Central venous catheters are often filled when not in use with an anti-coagulating fluid, usually heparinized saline, known as the locking fluid. However, the use of heparin locking fluid is associated with known risks, such as bleeding events, due to “leakage” of the lock. Previously, the physical mechanism of the leakage has been hypothesized, based on in vitro experiments, to be fluid motion driven by buoyancy forces between the heavier blood and the lighter locking fluid. However, previous experiments may not be physiologically realistic as these experiments placed heavier fluids inside the catheter which is the opposite of what occurs in vivo. A new hypothesis is proposed here to explain the lock fluid leakage; that the leakage is due to advective and diffusive mass transfer by blood flow around the catheter tip in situ.

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High and Low Frequency Subharmonic Imaging of Angiogenesis in a Murine Breast Cancer Model


Study: Comparing fractional tumor vascularity obtained from contrast-enhanced high frequency (HF) and low frequency (LF) subharmonic ultrasound imaging (SHI) to 3 immunohistochemical markers of angiogenesis in a murine breast cancer model.

Methods: 19 athymic, female rats were implanted with 5x10^6 breast cancer cells (MDA-MB-231) in the mammary fat pad. The contrast agent Definity (Lantheus Medical Imaging, N Billerica, MA) was injected in a tail vein (dose: 200 μl/kg) and low frequency pulse-inversion SHI was performed with a modified Sonix RP scanner (Ultrasonix Imaging, Richmond, BC, Canada) using a L9-4 linear array (transmitting at 8MHz and receiving at 4MHz) followed by high frequency imaging with Vevo 2100 (VisualSonics, Toronto, ON, Canada) using a MS-250 linear array transducer transmitting and receiving at 24 MHz in Nonlinear Contrast mode. The radiofrequency image data was filtered using an IIR Butterworth bandpass filter (11-13MHz) to isolate the subharmonic signal (from linear tissue and bubble signals). After the experiments, specimens were stained for endothelial cells (CD31), vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2). Fractional tumor vascularity was calculated as contrast enhanced pixels over tumor area for SHI digital images. Results were compared on per ROI basis using linear regression analysis.

Results: 16 rats of 19 showed tumor growth (84%) and 11 of them were successfully imaged. HF SHI demonstrated better resolution but weaker signals than LF SHI. The strongest correlation determined by linear regression in this breast cancer model was between HF SHI and percent area stained with VEGF (r = 0.38; p=0.034), while there was a trend towards significance for HF SHI vs CD31 and for LF SHI vs COX-2 (r=0.31; 0.07<p<0.09). Fractional tumor vascularity derived from contrast-enhanced HF SHI appears to be a better method than LF SHI for monitoring angiogenesis in a murine breast cancer model; albeit based on a limited sample size.

Linear regression results for FVs of LF SHI nad HF SHI for 3 immunohistochemical markers

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Effect of Rotary Bend Fatigue on the Corrosion Resistance of Common Medical Alloys

J. D. Weaver, C. Hambright, E. Gutierrez, M. Di Prima.

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Study: The effects of fatigue have been thought to be detrimental to corrosion resistance by damaging the surface oxide and through crack initiation, though little research has been done on the topic.

Methods: For this study 316LVM stainless steel, MP35N cobalt-chromium alloy, and nitinol wires were obtained. Given the sensitivity of nitinol behavior to surface finish, electro-polished, mechanically polished, and black oxide wires were obtained resulting in a total of five different wire materials/finishes. Prior to corrosion testing, wires were split into subgroups and subjected to either (1) high strain fatigue for several minutes; (2) phosphate buffered saline (PBS) soak for several minutes; (3) low strain fatigue for eight days; (4) PBS soak for eight days; (5) long-term PBS soak for seven weeks; or (6) nothing, i.e. as received. All wire fatigue testing was conducted with guided bend rotary bend fatigue testers in PBS at 37°C and at a test speed of 60 Hz; none of the fatigue samples fractured prior to corrosion testing. Potentiodynamic polarization testing was performed to ASTM F2129 for all wires and a post-test visual inspection was performed on all samples.

Results: Overall, any difference in the corrosion behavior could be accounted for by PBS soak time with minimal effect from fatigue. With the exception of the black oxide nitinol, the breakdown potential was not affected by any of the fatigue or soak conditions. While all materials had differing rest potential in the as received state, increasing PBS soak time showed a convergence of the rest potential to 0 mV for all materials. This led all materials except for the black oxide nitinol to have a normalized breakdown potential (difference in breakdown and rest potential) to converge to the vertex potential of the test, 1000 mV. Based on the materials and conditions tested, it appears that conducting fatigue testing on samples prior to corrosion testing does not greatly affect corrosion behavior.
Development of Noble Autologous Heart Valve (Biovalve)
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Study: A novel autologous aortic valve with a metallic stent (Biovalve Stent) was developed, using simple, safe and economical in-body tissue engineering. In this study, the long-term evaluation of the Biovalve Stent for transcatheter implantation was investigated in a goat model.

Methods: Biovalve Stents were prepared by 2-month embedding of the molds, assembled using plastic rods and a metallic stent, in the subcutaneous spaces of goats. After extracting the molds and removing the plastic rods only, Biovalve Stents with tri-leaflets similar to those of the native aortic valves were constituted from completely autologous connective tissues. Fourteen out of 19 Biovalve Stents were implanted in the aorta in situ and other 5 Biovalve Stents were implanted in the pulmonary artery (PA) in situ with transcatheter technique.

Results: In both aortic and PA cases, the Biovalve Stents were successfully implanted. Angiography showed smooth movement of the leaflets with a little regurgitation under the systemic and pulmonary circulation. The Biovalve Stents were extracted 1, 2 or 5 months after implantation. The leaflets of the Biovalve kept their shape and elasticity even after 5 months and neither calcification nor thrombi were observed. Histological examination showed the cell populations inside the valves and endothelial cells covering the laminar surface of the valve leaflets. In conclusion, the Biovalve Stent satisfied the higher requirements of systemic and pulmonary circulation in goats for 5 months with the potential for transcatheter implantation.

Evaluation of Functionality of Modified Red Blood Cells for Intravascular Drug Delivery
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Study: Drug delivery using autologous red blood cells (RBCs) as biocompatible vehicles is a promising novel technology which may enhance effectiveness and safety of intravascular drugs. It has been proposed that Camptothecin (an antitumor drug) incubated with dimethyl sulfoxide (DMSO) can be attached to NHS_BaPDMAA_Rodamine-B polymer that can in turn be attached to RBCs. One important issue for application of modified RBCs is preservation of their functionality. The major objective of this project was assessment of functionality of the modified RBCs via evaluation of their morphology and deformability.

Methods: RBCs were modified with a camptothecin monomer attached to the NHS_BaPDMAA_Rodamine-B polymer. Cell modification was confirmed by fluorescent microscopy, and deformability of the modified RBCs under shear was evaluated using the Linkam CSS450 optical shearing system. Images obtained at each shear stress were analyzed using ImageJ software. Samples were additionally analyzed on the second post-modification day to ensure stability of RBC/drug constructs. Statistical analysis was conducted using Student t-test.

Results: We found that modifying RBCs with a camptothecin-polymer construct did not significantly change the deformability (Figure 1, p>0.05) and morphology of the cells (Figure 2). These findings support the hypothesis that RBCs can be utilized for intravascular delivery of drugs where the integrity of the modified RBCs is maintained for at least 24 hours after modification.

Figure 1. Linkam photographs of modified RBCs show normal deformability under 100 s⁻¹ (left), 500 s⁻¹ (middle) and 1000 s⁻¹ (right).

Figure 2. Comparison of modified (left) and unmodified (right) RBCs.
A 0-D/3-D Multiscale Multiphysics Approach to Computational Fluid Dynamics Studies of Cardiopulmonary Bypass

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Study: Neurological complications often occur during cardiopulmonary bypass (CPB). Hypoperfusion of brain tissue due to diminished cerebral autoregulation (CA) and thromboembolism from atherosclerotic plaque reduce the cerebral oxygen supply and increase the risk of perioperative stroke. To improve the outcome of cardiac surgeries, computational fluid dynamic (CFD) models can be used to investigate the blood flow during CPB.

Methods: In this study, we established a CFD model of CPB which included cerebral autoregulation and movement of aortic walls. CA was represented with a 0-D control circuit model of the Baroreflex mechanism. The model parameters were assessed with respect to their physiological meaning and their influence on the cerebral blood flow (CBF). Additionally, a fully coupled Fluid-Structure Interaction (FSI) model taking the arterial compliance into account, was set up. Afterwards, the 0-D cerebral autoregulation model was transferred to 3-D FSI. The wall shear stress (WSS) distribution, a major risk factor of atherosclerotic plaque rupture, was computed for the whole FSI domain. Material parameters for the structural part of the simulation were identified with MRI measurements of the aortic arch cross section.

Results: The results show the advantages of a 0-D/3-D multiscale multiphysics approach for CFD simulations of CPB. The Baroreflex mechanism can mimic hypertensive and impaired autoregulation states. The effects of anesthetic agents on the dynamic CA can be reproduced as well. All parameters can be assessed with in vivo measurements of CBF and perfusion pressure. A transfer to the 3-D domain is feasible and delivers similar results of CBF as the 0-D representation. The FSI model delivers higher WSS and thus predicts a higher plaque rupture risk than rigid wall CFD. A neglect of wall movement is therefore a major limitation. The presented framework delivers a tool to identify an optimal perfusion technique based on non-invasive measurements.

Geometric Design of Spiral Groove Bearing to Reduce Hemolysis in a Hydrodynamically Levitated Centrifugal Blood Pump

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Study: The purpose of this study is to design the spiral groove geometry in a hydrodynamically levitated centrifugal blood pump for improvement of hemolytic property.

Methods: A numerical analysis based on a simplified viscous fluid dynamics equation was performed in order to examine the hydrodynamic force in a spiral groove bearing. The geometry parameter of the spiral groove was defined as the groove width. The outer and inner radii of the spiral groove were 18.5 and 8 mm, respectively, and the bearing gap was set at 5 μm. Two different spiral groove geometries were compared in the evaluation test. In the conventional model, the groove width is the same as the ridge width in the radius and circumferential direction. In the contraction model, the groove width decreased inwardly from 9.7 to 0 mm. In order to measure the bottom bearing gap, an impeller levitation performance test was conducted using a laser focus displacement meter at a pressure head of 200 mmHg and a flow rate of 4.0 L/min. An in vitro hemolysis test was also performed to evaluate the normalized index of hemolysis (NIH), at a pressure head of 200 mmHg and a flow rate of 4.0 L/min.

Results: As a result of the numerical analysis, the hydrodynamic force of the contraction model was approximately 8 times larger than that of the conventional model. In the impeller levitation performance test, the bottom bearing gap of the contraction and the conventional models were 90 and 26 μm, respectively. In the hemolysis test, the NIH values of the contraction and the conventional models were 0.027 and 0.411 g/100 L, respectively. In comparison, the NIH values of BioPump BPX-80 and Nikkiso HPM-15 were 0.043 and 0.030 g/100 L, respectively. These results indicate that the contraction model is effective at reducing hemolysis.

Conclusion: We confirmed that the contraction model for the spiral groove of a hydrodynamically levitated centrifugal blood pump achieved large bearing gap with enough hydrodynamic force and improved hemolytic property.
Hyperspectral Imaging of Thrombus Formation in a Hydrodynamically Levitated Centrifugal Blood Pump

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Study: Blood coagulation is one of the primary concerns when using mechanical circulatory support devices such as blood pumps. The objective of this study is to develop the optical non-invasive imaging of thrombus formation in a rotary blood pump.

Methods: In vitro antithrombogenic testing was conducted with a hydrodynamically levitated centrifugal blood pump developed by our laboratory using bovine whole blood in which the activated blood clotting time (ACT) was adjusted to 200 sec. The blood was circulated at 1.0 L/min against the 120 mmHg by the pump rotating at 2780 rpm. A halogen light including the wavelength from 400 to 800 nm was used for the light source. The backward scattering on the pump bottom area were imaged using a hyperspectral imaging (HSI) system (HSi-300, ChromoDynamics, Inc., USA). The system imaged the spectral picture at wavelength ranging from 600 to 750 nm. The changes in the spectrum in the pump during the experiment were analyzed.

Results: Although the normal 24 bits digital picture in Fig.(a) could not image the inside of the pump, HSI could image the impeller, the vanes, shroud pattern in blood as shown in Fig.(b). In the area of thrombus formation, the spectral gravity shifted to a longer wavelength. The index of the spectral shift is defined as τ, which is the wavelength when its intensity equals the intensity at 750 nm. Although the τ in the normal whole blood area was 644 nm, the τ was increased in the thrombus formation area. The spectral shift area was imaged as shown in Fig.(c).

Conclusion: HSI is useful for the evaluation of hemocompatibility of devices and the management of blood coagulation to avoid risk of infarction in the extracorporeal circulation therapies.

QuickSeeding Blood-Derived Endothelial Cells onto Ventricular Assist Device Surface Generates an Anti-Thrombotic Lining

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Study: The demand for heart donors for transplantation exceeds their supply by 50-fold. Promising alternatives to heart transplantation are ventricular assist devices (VADs). Yet, VAD therapy is limited by thrombosis complications. To reduce these, sintered titanium (Ti) surface was developed but thrombosis still occurs in 7.5% of patients during 1 year VAD support. To minimize thrombosis we have developed a QuickSeeding technology to rapidly endothelialize sintered Ti surface with blood-derived endothelial cells (ECs). We had previously demonstrated that QuickSeeding smooth Ti tubes with autologous porcine ECs prevents thrombosis in pigs.

Methods: Human ECs were isolated from umbilical cord blood and QuickSeeded (45 min) onto sintered Ti tubes (r= 0.63cm) with a rotating seeding device (1–4 x 10^6 ECs/ml, 10 Revolutions/hr). EC adhesion was evaluated with scanning electron and confocal microscopy and colorimetric metabolic assay after QuickSeeding and 20 hr exposure to 4.4 dynes/cm2 in a modified cardiopulmonary bypass circuit (L-15 medium + 3% dextran, flow rate= 2500 ml/min). To assess functionality, EC-seeded Ti was tested with a platelet adhesion assay after > 2 wk static culture (37oC, 5%CO2). After 20 hr 4.4 dynes/cm2, nitrite production was quantified as a marker of NO secretion.

Results: 77 ± 7% of QuickSeeded ECs adhered and grew to a confluent monolayer on Ti after 20 hr static incubation (Fig.1, n= 4). Following 20 hr of flow, 69 ± 1% ECs remained adherent on Ti (initial seeding density= 3.4 x 10^5 ECs/unadjusted cm2 surface area, n= 3). After > 2 wk static maintenance, significantly less platelets adhered on EC-seeded Ti than bare Ti (Fig. 2, n= 3, p<0.001, paired t-test). NO secretion increased significantly after 20 hr of flow as compared to static control (321 ± 255 vs. 2 ± 1 nmol/10^6 ECs, n= 3, p<0.001, paired t-test). Our results demonstrate the feasibility of rapidly seeding sintered Ti with blood-derived ECs to generate an anti-thrombotic surface.
Study on Evaluation of Cell Growth Potential With Cell Aging for Culture Process Simulation

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Study: In the rapid construction of the cell tissue, it is important to design a three dimensional structure of scaffold. However, the culture process simulating is difficult to evaluate cells within three dimensional structure, because individual cells change by growth potential in each. It is necessary to evaluate based on the cell behavior, which are evaluated by non-invasive visualization. In this study, the cells growth potential with cell aging has been evaluated by using newly index that cell migration flux was migration rate per projection area.

Methods: In order to evaluate cell behavior with cell aging, HPASMC cells was captured in each passage culture by using real time monitoring system. Cells migration rate and cells projection area were measured at early cell culture by using image analysis. The passage culture of HPASMC cells was shown that the ratio of individual cells with fast migration (over 72 μm/hour) decreased with increased of culture passage. Cells in an early culture passage indicated the average projected area increased over time. Moreover, the calculated cell migration flux as evaluation index for quantification of cell growth potential was investigated relation of residual number of cell divisions that is the cell aging.

Results: The migration flux of individual cells decreased with decreased residual number of cell divisions. In conclusions, it was suggested that migration flux can be evaluated cellular potential to measure migration rate and projected area at Elapse time in cell culture process. Additionally, it was suggested that cell migration flux was useful for evaluation of cell growth potential in cell culture process and quality evaluation.

Intraventricular Flow Patterns and Stasis in the LVAD-assisted Heart

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Study: Left ventricular assist device (LVAD) support disrupts the normal blood flow path through the heart, introducing flow patterns associated with thrombosis, especially in the presence of medical devices. The aim of this study was to quantitatively evaluate the flow patterns in the left ventricle (LV) of the LVAD-assisted heart, with a focus on alterations in vortex development and stasis.

Methods: Particle image velocimetry of a LVAD-supported LV model was performed in a mock circulatory loop.

Results: In the Pre-LVAD flow condition, a vortex ring initiating from the LV base migrated toward the apex during diastole and remained in the LV by the end of ejection. During LVAD support, vortex formation was relatively unchanged although vortex circulation and kinetic energy increased with LVAD speed, particularly in systole. However, as pulsatility decreased and aortic valve opening ceased, a region of fluid stasis formed near the left ventricular outflow tract. These findings suggest that LVAD support does not substantially alter vortex dynamics unless cardiac function is minimal. The altered blood flow introduced by the LVAD results in stasis adjacent to the LV outflow tract, which increases the risk of thrombus formation in the heart.

Mitral Regurgitation Compromises Cardiac Function During LVAD Support

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Study: Mitral valve regurgitation (MVR) is often present in patients at the time of LVAD implantation, and is expected to decrease as the LVAD is unloaded. However, in some patients, severe MVR remains, which represents a limitation for exercise capacity and recovery. The goal of this study was to measure the effect of MVR on the hemodynamics of the LVAD-supported heart using a mock circulatory loop.

Methods: A HeartMate II continuous flow LVAD was integrated into the SDSU cardiac simulator and the aortic valve was closed off to ensure series flow conditions. LV pressure, aortic pressure, and aortic flow were measured for an experimental matrix that included: 3 levels of cardiac function (Med, Low, Off), 3 levels of LVAD speed (7, 9, 11 krpm), and 4 levels of MVR (None, Moderate, Severe, Open).

Results: Transmissional pressure and flow increased with cardiac function and LVAD speed, and decreased with increasing MVR. Increased cardiac function augmented flow under all conditions except during the highest speed and greatest MVR. Pulsatility index was decreased by both increased LVAD speed and increased MVR. The results of this study provide some quantitative estimate of the impact of MVR on LVAD hemodynamics. The findings suggest that MVR decreases the augmentation of forward flow produced by improved cardiac function, diminishing exercise capacity. These results indicate that LVAD support is enhanced when the MV is able to hold pressure and should be repaired in LVAD recipients with a closed aortic valve.

The Effect of Mitral Incompetence During LVAD Power Loss In Patients With a Closed Aortic Valve

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Study: Aortic valve closure is performed in patients with aortic prostheses and in some with severe aortic incompetence. One concern in these patients is whether their native cardiac function could support sufficient cardiac output in the event that the LVAD loses power, as the only path for flow from the heart is through the LVAD. The goal of this study was to measure the effect of power loss on the hemodynamics of the LVAD-supported heart using a mock circulatory loop, and study the impact of mitral valve regurgitation (MVR).

Methods: A HeartMate II continuous flow LVAD was integrated into the SDSU cardiac simulator and the aortic valve was closed off. LV pressure, aortic pressure and aortic flow were measured for experimental conditions that included 2 levels of cardiac function (Med, Low) and 4 levels of MVR.

Results: The results show that a modest level of cardiac output through the LVAD can be maintained by the native heart when the LVAD is unloaded. However, in some patients, severe MVR remains, which represents a limitation for exercise capacity and recovery. The goal of this study was to measure the effect of MVR on the hemodynamics of the LVAD-supported heart using a mock circulatory loop, and study the impact of mitral valve regurgitation (MVR). The findings indicate that LVAD support is enhanced when the MV is able to hold pressure and should be repaired in LVAD recipients with a closed aortic valve.
In Vivo Validation of Ultrasound Image Velocimetry
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Study: Doppler ultrasound is currently the standard for measurements of blood velocity. An inherent limitation is that Doppler methods only measure the velocity component parallel to the ultrasound beam. Ultrasound Image Velocimetry (UIV) is an ultrasound technique in which regions of two sequential B-mode images are cross-correlated to calculate 2-D velocity vectors for a fluid containing scatterers. The aim of this work was to compare in vivo UIV measurements with Doppler ultrasound and invasive, transit time measurements of flow rate.

Methods: A rabbit was anesthetised and imaged through the abdomen using an Ultrasonix RPS500 with a linear transducer giving a longitudinal section through the aorta. Ultrasound contrast agent was administered as a continuous infusion via the ear vein using a syringe pump. A novel imaging sequence was used to interleave two ultrasound frames, effectively reducing the interframe time difference and enabling high arterial velocities to be measured across the entire field-of-view. Radiofrequency data were acquired at 7 MHz (sampled: 40 MHz) for ~100 cardiac cycles. The RF data were post-processed offline using in-house code which calculates the local correlation between successive frames, then sums the correlation results for identical phases of all the cardiac cycles. UIV results were compared with the Doppler spectrum as well as transit time flow measurements from a similar rabbit.

Results: The shape of the velocity waveform measured with UIV was in good agreement with the Doppler spectrum (within 10 cm/s) and peak systolic velocities were 99 cm/s and 104 cm/s with UIV and Doppler respectively. Peak systolic flow was calculated to be 175 ml/min, within the range found for similar anaesthetised rabbits.

Polymer-linked Argatroban Provides an Effective and Safe Nonthrombogenic Coating for Extracorporeal Circulation
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Study: Attempts to eliminate systemic anticoagulation for extracorporeal circulation (ECC) by creating a nonthrombogenic surface using heparin have been ongoing with limited clinical application. We propose a new polymer coating for a nonthrombogenic ECC circuit using a direct thrombin inhibitor, argatroban. Although heparin has long been in use, argatroban provides two significant benefits over heparin: it functions as a direct antithrombin inhibitor, not dependent upon plasma antithrombin III, and is not associated with a life-threatening allergic syndrome (heparin-induced thrombocytopenia). An in-vitro antithrombin chromogenic assay compared the effects of argatroban linked to a polymer versus an unlinked argatroban-containing polymer.

Methods: The in vitro assay consisted of formation of a chromophore (405 nm) from the reaction of the chromophore-containing substrate with 0.03 Units/ml of human thrombin. Argatroban inhibits this reaction. The synthesis of the argatroban-linked polyurethane/silicone polymer (CarboSi) polymer follows a two step process: 1) Carbosil underwent amidation with a linker, hexamethylene diisocyanate, followed by 2) binding of argatroban to the NCO-Carbosil polymer intermediate. The unlinked argatroban-Carbosil polymer was prepared as control. The amount of argatroban used ranged from 1 to 30 umoles in the unlinked polymer while 30 umole argatroban was used in the linked polymer. Both the linked and unlinked polymer were coated on the surface of 96 well plates.

Results: The assay showed antithrombin activity for both the argatroban bound via the linker and without linker. However, the plate without the linker showed after 24 h incubation at 37°C with buffer, 34 x more argatroban compared to the 24 h leaching of linked argatroban. This data suggests that a linker is necessary for argatroban binding to a polymer to achieve an effective and safe nonthrombogenic ECC circuit.
Ultraviolet Radiation Affects Thoratec© HeartMate II Driveline Tensile Properties

Study: Longevity and quality of life for left ventricular assist device (LVAD) patients are plagued by driveline exit site infections. Ultraviolet (UV) radiation is currently used in wound healing clinics as a method of treating dermal wounds and could potentially treat LVAD exit-site infections. However, the effect of UV radiation on the tensile properties of HeartMate II (HMII) driveline material is unknown.

Methods: The sleeve of a single HMII driveline was cut into 60 samples and distributed into 6 exposure groups (n=10/group, 5 exposed and 5 unexposed). The 6 groups were further divided into 2 treatment cohorts designed to replicate wound treatment schedules of post-implant LVAD patients. Treatment cohort 1 (groups 1–3) was exposed 3x a week for 4 weeks with exposure times of 60s, 120s, and 180s respectively. Treatment cohort 2 (groups 4–6) was exposed 2x a week for 6 weeks with exposure times of 240s, 300s, and 360s respectively. Strip biaxial tensile tests were performed on both unexposed and exposed samples to analyze changes in material elasticity (Young's modulus), point of deformation (offset yield), and breaking point. Repeated measure ANOVA calculations accounted for intra-driveline variability, and a p-value < 0.016 was considered significant after correcting with the Bonferroni approximation.

Results: After exposure the Young's modulus, offset yield, and break point had average changes of -5.6%, +43%, and -4.5%, respectively (n=60). Results of the ANOVA calculations are shown below comparing group as well as treatment cohort results.

<table>
<thead>
<tr>
<th>Changes in Baseline Material Properties After UV Exposure</th>
<th>Group Comparison (Groups 1–6) p-value</th>
<th>Treatment Comparison (Groups 1–3 vs. 4–6) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young's Modulus</td>
<td>0.011</td>
<td>0.012</td>
</tr>
<tr>
<td>Offset Yield</td>
<td>0.051</td>
<td>0.042</td>
</tr>
<tr>
<td>Breaking Point</td>
<td>0.273</td>
<td>0.280</td>
</tr>
</tbody>
</table>

Our data suggests that UV exposure changes the elasticity of the HMII driveline. However, the material endured aberrantly large forces and the properties remained within the safety threshold of device performance. Therefore, the changes are likely not clinically relevant and the efficacy and safety of UV for exit site infection treatment should be further explored in clinical trials.

Apico Aortic Blood Pump: Short Term in vivo Report

Study: Background: Apico Aortic Blood Pump (AABP) is a centrifugal intrathoracic Left Ventricle Assist Device. AABP's In Vitro studies have demonstrated that the device has adequate performance for use in Bridge to Transplantation Therapy. This work reports short term In Vivo experiments with AABP. Objective: Evaluate AABP's and organism responses to the implantation and also evaluate implant technique.

Methods: AABP was implanted in three pigs (female, ~140 lb). AABP's inlet cannula was inserted directly in the left ventricle, and outlet cannula was connected to the ascending aorta. After surgery, each animal was maintained for 6h, during this time, device performance and the animal were continuously monitored.

Results: In the first experiment, animal's heart fibrillated during anastomosis procedure. This fibrillation compromised animals's cardiovascular system and the experiment was interrupted. Anatomical studies indicated no abnormalities. In the second experiment, there was none registry of problems, device implantation time was 1h and total surgical time was 2h30. AABP's performance was satisfactory during the experiment and also no clinical abnormality was observed. For third experiment, a new outlet cannula connection system was implemented, which contributed to device implantation time reduction from 1h to 30 min, in this experiment, total surgical time was 2h. There was no device failure or clinical abnormality.

Conclusion: Through these experiments, it was possible to evaluate AABP surgical procedure and improve it with a new outlet cannula connection system. Clinical observations indicated no abnormal organism response. Also, AABP presented no performance failure during the experiments.
Control Strategy for Preventing Suction and Maintaining Physiological Perfusion With Rotary Blood Pumps

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Study: Rotary blood pumps have successfully demonstrated clinical benefit in the treatment of patients with advanced and refractory heart failure. However, potential risk of left ventricular suction events while maintaining adequate perfusion over a wide range of physiologic conditions remains a significant clinical concern. To address this challenge, we developed a suction prevention and physiologic control algorithm for use with axial and centrifugal left ventricular assist devices (LVAD).

Methods: A suction detection and physiologic control algorithm was developed using two gain-scheduled, proportional-integral controllers that maintain a differential pump speed (ΔRPM) above a user-defined threshold to prevent LV suction while also maintaining an average reference differential pressure (ΔP) between the LV and aorta to provide physiologic perfusion. Efficacy and robustness of the proposed algorithm were evaluated in-silico during simulated rest and exercise test conditions for (1) excessive ΔP/RPM setpoint (ES); (2) rapid eight-fold increase in pulmonary vascular resistance (PVR); and (3) ES and PVR. Characterizing hemodynamic waveforms (left ventricular pressure and volume; aortic pressure and flow) were simulated for up to 300 seconds, and analyzed for detection of suction event(s) and quantification of total flow output (pump + cardiac output).

Results: The computer simulation results demonstrated that the proposed algorithm prevented LV suction while maintaining physiologic perfusion for all tested conditions (Figure 1). The algorithm also offers the following advantages: ease of use and implementation, pump-independent, and may be applied to most current LVAD. The proposed algorithm may be implemented by estimating pump pressure head from intrinsic pump parameters only and does not require any external sensors.

Computational Simulations of Embolus Migration in the Inferior Vena Cava

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Study: Pulmonary embolism (PE) is estimated to be the cause of at least 100,000 deaths in the United States each year. Anticoagulation therapy is generally used to treat the condition. However, when anticoagulants are contraindicated, an inferior vena cava (IVC) filter is often placed as a prophylaxis. In some cases following IVC filter placement, PE still occurs. Many studies have investigated the hemodynamic effects of IVC filter implantation and embolus presence using rigid embolus and vein models in steady-state flows. However, no studies have addressed the transient hemodynamics that occur during embolus migration and capture, which determine the location and orientation of captured emboli, and the potential for flow-induced deformations that could lead to embolus escape, and ultimately, recurrence of PE.

Methods: This study investigates the migration and capture of deformable emboli in an IVC filter using a novel overset-mesh fluid-structure interaction (FSI) simulation approach. Specifically, the Bard G2 Express IVC filter is studied in an idealized IVC at a flow rate of 1.2 liters per minute. FSI is modeled using a tightly-coupled arbitrary Lagrangian-Eulerian formulation with an in-house finite-element code solving the structural equations and an open-source finite-volume code (OpenFOAM) solving the fluid equations (Navier-Stokes). Sugar++/DIRTlib provide overset mesh capabilities, which allow for large six-degree-of-freedom (6-DOF) motions of simulated emboli without remeshing.

Results: An overview and validation of the computational technique is presented, and simulations of the migration and capture of emboli are shown.
Designing and Developing a Mold for the Framework of an Artificial Bileaflet Mitral Heart Valve

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Study: The function of the heart’s valves is to assist the perfusion of blood through the body and prevent back flow into the heart. However, deficiencies in the heart valve such as stenosis, regurgitation, and prolapse, are prevalent throughout the world and especially in developing countries. Out of the heart’s 4 different valves, the mitral valve is by far the most difficult to reconstruct due to its unique saddle-shaped annulus and the mechanical stress induced on the tip of the leaflets. The purpose of this study is to develop the framework of the mitral valve using the shape memory alloy, Nitinol.

Methods: We designed a custom-made mold to constrain a piece of 0.51 mm diameter Nitinol wire using SolidWorks. The mold was 3D printed in 15-5 stainless steel due to its robustness and high melting point. After placing the wire into the mold, we heat treated it at 550 °C for 5 minutes to fine-tune the Nitinol wire’s transformation temperature.

Results: The 3D printed mold (1.65” x 1.65” x 1.17”) was developed with minor burns to the part. After the heat treating process, the Nitinol wire exhibited superelastic properties and conformed to the particular dimensions we specified in our CAD software. The Nitinol frame can pave the path for future studies with regards to developing a bileaflet bioprosthetic valve.

Further Development and Validation of RBC Mechanical Fragility Test

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Study: Andrew Wearden and Luke Ziegler are co-first authors. Characterization of red blood cell (RBC) susceptibility to mechanical shear stress, or RBC mechanical fragility (MF), is an important parameter in the assessment of blood quality and is of particular relevance to in vitro hemolysis testing of blood contacting devices. The rocker bead test with the calculated mechanical fragility index (MFI) has emerged as a simple method for the measurement of MF. MF tests have been used to compare the biocompatibility of blood contacting devices and to demonstrate the extent of sublethal membrane damage which occurs during RBC storage. Since the current test is hematocrit (Ht) dependent and requires ~20 mL of blood or RBC suspension, further development is necessary to reduce blood volume and enable intra-hematocrit comparison.

Methods: A test consists of five standard test tubes filled with blood, three of which contain five 1/8” stainless steel ball bearings, and rocked using a platform mixer (18 cycles/min, 17° angle) for one hour. MFI is computed as a function of total hemoglobin and the difference in free hemoglobin between rocked and control tubes. Experiments were performed using a normal donor pool at varying hematocrit values prepared by dilution with autologous plasma and at two sizes of test tube sample volumes.

Results: A strong exponential correlation ($R^2 = 0.85$) (Figure 1) was found between Ht and MFI, allowing for a correction factor. A linear relationship ($R^2 = 0.95$) was also seen between MFI values obtained using small and large sample volumes in parallel tests (Figure 2), establishing the validity of the reduced volume method to measure MF. With the increased interest in ex vivo organ perfusion as a method of donor organ preservation, work is ongoing investigating the MF of RBCs suspended in several commercial, clinical, and experimental organ perfusion solutions.
Comparative Evaluation of Nanoscale Surface Coatings on Silicon Substrates for Implantable Device Applications

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Study: Highly uniform silicon nanopore membranes (SNM) are under investigation for use in implantable devices for organ replacement functions. A robust, readily scalable, non-fouling surface coating is required to enhance SNM biocompatibility while preventing pore occlusion. We evaluated a number of thin-film surface coatings compatible with silicon processing techniques. Five candidate biocompatible coatings were optimized for sub-5 nm deposition and evaluated for protein resistance.

Methods: Silicon surfaces were modified using 1) surface grafted self-assembled monolayer polyethylene glycol (PEG); 2) RF plasma polymerized PEG; 3) poly(sulfobetaine methacrylate) (pSBMA) grown on surface via atom-transfer radical polymerization (ATRP); 4) poly(2-methacryloyloxyethyl phosphorylcholine) (pMPC) coated via ATRP; and 5) titanium oxide (TiO2) deposited via atomic layer deposition. Coating thickness was determined by ellipsometry. Protein adsorption was determined by enzyme-linked immunosorbent assays after 2-hour incubation in single protein solutions of human fibrinogen and albumin. All adsorption data was normalized to uncoated silicon substrates. Results: Average coating thickness for the coatings ranges between 0.7 nm to 4.7 nm (Figure 1). All coatings exhibited reduced protein adsorption compared to non-coated substrates (Figure 2). TiO2-coated silicon had the highest overall fouling, while pSBMA exhibited least fouling with an 84% reduction in human albumin adsorption and 98% reduction in human fibrinogen adsorption compared to bare silicon. The results demonstrate that pSBMA-coated surface exhibit superior non-fouling characteristics that make it suitable for application to SNM-based devices.

Heparin Leakage in Central Venous Catheters

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Study: Central venous catheters (CVCs) are used to provide vascular access during hemodialysis in patients with end-stage kidney disease. Despite several advantages and widespread use, CVCs have a high incidence rate of clot formation. In an attempt the prevent thrombosis at the catheter tip, hospitals routinely fill the catheter with heparin, an anticoagulant, during the interdialytic phase that usually lasts 48 hours - a procedure known as “heparin locking”. It has been reported, however, that up to 40% of the heparin solution will leak into the blood stream during the interdialytic phase, placing the patient at risk for systemic bleeding incidences. The aim of this study is to determine the role that advective-diffusive transport plays in the heparin leaking process and to quantify the amount of heparin lost during the interdialytic phase. This work is motivated in particular by pediatric hemodialysis where the risks associated with CVCs are exacerbated.

Methods: Planar Laser Induced Fluorescence (PLIF) is used to experimentally measure heparin transport from a CVC placed in an idealized Superior Vena Cava with physiologically accurate pulsatile flow conditions.

Results: Initial PLIF measurements show very high losses of heparin immediately following catheter filling (1–5 cardiac cycles), but this short period is followed by a rapid, almost exponential, decay of heparin flux. The advective flux caused by the flow in the central vein quickly lowers the concentration of heparin at the catheter tip and the diffusion-dominated transport inside the catheter lumen, where the concentration remains high, is insufficient to replenish the concentration at the tip. Although the risk of systemic heparinization seems to have been overestimated, the heparin concentration is effectively zero at the catheter tip for the majority of the interdialytic phase - possibly rendering the heparin locking procedure ineffective. This analysis is applied to multiple CVC configurations in the hope of improving catheter design and heparin locking procedures.
Magnetic Apheresis Device for Filtration of Malaria-Infected Red Blood Cells
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Study: The Plasmodium falciparum malaria parasite causes nearly one million deaths per year across over 100 countries. The parasite invades the host’s red blood cells (RBC), feeding off of the RBC’s hemoglobin and creates a magnetic byproduct. Severe malaria occurs when the concentration of infected RBCs (iRBC) exceeds 5%, often leading to death in less than 24 hours. Therapies include parental quinine or artesunate treatments. However, parasites have become resistant to these drugs thus limiting their effectiveness. Exchange transfusion (ET) has been used as an adjunct treatment yet its efficacy remains the subject of clinical debate. mPharesis, a magnetic dialysis-like device, is in development to remove a patient’s iRBCs without removing the healthy RBCs while minimizing plasma loss. The device provides a useful alternative to ET while being more accessible to low-resource settings where blood supply is limited. Here, preliminary data on an early device prototype is reported.

Methods: Experiments were conducted in-vitro using iRBCs and a blood analog composed of a mixture of healthy and methemoglobin RBCs (metRBC). Methemoglobin, created in-lab, is a modified form of hemoglobin with similar paramagnetic properties as iRBCs and occurs naturally in low percentages in humans. Tests were conducted with multiple hematocrits and flow rates.

Results: The concentration of metRBC was reduced by as much as 52.0% for 15%Hct and 10.7% for 40%Hct in a single pass at a flow rate of 0.05mL/min. Ongoing activities include design modifications to increase efficiency and throughput. In addition to malaria treatment applications, the mPharesis device could potentially be used as an alternative to ET with other disease management, such as Sickle-cell disease.

MVAD® Impeller Modification: Computational and Experimental Evaluation
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Study: Computational Fluid Dynamics (CFD)-based modifications of the MVAD impeller and corresponding hydraulic and hemolysis performance tests were conducted.

Methods: CFD was used to evaluate different impeller modifications. CFD-predicted HQ curves, velocity streamlines and shear stress contours were utilized as comparison indices. Hemolysis potentials were analyzed using the power-law based Eulerian method and the critical volume above the shear stress of 150 Pa. The thrust bearing design was revised based on the Reynolds’ equation calculations. The updated impeller design was fabricated and compared to the original design using nominal HQ measurements and in-vitro hemolysis experiments with bovine blood.

Results: The modified impeller doubled the calculated hydraulic efficiency, and reduced the required speed to achieve the same hydraulic condition by almost 3000 RPM. Front and rear edge modifications to the flow channels provided better streamlines and thus less shearing flow channels. The redesigned thrust bearings maintained the original radial stiffness. The critical shear stress volume was decreased by 75% and reflected in the calculated hemolysis index by a reduction of over 2.5 fold. The HQ experiments supported the CFD predictions on the hydraulic enhancement. The hemolysis tests indicated minimal red blood cell damage. CFD was successfully utilized to modify the MVAD impeller. As supported by the experimental data, the hydraulic and hemolytic performance of the MVAD Pump was significantly enhanced. Caution: Investigational device, limited by United States law to investigational use.
Changes Induced in Stem Cells Shape and Orientation Using Laser Patterning

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Study: Surface topography in the micron to nanometer range may improve biocompatibility. Polyurethanes (PU) are used in medical devices because of their good mechanical properties and biocompatibility. However, they may induce thromboembolic events and other undesirable surface-localized reactions. We hypothesised that topographical patterns produced on PU substrates by Direct Laser Interference Patterning (DLIP) technology may influence cell adhesion and growth.

Methods: Pillar- or line-like periodic micro-structured surfaces were obtained with a high-power pulsed (pulse duration: 10 ns; repetition rate: 10 Hz) frequency tripled Nd:YAG laser (Quanta Ray, Spectra Physics) to produce a linearly polarized beam of wavelength 266 nm. Laser fluence (F) was 700–1000 mJ/cm². After institutional approval, adipose tissue stem cells were collected from adult male Wistar rats and grown on PU substrates. We defined 5 groups: untreated PU as control, pillar-like structures of 10 µm width tracks, line-like structures with 10, 3 and 1 µm width tracks. Changes in cell area, ratio between axis and perimeter were measured with the Zen software (Zeiss, Germany) and data are summarized in the table. Statistical analysis was performed with ANOVA (SigmaStat 3.1, USA) and the Tukey test used for post hoc comparison. Results were considered significantly different from control at P < 0.05 and marked with an * in the table. Data are expressed as means ± SD.

Results: Cellular area was altered in the 10 µm track width groups but not in the 3 or 1 µm groups. As track width decreased, cells changed their shape to a more elongated shape, readily evident in the 3 and 1 µm track width groups, aligning with the direction of the pattern. A representative image of a 3 µm line-like pattern with cells is shown below:

<table>
<thead>
<tr>
<th>LASER pattern</th>
<th>Cell Area (µm²)</th>
<th>Shorter/Longer axis ratio</th>
<th>Cell Perimeter</th>
</tr>
</thead>
<tbody>
<tr>
<td>no pattern/control (n=131)</td>
<td>2008 ±770</td>
<td>0.75 ±0.1</td>
<td>253 ±86</td>
</tr>
<tr>
<td>pillar-like (n=94)</td>
<td>2573 ±966*</td>
<td>0.72 ±0.11</td>
<td>337 ±98*</td>
</tr>
<tr>
<td>10 µm width lines (n=113)</td>
<td>2327 ±757*</td>
<td>0.60 ±0.13*</td>
<td>345 ±110*</td>
</tr>
<tr>
<td>3 µm width lines (n=144)</td>
<td>1993 ±723</td>
<td>0.37 ±0.09*</td>
<td>339 ±107*</td>
</tr>
<tr>
<td>1 µm width lines (n=173)</td>
<td>2288 ±929</td>
<td>0.34 ±0.08*</td>
<td>375 ±125*</td>
</tr>
</tbody>
</table>

These findings support future approaches towards the use of micron and submicron topographical features to create functionalized medical implants.
Liposome-Encapsulated Hemoglobin Accelerates Skin Wound Healing in Diabetic db/db Mice

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**Study:** Liposome-encapsulated hemoglobin with extremely high \(O_2\)-affinity (h-LEH, \(P_{50O2}=10\) mmHg) has been reported to accelerate skin wound (ulcer) healing in normal mice (2009). We examined the effects of h-LEH in wound of diabetic db/db mice which exhibit severe wound-healing impairments as in human diabetics.

**Methods:** Full thickness dorsal wound of 6 mm in diameter with surrounding silicone stent (Fuji systems, Yokohama, Japan) was created in diabetic db/db mice (Day 0, \(n=14\)). Two days after wounding (Day 2), animals were randomized to receive intravenous h-LEH (10 mL/kg, \(n=7\)) or saline (\(n=7\)), which was repeated on Day 4. The size of the skin defect and ulcer analyzed by digital photometry and blood sampling for cytokines were repeated on Day 2, Day 4 and Day 7 post wounding, when animals were sacrificed for histological studies.

**Results:** The size of the skin defect remained relatively constant because of the attached silicone splint that prevents wound contraction (Fig-1, left). The size of the ulcer decreased on Day 4 in the mice treated with h-LEH as compared with animals receiving saline as the control (Fig-1, right). The difference was significant on Day 7, when the inflammatory cytokines were significantly suppressed in h-LEH-treated mice. Histological examination favored for the mice treated with h-LEH, which showed less inflammation and more granulation.

**Conclusion:** The results suggest that h-LEH (10 mL/kg, hemoglobin 600 mg/kg) early after skin excision may accelerate the wound healing in diabetic db/db mice as in the normal mice. The mechanism(s) of action appeared to be related to aerobic \(O_2\) metabolism and suppression of inflammation.

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3D-Flow Investigations In The Aortic Arch During Cardiopulmonary Bypass With Stereo-PIV

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**Study:** During open heart surgery patients are supplied with the cardiopulmonary bypass (CPB). Possible complications like stroke or hypoxia are related to the CPB. Reasons for these complications are amongst others the altered flow conditions by the cannula jet which is inserted in the aorta. Ongoing studies are investigating this issue with numerical simulations. As in vivo data with a satisfying resolution is not accessible, in vitro experiments are necessary to validate the numerical results. In this work the 3D-flowfield in a cannulated and a non-cannulated silicone replica of an aorta are investigated with stereoscopic Particle Image Velocimetry (PIV).

**Methods:** Two transparent silicone models were manufactured and integrated in a circuit separately. Flow, pressure and the fluid properties were adjusted in order to achieve physiological-like conditions. A laser and two cameras, which are required for stereo-PIV, were positioned around the silicone models, in order to record images of the particle-seeded flow. Multiple planes were recorded, which allowed a 3D reconstruction of the whole flow field in the aortic arch. Computer Fluid Dynamics (CFD) simulations with the same boundary conditions have been performed.

**Results:** Comparing the experimental flowdata in the non-cannulated and cannulated aorta, the significant higher velocities produced by the cannula jet are clearly visible. The jet also leads to higher turbulences. Comparison of experimental und numerical data shows good agreement and allows further numerical investigations. The applied technique shows to be a valuable in vitro tool for investigating highly three-dimensional flow and is applied in ongoing studies.
Liposome-Encapsulated Hemoglobin Improves Tumor Oxygenation as Detected by Near-Infrared Spectroscopy (NIRS) in Colon Carcinoma in Mice

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Study: Liposome-encapsulated hemoglobin with high (h-LEH, P50=12 mmHg) or low O2-affinity (l-LEH, P50=40mmHg) may improve O2 delivery to sensitize tumor tissues for radiotherapy and/or chemotherapy.

Methods: Ten mL/kg of h-LEH, l-LEH, or red blood cells (RBC) was infused in mice transplanted with murine colon carcinoma with the NIRS detector set at the tumor and intact muscle. NIRS recorded changes in the amount of oxy-hemoglobin (OxyHb), DeoxyHb and sum (tHb). Then, inspiratory gas turned to pure O2 and back to room air. The tumor was finally excised for the weight and histological examination.

Results: In the intact muscle, tHb increased after LEHs than RBC infusion while OxyHb increased in the order of h-LEH>RBC>l-LEH. In response to O2 inspiration, OxyHb increased but DeoxyHb decreased more, resulting in a decrease in tHb in all. In the tumor, tHb increased after LEHs but not after RBC. DeoxyHb increased more than OxyHb with tHb increased in all, but the magnitude was smaller than in intact muscle (h-LEH, n=18, Figure). In response to O2 inspiration, changes in OxyHb and DeoxyHb were similar with a smaller magnitude, but tHb increased in all.

Conclusion: The results suggest that nanometer size of LEHs may result in an increase in tHb in tumor < muscle. Relative change in OxyHb and DeoxyHb appeared to depend on muscle PO2 to O2-affinity of infusates while DeoxyHb increased in all in the tumor, suggesting tumor PO2<12 mmHg. In all, LEH appeared to increase O2-delivery to the tumor but not to the intact muscle.

Figure 1. A, H&E, 2x. B, H&E, 10x. C, Elastic, 40x. D, Factor VIII, 40x. E, MSA, 2x. F, SMA, 20x.

Full Regeneration of the Aorta in a Porcine Model with Small Intestinal Submucosa Vascular Grafts

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Study: Autologous grafts remain to be the gold standard for vascular replacement surgery; however, their availability is limited. Alternative synthetic scaffolds have varying degrees of success in large diameter vessel implantation. Biological decellularized tissues such as small intestinal submucosa (SIS) are a promising option that provide structural strength and present mechanical and biological signals that may guide vascular tissue regeneration.

Methods: We evaluated the remodeling of a large blood vessel with SIS (ID 8mm, n=9) in an abdominal aorta swine model after a 20w implantation period. Dacron was used as a control (n=5). Patency was periodically examined using Doppler Ultrasound. After implantation, regeneration of the vascular wall was assessed with hematoxilin-eosin (H&E), Masson’s trichrome, elastic, muscle specific actin (MSA), alpha smooth muscle actin (SMA) and Factor VIII staining.

Results: Preliminary results after 8w in a subject euthanized early (for non graft-related reasons) showed the full remodeling of the vascular wall, where tunica intima, media and adventitia and internal elastic lamina were clearly discernible (Fig. 1.A-C). The regenerated tissue stained positive for endothelium (Fig. 1.D.), myofibroblasts (Fig.1.E,F), vasa vasorum (Fig. 1.A,B,D,F) and nervous fillets (Fig. 1.A,E). So far, our ongoing study shows strong evidence for SIS vascular grafts to be an excellent option for large diameter vessel remodeling.
Minimally Invasive Handheld Balloon Sinuplasty Device
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Study: Purpose: Sinusitis is an inflammation of the sinus cavities, which occludes the passageways connecting the sinus and the nasal cavity, causing a buildup of mucus, pressure and increasing the risk of infection. Sinusitis affects approximately 37 million Americans each year, which accounts for $5.8 billion in annual healthcare costs. The goal of this project is to design a hand-actuated device that dilates the frontal sinus tract.
Methods: Frontal sinus drainage is generally improved by removing the soft tissue, lining the medial wall of the agger nasi using a microdebrider. Another method of dilating the frontal sinus involves navigating a balloon catheter through the ethmoids and dilating the balloon to compress the sinus tissue. Dilation is less traumatic, resulting in less scarring. Overall, the microdebrider procedure has a success rate (no reoccurring chronic sinusitis systems) of 85%, while a hybrid procedure has a success rate of 93%, and balloon catheter devices have a success rate of 77%.
Results: Design: The device has a dual lumen catheter with a semi-rigid distal tip incorporating a dilation balloon. It allows for suction to be used in conjunction with the balloon catheter, to greatly reduce the time spent in instrument exchanges during the procedure. The device also provides tactile feedback to the user, eliminating the need for an endoflator system and additional operators. The physician has greater control maneuvering through the nasal tract and is able to feel the force of the balloon against the agger nasi. To mitigate the high cost associated with current devices, the design incorporates a reusable handle with a single use balloon distal end. Conclusion: The proposed balloon sinuplasty device is designed for better ergonomics when restoring the luminal diameter, while providing tactile feedback to a sole operator and reducing system cost and complexity.

Hemodynamic Factors That Affect Hemolysis in Turbulent Shear Flows
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Study: In designing ventricular assist devices (VAD), minimizing hemolysis that occurs as blood flows through the device is an important concern. Understanding flow conditions in the device, thus, becomes important in any hemolysis study. Many VAD devices contain parts where Taylor-Couette flow occurs. In this study, simulation of a Taylor-Couette flow is performed to determine flow parameters of interest for hemolysis study.
Methods: Common flow structures are found to be the same between a Taylor-Couette flow and a plane Couette flow, so long as the box length of the plane Couette flow is long enough. Therefore, a plane Couette flow is simulated herein to capture the flow characteristics using a Direct Numerical Simulation (DNS). DNS is a computational method that is widely used in turbulence community, because of its ability to solve the Navier-Stokes equation directly, with high fidelity and without modeling small scale turbulence. Our method is based on a pseudo-spectral numerical technique that has been validated with experimental results in earlier studies. Using this method, a complete velocity field in the channel is obtained at each location. Parameters of interest can then be calculated. Flow fields at different Reynolds and Taylor numbers are simulated, in order to capture the development of the flow from transitional state to turbulent regime.
Results: Current dimensionless results from plane Couette flow at frictional Reynolds numbers of 150 and 300 show that Kolmogorov length scales from 6 to 8 micrometers are present in the flow fields, which could lead to hemolysis. High values of turbulent stress are found in the center region of the channel, while turbulence dissipation rate reaches maximum in a near wall region. Further study will give information of distribution of interested parameters in the whole channel at a wide range of Reynolds numbers. By applying appropriate hemolysis models, predictive hemolysis values in a whole device operating at different conditions would then be obtained.
Multi-species in vitro Assays for Platelet Activation and VWF Degradation for in vitro Safety Assessment of VADs
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Study: Thrombosis and bleeding remain common complications in heart failure patients with implanted ventricular assist devices (VADs). These complications are likely due to high shear stress causing damage to blood cells and proteins such as platelets and von Willebrand factor (vWF). The purpose of this study was to determine the effect of controlled levels of shear stress and exposure time on platelet activation and vWF structure and function. An additional purpose was to elucidate any differences in the response of the animal species used commonly for pre-clinical safety assessment.

Methods: Human, bovine, ovine and porcine blood was subjected to non-physiological levels of shear stress using a rheometer. Flow cytometry was used to determine the vWF activity and platelet activation and the presence of high molecular weight (HMW) vWF multimers was detected through immunoblotting.

Results: The results show that vWF activity decreased and platelet activation increased under shear stress in all species whereas these remained the same in blood not exposed to shear stress. Flow cytometry platelet aggregation results were substantiated with immunoblotting to show that the rate of loss of HMW vWF multimers was directly linked to the loss of vWF activity. In conclusion, this method enables us to quantify the effect of different levels of shear stress on key components of blood coagulation and compare between species to optimize pump design to avoid certain ranges of shear stress and identify the species with the most similar response to humans for pre-clinical VAD safety assessment.

Mechanical Characterization of Alginate/Chitosan-Based Bone Adhesives for Trauma Surgery
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Study: Complex fractures with high bone fragmentation are very difficult to treat and can limit the functionality of the affected limb. For example, current solutions for articular comminuted fractures fail to fix and attach the smallest fragments. An adhesive would be an easy and safe alternative for the treatment of many of these fractures. A critical aspect in the development of these adhesive joints is to characterize the mechanical performance of the adhesion system and the adhesive itself. This project is directed to evaluate the tensile and shear joint strength and the mechanical properties of bulk specimens in a tensile test of the adhesive alone.

Methods: Cancellous bone extracted from the bovine proximal humerus condyle is used to evaluate the adhesion strengths on a specific joint geometry. Three formulations of adhesives based on chitosan and three based on alginites were used, each one mixed with calcium carbonate and hydroxyapatite (HA) at different concentrations. In order to achieve a variety of stress conditions using a tensile test, three controlled adhesion joints at 90°, 45° and 0° relative to the load direction were used (TT90, TT45 and TT0). Alongside adhesive joints tests, bulk specimens for each adhesive (n=5) were manufactured by injection into 5.0 x 5.0 cm PEHD molds and after 15 hours of curing, die forming was executed to produce the specimen’s final geometry. Test where conducted at a constant displacement rate of 1mm/min until fracture. The joint strength and adhesive Young’s modulus were compared using ANOVA (p < 0.05) and a post-hoc test (Tukey).

Results: Results showed that adhesives under TT90 support a higher load (33.2 ± 4.2 N) than TT45 (18.6 ± 1.2 N). Adhesives based on alginate with high and low HA concentration shows a lower joint strength (27.9±0.3N) compared to others adhesives (p < 0.05). Mechanical characterization using TT0 joints and bulk tensile test is currently under way, and these combined results will be used to further optimize the adhesive formulation.
Housing Design for Cavopulmonary Assist Device to Provide Chronic Fontan Biventricular Maintenance: a Computational Study

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Study: Fontan failure and attrition is emerging as a clinical problem for which there is no primary or preventive therapy. A permanent right-sided circulatory power source that provides modest augmentation of cavopulmonary blood flow would beneficially maintain the circulation in a more stable biventricular state. Safety in device design must account for physiologic needs unique to Fontan, including the housing design which must be optimized for fluid flow in both active and passive (failed) states.

Methods: A rotary blood pump, based on the von Karman viscous impeller pump (VIP), is modeled in the center of a total cavopulmonary connection (TCPC) housing. TCPC housing is optimized using computer aided design (CAD). Four housing geometries are studied: 1) idealized TCPC (no angulation or offset of the pulmonary arterial outflow), 2) TCPC with angulation, 3) TCPC with offset, and 4) TCPC with angulation and offset. Computational Fluid Dynamics (CFD) is used to assess performance, flow field, and shear stresses under rotating and static conditions.

Results: CFD simulations allow an optimized housing geometry that provides ideal performance while reducing risk of blood damage for both rotating and static cases. In the non-rotating case, a stationary VIP reduces hydraulic energy loss and streamlines passive TCPC flow as a flow diverter. Shear rates predict low thrombogenicity risk at the high impact strike zones for flow coming off the VIP.

Summary: Long-term biventricular maintenance of univentricular Fontan circulation is feasible using a VIP implant design that presents no risk of venous pathway obstruction whether the device is functional or not. Both angulation and offset of the housing outlets are beneficial design features. Clinical translation of this technology will make it possible to reverse the Fontan paradox, reducing the need for transplant, and improving quality of life and lifespan for patients with functional single ventricle.

Modified RBCs for Modeling Malaria Infected Erythrocytes to Test Magnetic Cell Separation Device

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Study: The Plasmodium falciparum malaria parasite infects erythrocytes and causes these cells to become paramagnetic with reduced deformability. This study develops and examines the potential of glutaraldehyde (GTA) fixed, methemoglobin (metHb) containing red blood cells (RBCs) as a safe analogue for P. falciparum infected erythrocytes, to test microfluidic devices for magnetic separation of infected cells.

Methods: Cells are converted in a two-step process. Hemoglobin is first oxidized to methemoglobin, followed by fixation via GTA. An efficient large scale protocol for the conversion of oxyHb to metHb was developed, using sodium nitrite as the oxidizing agent. A suspension of washed human RBCs in PBS is mixed (1:9) with 0.11 M NaNO₂ (in PBS) and rocked for 1.5 hr. The cells are then washed three times with PBS to prevent further reaction by NaNO₂. The resulting cells are mixed (1:19) with 0.015% glutaraldehyde and incubated at room temperature for 30 min, then washed three times with PBS. Cell deformability is analyzed using a Linkam shearing stage.

Results: Preliminary results indicate that the above protocol successfully converts all oxyHb to metHb, as measured by an OSM-3 hemoximeter. Results reveal that while metHb cells display a somewhat reduced deformability when compared with healthy cells, GTA cells containing metHb are practically nondeformable even under high shear stress. Thus, GTA fixed, metHb erythrocytes show potential to be a safer analog for P. falciparum infected erythrocytes in both their magnetic and mechanical properties. The ongoing study is investigating the magnetic properties of the modified RBCs, and their behavior in microflow devices where a mixture of normal and modified RBCs is exposed to a strong magnetic field gradient. Supported by grants 1R43HL110508-01A1 and R01 HL089456. Figure 1. Normal RBCs subjected to 15 Pa shear stress Figure 2. Modified RBCs subjected to 15 Pa shear stress.
Hydrodynamic Performance and Hemolysis Tests Comparing Different Impeller Angles of a Centrifugal Blood Pump to be Used as Bridge to Decision or Recovery

Study: Department of Bioengineering at Institute Dante Pazzanese of Cardiology has been developing and evaluating a new model of centrifugal blood pump for bridge to decision or recovery. This pump can be used extracorporealy with or without membrane oxygenator. Device design is based on centrifugal pumping principle associated to the usage of ceramic bearing to achieve durability up to 30 days. Rapid prototyping technology has been used for prototypes production with three different impeller angles: with four straight blades, with four 90º curved blades and with four 180º curved blades.

Methods: Hydrodynamic performance tests were conducted with those prototypes, using a mock loop system composed by Tygon® tubes, 500 ml flexible reservoir, digital flow meter, pressure monitor, electronic driver and adjustable clamp for flow control, filled with water/glycerin/alcocol solution, simulating blood viscosity and density. Flow versus pressure curves were obtained for rotational speed of 1000, 1500, 2000 and 2500 rpm. Hemolysis tests were conducted with same prototypes and same closed circuit, however, free of air and flow fixed at 5 L/min against total pressure head of 100 mmtg, filled with bovine blood.

Results: Results showed that rotor with straight blades, 90º and 180º curved blades provided similar hydrodynamic performance for lower rpm, but pump with straight blades showed better hydrodynamic performance for higher rpm. Hemolysis tests showed best results for 180º curved blades, with normalized index of hemolysis of 0.004±0.003g/100L.

In-Vitro Shear Stress-Induced platelet activation: Differences between Species: Human, Ovine, and Porcine
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Study: Platelet activation caused by mechanical forces plays an important role in physiological hemostasis and pathological thrombosis in patients treated with blood contacting artificial organs. In vitro and in-vivo animal tests are commonly performed to evaluate the hemocompatibility of these devices before they are used clinically in humans.

Methods: The purpose of this study was to investigate the sensitivity and dependency of shear-induced platelet activation on shear stress in the three species. The experiments were carried out using two flow-through Couette-type blood-shearing devices. Two commonly used markers (surface expressed P-selectin (CD62p) and soluble P-selectin) were used to indicate the shear-induced platelet activation and were quantified at a matrix of exposure time (0.039 to 1.48 s) and shear stress (50 to 320 Pa).

Results: The results showed that the level of surface expressed P-selectin increased appreciably in human and porcine blood after exposed to shear stress above 75 Pa. Surface P-selectin was a less sensitive marker for shear-induced platelet activation for ovine blood. The level of surface P-selectin in ovine blood did not increase as high as that in human and porcine blood. Relatively, soluble P-selectin in blood increased in the three species after being exposed to shear stress level above 75 Pa for duration longer than 0.5 sec. The data from these in-vitro experiments indicated that human blood is more susceptible to shear-induced platelet activation than porcine and ovine, the surface and soluble P-selectin response of porcine blood to shear stress is similar to the human blood. The differences in platelet activation markers between human, ovine and porcine platelets suggest that porcine blood might be the best species to evaluate biocompatibility related platelet activation of human.

Development of The Calon Minivad™- A Novel LVad With Potential for a Lower Cost and Reduced Complications
G. D. Foster. Calon Cardio-Technology Ltd, Swansea, UNITED KINGDOM.

Study: The MinivAD™ is a new LVAD that utilises a novel layout to potentially improve implantability, manufacturability and haemocompatibility. It is hoped that this will lead to commensurate improvements to the device cost and complication rate, improving the overall health-economic proposition.

Methods: The performance of the MinivAD has been evaluated invitro against a series of well-established metrics and also against novel assays developed by our group to gain better insight into haemocompatibility.

Results: Current results indicate that the MinivAD performs competitively against all key performance and haemocompatibility metrics currently tested: Power: <1W/l/m @ 100mmHg Hydraulic characteristic: 0 - 8L/m average flow range with ‘flat’ HQ curve, low shut off pressure and good pre-load / afterload sensitivity. Physical size: <100g weight; 15mm depth x 35mm diameter package (outside of heart); 30mm length x 22mm diameter inflow cannula (implanted into ventricle). The MinivAD can be implanted inside pericardium with convenient siting of outflow cannula (centrifugal outflow) and is suitable for less invasive techniques such as a mini thoracotomy. Haemolysis: <0.002 g/100L NIH, bovine blood, 6h loop test, 500ml loop, 5/l Platelet activation: 11% compared to 9% in CentriMag and 6% in static (BAQ125, bovine blood, at 6h). Leukocyte damage: 8% compared to 5% in CentriMag and 6% in static (7AAD, bovine blood, at 6h). The haemocompatibility of the small, implantable MiniVAD is comparable with good, and substantially larger, extra-corporeal blood pumps such as the CentriMag and the Rotaflow. Further in-vitro evaluations are ongoing and in-vivo evaluations are planned for quarter four 2014.

Importance of a Rotational Speed Control System for Implantable Centrifugal Blood Pumps
T. Leão, J. Fonseca1, J. Leme1, B. Utiyama1, E. Bock1, R. Sá1, E. Drigo1, A. Andrade1.1 Institute Dante Pazzanese of Cardiology, São Paulo, BRAZIL, 2Federal Institute of São Paulo, São Paulo, BRAZIL.

Study: An Implantable Centrifugal Blood Pump (ICBP) has been developed in our institution to be used as Left Ventricle Assist Device (LVAD) in Bridged to Transplant (BTT). Actually the pump electronic control strategy is being studied used a Hybrid Cardiovascular Simulator (HCS) a tool that allows the physical connection of the ICBP under evaluation. Also, HCS allows to change some cardiovascular parameters in order to simulate specific heart diseases. This study shows different modes of ICBP actuation and its consequences for left ventricle and for cardiovascular system.

Methods: Controller adjusts the rotational speed depending on the heart rate. Tests were performed using HCS on specified heart rate and simulating failing heart. These test parameters were based on the patient natural activity.

Results: The results of controller action showed important for application, increasing rotational speed to avoid backflow and decreasing rotational speed to avoid aortic valve dysfunction. Future studies are in progress to improve the sensing and control algorithm.
Computational and Theoretical Approach to Determining Radial-Coordinate Spring Constant in Universidad de los Andes’ Nitinol Cardiovascular Occluder Devices.
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Study: The cardiovascular occluder devices developed by our group are small Nitinol double-helix springs implantable through catheterization. The radial coordinate spring constant can be used to optimize the ratio between the device diameter and the artery’s diameter; an optimization that guarantees that the device will be large enough to hold out the drag force generated by the blood flow, without tearing or damaging the arterial tissue. The ideal size of these cardiovascular devices is an empirical approximation, as well as the ratio between diameters, and research around this topic has been mainly experimental so far. This project represents the first step into a theoretical and computational analysis that allows the determination of the spring constant to furthermore optimize the number ratio between device and artery diameters.

Methods: The 3D CAD model of the spring is built through simple to complex geometric iterations, using the constant-diameter-simple-helix spring as the starting solid. While the theoretical section of the study focuses on this geometry only, which in turn serves as a validation of the computational and former experimental results, the FEM analysis covers every model, including the actual device geometry. This research defines the spring constant for each of the different springs and shows the static structural results obtained through ANSYS, Inc. These results allow spring constants to be determined mathematically.

Results: The obtained values of spring constants match the previous experimental in vitro results. These values were operated to determine the ideal ratio between the diameters: the smallest size of the device was determined by the reducing its dimensions to the point where friction between surfaces is equal to blood flow drag force, and common artery tissue mechanical properties were the determining factor when estimating the device’s largest dimensions.
Sterilization Study of Perfluorocarbon (PFC) Emulsions Used as Oxygen Carriers
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Study: Clinical sterilization is a method that ensures destruction and suppression of all forms of microbial growth avoiding the presence of pyrogens. The main problem during moist heat sterilization in autoclave is the exposure to high temperatures that could change the system initial properties. In this paper, the effect of sterilization on stability of an intravascular emulsion composed of water, PFC and egg yolk lecithin is evaluated.

Methods: To achieve this goal, two conditions of moist heat sterilization were studied, reporting physicochemical changes in droplet size, zeta potential, viscosity and pH for a period of 42 days. Sterilization conditions studied were 100°C for 40 minutes and 121°C for 20 minutes. Sterility was evaluated by the suggested World Health Organization test, culturing samples in thioglycollate and soybean casein.

Results: Results showed that a process carried out at 121°C for 20 minutes ensures sterility, as the European Pharmacopoeia suggest. Physicochemical changes in droplet size, zeta potential, viscosity and pH were found. Changes in pH were the most significant after sterilization, changing from 7.85±0.07 to 5.69±0.01. The decrease in pH was associated with the increase of free fatty acids in the emulsion due to the elevated temperatures effect during sterilization, as demonstrated by chemical analysis by titration with KOH to determine the acid value of the emulsion. Acid value changed from 1.13±0.03 mg KOH/g to 11.33±0.3 mg KOH/g. Results show the need of effective sterilization protocols to grant safety to the emulsion, that simultaneously cause minimum impact on the physicochemical stability. Further studies to understand, characterize and control free fatty acids generation in lipid complex systems are required to maintain pH in a physiological value and to prolongate shelf life of the emulsion after sterilization process.

Hemodynamic Response of the qPulse™ Algorithm with the HeartWare MVAD® Pump in an Acute Heart Failure Ovine Model
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1HeartWare, Inc, Miami Lakes, FL, 2Texas A&M Institute for Preclinical Studies, College Station, TX.

Study: The qPulse algorithm promotes aortic valve (AV) opening via intermittent reduction of pump speed. The purpose of this study was to better understand the hemodynamic response to the qPulse algorithm in an acute heart failure ovine model.

Methods: Three animals (71.8 ± 4.3 kg) were implanted with the MVAD Pump. Acute heart failure was induced via coronary artery ligation. Testing was conducted over a speed range of 10 to 20 kRPM (or until suction). Five-second speed decrease intervals of 15% and 20% were performed with a 10 second offset in between each cycle. Pump parameters, pump flow, pulmonary artery flow (PAF), aortic pressure (AOP), and PV loops were captured using Powerlab and a proprietary data logging system. Echocardiography was used to determine AV function.

Results: The qPulse algorithm opened the AV of an unloaded heart in two of the three animals tested. For the case where the algorithm was unsuccessful, the animal was in severe HF and the speed ramp could only be increased to 12 kRPM. For the three animals, qPulse settings of 15% and 20% resulted in an average decrease in pump flow of 0.9 ± 0.3 LPM and 1.2 ± 0.4 LPM, respectively. The maximum pump flow decrease observed was 1.8 ± 0.1 LPM at 20 kRPM with the 20% qPulse setting. Minimal (< 0.5 LPM) changes were observed in PAF, indicating that overall system flow remained unaffected. qPulse settings of 15% and 20% resulted in an average decrease in pump flow of 0.9 ± 0.3 LPM and 1.2 ± 0.4 LPM, respectively. The maximum pump flow decrease observed was 7.8 ± 1.0 mmHg at 20 kRPM with the 20% qPulse setting. Minimal (< 0.5 LPM) changes were observed in AOP, indicating that overall system flow remained unaffected. qPulse settings of 15% and 20% resulted in an average decrease in AOP of 2.3 ± 1.6 mmHg and 3.3 ± 2.0 mmHg, respectively. The maximum pressure decrease observed was 7.8 ± 1.0 mmHg at 20 kRPM with the 20% qPulse setting. A significant increase in left ventricle stroke work was observed during the qPulse cycle, both when the AV was consistently closed or was closed and then induced to open as a result of the algorithm.

Conclusions: In these preliminary studies, the qPulse algorithm was capable of opening the AV in two of three animals with minimal changes to systemic hemodynamics. Caution: Investigational device, limited by United States law to investigational use.
Assessing the Acute Thrombogenicity of Clinically-Relevant Opaque Materials

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Study: Although a wide array of approaches have been investigated to reduce material thrombogenicity, thrombosis complications remain of clinical significance for many cardiovascular devices, i.e. ventricular assist devices (VADs). Thus surfaces with improved biocompatibility, as well as methods to quantify such improvements, remain of interest to the cardiovascular device community. This study was conducted to perform a systematic, real-time comparison of candidate, opaque materials currently being considered for application in VADs.

Methods: A blood analogue consisting of fluorescently labeled platelets and optically transparent hemoglobin depleted red blood cells, was perfused across 6 materials (titanium alloy (Ti6Al4V), silicon carbide (SiC), alumina (Al₂O₃), 2-methacryloyloxyethyl phosphorylcholine polymer coated Ti6Al4V (MPC), yttria partially stabilized zirconia (YZTP), and zirconia toughened alumina (ZTA)) for 5 min at wall shear rates of 400 and 1000 sec⁻¹. Fluorescent micrographs were acquired in real-time and analyzed for platelet surface coverage.

Results: MPC, Al₂O₃, YZTP, and ZTA had significantly decreased platelet deposition when compared to Ti6Al4V at both shear rates and SiC at 400 sec⁻¹ (P <0.01). Increasing the wall shear rate from 400 to 1000 sec⁻¹ produced a trend of decreased platelet adhesion to the test surfaces. Embolization of fragments and entire thrombi were observed sporadically with the Ti6Al4V, SiC, YZTP, and Al₂O₃ samples. This may present a clinical risk should the phenomenon occur in vivo and allow the shedding of emboli large enough to trigger tissue ischemia. The observed reduction in platelet deposition at the elevated wall shear rate suggests that the blood biocompatibility of VADs may be improved by minimizing the areas of low shear blood contact. This technique revealed that MPC and ZTA have improved thromboresistance when compared to the other surfaces and, thus, could be considered for implementation in future VAD designs.

Vascular Adaptation to Pulsatile Endothelial Shear Stress Plays a Central Role in the Physiological Response to Continuous-flow VADs

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Study: Implantation of continuous-flow VADs (CFVADs) is associated with significant incidence of gastrointestinal arteriovenous malformations. Although decreased pulsatility has been implicated as a possible cause, basic research in vascular biology offers a potential mechanism: vascular remodeling via endothelial shear stress. Controlled cellular mechanobiology studies have suggested that pulsatile shear stress is a more potent mechanical stimulus than mean shear stress, but the implications have never been explored, perhaps because mean and pulsatile blood flow are usually coupled.

Methods: We therefore expanded our multiscale cardiovascular model to include a single, critical assumption-microvascular radii increase with pulsatile shear stress. Utilizing the model, we tested this adaptive response in the lumped vascular system, microvasculature, and interstitial fluid compartments.

Results: This adaptive behavior predicts normal microvascular architecture, tissue perfusion, and interstitial fluid volume. Furthermore, we found that decreasing pulsatility decreases microvascular radii, shunts blood through the microvasculature, and may disrupt tissue perfusion, increase venous pressures, and ultimately introduce structural abnormalities analogous to arteriovenous malformations. Taken together, these results imply that pulsatile shear stress plays a central role in the physiological response to CFVADs. Not only has integrating the disparate fields of pulsatile hemodynamics, microvascular physiology, and interstitial fluid balance translated basic vascular biology research into common pathologies, it promises to offer concrete solutions: 1) informed design of pulse modes to increase flow pulses transmitted to the microvasculature and 2) targeted pharmacological intervention to increase the sensitivity to pulsatile shear stress.
The Role of Neutron Activation Analysis in Pathological Evaluation of Silver-Eluting Biomedical Devices
T. Lancon, F. J. Clubb, Jr. Nuclear Engineering, Texas A&M University, College Station, TX.

Study: A major problem with implantable biomedical devices is the prevalence of bacterial infection following implantation, particularly with regards to electrical drivelines. Device manufacturers have long utilized the antimicrobial properties of silver to combat this impediment. Prior to approving devices that elute antimicrobial agents, the FDA questions the agent’s toxicity and the amount that is eluted into adjacent tissues. Neutron activation analysis (NAA) has been shown to provide these answers for colloidal gold when correlated with routine pathology. This research aims to determine the feasibility of NAA to answer these questions and correlate to routine pathology procedures for silver-eluting devices in the context of the cost and volume demands associated with preclinical trials.

Methods: Plugs of skin containing silver-embedded drivelines were explanted from a porcine model. One plug contained a control that was known to elute silver, and one plug contained a form of silver hypothesized to remain local to the device. Samples of tissue were taken for scanning electron microscopy with x-ray microanalysis (SEM/EDS), transmission electron microscopy (TEM), and NAA at 2 mm and 6 mm in the same direction from each device. The NAA procedure was designed to mimic the time and cost limitations faced by a company performing a preclinical trial. Results from these modalities were correlated. A SIMULINK model was built to analyze NAA results.

Results: SEM/EDS and TEM provided valuable qualitative information regarding the distribution of host and response to eluted silver. NAA yielded inconclusive results due to poor experimental design. SIMULINK results provided feedback that will allow improved experimental design in future work. Currently NAA is thought to be useful for silver-eluting device manufacturers wishing to explore device designs in low-volume, exploratory studies.

Effects of Turbulent Eddy Structures on Hemolysis

Study: Purpose of study: Turbulence often occurs with ventricular assist devices, artificial hearts, blood pumps, and artificial valves. Locally high shear stresses and significant pressure fluctuations are some of the negative effects of turbulence in blood. Design of devices to avoid hemolysis, therefore, depends on understanding and predicting the effect of turbulent shear stresses on RBC. In order to understand better the structure and effects of turbulence on the cells, we relate the hemolysis observed for 5 Couette experiments to the characteristics of turbulence in the flow as captured by computational models. A number of groups have explored Kolmogorov length scale, KLS, as an indicator of hemolysis. In this study, we have searched for relationships with hemolysis using extensive quantities such as the total surface area from subpopulation distributions of eddies with different KLS.

Methods: A computational technique (FLUENT with kappa-epsilon model) that can predict the detailed structure of turbulence has been used to investigate the effect of turbulent eddy structures on cell damage. This study emphasized characteristics other than the KLS. Instead, observing extensive measures like total eddy areas for specific KLS were used to provide a more general understanding of hemolysis. A number of groups have explored Kolmogorov length scale, KLS, as an indicator of hemolysis. In this study, we have searched for relationships with hemolysis using extensive quantities such as the total surface area from subpopulation distributions of eddies with different KLS.

Results: Results showed that hemolysis correlated directly with the total area of eddies up to 6 micron KLS. A correlation was not evident for any KLS of 7 microns and above. Similar relationships are observed with total volume of eddies and number of eddies. Further development of these relationships will require adding the dimension of exposure time and then testing the ability to predict hemolysis for various flow conditions.
Simulation of Blood Platelet Aggregation
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Medicine, Pittsburgh, PA.

Study: Blood platelets may be activated by mechanical stresses produced
by cardiovascular devices. Activated platelets can aggregate when they
collide against either single platelets or aggregates of multiple platelets.
The collision of platelets and aggregates depends on the blood flow
velocity gradient, or shear rate. However, this may not necessarily mean
that aggregates will end up blocking smaller vessels. Aggregates may
break up as a result of shear stresses which are higher at smaller vessels.

Methods: We created a dynamic model to predict the size distribution of
platelet aggregates according to the flow condition. The aggregation rates
can be predicted by the Smoluchowski aggregation model, whose rates
are based on the probability of collision between particles of different
sizes. The disaggregation rates depend on the size of the aggregate and
shear stress. To validate our model, we observed platelets aggregating
and disaggregating in a rheoscope. Image sequences were recorded
during each shear profile. The images were analysed to count and classify
aggregates by size. The image processing algorithm returned a set of time
series of aggregate classes.

Results: In preliminary results with stress-activated platelets, we
observed breakup of large aggregates at shear stresses higher than 1 Pa.
Moreover, aggregate sizes returned to the initial equilibrium state after
low shear rate. The figure shows the model reproducing the dynamics
of our experiment. Our mathematical model has the advantage of being
determined by just four parameters: platelet concentration, activation
level, shear stress, and aggregate size. When fully developed, this model
may significantly advance the power of prediction of blood damage in
medical devices using CFD modelling.

Particle Image Velocimetry Flow Studies on a Pulsatile Pediatric
Ventricular Assist Device
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BRAZIL, 2Institute of Physics, University of Sao Paulo, Sao Paulo, BRAZIL,
3Department of Mechanical Science and Engineering, University of Illinois,
Urbana, IL.

Study: The utilization of VADs may increase the chance of
pretransplantation survival in children awaiting for a heart transplant.
First generation pulsatile devices lead the application in small pediatric
patients while second- and third-generation devices are being introduced.
We report results of in vitro flow studies using two-dimensional phase-
locked particle image velocimetry (PIV) measurements on a 30 mL
diaphragm type pump fitted with bovine pericardium valves driven by an
external pneumatic unit.

Methods: Phase-averaged velocity fields were obtained in 3 planes
parallel to the diaphragm and in one plane on the center of the inlet valve
orifice at six different stages during filling and ejection of the pump. The
experimental set up include pulsed Nd:YAG lasers, a CCD camera and an
optically transparent model of the pump placed on a mock circulatory
operating at 8 mm Hg pre-load and 80 to 120 mmHg pulse after load, at
beating frequencies of 80, 100 and 120 bpm.

Results: Peak phase-averaged velocities measured in the planes parallel
to the membrane show comparable profiles with an acceleration followed
by a deceleration phase and peak magnitudes that may exceed 1 m/s in
late ejection, the largest mean velocity magnitude was 1.66 ± 0.21 m/s
at 80 bpm. The overall flow pattern during ejection shows fixed vortices
that drive the bulk of flow within the blood chamber with no significant
stagnation except in the region near the wall between the inlet and
outlet valves and no turbulences. During the filling phase a cycle-to-cycle
variability was found in the instantaneous velocity with turbulent shear
stress exceeding 300 dynes/cm2. The turbulence was coincident with
the movement of the diaphragm that seems to destabilize the flow. Flow
visualization studies and computational models are being developed to
optimize fluid-structure interactions in this device.
Comparison of Bovine and Ovine Erythrocyte Mechanical Fragility Using the Hemolyzer
B. Lukic, M. Stauffer, W. J. Weiss, R. Newswanger, G. Rosenberg. Surgery, Penn State University, Hershey, PA.

Study: In vitro hemolysis testing using animal blood is a common method to evaluate circulatory support devices. This study compared mechanical fragility of bovine and ovine erythrocytes, as well as donor animal variability, at three different shear stress conditions, using a novel device known as the Hemolyzer.

Methods: The Hemolyzer consisted of a stationary inner and a rotating outer cylinder modified at their ends in order to provide a uniform shear stress throughout the encapsulated volume (14 ml). Fresh bovine or ovine blood was tested 10 times at one speed condition during each experimental day. Each blood type was tested at three different speed conditions: 1500, 4000 and 5500 RPM, while keeping constant exposure time of 60 seconds. Assuming a viscosity of 3.5 cp, these three speed conditions corresponded to shear stresses of 416, 1111 and 1527, respectively. The low shear stress condition was tested 3 times, while the two higher shear test conditions were tested 5 times for each blood type. The average plasma hemoglobin was used to express mechanical fragility. A single factor analysis of variation was used to determine the statistical differences between species as well as donor variability within each experimental group.

Results: The measured hematocrit (mean and standard deviation) of fresh bovine and ovine blood were 26.5±2.1 % and 25.3±2.9 %, respectively. There was no correlation found between hematocrit and mechanical fragility at the same strain rate and the results were not normalized for hematocrit. A statistically significant difference between species (p<0.05) was only found at the high shear stress condition (1527 dynes/cm²). A statistically significant difference was observed between individual experiments at each shear stress condition for both species, although it was minimal for bovine blood at 1111 dynes/cm² (p=0.053).

Decreased Platelet Aggregation Following Single Pass Exposure to Elevated Shear Rates
A. Houzelle1, C. S. Lewis2, T. A. Snyder3, D. W. Schmidtke2. 1Bioengineering, University of Oklahoma, Norman, OK, 2School of Chemical, Biological, and Materials Engineering, University of Oklahoma, Norman, OK, 3Advanced Cardiac Care, Integris Baptist Medical Center, Oklahoma City, OK.

Study: Ventricular assist devices (VADs) are a reliable option to treat heart failure patients waiting for transplantation. Despite significant advances in VAD performance, complications still exist. VAD patients exhibit a loss of high-molecular-weight von Willebrand factor multimers leading to a 30% non-surgical bleeding rate. It is hypothesized that exposure to high shear conditions in VADs plays a role in this bleeding but the mechanisms remain unclear. In this study we investigated the role of short duration high shear rate exposure on platelet adhesion and aggregation.

Methods: Mepacrine labeled whole blood was perfused through microfluidic devices that consisted of a high-shear region (40,000 - 100,000 s⁻¹) placed between two low-shear regions (100 - 2500 s⁻¹). We investigated the effects of shear rate and high shear exposure time (1–30 ms) on platelet function by using epifluorescent and differential interference contrast microscopy to quantify platelet adhesion upstream and downstream of the constriction.

Results: Blood exposure to high shear rates produced decreased platelet aggregation downstream of the constriction when compared to aggregation upstream of the constriction. Whether platelet aggregation was decreased downstream was dependent upon shear rate (60,000 - 100,000 s⁻¹) and exposure time (1–30 msec). Lower shear rates did not produce a change in aggregation, suggesting a potential threshold for the onset of the platelet aggregation defect. Conclusions: We observed decreased platelet aggregation on immobilized collagen downstream of a high shear rate for exposure times relevant to continuous flow VADs. These findings suggest that normal platelet aggregation is impaired after a single exposure to high shear and that there may be a threshold for platelet dysfunction, providing new design criteria for future VAD development. The body of investigation could provide insight on the mechanisms of non-surgical bleeding and how to reduce them in VAD patients.
ETHICON™ OMNEX™ Surgical Sealant Achieves Greater Than 98% Reduction in Suture Hole Bleeding on Average in an ex-vivo Porcine Aortotomy Closure Model

J. Matonick1, M. Pfefferkorn1, R. Kocharian2, M. Picone1, J. Riebman2, L. Johns1, D. Stoloff1, B. Patel5.

Study: ETHICON™ OMNEX™ Surgical Sealant is a 2-octyl cyanoacrylate-based bioabsorbable synthetic surgical tissue adhesive for vascular reconstruction. The sealant can be applied to an anastomosis to create a flexible physical seal independent of the body’s clotting mechanism to prevent suture hole leakage.

Purpose: The purpose of this study was to measure the suture hole leak rate of a sutured transverse aortotomy in explanted porcine aorta with and without a topical application of ETHICON™ OMNEX™, at normal and elevated blood pressure levels, in an ex-vivo cardiopulmonary bypass pulsatile flow loop with heparinized porcine blood.

Methods: A transverse aortotomy, involving 50% of the circumference, was created on a section of ex-planted thoracic aortas from 40 pigs and closed with PROLENE® Polypropylene Suture (size 4-0) using a continuous suture pattern. The surgeon was blinded to the group assignment of each sample. The sutured aortas were then divided into two groups of 20 samples each, a control group and a treatment (ETHICON™ OMNEX™) group. The aortas were individually placed on the cardiopulmonary bypass (CPB) model and the suture hole leak rate measured at normal blood pressure. Sealant was then applied to the anastomosis in the treatment group, per the instructions for use, and the leak rate was re-measured post-treatment at normal and elevated blood pressure levels.

Results: Data Summary.

<table>
<thead>
<tr>
<th>Blood Pressure (mmHg)</th>
<th>Suture Hole Leak Rate (ml/min)</th>
<th>Control group (n = 20)</th>
<th>ETHICON™ OMNEX™ group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120/80</td>
<td>55.80</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>240/200</td>
<td>107.77</td>
<td>1.42</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: The application of ETHICON™ OMNEX™ provided on average greater than 98% reduction in leakage compared to the control samples from normotensive through hypertensive blood pressure levels in a heparinized model with physiological blood pressures, pulse rate, and temperature.
Effect of High Shear Exposure on Neutrophil Rolling Behavior
C. S. Lewis¹, A. Houzelle², T. A. Snyder², D. W. Schmidtke³. ¹School of Chemical, Biological, and Materials Engineering, University of Oklahoma, Norman, OK, ²Bioengineering, University of Oklahoma, Norman, OK, ³Advanced Cardiac Care, Integris Baptist Medical Center, Oklahoma City, OK.

Study: Despite the success of ventricular assist devices (VADs) in recent years, infection is the most frequent complication of VAD support, occurring in 30% of patients annually. These complications suggest a disruption of the immune system following exposure to the VAD, including foreign materials and blood exposure to supraphysiologic shear rates. Elevated shear potentially damages blood elements, including neutrophils, a first responder to infection. The capture and rolling of neutrophils on vascular endothelium is the 1st step of the adhesion cascade whereby neutrophils migrate from the bloodstream to sites of infection, a process controlled by the interaction of PSGL-1 on the neutrophil surface and P-selectin on activated endothelial cells.

Methods: Microfluidic chambers were designed with a low shear (100s-1) region coated with P-selectin to allow for the observation of neutrophil rolling, a high shear exposure constriction with exposure time determined by the length, followed by a 2nd identical low shear region. This design allows for the examination of neutrophil rolling both before and after high shear exposure.

Results: Exposure to a 4000s-1 constriction for 470 msec yielded an almost two-fold increase in the rolling velocity. Corresponding straight channel controls with no high shear exposure (chamber with fixed width and constant 100s-1 shear rate) yielded no significant change in rolling velocities. Conclusions: Increased rolling velocities following a short exposure to high shear conditions suggest a possible alteration to neutrophil rolling and extravasation behavior. The increased velocity could translate into fewer neutrophils extravasating to the site of an infection, reducing the immune response and permitting extended microbial presence in the body. This dysfunction induced by hemodynamic conditions is independent of the foreign material surfaces of the VAD; and thus, identify a novel mechanism of potential infectious vulnerability within VAD patients.

Effects of Hydration State and Preserved Intestinal Layers on the Mechanical Properties of SIS Vascular Grafts
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Study: Small intestinal submucosa (SIS) has produced variable patency in vascular regeneration depending on graft fabrication techniques. The effect of fabrication on mechanical properties was evaluated in an experiment that combined: 1) preservation (P) or removal (R) of the intestinal layer stratum compactum (SC), and 2) dehydrated (D) or hydrated (H) state, into four study groups PD, RD, PH, RH.

Methods: P membranes were obtained by mechanically and chemically removing all intestinal layers except the SC and submucosa, while only the submucosa was preserved in R samples. D grafts were obtained by wrapping H membranes around cylindrical mandrels (OD 4.5mm) and air drying. H grafts were shaped in the operating room by the surgeon using H membranes and suturing along the edges. Grafts were implanted in carotid arteries (CA) of swine (ID 4.5mm, n=4) for 7d and collected afterwards with adjacent arterial segments. Biaxial mechanical testing was performed in the longitudinal (X1) and circumferential (X2) directions of the grafts. An anisotropy ratio (AR = (X2max-stretch)/(X1max-stretch)) assessed the preferential fiber orientations.

Results: Stress-stretch results before implantation (BI) showed X1 as the preferential direction in all scaffolds, H being more elastic than D grafts. There was no distinction after implantation (AI) between H and D groups, while P were stiffer than R grafts. Also properties in P grafts became inverted (the X2 direction became preferential, AR <1), whilst R grafts maintained an X1 preferential direction. RD grafts were the most elastic and had the closest behavior to that of CA. We concluded that fabrication parameters significantly affected the mechanics over 7d and were found closest to that of CA in RD grafts, yet, they might continue to evolve since final properties of the reconstructed tissue should be influenced by the arterial loading state. The progression of R groups towards CA behavior is a positive step towards vessel regeneration using SIS.
Ventricular Unloading by Continuous Flow Blood Pump and its Effect on Myocardial Wall Stress: Finite Element Analysis

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Study: This study investigated the effect of systematic LVAD unloading on the 3-dimensional myocardial wall stress by using a finite element method taking the myocardial fiber structure into account. We hypothesized that left ventricular assist device (LVAD) support unloads left ventricular (LV) pressure and volume, thus, decreases the myocardial wall stress.

Methods: The HeartMate II® (Thoratec, Inc., Pleasanton, CA) was used for LV unloading. The model geometries and hemodynamic conditions for baseline (BL) and LVAD support (LVsupport) were acquired from a Penn State mock circulatory cardiac simulator. We employed finite element models containing layered fiber structure, active contractility, and passive stiffness. Myocardial wall stress of BL was compared with that of LVsupport at 8000, 9000, 10000 RPM providing mean pump flow (Qmean) of 2.6, 3.2, and 3.7 l/min, respectively.

Results: LVAD support was more effective at unloading during diastole as compared to systole. Approximately 40%, 50%, and 60% of end-diastolic wall stress reduction was achieved at Qmean of 2.6, 3.2, and 3.7 l/min, respectively, as compared to only a 10% reduction of end-systolic wall stress at Qmean of 3.7 l/min. There was a stress concentration during systole at the apex due to the cannulation and reduced boundary motion. Since the traditional methods for interpreting the LV mechanics derived by the force balance (i.e., Laplace's law) are insufficient to characterize the true wall stress especially in mechanically supported hearts, the utility of the myocardial fiber structure based numerical method will greatly enhance the current understanding of the LV mechanics for the LVAD recipients. This model can be used to further understand optimal unloading, pump control, design of cannula, and patient management.

Impact of Outflow Restriction on the HeartWare HVAD® Pump Flow Estimation Accuracy


Study: Advancements in miniaturization of continuous flow ventricular assist devices have led to less invasive and alternative surgical procedures, increasing the available patient population. Outflow graft restriction has been commonly used by implanting sites to mitigate the lower physiological resistance encountered in some patients. The objective of this preliminary study was to measure the impact of outflow restriction on the HVAD Pump Flow Estimation accuracy.

Methods: HVAD Pump Estimated Flow was compared to Transonic (Ithaca, NY) measured flow in a steady state in-vitro flow loop with a blood analogous fluid (40% by vol. glycerol solution at 37°C). Controller settings were set to match the test conditions at 30% hematocrit. The flow measurements were taken for outflow restriction ranging from 0–100% and pump speed between 1800 and 4000 RPM in 200 RPM intervals.

Results: HVAD Pump Estimated Flow remained within the specified accuracy error of +/- 1 LPM or 20% across all speed and flow ranges tested as depicted in the Figure below.

Conclusions: Restriction of the HVAD Pump outflow does not impact flow estimation accuracy. Less invasive surgical techniques and alternative pump configurations may benefit from using flow estimation as an indicator of pump support.
Study on Early Cellular Adhesion During the Development of 3D Small Intestinal Submucosa Scaffolds
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Study: Small intestinal submucosa (SIS) is an extracellular matrix used for tissue regeneration, with current limitations due to its laminar geometry. We have obtained porous SIS scaffolds by tuning reported protocols and introducing a new pulverization technique. By altering SIS concentration and cross-linking agent, we aim to produce a regenerative scaffold that has pore size suitable for cellular intercalation, optimizes cellular adhesion and preserves collagen structure throughout manufacture.

Methods: 3D scaffolds were obtained by pulverization, gelification, cross-linking and lyophilization of porcine SIS membranes. Pulverization was performed by mechanical abrasion of dry SIS under controlled temperature. The powder was then solubilized in acetic acid and pepsin. Two solutions of SIS powder were studied: 0.5% w/v (S0.5) and 1% w/v (S1). The solutions were then cross-linked with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) or glutaraldehyde (GA) producing four groups: S0.5GA, S1GA, S0.5EDC, and S1EDC. Stability was assessed by rehydrating in deionized water and hierarchical structures characterized by Scanning Electron Microscope (SEM). Kidney fibroblasts were finally cultured for 3d to study early cellular adhesion and biocompatibility, using hematoxylin-eosin staining [H&E] to identify adhered cells and collagen.

Results: GA samples had defined interconnected pores, whereas EDC samples showed scale-like walls around the empty portions of the scaffolds. S1GA lost structural coherence after 72h in water, whereas S0.5GA, S0.5EDC and S1EDC samples maintained their structure. H&E revealed limited adhesion of fibroblasts, with EDC samples showing healthy growing cells and GA scaffolds presenting fragmented apoptotic cells. Due to the cytotoxicity associated with the GA samples, EDC seems advantageous as a cross-linking agent. Further mechanical, chemical, and biological characterization is currently underway to assess medical viability.

In Vitro Analysis of Thrombi Growth Using PDMS Models

Study: Heart disease is leading cause of death amongst individuals in the United States. Cardiovascular devices offer hope to treat individuals suffering from heart disease. However, the inherent geometry of these devices often promotes the generation of recirculation regions where blood flow becomes stagnant, leading to the formation of blood clots. Additionally, recirculation regions develop downstream of atherosclerotic plaques leading to thrombosis and potential embolization. A better understanding of the growth pattern of thrombi in these recirculation regions is needed.

Methods: To help verify previous growth models, an in vitro study is performed using modeled clots in a sudden expansion geometry. Previously obtained MRI data is analyzed and 3-D surface models are developed using the data visualization and analysis software Avizo. Negatives of these models are created and sterilization molds are produced allowing for creation of clot models. Clot models are formed using polydimethylsiloxane and are coated with collagen in order to promote thrombus growth on the exposed surface of the clot model. The clots are then placed into the recirculation region of the sudden expansion model. An in vitro flow loop containing a backward facing step is constructed and whole bovine blood is used to produce thrombus on the surface and downstream of the clot models. The flow loop is operated at 0.76 L/min for times between 15 and 45 minutes. Once the specific time is complete, PBS is flushed through the system and MRI imaging of the resulting model and thrombus growth is obtained.

Results: Volume and surface area analysis show consistency with previous growth data that was obtained from clots that were just formed in the recirculation region without the models. These models provide a basis for future computational simulations.
324

Advanced Pathology Analysis of a Feline Microchip-Associated Fibrosarcoma
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Study: Microchips are passive RFID devices consisting of an integrated circuit, an inductor, and a capacitor encased in a biocompatible substrate and placed subcutaneously in domestic animals for identification purposes. An association between vaccination and the development of aggressive fibrosarcomas has been recognized in cats and may be due to the inflammatory provocations in a genetically susceptible individual. Two previous case reports in cats have reported fibrosarcomas near or directly associated with subcutaneous microchips, but standard paraffin embedding and routine processing requires removal of the microchip. The objective of this project is to evaluate a feline microchip-associated fibrosarcoma with the microchip in situ.

Methods: A histologically confirmed fibrosarcoma surrounding a microchip was embedded in a methacrylate-based plastic resin (Technovit 7200 VLC) and sections microground for histology. Routine H&E staining was used for tissue staining; a trichrome stain was attempted. Microcomputed tomography (micro CT) and scanning electron microscopy were performed prior to embedding. Energy dispersive x-ray spectroscopy (EDX) was used to evaluate the elemental composition of peri-microchip tissue.

Results: Plastic embedding followed by microground sectioning provided good preservation of the microchip housing in situ and allowed direct histologic evaluation of neoplastic tissue surrounding the microchip. EDX did not identify any apparent elemental elution from the microchip. SEM and trichrome staining did not aid pathologic evaluation, while micro CT was useful to determine the microchip structure and orientation. This is the first case of a feline microchip-associated fibrosarcoma with the microchip evaluated in situ.

326

Comparison in the Dosification Strategy Of Nitric Oxide (NO) During Resuscitation From Hemorrhagic Shock (HS): Inhaled NO and NO Nanoparticles (NO-np)
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Study: This study investigated the systemic and microvascular hemodynamic changes related to increased availability of NO after resuscitation from HS. NO is made available by inhalation (90 ppm and 180 ppm) and by infused NO-np (1 mg/kg, 10 mg/kg, 20 mg/kg and 40 mg/kg). Methods: Syrian hamsters instrumented with a window chamber were used to study microhemodynamic parameters. HS is performed by withdrawing 50% of the blood volume. After 1h, resuscitation with HS is performed with half of the lost blood volume. The animal is observed for 90 min. The NO is administered as a coadjutant, through inhalation or NO-np infusion. Mean arterial pressure (MAP) and heart rate (HR) are monitored. Hematocrit, blood gases and pH are measured. Microhemodynamic parameters are observed by intravitreal microscopy: functional capillary density (FCD), vascular diameter and RBC velocity.

Results: A scorecard was constructed to compare the different NO therapies. The highest scores were obtained by NO-np infusion of 20 mg/kg and 10 mg/kg respectively. Systemic and microvascular parameters are improved by NO therapy with values compared to control group and up to 3 times higher. NO promotes vasodilatation and increases perfusion, altering organ function by regulating regional blood flow and organ perfusion. NO prevented cardiovascular collapse, maintaining blood volume and stabilizing hydrostatic capillary pressure, allowing animals to maintain superior systemic and microvascular hemodynamic conditions. This was evidenced in the maintenance of heart rate, blood pressure, microvascular function and FCD.

327

Preparation, Characterization and Evaluation of Scaffolds Produced From Small Intestinal Submucosa and Hyaluronic Acid for Potential Use in Tissue Regeneration
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Study: The lack of organ donation and limited capacity of regeneration of some tissues has increased interests in finding new alternatives. Given their extracellular matrix-like environment, natural materials, such as small intestinal submucosa (SIS) and hyaluronic acid (HA), are currently used as scaffolds. In this paper, we developed and characterized porous scaffolds from SIS and HA for use in tissue regeneration.

Methods: Four formulations were prepared with two levels of SIS (0.5 and 1% m/v) and HA (7.5 and 15% m/v). SIS powder was initially characterized using X-ray diffraction (XRD). For the resulting scaffolds, cross-linking of SIS and HA was analyzed by Fourier Transform Infrared Spectroscopy (FTIR), water uptake quantified, bulk porosity measured, and the pH of the aqueous environment monitored to test stability.

Results: XRD pattern of SIS showed the typical peak of native collagen, implying that no structural changes were caused in the protein during the pulverization process. For the resulting scaffolds, FTIR showed the presence of amide links, which can indicate that the SIS was being cross-linked with HA. Water uptake ranged from 3000–5000%, inferring sufficient capacity for cellular medium uptake. Furthermore, all scaffolds presented bulk porosity over 97%. Additionally, all samples showed a pH decrease at 24h. Generally, the scaffolds present a water uptake and porosity in line with other biomaterials that allow for cell proliferation. These initial results indicate that the composite material has potential, but the lack of differences shows that the crosslinking concentrations and protocols should be refined. It is therefore necessary to evaluate new formulations in order to understand the overall effect of HA. Furthermore, degradation should be assessed in vitro to test regenerative capacity.

329

Systems Biology Approach to Identify Critical Risk Factors for Pulmonary and Intestinal Edema With Continuous-flow LVADs
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Study: Heart failure and subsequent implantation of c-LVADs results in significant alterations in hemodynamic variables associated with pulmonary and intestinal interstitial fluid balance. In particular, the heart, LVAD, vasculature and kidneys, interact in a complex fashion to modulate capillary and central venous pressure. Although it is well established that elevated capillary pressure increases microvascular filtration into interstitial spaces and elevated central venous pressure inhibits lymphatic drainage, critical fluid balance parameters characterizing microvascular, interstitial, and lymphatic function are difficult to measure and impossible to alter independently in vivo.

Methods: By integrating our previously reported mathematical models of LVAD interacting with the blood vasculature and interstitial compartments, we reproduce the obvious results that c-LVADs can prevent edema by lowering capillary and central venous pressures. However, such predictive models can identify critical risk factors that predispose particular patient groups to risk of edema. In addition, we have expanded our modeling to include the effect of pulsatility on vascular radii and microvascular permeability.

Results: Results suggest the diminution of pulsatility has an additional benefit of decreasing the capillary filtration coefficient and increasing arterial resistances, both of which delay the manifestation of edema in the lungs and intestines. Our systems biology approach thus allows translation of research in basic biology to implication for clinically-relevant outcomes, decrease in pulmonary edema and restoration of intestinal function. With these insights, we have a framework to 1) identify adjunctive pharmacological therapy, 2) optimize preclinical animal studies, and 3) identify critical risk factors for patient selection for clinical trials.
Blood Substitute With Vasodilatory, Antioxidant and Anti-inflammatory Properties: From Concept to Bedside  
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Study: Regardless of previous commercial setbacks, blood substitutes still remain a viable solution to the current transfusion medicine challenges. Armed with an awareness of the problems with first generation Hb-based blood substitutes, we created a unique pharmacologic cross-linking technique to modify the Hb molecule providing it with new physico-chemical and medicinal properties that eliminate Hb’s intrinsic toxic effects without interfering with its respiratory function. In this bovine Hb-based blood substitute, ATP prevents Hb dimerization, and adenosine allows formation of polymers and inhibits the vasoconstrictive and pro-inflammatory properties of Hb by activation of adenosine receptors. ATP also regulates vessel tone through activation of P2Y receptors. GSH adds electronegative charge onto the Hb surface blocking Hb’s transglomerular and transendothelial passage and shielding heme from nitric oxide and reactive oxygen species.

Methods: This blood substitute and its manufacturing technology have been extensively examined by GLP certified laboratories including viral and prion clearance validation studies and various non-clinical pharmacology, toxicology, genotoxicity and efficacy tests. The clinical proof-of-concept was performed abroad in sickle cell anemia patients. This product is currently completing requirements for being tested clinically in the US.

Results: Preclinical and clinical studies indicate that this blood substitute is nontoxic, possessing vasodilatory, antioxidant and anti-inflammatory characteristics, and stimulates erythropoiesis. The first clinical indication set up for this product, due to its pharmacologic features, is perfusion fluid for percutaneous coronary intervention procedures.

Development of a Jet Flow Circulation System for Preventing Filter Clogging During Cell-Free and Concentrated Ascites Reinfusion Therapy (CART)  
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Study: Cell-free and concentrated ascites reinfusion therapy (CART) involves the filtration, concentration, and reinfusion of drained ascites during the replacement of autologous protein. The clogging of the filter makes the reuse of a reasonable quantity of the ascites difficult. Furthermore, because the clogging produces toxic substances that cause side effects, it constitutes one of the critical problems that should be resolved for safe application of CART. To prevent clogging of the filter, we developed a novel jet flow circulation system that causes the ascites to circulate through the filter and the circulation circuit. The objective of this study was the use of computer simulation to optimize the structure of the jet flow system to increase the circulation flow rate, and the evaluation of the circulation flow rate using in vitro circulation models.

Methods: The simulation method was based on the Hagen-Poiseuille tube flow, and the jet flow was based on flow from a nozzle. The circulation model consisted of a jet pump, roller pump, connecting tubes, and filter. Jet pumps of several sizes were developed and experimentally evaluated. The flow rate of the roller pump was adjusted to 100 mL/min. The filter was considered a resistive element in the calculation of the circulation flow rate, and its resistance was measured using two liquids of different viscosities, namely, physiological saline and 1% lipid emulsion. Experiments were conducted to verify the simulation results using the same liquids.

Results: The results of the simulation showed that the circulation flow could be increased very efficiently by reducing the internal diameter of the nozzle. Using jet flow circulation for the experiments, 1% liquid emulsion could be circulated at over 30 mL/min. These results indicate that the jet flow circulation system can maintain the circulation through the filter and prevent filter clogging during CART.
Development of New Artificial Nerve: Influence of Sodium Chloride in the Scaffold

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Study: Peripheral nerve has a potential to regeneration. Using this potential, nerve conduit has been applied for repair of peripheral nerve defect. After experimental studies in canine with 80-mm peroneal nerve gap, the nerve guide tube made from polyglycolic acid tube stuffed with collagen (PGA-C tube) moved to clinical application in 2002, where the collage was used as a scaffold of tissue regeneration. However there has been no detailed evaluation of NaCl concentration in the scaffold. The aim of the present study was to evaluate the influence NaCl concentration in the collagen scaffold of the artificial nerve.

Methods: Three types of nerve conduits were prepared; one was PGA-hollow tube (tube A), another was PGA tube stuffed with a collagen with a NaCl concentration of more than 4% (tube B), the third was PGA tube stuffed with a collagen with a NaCl concentration lower than 1.0% (tube C). Ten tubes with a diameter of 2 mm, 15 mm length were implanted into the 10mm defect of the sciatic nerve on each groups (A, B, C). After 180 days, nerve conduction velocity (NCV) on the reconstructed sites of the sciatic nerves was measured on all rats, and then the animals were sacrificed for the pathological examination of the nerve regeneration on the reconstructed sites.

Results: In all tube A, B, and C the sciatic nerve was regenerated. NCV of the tube A, was lower than other two tube (B, C). Though average value of NCV of group B was higher than that of group C, there was no statistical difference between two groups. The pathological findings coincide with the NCV values, namely the regeneration of the axon had a corresponded the NCV on the regeneration sites. Conclusion: These results suggest that the collagen staffed in the tube promoted nerve regeneration and that the regeneration was not influenced with NaCl contained in the collagen scaffold at 1% and 4%.

Augmented Pulsatility by Modulating Pump Speed in Bovine Ischemic Heart Failure Model

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Study: Rotary blood pumps operate at a constant speed (rpm), which significantly diminishes pulsatility and may be associated with aortic insufficiency, gastrointestinal bleeding, and stroke. We hypothesize that modulation of pump speed will augment vascular pulsatility, helping to reduce the incidence of these adverse events. In this study, ten candidate speed modulation algorithms were investigated in a chronic ischemic heart failure (IHF) bovine model to quantify pulsatility and hemodynamic efficacy.

Methods: IHF calves (n=10) were acutely supported with clinical-grade centrifugal LVAD. Aortic and left ventricular (LV) pressures, and pulmonary artery, distal aortic, and LVAD flows were recorded at IHF baseline, constant pump speeds, and asynchronous (19–60 cycles/min) and synchronous modulation profiles (±25–38% rpm change). Hemodynamic and LVAD parameters were calculated to characterize aortic pulse pressure (ΔP), surplus hemodynamic energy (SHE), and pump performance for IHF baseline and each pump speed profile.

Results: Centrifugal LVAD augmented ΔP and SHE for all flow modulation profiles compared to constant pump speed. At 3200 rpm mean support using ±25% rpm modulation, the ΔP were significantly greater than constant pump speed (all asynchronous, †p<0.01; and synchronous copulse, ††p<0.001). Asynchronous modulation at 19 cycles/min produced the largest pulsatility (ΔP = 25.1±3.70 mmHg; SHE = 4.01±1.02*10³ erg/cm³). However, ±38% rpm modulation required 22±6.7% more power than that of matched constant pump speed, whereas ±25% rpm modulation only increased power consumption by 4.8±1.1%. While operation of rotary blood pumps at constant speed delivers flow with a ‘diminished pulse’, speed modulation has the potential to restore vascular pulsatility at equivalent mean flow. Future studies of chronic LVAD speed modulation will determine if there is a significant impact on LV unloading and end-organ perfusion, and a reduced risk of adverse events.
Soft Robotic Actuators for Cost-Effective Prostheses
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Study: Functional upper limb prostheses are prohibitively expensive, especially for children who require prosthesis refitting as their bodies grow throughout adolescence. A novel prosthesis design incorporating strength-enhanced soft robotic actuation technology is described in this study. Soft robotic actuators resembling fingers replicate the bending motion of finger joints through inflation of pneumatic chambers. This cost effective, simple, durable design has improved grip strength and is suitable for children's lifestyles involving frequent physical activity. We report the design of a pneumatic actuator with grip strengths that demonstrate viability for use in children’s upper limb prostheses.

Methods: Soft pneumatic actuators were designed by casting liquid elastic silicone rubber into 3D-printed plastic molds. Upon solidification, the actuators were removed from the mold and pressurized with an external air source for experimental validation of performance. Actuator strength was improved by incorporating reinforcing fabric layers around the molded silicone rubber, thus preventing material failure associated with internal pressures required to maintain high grip strengths. Prototypes were tested by measuring internal pressures required to both hold static loads and lift free-hanging weights.

Results: Soft pneumatic actuators were designed with improved grip strength for application as fingers in children’s prostheses. Incorporation of fabric reinforcing layers around rubber actuators resulted in a 2.5-fold force increase. Using this novel actuator design, we plan to build a prosthetic hand prototype with basic gripping functionality as a proof-of-concept alternative to traditional prostheses. Furthermore, this actuator can be easily customized in shape due to its simple, low-cost of design. Our strength-enhanced pneumatic actuators are relevant not only for prostheses, but also for medical applications such as surgical assist devices requiring single-use, custom gripping tools.

Oxygen Therapy Burn Prevention
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Study: Patients who have difficulty breathing normally due to pulmonary diseases, such as COPD, are often put on oxygen therapy[1]. Oxygen therapy generally involves an oxygen tank and tubing to deliver the oxygen from the tank to the patient via the nose or mouth. The most common tubing is the nasal cannula (Figure 1) which sits on the upper lip, directing highly concentrated oxygen into the nostrils (Figure 2). The problem that we are addressing arises mainly from the fact that a large number of these patients are smokers, and they continue to smoke while on oxygen therapy. Since oxygen acts as an accelerant for flames, patients are at a high risk of causing flash burns while lighting cigarettes. This can lead to burns to the patient’s face, singed hair, ignition of clothing, and melting of the nasal cannula onto the skin, which sometimes requires surgery (as seen in Figure 3).

Methods: Statistics: In a 2008, National Fire Prevention Association wrote a journal containing reviews of fire and medical literature and statistics of burns and fires involving medical oxygen in the U.S. Emergency rooms saw an estimated average of 1,190 burns per year involving medical oxygen in 2003–2006. Figure 4, listed below, shows what heat sources are seen in medical oxygen related burns at hospital emergency rooms.

Results: Using 2 IR sensors mounted on the nasal cannula around the cheek, we can create a system that can detect flames specifically near the face. The IR sensors can be used to trigger an automatic shutoff valve, thereby stopping the O2 flow whenever a flame is detected. Because flames release a lot of IR radiation, the system should be able to detect flames consistently and very quickly. This will also require a microcontroller connected to the IR sensors and the automatic shutoff valve, as the microcontroller will control the valve after receiving the inputs from the IR sensors.
Nanofiber Manufacturing Device for Stem Cell Studies
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Study: The purpose of this study is to engineer a robust method of consistently reproducing biodegradable and biocompatible nanofiber scaffolds that mimic the microenvironment of the extracellular matrix of tendon. Our objective is to develop a nanofabrication device that manufactures a scalable and parallel aligned nanofiber scaffold; the scaffold will be used as a platform to cultivate stem cells that will differentiate into tendon. We have found that applying an electrospinning methodology would be the optimal means of fulfilling our client’s criteria.

Methods: Our electrospinning apparatus includes a rotating, surface-patterned mandrel and mobile spinneret. The mandrel will be connected to the grounded lead of a high voltage DC power supply, and its rotation will be driven by a DC motor. A microcontroller will control the rotation speed of the motor and the x-y movement of the syringe. The syringe will expel a polymeric solution (consisting of PLGA and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)) onto the mandrel. The positive lead of the DC power supply will charge the polymeric solution through its connection to a conductive needle tip; this will cause a jet of fibers to eject from the syringe and onto the mandrel. Subsequently, the scaffold may be removed from the mandrel and seeded with stem cells.

Results: We expect to produce 8"x6" sheets of nanofibers. We will execute scanning electron microscopy and liquid intrusion tests to verify the nanofibers' alignment, scaffold porosity, and nanofiber diameter (200–600 nm). The parameters we will consider in order to produce such results include but are not limited to: concentration of PLGA, flow rate of the polymeric solution, and rotation speed of the mandrel.
Pulsatile Modulation of Centrifugal LVAD Improves Left Ventricular Unloading and End-Organ Perfusion in Ischemic Heart Failure
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Study: Left ventricular assist devices (LVAD) are operated clinically at constant speeds to improve end-organ perfusion, however associated complications such as myocardial weakening, aortic valve stasis, and diminished end-organ perfusion have been reported. We hypothesize that modulating LVAD speed will enable periodic reloading of the left ventricle (LV) to minimize these complications. In this study, we investigated the effects of LVAD speed modulation on LV external work (LVEW), LV oxygen consumption (LVVO\textsubscript{2}) and end-organ perfusion in an ischemic heart failure (IHF) animal model.

Methods: IHF calves (n=4) were acutely supported with clinical-grade centrifugal LVAD. Speed modulation was accomplished by asynchronous (19–60 cycles/min) and synchronous symmetric modulation. LVAD speed was set at high rpm (3200 rpm) ±25% step change and moderate rpm (2900 rpm) ±38% step change for each modulation profile. Aortic and LV pressures, pulmonary artery flow, coronary artery flow, LVAD flow, and LV volumes were recorded. Arterial and coronary sinus blood samples were collected to calculate LVVO\textsubscript{2}. End-organ perfusion was quantified by injection of fluorescently-labeled 15μm spheres.

Results: All speed modulation profiles at moderate rpm (±38% rpm) resulted in significantly reduced LVEW and LVVO\textsubscript{2} compared to IHF baseline (**p<0.01). Synchronous modulation demonstrated significantly less LVVO\textsubscript{2} than constant rpm (†p<0.05) but neither synchronous counterpulse nor copulse reduced LVEW below constant rpm. Speed modulation provided significant increases in end-organ perfusion. Asynchronous flow modulation (±25% rpm) increased LV tissue perfusion by 45±28% (60 cycles/min) and 62±43% (19 cycles/min) compared to constant pump speed. Continuous LV unloading during LVAD support may impair end-organ perfusion. Regulating the mean pump speed and speed modulation profiles may allow for better control of LV workload and improved end-organ perfusion.

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Splenectomy for Surgical Training

Study: The goal of SimuCut was to create a device that allows surgical trainees to develop and refine techniques by practicing on a simulator that mimics tactile and aesthetic experiences of performing surgery. Providing a controlled surgical environment improves efficiency and performance of procedures, resulting in fewer surgical errors. The focus was to develop a reusable, cost-effective splenic system and abdominal cavity that has similar shape and mechanical properties as a human abdomen.

Methods: Literature values of the mechanical properties of a human spleen and connective tissues were used to benchmark materials for stiffness and hardness. Three prototypes of different materials were user tested with a focus group to determine which materials would provide the most realistic surgical experience. Importantly, circulation and adipose tissue are incorporated into the splenic simulator.

Results: With the development of a spleen, vasculature, abdominal cavity, connective and adipose tissues, a solid foundation was set for the development of a full abdominal organ simulator. The final product will be used at hospitals as an alternative for animal and cadaveric practice.
Do the Difference of HQ Curve Gradient and the Stiffness of Rotational Speed Control for Rotary Blood Pump Make Any Change on Blood Flow on an End Organ?
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Study: Rotary blood pumps employed as LVADs have distinctive hydraulic characteristics with respect to the design and control. Pump performance is generally expressed by an HQ curve under steady flow conditions. In physiological conditions, the cardiac beat makes the head pressure change and rotational speed variation. In this study, we examined the effects of the HQ characteristics on the peripheral perfusion of end organs using the centrifugal blood pump (EVAHEART LVAS) under the different stiffness conditions in the rotational speed variations.

Methods: The pump, which has a flat HQ curve which enables to create pulsatility with constant speed, was implanted in an adult goat. Firstly, a beta-blocker was administered intravenously as a bolus in order to decrease the heart function as well as to achieve the low peripheral resistance condition, and the aortic and renal artery pressure and flow waveforms were measured simultaneously. Secondly, we increased internal pump resistance by narrowing the outlet conduit. Moreover, we altered parameters of the PID controller to change the pump speed variation range in one cardiac cycle.

Results: Altering the outlet conditions made the HQ curve steeper like the axial flow pump. The changes in aortic and renal impedance were analyzed by FFT and the input impedance at the ascending aorta decreased in high frequency ranges under the flat-HQ curve condition, whereas the renal impedance exhibited the smaller values at lower frequency compared with the control condition. On the other hand, with flexible control conditions, modulus of both aortic flow and renal artery flow were low and flat. Therefore, it was indicated that the vascular bed decreased the peripheral wave reflections under the cardiac assist condition with the flexible controlling method. In summary, flat HQ curve characteristics and stiff rotational speed control might deliver the flow with pulsatility to the peripheral circulatory systems.
Use of HVAD® Controller Log Parameters to Identify Suction Events with a Novel Index
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Study: The HVAD Controller is capable of capturing log file trend data, which contains historical VAD operating parameters. Current logged VAD parameters include estimated flow, flow pulsatility (waveform amplitude), and flow trough (waveform minimum). Retrospective analysis of HVAD controller log data was conducted to characterize these parameters for normal operation and suspected suction conditions.
Methods: Normal events were classified as any stable waveform regions lasting at least 12 hours. Suction conditions were defined as any sudden, intermittent decreases in average flow greater than 1 L/min. A total of 200 patients were analyzed for normal and suction events, yielding n=770 normal data points and n=172 suction data points. Using pulsatility, trough, and average flow, the “waveform index” is calculated as defined in Figure 1. Due to the duty cycle of the cardiac cycle, we hypothesized the waveform index will be greater during suction events.

Figure 1. Identifying the Waveform Index

Results: Normal operating conditions produce a waveform index that is lower on average with a greater density when compared to suction conditions (0.41 ± 0.04 vs. 0.52 ± 0.13; p<0.001). Normalized distribution curves for normal and suction conditions are shown in Figure 2.

Figure 2. Normal Distribution Curves

Conclusion: The waveform index may helpful in future algorithms to minimize false positive events and allow for better patient management.

Patients Listed with Status 2 had a Poor Prognosis without Mechanical Circulatory Support - How to Indicate Device Implantation among Them?
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Study: Indication for mechanical circulatory support (MCS) has been a matter of debate in less sick status 2 patients. Therefore, we here tried to find out a therapeutic borderline between medical and MCS therapy in status 2 patients.
Methods: Data were obtained and calculated from consecutive 183 patients assigned stage D heart failure (HF) who were evaluated by the institutional review board of the University of Tokyo Hospital and then listed for heart transplantation as status 1 or 2 of Japan Organ Transplant Network, which were equivalent to United Network Organ Sharing status code 1 or 2, respectively.
Results: Patients with status 2 (N=38) had a prognosis as poor as those dependent on inotropes (N=54) or MCS (N=91) (p=0.615 by log-rank test), along with only four eventual ventricular assist device (VAD) implantation (10.5%). Patients who eventually received VAD (N=92) had better 4-year survival over those without MCS among status 1 and 2 group (p=0.030 by log-rank test). Cox regression analyses demonstrated that plasma BNP level >740 pg/mL was an only significant predictor for 4-year mortality among status 2 group (p=0.014; hazard ratio, 8.267). Ten patients with status 2 deceased, 6 due to acute hemodynamic compromise and 4 due to ventricular fibrillation. In conclusion, prognosis in patients with status 2 was as poor as those dependent on inotrope infusion or VAD mostly because of out-of hospital sudden death without MCS. Status 2 patients with considerably high levels of plasma BNP may be good candidates for continuous flow VAD therapy.
Extracorporeal Membrane Oxygenator (ECMO) Support as Bridge to Implantation of Durable Mechanical Circulatory Support (MCS) in Patients with Advanced Cardiogenic Shock (ACS)

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Study: Implantation of durable MCS devices in the setting of advanced cardiogenic shock complicated by multi-organ failure remains controversial because of high mortality and morbidity. We describe our institutional experience of patients bridged with peripheral veno-arterial (VA) ECMO to durable MCS.

Methods: Since July 2008, 18 patients with advanced cardiogenic shock were bridged using peripheral VA-ECMO to long-term MCS. We performed a retrospective chart review to determine the short and long-term outcomes of this subgroup of INTERMACS category 1 patients.

Results: All patients were in advanced ACS with ≥2 inotropes and multi-organ dysfunction, with mean lactate of 5.1 mmol/l, AST 340 mmol/l, ALT 194 mmol/l and Cr 1.8 mg/dl. The mean age was 59.8 years (range 39–74). There were 7 males (94.4%). Etiology of ACS was ischemic in 10 (55.6%) and non-ischemic in 8 (54.4%). Duration of ECMO support was 9.3 days (range 1–27). Implanted devices were HeartMate II (13), Heartware (3) and Syncardia TAH (2). Re-operation for bleeding occurred in 6/18 (33.3%), and right ventricular failure requiring short-term mechanical support occurred in 4/16 (25%). 30-day survival was 88.9%. Long-term survival after a mean follow up of 381 days (range 5–1922) was 51.6%. Three patients were transplanted after mean of 190 days (range 109–255), of whom 2 are alive after mean follow up of 1142 days.

Conclusion: Application of peripheral VA-ECMO to bridge patients with advanced cardiogenic shock to durable MCS devices results in excellent short-term and long-term outcomes.

Improved Survival in Postcardiotomy Shock Using Modern ECMO

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Study: Postcardiotomy shock occurs in 3–5% of patients undergoing cardiac operations. It is associated with poor survival with mortality rates between 16–41%. However, newer ECMO circuits and blood pumps may help improve patient survival. We reviewed the survival to discharge of patients placed on modern ECMO circuits.

Methods: Between 7/08 and 8/12, all patients put on veno-arterial ECMO for postcardiotomy shock were included in the study. These patients were all operated on at a single institution. All patients were unable to be weaned from bypass despite at least 2 high dose inotropes and/or an intraaortic balloon pump. A Bioline coated Quadrox-D oxygenator, Bioline coated tubing, Carmeda coated cannulas, and current centrifugal blood pumps were utilized as the ECMO circuit. Heparin was used and titrated to a partial thromboplastin time between 40–60 sec. The patients were maintained on ECMO until recovery and ECMO explantation or death. Survival to discharge was analyzed.

Results: 31 patients were included in the study with an average age of 53.9 yrs (range 19–79 yrs). 23 were male and 8 were female. The average BMI was 27.9 Kg/m² ± 5.9 and 13% (4 of 31) had peripheral vascular disease. 26% (8 of 31) had diabetes and 61% (19 of 31) had hypertension. The average systolic pulmonary artery pressure was 42 ± 10 mm Hg and the average Euroscore II was 14.3 ± 13.7 %. 25 operations were urgent or emergent. 26 were cannulated via femoral artery and vein and 5 were cannulated centrally. 6 of 31 were supported by ECMO and IABP. The operations requiring postcardiotomy ECMO were cardiac transplant n=10, Coronary artery bypass grafting (CABG) n= 9, single valve/CABG n=5, multi-valve replacement n=2, aortic root replacement n=2, multi-valve/CABG n=1, single valve replacement n=1, and right heart failure n=1. The average duration of support was 5.1 days (range 1–15 days). 20 pts survived to discharge and 11 expired for a survival rate of 64.5%. Using modern ECMO circuits we have observed a significant increase in survival.
Prospective Characterization of Power Utilization and Temporal Correlation with Indices of Hemolysis, Coagulation Status, and Adverse Events in a Continuous Axial Flow Pump

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Study: Power elevations in continuous flow rotary pumps are concerning for thrombosis. Evaluation of these events has been limited in previous retrospective studies. Our aim was to prospectively characterize the pattern of power utilization early after LVAD implant and correlate with coagulation status, hemolytic indices, and adverse events.

Methods: Power utilization was digitally captured every 15 seconds in the post-operative period in patients implanted with the HM2 LVAD (n=14). INR, PTT, LDH, and adverse events related to thromboembolic complication were collected. Data was recorded for an average of 6.1 days (range 1.5–16.5). Mean follow-up was 5 months (range 1–8).

Results: Three different power utilization patterns were observed: stable power utilization over time (Group 1; n=7); power utilization >2W above baseline or >10W for less than 24 hours (Group 2; n=5); and sustained power elevations >24 hours (Group 3; n=2) (Figure 1). Patients in Group 2 had a mean INR of 2.9 (Range 1.1–5.9), PTT of 43 (26–79), and LDH of 345 (232–466) at initial elevation. Patients with sustained elevations had INRs of 2.8 and 1.1, PTTs of 76 and 46, and LDHs of 282 and 252, respectively, at the time of initial elevation. Mean LDH on discharge for patients without elevations was 404 (Group 1). Mean peak LDH levels were 580 U/L (Range 369–1136) for Group 1, 850 U/L (387–2038) for Group 2, and 424 U/L (369–479) for Group 3. Thrombus within the pump was noted in one patient in group 2 at routine heart transplantation, although the patient had no clinical symptoms prior to explant.

Use of a Simple Modified Outpatient Ramp Study to Identify Patients with an Improperly Functioning LVAD

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Study: Patients with a ventricular assist device (VAD) are at risk for persistent heart failure symptoms and thromboembolic complications if the VAD is not functioning properly. Our goal was to develop a simple ramp study without echocardiography to screen patients for VAD malfunction.

Methods: Patients in the ambulatory clinic with a Heartmate II LVAD had their speed increased at 200 RPM intervals starting at 600 RPMs below baseline and going to 400 RPMs above baseline. Flow was plotted at each speed. Flow slope was defined as (maximum flow - minimum flow)/200RPM. Results from the most recent echocardiogram, right heart catheterization, and adverse events were evaluated.

Results: Thirty-one patients were enrolled, 28 were male, mean age was 56. The average duration between implant and ramp study was 14 months (range 1–41). The average flow slope was 0.21 (Liters/min)/200RPM (SD=0.07). Four of ten patients (40%) with a flow slope <0.20 had an issue with their pump including cannula malposition (n=2) and pump thrombosis (n=2). Two of twenty-one patients (4.7%) with flow slope ≥0.20 had confirmed pump thrombosis (n=1). A significant decrease in the slope of the flow curve was seen in patients with an increased transpulmonary gradient (p=0.01) and increased pulmonary vascular resistance (p=0.01). LVEDD, RV failure, mean RA pressure, and BMI were not associated with a change in flow slope. No significant difference in flow slope was found for patients who remained in class IV heart failure.
Optimized Post-Cardiopulmonary Bypass Biventricular Pacing Improves Hemodynamics Despite QRS Widening: Results From The BiPACS Trial


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Study: Biventricular pacing (BiVP) post-cardiopulmonary bypass (CPB) improved hemodynamics acutely in our recently published trial. The relationship between QRSd and hemodynamics was explored in this post-hoc analysis.

Methods: Patients (n=43) with preoperative EF <40% and QRSd >100 ms underwent a hemodynamics-based BiVP optimization protocol 1,2 and 18±6 hours after CPB (Phases 1, 2 and 3, respectively) and subsequently compared during no pacing (NoP), atrial pacing (AAI) and optimized BiVP settings. Patients were also randomized to continued BiVP or standard postoperative care between measurements. Surface ECGs were recorded throughout the study. The QRSd was calculated from averaged complexes and compared to pre- and postoperative ECGs. Within phase comparisons were done with a paired t-test and between phase comparisons were done with a mixed effects model.

Results: QRSd was prolonged in BiVP over AAI in phase 1 116±4 vs 139±6 (p=0.005), despite a 10±3% (p=0.003) increase in Cardiac Output. Similar QRSd prolongation was seen in later phases without hemodynamic benefit. There was no significant correlation between preoperative or intraoperative QRSd and hemodynamic benefit. Patients undergoing aortic valve surgery had the greatest hemodynamic benefit but no intraoperative QRSd and hemodynamic benefit. Patients undergoing biVP or standard postoperative care between measurements. Surface optimized BiVP settings. Patients were also randomized to continued BiVP or standard postoperative care between measurements. Surface ECGs were recorded throughout the study. The QRSd was calculated from averaged complexes and compared to pre- and postoperative ECGs. Within phase comparisons were done with a paired t-test and between phase comparisons were done with a mixed effects model.

Experience of The MERA, Pivot-bearing Centrifugal Pump System For Short-term Circulatory Support

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Study: Bridge to decision with short-term circulatory support is an evolving paradigm in the management of patients who present in acute refractory cardiogenic shock. MERA HCF-MP23 (Senko Medical Instruments, Japan), which is a pivot-bearing centrifugal pump designed for open-heart surgery, and bridge to decision for up to 4 weeks, is our device of choice.

Herein we present our experience with the MERA HCF-MP23 in patient with heart failure for the purpose of bridge to decision.

Methods: From December 2012 to November 2013, 8 patients underwent MERA placement as bridge to decision. 2 dilated cardiomyopathy; 2 fulminant myocarditis; 1 DuraHeart pump pocket infection; 1 multiple cerebral infarction after Nipro VAD installation; 1 uncontrollable anti-coagulation after Nipro VAD installation; and 1 ischemic cardiomyopathy. Mean age was 43.8 years (range 30–55 years). 5 underwent salvage with a MERA; 3 were converted MERA from a DuraHeart and 2 Nipro VADs. Target ACT was between 180–220 seconds with heparin or argatroban.

Results: Mean mechanical circulatory support was 24.2 days (range 2–62 days). Mean pump flow was 2.5 l/min/m². Operative (30-day) mortality was 12.5%. 5 patients were converted to long-term assist devices (HeartMate II, DuraHeart, and 3 Nipro VADs). Two patients were weaned from MERA following recovery of cardiac function. Two patients died due to mediastinitis 87 and 109 days after MERA removal. Overall survival was 62.5%. 1 patient had a cerebral infarction after 15 days. 1 patient had re-exploration for cardiac tamponade after 8 days. No mechanical failures occurred. There were no thrombus formations in the pump when the systems were removed. No hemolysis occurred. MERA provided satisfactory short-term support for patients with cardiogenic shock or those with LVAD related complications with a low incidence of device-related complications and no device failures. Further clinical experience is still needed.
The Improvements of Hemodynamic Performance of the Synchronized Bileaflet Mechanical Heart Valve

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Study: Cavitation, intermittent regurgitation and rebound are issues to be resolved for St. Jude Mechanical (SJM) bi-leaflet valve, which is the most widely implemented mechanical heart valve in clinical application. Our novel synchronized bi-leaflet valve provided the solution for these problems.

Methods: The opening and closing motion of the leaflets of SJM and synchronized valves were closely observed using ultrahigh-speed camera in the test chamber along with the flow channel which was piped by a water pump. The hemodynamic performance and characters of these two valves were analyzed and calculated using an adult mock circulation simulator at heart rates of 70 and 110 bpm at various cardiac outputs, respectively. We also compared the occurrence of in vitro blood hemolysis between these two valves in the mock system using porcine blood under physiological conditions.

Results: There was a 28–30 mSec gap between complete closures of both leaflets of the SJM valve. However, the two leaflets of our synchronized valve were closed simultaneously. The time-gap might be the reason of the intermittent regurgitation for the SJM valve. On the mock model, we found that the valve opening pressure of our synchronized valve was significantly decreased, the stroke volume was elevated, and the regurgitant volume was decreased, compared to those of the SJM bi-leaflet mechanical valve. The increased effective energy and decreased energy loss of the synchronized valve might also result from the time-gap of closure of the leaflets of the SJM valve. The calculated effective orifice area and occurrence of hemolysis were significantly better with the synchronized bileaflet valve. In conclusion, our Synchronized valve could improve the performance of the ventricle with less opening pressure, end-systolic volume and much larger stroke volume. Further study of the performance of the synchronized valve on the failed heart will be performed.

The Amelioration of The Structure of Intraaortic Axial Flow Pump for Improving Its Hydrodynamic Performance

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Study: Previously we proposed a unique LVADs, termed as “intraaortic axial flow pump", which is simply an cage supported impeller posting inside the lumen of the ascending aortic and driven by an extra corporeal electric-magnetic device. We seek to ameliorate the structure for further improving its hydrodynamic performance.

Methods: The intraaortic axial flow pump is composed of a fan-like impeller, a supporting cage and a diffuser. The impeller, with an outlet diameter of 18mm and a length of 10mm, locates inside the supporting cage and sustained by a shaft through a pair of sliding bearing. The impeller, made of titanium, is equipped by a column of permanent magnet at its center and, therefore can coupled with an alternative magnetic field for whiling. The alternating magnetic field would be generated by a nearby magnetic device, extracorporeal arranged in conceivability. A diffuser is located downstream to the impeller by fixing to the supporting cage. This setting was anticipated to improve hydrodynamic performance. The new device was tested and compared with an original prototype in a mocking circulatory line with the solution of 33% glycerol.

Results: The new device, totally weights 20 gram and has a diameter of 22mm and length of 30 mm, is feasible for implanted inside the ascending aorta. The output reached 5L/min against a 100mmHg afterload at the rotational speed of 14100rpm, that corresponded to a hydrodynamic efficiency of 10.5%. Contrastively, originally proposed prototype produced same output at a rotational speed of 17300rpm, only with a hydrodynamic efficiency of 9%.

Conclusion: The present study suggested that a diffuser is beneficial for improvement of hydrodynamic performance for an intraaortic axial flow pump, in contrast to the previously proposed model without a downstream diffuser.
High Oxygen Partial Pressure Promotes an Inflammatory Response During Extracorporeal Circulation in a Rat Model

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Study: Systemic inflammatory responses in patients receiving cardiac surgery supported by extracorporeal circulation (ECC) significantly contribute to ECC-associated morbidity and mortality. We hypothesized that high oxygen partial pressure condition aggravates the inflammatory responses and organ damage during ECC. To verify this hypothesis, we investigated the inflammatory responses at high and normal levels of PaO2 in the rat CPB model.

Methods: Rats were divided into a SHAM group (n=5), a hyperoxia CPB group (n=7, PaO2 > 400mmHg), and a normoxia CPB group (n=7, PaO2:100-150 mmHg). We measured the serum cytokine levels of (TNF-α, IL-6, IL-10) and biochemical markers (LDH, AST, ALT) before, 60 and 120 min after the initiation of ECC. We also measured the wet-to-dry weight (W/D) ratio of the left lung and performed dihydroethidium (DHE) stain reflecting superoxide generation in the lung and liver tissues postmortem after 120 min ECC.

Results: In the hyperoxia group, the pro-inflammatory cytokines and biochemical markers significantly increased during the ECC compared to the SHAM, but such increases were significantly suppressed in the normoxia group (TNF-α: hyperoxia vs normoxia: 1237 ± 62 pg/ml vs 834 ± 110 pg/ml). On the other hand, the increase in anti-inflammatory cytokines was more suppressed in the hyperoxia group than in the normoxia group (IL-10: hyperoxia vs normoxia: 632 ± 40 pg/ml vs 1002 ± 36 pg/ml). The W/D ratio increased significantly more in the hyperoxia group than in the normoxia group (hyperoxia vs normoxia: 6.01 ± 0.11 vs 5.57 ± 0.08). In addition, the DHE fluorescence predominantly increased in the hyperoxia group compared to that in the normoxia group. The present study strongly indicates that too much oxygen insufflation during ECC may result in organ damages due to inflammatory responses associated with superoxide production.

Development of a Compact Pneumatic Drive Unit With a DC Servo Motor for a Ventricular Assist Device

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Study: Currently, a pneumatically driven extracorporeal VAD is still widely used for the treatment of acute severe heart failure patients or patients who are not eligible for an implantable VAD in Japan. Conventional pneumatic VAD drivers which have a sufficient performance are used for these patients, but they are large (more than 30x43x24 cm) and heavy (more than 14 kg) and restrict patient’s freedom of movement. To improve the QOL of patients, we have been developing a novel pneumatic driver with a direct current (DC) servo motor, and we evaluated its performance in in vitro experiments.

Methods: The size and weight of core unit of the developed driver are 22x24x14 cm and 2.8 kg, respectively. The core unit is constructed from a cylinder-piston, a crankshaft and a DC servo motor. Driving air pressure is generated by the cylinder-piston and crankshaft driven by the DC servo motor and the beating rate and systolic ratio of the driving air pressure can be changed arbitrarily by controlling the rotational speed of the DC servo motor. The ranges of reproducible beating rate and systolic ratio and the pump performance of the developed driver were examined using a mock circuit.

Results: The range of the reproducible beating rate and systolic ratio in the developed driver was from 10 to 25% at minimal beating rate of 30 bpm and was from 30 to 52% at maximal beating rate of 100 bpm. The pump output ranged between 1.8 and 5.7 L/min at the systolic ratio of 30–52 % at beating rate of 100 bpm when the preload and afterload of the pneumatic VAD were 10 and 120 mm Hg, respectively. More than 5 L/min of pump output was obtained at the systolic ratio of more than 44 %. Thus, the developed driver has the equal functions and performances, and offers a small size and lightweight, as compared with conventional pneumatic VAD drivers. It was shown that developed driver has the potential to improve the QOL of patients with a pneumatic VAD in Japan.
Association of Left Ventricular Assist Device Speed and Risk of Hemorrhagic Stroke

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Study: High LVAD speeds predisposes patients to increased bleeding, particularly in the gastrointestinal tract. The relationship of LVAD speed and bleeding from other sites has not been well characterized. We investigated the association of LVAD speed and hemorrhagic stroke (HCVA).

Methods: We retrospectively reviewed patients implanted with a continuous-flow LVAD at our center between 2005-September, 2013 who survived to discharge. Patients were stratified into the “high speed” group if their LVAD speed at discharge was greater than the median (> 9200 RPM for Heartmate II (HM2); >2800 RPM for HVAD). The effect of high vs. low speed on the risk of HCVA was modeled with logistic regression and time to HCVA was modeled with Kaplan-Meier analysis.

Results: 270 patients were included (median 62 years, 77 % male, 83% destination therapy, 54% ischemic, 84% HM2) and followed for a median of 1.5 years. 13 patients (5%) suffered HCVA. High-speed patients (n=118) were more likely to be male (p=0.03), have a higher body mass index (p<0.001) and have a higher creatinine at discharge (p=0.004). They tended to be older and have more diabetes (p=0.06 for both). There was no difference in history of stroke between the groups (p=0.22). High LVAD speed was a strong predictor of incident HCVA (OR 17.1; 95% CI 2.2–133.5; p<0.01). There was no association between high LVAD speed and ischemic stroke (p=0.75). Among the subgroup of HM2 patients, speed as a continuous variable predicted HCVA (OR 1.6 per 200 RPM; 95% CI 1.1–2.3; p=0.01). Discharge MAP was the only other univariate predictor of HCVA (OR 1.06; 95% CI 1.01–1.12; p<0.01). High speed remained significant in a multivariate model including age, gender and MAP (OR 15.2; 95% CI 1.9–122.5; p=0.01). The high-speed group had an increased hazard for time to HCVA compared to the low-speed group (log-rank p=0.001; Figure). Conclusion: High LVAD speeds are correlated with increased risk of HCVA. Further investigation is needed to determine the mechanism underlying this association.

Comparison of the Impella and TandemHeart: Numerical Simulation of Unloading

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Study: To compare the effect on cardiac energetics between a centrifugal pump across the LV (TandemHeart) and an axial pump in the LV (Impella), we developed a mathematical model of pressure-volume (PV) loops to compute relative unloading and to allow animal validation.

Methods: The simulation uses a time-varying elastance model to determine pressure and volume within the left ventricle at each time throughout the cardiac cycle. A Windkessel model simulates arterial vasculature. Device pressure-flow curves determine pump flow rate as the cardiac and arterial pressures vary throughout the cardiac cycle. LV work load results from the combination of instantaneous LV volume and pressure gradients. Stroke work (SW) comparisons were evaluated in both healthy and injured hearts.

Results: Device activation reduced end diastolic volume with each device, yet distinct differences were found between the PV loops of the different therapies. The aortic valve device removes volume during diastole and isovolumetric filling and emptying phases, resulting in a triangular PV loop shape. In contrast, the LA device maintains the isovolumetric phases but reduces LV load throughout all phases of the cycle. The centrifugal pump maintains consistent flow during diastole and the in-LV device requires more native LV contraction effort to overcome the pressure gradient to the aorta. The net result is greater workload reduction for the centrifugal, LA device. Experimental comparisons between the devices in animals is ongoing.
Aortix Percutaneous Circulatory Assist Device Decreases Afterload, Improves Renal Function in Chronic HF
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Study: Aortix is a catheter based intra-aortic circulatory assist device for ambulatory, semi-durable treatment of heart failure patients with cardiorenal syndrome. Aortix minimizes risk for Class III heart failure patients with a non-surgical approach that has zero thrombotic stroke risk. Aortix preserves the natural physiology of the circulatory system, rehabilitating the failing heart and pump failure is not a safety concern, since the device does not occlude the aorta. Our study aims to show the acute cardiac and renal benefits of Aortix in a model of chronic heart failure.

Methods: Aortix was implanted via catheter into the descending aorta of an ovine micro-embolization chronic heart failure model (n=4), upstream of the renal arteries and downstream of the carotid arteries. Acute hemodynamic measurements included sonomicrometry crystal PV Loops, proximal, distal, and ventricular pressures, urine output, GFR, myocardial oxygen consumption, and microsphere organ perfusion studies. A 30-minute baseline period was followed by Aortix deployment and activation for two 30-minute periods. Further cardiac parameters were calculated from PV loop data and balloon occlusion of the IVC at the end of each 30 minute period.

Results:
Our results show significant improvements in cardiac energetics, performance, and renal function. Overall energy consumption was decreased by 39%* while CO and EF were improved by 14% and 28%*, respectively. Despite a 5.5% decrease in coronary perfusion, Aortix decreased myocardial oxygen consumption by 24%*. Urine output doubled* and GFR showed a 23% improvement. (*=p<.05) An ideal ambulatory device for cardiorenal HF patients reduces afterload, improves kidney performance, and has a low risk profile. The present work suggests that Aortix can acutely meet these goals.

Progress in the Development of a Pneumatic Extracorporeal Ventricular Assist System
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Study: In vivo evaluation of an extracorporeal ventricular assist device with a pneumatically actuated bladder (EVAD-P), with integrated silicone tri-leaflet valves (Vitalmex, Mexico City, MX). The system incorporates an exchangeable and disposable bladder and hard-shell housing to greatly reduce cost.

Methods: The EVAD-P was evaluated in 3 separate groups of healthy adult sheep. Beat rate, stroke volume (SV), and device flow were continuously monitored throughout the duration of all studies. Group I studies (n=8) were evaluated in durations up to 30 days. Group II studies (n=2) were evaluated in study durations up to 49 days. Following a system redesign, Group III studies (n=5) were conducted up to 93 days.

Results: In group I, 5 out of 8 animals survived 27–30 days. Three studies were terminated early; 2 for reasons not related to device function and 1 as a result of an acute celiac artery thrombus. A fixed rate of 90 bpm was maintained, with a SV of 45.2±2.39 ml (mean blood flow 4.1± 0.33 L/min). Group II (n=2) animals were terminated at 28 and 49 days due to device thrombus. Subsequently, system modifications were made which included: redesigned inflow cannula, decreased beat rate, increased SV, and controller software revisions.

In Group III (n=5), three sheep were terminated due to morbidities not related to the system. Two sheep survived for 91 and 93-days, at a fixed beat rate of 56 bpm and a SV of 58± 0.6 ml, with a mean flow of 3.6± 0.01 L/min. In all study-term animals, hematologic and biochemical values were within normal range. At necropsy all major organs were unremarkable, however, there were small renal infarcts found in 4 animals which did not affect in-life renal function. There were small adherent thrombi in some pumps, which did not affect pump function. Initial results are encouraging, but additional studies are warranted.
Unplanned Hospital Readmissions After Continuous Flow Left Ventricular Assist Device Implantation

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Study: Continuous flow ventricular assist devices (VAD) improve survival in pts with Stage D heart failure. Though not extensively studied, recurrent hospital admissions in VAD pts remains a concern given the impact on pt quality of life and rising health care costs. We sought to define the incidence and patterns of hospital readmissions in a large cohort of VAD pts.

Methods: Between 2008 and 2013, 167 pts implanted with a VAD and surviving to hospital discharge served as our study cohort. We analyzed our VAD database to determine the frequency, etiologies, and notable patterns of all VAD unplanned hospital readmissions.

Results: Mean age was 60 yrs, 78% were men, 54% were Caucasian, and mean INTERMACS score at time of implant was 2.3±1.0. Indication for VAD was DT in 90 pts (54%) and BTT in 77 pts (46%). 147 pts (88%) had a total of 561 hospital readmissions during 546±388 days of VAD support. This resulted in a median of 3.0 (1.0–5.5) readmissions per pt (range 0–21), a median time to 1st readmission of 75 (35–160) days and median length of stay of 6 (3–13) days. No diff in annual readmission rates was seen between DT and BTT pts (3.5±2.9 vs. 3.3±2.3, p=0.67).

While readmissions accounted for a total of 5,476 hospital days, pts spent 85,709 days (94% of days on VAD support) out of the hospital. Also, 83 pts (50%) had <2 readmissions while only 10 pts (6%) accounted for 116 (21%) of all readmissions. In our large VAD cohort, unplanned hospital readmissions were common, though a disproportionate number occurred in a minority of pts. Improvements in VAD technology and management strategies, coupled with refinements in pt selection may reduce VAD related hospital admissions in the future.

Sequential Conditioning of the LVAD-supported Heart as a Strategy for Facilitating Myocardial Recovery

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Study: The Jarvik 2000 left ventricular assist device (LVAD) differs from other continuous-flow LVADs in that it allows for the patient to adjust the speed. These variable speed options correlate to substantial changes in flow rate, allowing decreases in flow to minimal values (1–2 Liters/min). We report the use of a Jarvik 2000 LVAD and a “turn down” strategy for bridging to recovery in a patient with cardiomyopathy.

Methods: A 16 year-old male with non-ischemic, dilated cardiomyopathy underwent implantation of a Jarvik 2000 LVAD for cardiogenic shock. Early in his postoperative course, he required high LVAD speeds (speed 4; 11,000 rpm) to perform daily functions. This corresponded to an ejection fraction (EF) of 16%. His initial left ventricle internal dimension-diastole (LVIDd) was 6.6 cm, which decreased to 5.4 cm over the first 6 months of support. Over the following months, his heart failure (HF) medicines were increased and his LVAD settings were sequentially decreased. Based upon his symptoms, his speed was decreased at night and returned back during the day. He began at speed 4 during the day, speed 3 at night. This approach continued until he was at speed 2 during the day, speed 1 at night. He tolerated these changes and underwent pump-off evaluation that demonstrated an EF of 61%, LVIDd of 4.7 cm, VO2 max of 20 cc/kg/min, and a right heart catheterization that showed a central venous pressure of 3 mmHg, pulmonary artery pressures of 26/19 mmHg, pulmonary capillary wedge pressure of 14 mmHg, and cardiac index of 2.9 L/min/m^2. His LVAD was explanted via left mini-thoracotomy and the patient was discharged home on post-operative day 7. He is now two months post-explant, tolerating titration of HF medications, and remains NYHA class I.

Results: Sequential conditioning of the LVAD supported heart - and in this situation using a device that allows for flexible, patient-controlled speed variability - is a promising strategy for bridging patients to recovery and pump removal.
Valve Surgery in Hemodialysis Patients: Surgical Outcomes and Risk Factor Analysis

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Study: Valve surgery in hemodialysis dependent patients is associated with postoperative complications and a high mortality rate. This study was performed to determine the pre- and intra-operative risk factors associated with hospital mortality in hemodialysis dependent patients after valve surgery.

Methods: The pre- and intra-operative statuses, and short- and long-term surgical results of 78 dialysis patients who had undergone valve surgery between 1998 and 2014, were retrospectively reviewed. Fifty perioperative risk factors were used in the statistical analysis for the prediction of hospital mortality. Risk factors for mortality were investigated with univariate and multiple logistic regression analyses.

Results: The in-hospital mortality rate including operative death was 12.8% (10 patients) and the actuarial survival rate (including in-hospital death) was 36.1 ± 7.6% at 5 years. Univariate analysis revealed the following 8 statistically significant risk factors as predictors of hospital death: emergent surgery, cachexia (BMI <17.6), New York Heart Association (NYHA) grade 4, amount of blood transfusion during surgery, total cholesterol, albumin, and serum calcium levels, and history of gastrointestinal disease (p < 0.05). Multiple logistic regression analysis confirmed cachexia and low serum cholesterol level to be statistically significant independent risk factors for hospital death (p < 0.05).

Conclusions: The surgical outcome of valve surgery in dialysis-dependent patients remains poor. These results suggest that surgical factors do not affect the outcome; however, patient status, including nutriure (cachexia and low serum cholesterol level) impacts the surgical outcome. Our findings will contribute to the estimation of operative risk in hemodialysis patients.

Use of a Single Circuit to Provide Temporary Mechanical Respiratory and Circulatory Support in Patients with LV Apical Thrombus and Cardiogenic Shock

G. Yost, B. Mohamedali, G. Bhat, A. J. Tatooles. Center for Heart Transplant and Assist Devices, Advocate Christ Medical Center, Oak Lawn, IL.

Study: We describe a novel method of biventricular mechanical cardiopulmonary support (MCS) in patients with left ventricular (LV) apical thrombi.

Methods: Two patients were admitted to our institution with refractory cardiogenic shock. The first patient was a 40 year old woman 3 days after a left main myocardial infarction. The second patient was a 56 year old man with a new diagnosis of cardiomyopathy and cardioversion refractory atrial fibrillation. Both were in cardiogenic shock with multisystem organ failure. Temporary MCS as a bridge to decision with left ventricular assist device (LVAD) and extracorporeal mechanical oxygenation (ECMO) were instituted. Both patients were noted to have LV apical thrombi. Instead of the traditional LV apical cannulation for LVAD, the left atrium (LA) was cannulated. The LA cannula was then integrated with the ECMO circuit with a “Y” connection to a percutaneous right atrial cannula. This circuit enabled optimal drainage of both sides through a single CentriMag® pump and ECMO. Oxygenated blood was returned to circulation via the aorta. (Figure 1)

Results: The first patient was converted to a durable LVAD and successfully transplanted while the second patient was successfully explanted after demonstrating significant LV recovery.

Conclusion: We demonstrate successful use of MCS as a bridge to decision in patients with LV thrombi utilizing biatrial cannulation with a “Y” connection to drain both right and left sided circulation through a single circuit.
Effectiveness of Protocol Guided Heparin Anticoagulation in Patients With TandemHeart Percutaneous Ventricular Assist Device

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Study: The TandemHeart is a percutaneous ventricular assist device that can be used to provide cardiac support to patients with severe refractory cardiogenic shock. The manufacturer of the TandemHeart recommends the use of a standard heparinized device infusate and the addition of peripherally administered heparin if necessary to maintain therapeutic anticoagulation. In current literature, there is no standard anticoagulation protocol for the TandemHeart. The purpose of this study is to assess how well heparin anticoagulation is managed in patients for which the institution’s TandemHeart heparin protocol was implemented compared to those managed without any heparin protocol.

Methods: This single center, retrospective cohort study included adult patients who received circulatory support with the TandemHeart from March 1st, 2012 to August 30th, 2013. Patients were excluded if they were under 18 years of age, received TandemHeart support for less than 24 hours, were anticoagulated with bivalirudin, or were managed with heparin protocols other than the TandemHeart heparin protocol. The case group was managed under the institution’s TandemHeart heparin protocol (Table 1) and the control group received heparin for anticoagulation without any heparin protocol. Electronic medical records were reviewed for demographic data, presence of heparin protocol, aPTT and clinical outcomes including thrombosis and bleeding. The aPTT values were collected from 6 to 48 hours after the initiation of the TandemHeart support.

Results: There were 15 patients in the case group and 10 patients in the control group. Patients who were managed with the institution’s TandemHeart heparin protocol had a significantly higher percentage of therapeutic aPTT and a lower percentage of supratherapeutic aPTT compared to the control group. (Table 2) Time to first therapeutic aPTT, time in therapeutic range and clinical outcomes did not differ significantly between groups.

Thoratec HeartMate II to HeartWare HVAD Ventricular Assist Device Exchange Experience

Mid-Term Outcomes Following Left Ventricular Assist Device Therapy: A Single Center Experience
B. Mohamedali\textsuperscript{1}, A. Tatooles\textsuperscript{1}, P. Pappas\textsuperscript{2}, G. Bhat\textsuperscript{2}, G. Sayer\textsuperscript{2}. \textsuperscript{1}University of Illinois at Chicago, Chicago, IL, \textsuperscript{2}Advocate Christ Hospital, Oak Lawn, IL.

\textbf{Study:} Continuous-flow LVADs (CF-LVAD) are increasingly being implanted as destination therapy, raising the expectation of longer therapy duration. We report our single-center experience with LVAD patients followed for a minimum of three years.

\textbf{Methods:} Data was retrospectively collected in consecutive patients who received the Heartmate II LVAD between 2005–2011. Patients were excluded if they were transplanted (n=16) or explanted (n=4) prior to three years follow-up. Characteristics of survivors and non-survivors were compared using chi-square and the Mann-Whitney U test.

\textbf{Results:} 110 patients were included in the analysis, with 54 (49\%) surviving to three years (Table). No significant differences were seen in baseline characteristics between survivors and non-survivors, although survivors had a trend towards a better baseline GFR (55 vs. 46; p=0.08). At the time of discharge from the index hospitalization, the aortic valve was closed in 78\% of survivors as compared to 53\% of non-survivors (p=0.006). Pulsatility index (PI) was significantly lower in the survivor cohort as well (median 4.8 v. 5.3; p=0.002). No differences were noted in LVAD speed or flow. Approximately half of CF-LVAD patients in our cohort survived to three years. Survivors were more likely to have a closed aortic valve and lower PI at the time of hospital discharge, suggesting a potential management strategy for promoting longevity on device. Further studies are needed to validate our findings.

<table>
<thead>
<tr>
<th>Table: Pre-LVAD Characteristics of 3-year Survivors (N=54)</th>
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Left Ventricular End-diastolic Pressure-dependent Passive and Active Flow Adjustment Scheme In Continuous-flow Left Ventricular Assist Devices
V. Tchantchaleishvili\textsuperscript{1}, S. W. Day\textsuperscript{2}, H. T. Massey\textsuperscript{1}. \textsuperscript{1}University of Rochester, Rochester, NY, \textsuperscript{2}Rochester Institute of Technology, Rochester, NY.

\textbf{Study:} Adjustable output is becoming increasingly important in left ventricular assist device (LVAD) development. Continuous flow LVADs inherently possess an autoregulatory potential that allows them, to a certain extent, to adjust LVAD flow on the basis of venous return without change in the pump speed. This “passive” pressure responsiveness of LVADs is, however, unlikely to accommodate the degree of variability that would be compatible with long term mechanical circulatory support. Left ventricular end-diastolic pressure (LVEDP)-based automatic adjustment of the LVAD pump speed could provide a solution to this problem.

\textbf{Methods:} Using the head flow curves available for HeartMate II LVAD we mathematically estimated the change in LVAD flow both in case of passive autoregulatory response (constant LVAD speed) as well as active LVEDP-based pump speed adjustment to regulate the demand-based LVAD flow. In our hypothetical example, a failed left ventricle (LV) supported with HeartMate II LVAD saw a mean aortic pressure (AoP) of 100 mmHg, and the LVEDP ranged between 8–12 mmHg at rest and rose to 15–45 mmHg with exercise.

\textbf{Results:} At rest, with LVEDP 8–12 mmHg, AoP 100 mmHg, and a minimal residual left ventricular function, LVAD flow was approximately 5 liters per minute (LPM) at 10000 rotations per minute (RPM), with mean pump differential pressure (dp) of 70 mmHg. During exercise, with AoP remaining at 100 mmHg and LVEDP varying between 15–45 mmHg, the LVAD dp decreased to 55 mmHg and the LVAD flow increased to 6 LPM with passive autoregulation only, at unchanged LVAD speed (10000 RPM). An increase in the pump speed to 10600 RPM with LVAD dp remaining at 55 mmHg, resulted in the LVAD flow increase to 7 LPM. An in vitro model is presented to support this passive and active LVAD flow adjustment scheme. The active LVEDP based pump speed controller shows promise as a method of LVAD output adjustment during long term mechanical circulatory support.

Berlin Heart Innovation Pipeline
F. J. Morales Serrano. R&D, Berlin Heart, Berlin, GERMANY.

\textbf{Study:} Berlin Heart is a world leader in the treatment of patients with heart failure, providing unique solutions for unique, individualized situations.

\textbf{Methods:} Berlin Heart is the only company worldwide with both FDA and CE approval for a paediatric mechanical circulatory support device, the EXCOR Pediatric, providing options for patients of every size and age.

\textbf{Results:} During this presentation, Berlin Heart will share our innovation pipeline including a new patient mobilization option and our ground-breaking solutions for our 3rd generation implantable technologies.
Thrombosis in Ventricular Assist Devices


Department of Biomedical Engineering, Texas A&M University, College Station, TX; College of Veterinary Medicine, Texas A&M University, College Station, TX; Department of Veterinary Pathobiology, Texas A&M University, College Station, TX.

Study: Ventricular assist devices (VADs) have become an effective treatment method for heart failure patients as they await cardiac transplantation. With each generation of devices, VAD developers and manufacturers are continually striving to make VADs safer and more effective. Mural thrombus formation and embolization have been issues consistently facing VAD manufacturers; these issues commonly cause problems during VAD implant/exchange procedures and throughout the duration of mechanical support.

Methods: To understand the effects of thromboembolism in VADs, a method to create thrombi in vitro was developed. Fibrin thrombi were made in vitro from equine donor blood. Shear forces were applied to the clotting blood using a motor capable of up to 300 rotations per minute. The resulting thrombi were processed and embedded in paraffin, then sectioned and stained with hematoxylin and eosin. Each thrombus created in vitro was compared to thrombi observed within VADs (in vivo) during post-explant pathological evaluation.

Results: The thrombi created in vitro shared similar gross and microscopic characteristics to those seen clinically (Fig. 1A in vitro, 1B in vivo).

Blood Product Utilization in VAD Patients at Time of Transplant and the Effect on Post-Transplant Outcomes


Transplant Program, Inova Fairfax Hospital, Falls Church, VA.

Study: Ventricular assist devices (VADs) are frequently used as a bridge to cardiac transplant. The removal of a VAD at time of transplant often requires blood transfusion due to anticoagulation and adhesions. With other cardiac surgeries, perioperative blood transfusions are associated with increased morbidity and mortality. We compared the number of blood transfusions at time of transplant and post transplant outcomes between patients with and without a VAD.

Methods: Between January of 2008 and 2014, we performed 101 orthotopic heart transplants. We performed a retrospective analysis of blood products transfused and post transplant outcomes of patients bridged to transplant with a VAD compared to those who went direct to transplant. We excluded patients who received biventricular VAD support, a pulsatile VAD, dual-organ transplants and re-transplants. Eighty nine patients were included in this analysis.

Results: Baseline characteristics are presented in table 1. Post-transplant outcomes including the Kaplan-Meier survival estimates are in table 2 and figure 1. Adjusting for a history of prior sternotomy had no effect on blood product utilization which continued to be higher in VAD patients.

Conclusion: VAD patients required a higher number of blood transfusions at time of transplant, however there was no effect on the one-year incidence of allograft rejection and post-transplant survival when compared to patients who went directly to transplant.
Hemodynamic Transesophageal Echocardiography after Left Ventricular Assist Device Implantation

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Study: The clinical profile of patients who receive hemodynamic transesophageal echocardiography (hTEE) after continuous flow left ventricular assist device (CF-LVAD) implantation is unclear. We sought to determine the clinical profile of patients who received hTEE after CF-LVAD implant and whether hTEE changed clinical management in the intensive care unit (ICU).

Methods: We retrospectively analyzed hTEE utilization in 100 patients (53±11 years, 83% male) implanted with a CF-LVAD (HeartMate-II (HM-II) n= 54, 54%; HeartWare (HW) n=46, 46%) between April 2009 and September 2013. Patients were analyzed in 2 groups according to clinically driven hTEE use: 41 patients received hTEE (hTEE group), while 59 patients did not receive hTEE (No hTEE group). Change in clinical management was defined as hTEE directed titration of vasopressors, volume (diuretic or blood product/fluid administration) or CF-LVAD speed.

Results: Significant preoperative, intraoperative, and postoperative differences were observed between hTEE and No hTEE groups, suggesting that patients who received hTEE had greater overall critical illness (Figure 1). Thirty-three patients received 68 (mean 1.9±1.2) hTEE studies. The most frequent indication for hTEE was unexplained postoperative hypotension (61%), while the most frequent hTEE findings were hypovolemia (33%) and RV dysfunction (33%). Information obtained from hTEE changed ICU management in 72% of studies. Interestingly, in patients who received multiple hTEE studies (n=35, 51%), information from hTEE continued to change management in >66% of studies. Within the hTEE group, patient characteristics between device types (HM-II and HW) were comparable (p>0.05). Conclusion: Post-operative hTEE is common after CF-LVAD implantation and frequently leads to changes in ICU clinical management. Our data suggests that decisions to utilize hTEE after CF-LVAD implantation are driven by increased severity of clinical illness.

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*p-value<0.05

Paracorporeal Vad For Left And Right Heart Support


Study: Right ventricular failure (RVF) presents significant problems for LVAD therapy. It has been reported that RVF affects 20–50% of LVAD patients and negatively impacts their morbidity and mortality. For LVAD patients who experience RVF, a tempooral right ventricular assist device (RVAD) support is required. Almost all durable VADs are designed for left heart support. Options for RVAD support are limited; and due to their large size, patients are often bedridden with limited mobility.

Methods: MiTiHeart® is currently developing paracorporeal, wearable, short-term, magnetically levitated blood pump as a versatile circulatory assist device for RHF or LHF support. The new conceptualized device is based on our successful MiTiHeart® LVAD platform technology. Due to a centrifugal pump design with a simple and direct wash-flow path the pump is well suited for a wide range of operating conditions.

Results: Hemolysis test results confirm that low blood damage is experienced over a wide range of operating speeds. Based on data from HQ testing at speeds from 1,000 rpm to more than 8,000 rpm, the MiTiHeart VAD has demonstrated stable hemodynamic at the low head requirements of RVAD support. The same VAD is also capable of producing more than 400 mmHg differential pressure, at 5 L/min output for application with extracorporeal devices such as cannulated acute support or in tandem with artificial lung support systems.
Centrifugal Pumps for ECMO are Associated With Higher Incidence of Pulmonary and Neurologic Hemorrhage

I. Halaweish, A. Cole, J. W. Haft. Cardiac Surgery, University of Michigan, Ann Arbor, MI.

Study: There has been an increased use of centrifugal pumps in extracorporeal membrane oxygenation (ECMO) circuits. However, continuous rotary pumps are associated with acquired von Willebrand deficiency and bleeding complications. This study was undertaken to compare adverse bleeding complications with use of centrifugal and roller pumps in patients supported with ECMO.

Methods: The records of all adult ECMO patients from June 2002 to 2013 were reviewed using the University of Michigan Health System database and the Extracorporeal Life Support Organization registry, focusing on patients supported for at least 7 days.

Results: Ninety-five ECMO patients met criteria for inclusion (48 roller vs. 47 centrifugal pump). Indications included pulmonary (79%), cardiac (15%), and extracorporeal cardiopulmonary resuscitation (6%), without significant difference between the two groups. Despite lower heparin anticoagulation (9.9 vs 13.4 IC/kg/hr) with centrifugal pumps, there was a higher incidence of neurological hemorrhage (5.5 vs. 0 events/1000 patient-days, p = 0.083), pulmonary hemorrhage (14.2 vs. 5.5 events/1000 patient-days, p = 0.12), and gastrointestinal hemorrhage (5.5 vs. 3.6 events/1000 patient-days, p = 0.62), although not statistically significant. There was a higher rate of RBC transfusions with use of roller ECMO pumps (1.89 vs. 2.87 units/day, p = 0.016). Patients on centrifugal pumps had lower post-ECMO platelet counts (96 vs. 130 k/mm^3, p = 0.003), and higher INR (1.45 vs. 1.14, p = 0.006). CONCLUSION: Despite reduced anti-coagulation, centrifugal ECMO pumps are associated with a higher incidence of non-surgical bleeding.

The Use of Probiotics Does Not Reduce Gastrointestinal Bleeding in Patients with Continuous Flow Left Ventricular Assist Devices


Study: Gastrointestinal (GI) bleeding after placement of a continuous-flow (CF) left ventricular assist device (LVAD) is a well-described problem. We hypothesize that disruption of GI flora may be associated with increased rates of GI bleeding. This study sought to evaluate the effects of probiotics on GI bleeding in LVAD patients.

Methods: A retrospective cohort study of all CF LVAD patients at our institution who survived to discharge between January 1, 2011 and November 15, 2013 was performed. Patients were divided into two groups: those that received probiotics (PB) at hospital discharge following LVAD implantation and those who did not (NPB). Patients in the NPB group who crossed over to probiotics after discharge were censored at time of crossover.

Results: A total of 82 patients (34 PB, 48 NPB) with 68.4 years of follow-up were analyzed. There were no differences between the groups with regard to age, sex, device type, or heart failure etiology. An indication for bridge to transplant was more likely in PB patients than in NPB patients (23/34 or 67.6% vs. 21/48 or 43.8%, p=0.033). 17.6% (6/34) of PB patients and 27.0% (13/48) of NPB patients had one or more GI bleeds (p=0.318). At 1.17 years of follow-up, freedom from GI bleeding was 77.2% in the PB group and 71.9% in the NPB group (p=0.921). Accounting for patients with multiple bleeds, PB patients had a mean GI bleed rate of 0.38 ± 1.02 bleeds/patient-year compared to 0.48 ± 0.95 bleeds/patient-year (p=0.650) in the NPB group. Seven patients in the NPB group who had GI bleeds were analyzed after crossover to probiotics. Rates of GI bleeding before probiotics were 1.71 ± 0.76 bleeds/patient-year and 1.57 ± 1.90 bleeds/patient-year after probiotics (p=0.869). Probiotics do not reduce rates of GI bleeding in CF LVAD patients. For the small sample of patients who had already experienced GI bleeding, the addition of probiotics was not beneficial. Further investigation into methods of reducing GI bleeding is needed.
A 28-Year Experience with Emergent Percutaneous Cardiopulmonary Bypass for Cardiovascular Collapse


**Study:** Non-cardiac surgery patients who experience in-hospital cardiac arrest or suffer from refractory shock have high expected mortality. We have implemented a system that provides for emergent institution of percutaneously placed cardiopulmonary support (CPS) as a salvage measure when other interventions have failed to rescue a patient from life threatening cardiovascular collapse or sepsis.

**Methods:** In 1986, a protocol for initiating CPS was developed where in house surgery, cardiology, and emergency room physicians percutaneously place cannula for emergent CPS while trained critical care nurses prime an extracorporeal life support circuit. All patients who had CPS initiated were entered into a prospective registry. Patients requiring CPS following cardiac surgery are included in a separate registry. Patients were characterized as long-term survivors (LTS) (>30 days, CPS weaned), short-term survivors (STS)(<30 days, CPS weaned), or expired on CPS. We divided the time frame into two study periods, the first 18 years (1986–2004) of the program and the last 10 years (2004–2014).

**Results:** Two hundred seventy two (272) patients were placed on CPS, 150 of which were in the first 18 years. There were 41 (27.3%) LTS and 23 (15.3%) STS during this time period. The mean time of support in hours for LTS, STS and expired were 28.9 ±39.9, 38.2 ±46.1 and 25.1 ±47.2 respectively. During the last 10 years, 122 patients were initiated on CPS. There were 35 (28.6%) LTS and 35 (12.3%) STS. Total support time in hours for LTS, STS, and expired were 48.2 ±43.8, 81.4 ±70.4 and 48.1 ±73.3 respectively. During the two time periods, circulatory support times became longer in LTS, STS and expired patients while the overall survival and rates of weaning CPS remained unchanged. These findings demonstrate that we have been able to increase the length of support on CPS without affecting survival significantly. Additional work is needed to determine the reason for the differences and to improve survival.

Temporary Biventricular Mechanical Support With CentriMag as Bridge to Decision

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**Study:** Temporary mechanical assist devices are increasingly being used as lifesaving bridge to decision in patients requiring cardiopulmonary resuscitation. We report our single center experience with biventricular CentriMag pumps over a five-year period.

**Methods:** Data was retrospectively collected in consecutive patients who required biventricular support from 2008–13. Patients who were supported with central cannulation using the CentriMag system were analyzed. In addition to demographic information, data pertaining to indications, outcomes, and mortality were collected. A non-parametric Mann-Whitney U test was used to evaluate risk profiles for patient demographics.

**Results:** The cohort consisted of 46 patients (18 women and 28 men, mean age of 56 years). The median duration of support was 13 days. The median duration to patient expiration while still on Centrimag was 14 days. Thirty-day survival was 54% (25/46), while long-term survival was 37% (17/46). Seven patients were explanted to recovery, while 21 patients either underwent heart transplantation, or were converted to a durable LVAD. We stratified patients into two groups. Group I comprised of patients who were either explanted to recovery, converted to durable LVAD or transplanted (21/46), and group II consisted of patients who died on CentriMag (25/46). A multivariate risk stratification did not reveal any statistically significant differences in survival between the two groups in terms of age, sex, etiology, hemodynamics, and co-morbidities.

**Conclusion:** Biventricular CentriMag can be used as a bridge to decision in patients with thirty day survival of >50%. No risk factors were identified to predict longevity in the two cohorts.
Analysis of Specific Absorption Rate and Internal Electric Field in Human Muscle Tissue Surrounding Air-core-coil Type Transcutaneous Energy Transmission Transformer

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Study: To provide protection against all of the established adverse health effects caused by electromagnetic induction, we sought to analyze the specific absorption rate (SAR) and internal electric field of human muscle tissue surrounding the air-core coil of a transcutaneous energy-transmission transformer.

Methods: By using an electromagnetic simulator based on the moment and finite element method, we created a muscle-tissue model that consisted of a primary coil located on the surface of the skin and a secondary coil located subcutaneously inside the tissue. The values of the SAR and internal electric field of the muscle tissue between the frequencies of 100 kHz and 1.5 MHz were analyzed. The transmitting power was 15 W, and the load resistance was 38.4 Ω.

Results: The results showed that the values of the SAR and internal electric field increased with an increase in the transmission frequency. The SAR values were well below the basic limits specified by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) for occupational and general public exposure between the frequencies of 100 kHz and 1.5 MHz, whereas the internal electric fields were well below the basic limits specified by the ICNIRP for occupational and general public exposure between the frequencies of 300 kHz and 1.5 MHz. This study showed that it is possible to transmit 15 W of power at frequencies between 300 kHz and 1.5 MHz.

Development of a Mock Extra Corporeal Membrane Oxygenation (ECMO) Circuit to Assess Recirculation and Cerebral Perfusion

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Study: We compared cannulation strategies for combating recirculation of newly oxygenated blood back to the veno-venous ECMO (VV-ECMO) circuit. We also investigated a correlation between cardiac output and impairment of cerebral oxygenation during veno-arterial ECMO (VA-ECMO) with femoral arterial cannulation.

Methods: We used an artificial simplified circulation (mock circulation loop - MCL) on VV-ECMO and VA-ECMO for the recirculation and cerebral perfusion experiments respectively, monitored with ultrasonic flow probes and pressure transducers to ensure physiological parameters. For VV-ECMO we tested recirculation proportions with the femoro-jugular and femoro-femoral cannulation configurations and the Wang-Zwische double lumen cannula. For the cerebral perfusion experiment we utilised the femoral vein and artery cannulation configuration. Both measured ECMO infusion distribution using oxygen partial pressure and flow measurements.

Results: We found the Wang-Zwische dual lumen cannula to have lower mean recirculation proportions (4.00±1.77, n=7) in the acute setting for VV-ECMO (ANOVA, F=14.25; p = 0.0001) than both the femoro-jugular (15.23±7.00, n=8) and the femoro-femoral cannulation configuration (13.49±1.44, n=8). There was no significant difference between the latter two configurations. A linear regression analysis showed a rapid decline of the proportion of infused solution from the VA-ECMO circuit reaching the cerebrum with increasing cardiac output (n = 19, R² = 0.6709, p <0.0001).
In vitro Evaluation of a Physiological VAD Controller under Fibrillation, Tachycardia, Hypovolemia, and Hypertension Conditions

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Study: In a previous publication, we proposed the preload-responsive speed (PRS) controller, which adapts the speed of a turbodynamic VAD based on a measurement of the left ventricular volume. Thereby, the controller imitates the Frank-Starling law of the heart. In order to evaluate the reliability of the PRS controller, we tested its behavior under fibrillation, tachycardia, hypertension, and hypovolemia conditions in vitro and compared its behavior to a VAD operated at a constant speed.

Methods: Experiments were conducted on a hybrid mock circulation, which consists of a numerical and a hydraulic part. The numerical part simulates the human cardiovascular system in real time and interacts with the hydraulic part, which consists of two pressure controlled reservoirs and a modified Deltastream DP2 blood pump. Tachycardia, hypovolemia, and hypertension could be simulated by numerically changing the heart rate, the unstressed volume of the systemic veins, and the systemic arterial resistance, respectively. Ventricular fibrillation was implemented by reprogramming the time-varying elastance function.

Results: When the preload drops due to a simulated blood loss of 700 mL, the speed is automatically reduced by the PRS controller such that no suction occurs. However, the cardiac output (CO) reduces to 1.08 L/min. When the systemic arterial resistance is increased from 1.1 to 3 mmHg•s/mL to simulate hypertension, the PRS controller increases the pump speed and the CO stays above 3.65 L/min, but the arterial pressure increases to 188 mmHg. The experimental results confirm that the response of the PRS controller is similar to that of the native ventricle, but this reaction may not be ideal in any situation. However, any VAD controller can solely change the speed of the VAD and such situations can only be resolved by an external intervention rather than the VAD controller. In conclusion, the PRS controller operates safely also under abnormal conditions.

Influence of Intermittent Pump Speed Reductions on Pump Flow and Aortic Valve Opening in Rotary Blood Pump Recipients

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Study: During prolonged left ventricular support abnormal aortic valve (AV) opening is related to adverse events as commissural leaflet fusion, aortic insufficiency and thrombus formation in the aortic root. Intermittent pump speed reductions for frequent AV opening might reduce the occurrence of such adverse events. In this study the required degree as well as the duration of such a speed reduction to enforce an AV opening was investigated.

Methods: Step-like pump speed reductions were performed in 15 patients with a HeartWare Ventricular Assist Device implanted. The AV status was continuously monitored using M-mode echocardiography; simultaneously the estimated pump flow signal was recorded. 78 pump speed steps were analyzed, especially for the time immediately following the speed reduction.

Results: Pump flow was 5.1±0.8 L/min at baseline pump speed of 2.7±0.2 krpm. Pump flow highly correlated with speed (0.88±0.08), regression analysis indicated a slope of 2.8±0.6 L/(min•krpm). In 11 of the 15 patients the AV was mainly closed at baseline speed and opened at a pump speed of 2.1±0.2 krpm (range: 1900–2400). The AV opened within the first two beats following a speed reduction. In all patients an opening of the AV could be enforced, however, diverse degrees of speed reductions were required. The AV opened immediately after a speed reduction; therefore, speed reductions for intermittent AV opening can be potentially kept short. Since the pump flow is highly dependent on speed, simultaneous non-invasive monitoring of the AV state based on pump signals to prevent excessive speed reduction and consequently an insufficient perfusion seems mandatory.
Reduction of the Radiation Magnetic Field from a Transcutaneous Energy-Transmission Transformer Using a Three-Phase Alternating Current - Analysis and Measurement -
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Study: Transcutaneous energy transmitting systems (TETS) allow a cable-free supply of energy through the skin to a ventricular assist device (VAD). They carry a lower risk of infection than cable-based energy supplies because there is no skin penetration. However, the magnetic field emitted from conventional TETS exceeds the standard set by the International Special Committee on Radio Interference (CISPR) pub. 11. We propose a three-phase TETS to achieve lower magnetic fields.
Methods: The three-phase TETS has three pairs of transformers and is driven by three alternating currents with different phases. The external coil diameters are each 70 mm. The radiation magnetic field is reduced by the three-phase alternating magnetic field. The magnetic field was analyzed using an electromagnetic simulator, using the method of moments (MoM). A magnetic field emitted from a conventional TETS and from a three-phase TETS were simulated and compared. In addition, the magnetic fields were also measured experimentally with a spectrum analyzer and a closed-field probe.
Results: The simulated magnetic field for a conventional TETS ranged from 46.3 to 56.91 dBμA/m, and for a three-phase TETS from 16.37 to 26.26 dBμA/m, when transmitting 5 W at frequencies between 150 kHz and 500 kHz. Corresponding measurements on conventional TETS ranged from 41.82 to 59.96 dBμA/m, and on a three-phase TETS from 13.44 to 21.82 dBμA/m, i.e., below the standard level at all frequencies. The average measured magnetic field emitted by a three-phase TETS was 29.52 dBμA/m, lower than with a conventional TETS, when transmitting 5 W power.

Are Flow Measurements Obtained from Continuous Flow Left Ventricular Assist Devices Accurate?
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Study: Blood flow in a continuous flow left ventricular assist device (cfLVAD) is estimated based on the power waveform and speed of the assist device. However, this is not a direct measurement of blood flow and the accuracy of this estimate has not been studied in detail. This study evaluates the correlation between the thermodilution cardiac outputs (tdCO) with flow measurements of the ventricular assist device.
Methods: This is a retrospective study involving 83 consecutive LVAD implants from 2012–2013. Cardiac outputs were obtained using a thermal dilution method by routine clinical care practices in the ICU, while cfLVAD flow measurements were obtained from the bedside ventricular assist device controller. Measurements were obtained on the day of implant and post-op day 1 and 3. Echocardiograms which were routinely obtained at the time of implant or for clinical indication thereafter were reviewed for aortic valve opening. Only patients implanted with a HeartMate II device in whom simultaneous measurements were taken, the aortic valve did not open and no significant aortic regurgitation (<2+) was present were used for this analysis.
Results: A total of 86 measurements from 32 patients were used for this analysis. The mean age was 62 +/- 12 years and 81% were male. The tdCO and flow measurements are shown in the figure. Although there is a correlation between the two measurements of blood flow, the slope of the relationship is not unity.
Conclusion: While flow measurements from a cfLVAD do appear to trend with tdCO, the relationship should not be used quantitatively.
Flow in a Wound Fiber Membrane Oxygenator: Particle Image Velocimetry for the Validation of Computational Fluid Dynamics


Study: Computational Fluid Dynamics (CFD) is routinely used for the investigations of the blood flow in fiber membrane oxygenators. Results from these investigations may help to improve the flow and decrease blood damage. However, the numerical approaches are based on hydraulic simplifications regarding the fiber bundle and are predominantly only validated by the pressure drop. In this study, a direct validation of the velocity field from CFD simulations through flow visualization was performed.

Methods: Therefore, Particle Image Velocimetry (PIV) was applied on a wound fiber membrane oxygenator model. With respect to the similitude theory, an upscaled and transparent model of the oxygenator was built that satisfies the requirements of the optical measurement method. For the optical accessibility all relevant parts including the fibers were made from PMMA. For the reconstruction of the in-plane velocity component, a stereo-PIV technique was applied. The 3D velocity field is used for the validation of the numerical results. For the numerical approach the flow field was computed using CFD for the original size geometry. The fiber bundle was modeled as an isotropic porous media defined by the pressure drop.

Results: An approved optical measurement method for flow visualization was successfully applied on a transparent upscaled model of a wound fiber membrane oxygenator. The similitude theory ensures the transferability of the results. The PIV measured flow field allows the identification of stagnation areas as well as critical areas with high velocity flows associated with high shear rates. Changes in the velocity and also direction on short distances occur in the PIV fiber bundle. The smooth character of the CFD simulated flow cannot be confirmed. Though, on a macroscopic level, a similar flow distribution as predicted through the CFD study can be observed. A further quantitative validation is still in progress and will be presented at ASAIO 2014.

Performing DT Alone - Kazakhstan’s Experience


Study: The aim of this study was to evaluate the first results of VAD program without a developed transplant program.

Methods: Our Center is the sole coordinator of the program in Kazakhstan. Over two years (2011 - 2013), the Center has implanted 100 VAD in 95 patients with end-stage heart failure. There were 87,37% males (n=83). Mean age was 49,5 ± 13,9 years (11 - 73). Mean ejection fraction was 22,79±5,72%; 47,37% had an ischemic etiology. INTERMACS patients profile was 1, n=7 (7,37%); 2, n=16 (16,84%); 3, n=16 (16,84%); 4, n=52 (54,74%); and 5, n=4 (4,21%).

Results: The most common adverse events within the first 30 days after VAD implantation were right ventricular failure (n=8) and bleeding (requiring surgery=11, requiring packed red blood cells transfusion=14). After 30 days the most common complication were driveline infections (n=18, 21,05%). There was 1 incidence (1,05%) of pocket infection. Survival at 3, 6, 9 months after VAD implantation is 72,29%, 71% and 73,33% accordingly. It is noteworthy that 12 month survival rate improved till 80%. There is about 14–15% decrease of 1-year survival of patients in INTERMACS 1 and 2 compared to INTERMACS 3 and 4. The main causes of the death were multorgan failure (n=8) and stroke (n=6).

Survived patients were defined by postoperative NYHA I-II symptoms.

CONCLUSIONS: The Centers experience shows that hospital can perform destination therapy (DT) alone. Thus, Kazakhstan has established a VAD program with the first outcomes that are comparable to those in existing world centers of excellence.
**Design and Development of a Durable, Percutaneous, Wireless Left Ventricular Assist Device**

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**Study:** Current permanent LVAD devices are hampered by invasiveness associated with implantation, tethered operation and cumbersome peripherals. In spite of miniaturization, delivery and deployment still requires a thoracotomy, whereas percutaneous devices are hampered by durability. We have developed an endovascularly deployable micro-LVAD with a durable design.

**Methods:** The base unit of the pump consists of a fully sealed motor and drive shaft magnetically coupled to a bearing-less freely spinning impeller. SolidWorks 2013 Computer Aided Design software was utilized to model various configurations of the drive shaft magnet enclosure, impeller magnet enclosure, and pump housing. An Objet 30Pro 3D Printer was used for the rapid prototyping of these components. Various magnetic coupling configurations were compared.

**Results:** Preliminary in vitro tests of pump performance were performed. The magnetic coupling system provided adequate strength to stabilize the impeller without additional bearings. Several iterations of modeling, rapid prototyping, and testing were performed to achieve progressively smaller footprints. Initial prototypes focused on magnetic coupling of a 20mm diameter version. Bar and cylindrical magnetic arrangements were tested with axial and radial polarities as well as with continuous and alternating arrangements. This was followed by a 14mm diameter and finally 8mm diameter pump, which required the use of alternative housing materials due to wall thickness reaching 0.5mm. The small footprint allows the device to be delivered via the femoral artery or subclavian artery. Further studies will focus on optimizing impeller geometry and outflow design to improve pump performance. By completely sealing the motor, this design eliminates the need for a purge fluid line present in current temporary percutaneous devices. Combining this with a wireless energy transfer system allows for a completely wireless intermediate- to long-term minimally invasive solution.

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**A Predictive Model for Mortality Post Continuous Flow LVAD Implant using Bayesian Analysis: the First Application to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Database**

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**Study:** Existing risk scores for prediction of mortality post-implant have several limitations in that they were derived from older generation pulsatile pumps, from single center studies having considered a limited set of data elements, and calculated using traditional statistical methods. Our study aims to use a modern machine learning approach, by performing Bayesian analysis on the INTERMACS dataset, which overcomes all these limitations. We have previously demonstrated the feasibility of Bayesian analysis to predict 90-day outcomes from 2 LVAD centers.

**Methods:** We retrospectively analyzed data from 8050 continuous flow LVAD patients between 2006–2013 from INTERMACS. 226 pre-implant variables were screened and ranked based on their predictive power and their completeness of at least 50% of the patient records. 111 variables were included. Missing values were replaced with either the mean or mode if the variable was either continuous or discrete, respectively. Bayesian analysis was applied to derive predictive models for mortality at each of five endpoints post-implant.

**Results:** The final Bayesian model for each of the five endpoints (30 day, 90 day, 6 month, 1 year and 2 year post-LVAD implant) achieved accuracies of 95, 90, 90, 83, and 78%, Kappa values of 0.43, 0.37, 0.37, 0.45, and 0.43, and area under the ROC of 91, 82, 82, 80 and 81%. See Figure for ROC plot of the models. This study is the first application of sophisticated machine learning algorithms to a comprehensive, large LVAD patient database. Bayesian models have the ability to handle uncertainty and missing data allowing for high predictive accuracy and the ability to represent the complex causal relationships of multiple variables on clinical outcomes. Their potential to develop a reliable risk stratification tool for use in clinical decision making on LVAD patients encourages further investigation.
Comparison of Intraplatelet Reactive Oxygen Species, Mitochondrial Damage and Platelet Apoptosis after HeartMate II, Jarvik 2000 and HeartWare Left Ventricular Assist Device Implantation

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Study: Differences in the design of continuous-flow left ventricular assist devices (CF-LVADs) may exert variable effects on platelet function. Understanding the role of platelet functionality after LVAD implantation is crucial for patient management to reduce adverse events, especially bleeding and stroke complications. In this study we longitudinally compared the platelet functionality of patients who received 3 CF-LVADs: HeartMate II (HMII; Thoratec Corp, Pleasanton, CA), the Jarvik 2000 (Jarvik Heart, New York, NY) and the HeartWare HVAD (HeartWare International Inc, Framingham, MA).

Methods: Twenty patients who underwent CF-LVAD implantation with HeartMate II (n=7), Jarvik 2000 (n=7) or HeartWare (n=6) devices were enrolled in this study. Intraplatelet ROS generation, platelet mitochondrial damage and platelet apoptosis were quantified by flow cytometry and compared according to devices before and after the implantation at every week up to 1 month.

Results: Overall, the baseline characteristics, demographics, routine laboratory values were comparable among the three groups. The HeartWare group showed significant decreased in platelet numbers after the implantation compared to the other two devices. Intraplatelet ROS generation, platelet mitochondrial damage and platelet apoptosis remained significantly elevated in the HeartWare group in comparison to the other two devices before and after the implantation at every week up to 1 month.

Conclusion: Data from this preliminary study suggests that CF-LVAD design may exert different effects on platelet function. Further studies with higher numbers of patients are needed to elucidate these effects and their clinical relevance.

Low Incidence of Driveline and Pump Pocket Infections in a Start-Up LVAD Program

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Study: The incidence of infection in patients with mechanical circulatory support systems ranges from 7% to 59%. Prevention of device-related infection is crucial to cost-effective use of left ventricular assist devices (LVADs) and patient survival.

Methods: We analyzed the incidence of LVAD-related driveline and pump pocket infections in 45 patients who received LVADs from May 2012 to November 2013 at our institution. Our established measures to limit the incidence of infections in our patient population included both meticulous surgical technique and, more specifically, placement of the driveline tunnel between the anterior and posterior rectus sheath and into the LVAD pocket through the rectus muscle. Discharge planning included extensive training for both patients and their caregivers. Furthermore, we provided patients with dressing changes for the driveline exit site rather than relying on patients to purchase on their own dressings.

Results: Forty-two men and 3 women (mean age: 55±11 years) underwent LVAD implantation. Of those 45 patients, 1 patient (2%) developed a driveline infection after 183 days on LVAD support, and 1 patient (2%) developed a pump pocket infection after 269 days on LVAD support. The incidence of infection was 0.022 per 100 LVAD days and 0.08 per patient year. The patient who had the driveline infection is doing well at home on LVAD 23 days after infection resolution. The patient who recently developed the pump pocket infection is still waiting for a heart transplant in our hospital. Our observations suggest that with thorough surgical planning, care, and education, the incidence of LVAD-related driveline and pump pocket infections can be minimized.
Safety Assessment of Heartmate III LVAS, a 60-day Chronic Bovine GLP Study

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Study: The Thoratec HeartMate® III Left Ventricular Assist System (HMIII LVAS) is a set of equipment and materials that together comprise a medical device designed to provide therapeutic benefit to those afflicted with advanced heart failure. This study was performed to assess the safety of the HM III LVAS in a bovine model for a period of 60 (+5) days.

Methods: The protocol was conducted using Good Laboratory Practices (GLP). Ten implants were performed at the Texas Heart Institute (n=8) and the Texas A&M Institute for Preclinical Studies (n=2) in calves weighing 80-100kg. Each calf was continuously monitored, with the pump target flow set to 5.4±1Lpm. Data collection included pump flow, pulmonary artery flow, pump speed, pump power, pump voltage, and motor temperature. Physiologic data collection included but was not limited to: hematology, chemistry and coagulation profiles, PfHgb, and adverse events (AEs).

Results: Eight of ten animals survived to the planned explant date. Two animals expired on Post-op Day 0, due to complications unrelated to the HM III LVAS. There were no device malfunctions reported. There were 9 reported AEs, with only one event determined to be device related (a driveline infection). No AE was determined to be serious. Average PfHgb levels were <8g/dL. Gross necropsy results showed there were no downstream or systemic effects on the end organs following chronic implantation of the HM III LVAS. In conclusion, the GLP study data shows that the HM III LVAS does not pose any undue safety risks when implanted in a calf for a period of 60(+5) days.

Development of an Implantable Compliance Chamber for a Total Artificial Heart

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Study: Cardiovascular diseases are the most frequent cause of death in the western world. Due to a lack of donor hearts, not all patients in need of heart replacement can be treated. Among others, an alternative treatment option is a total artificial heart (TAH). Such a device is under development and currently undergoing chronic in-vivo animal trials at the RWTH Aachen University. The TAH consists of a linear drive in between two ventricles. For a clinical use of an implantable TAH a compliance chamber (CC) is required, which is connected to the drive unit. It lowers pressure peaks in the drive unit, supports the filling of the ventricles and creates a balance between systemic and pulmonary output. This study focusses on an anatomical fit design and parameter variations for optimum TAH output.

Methods: Clinical CT data was analyzed to adapt the geometry of the CC to the human thorax. An active mock circulation loop was used to measure the pressure peaks in the TAH drive unit and the corresponding blood flows. The same measurements were performed with and without connected CC. Parameters such as CC pressure and volume were varied to study their effect on the TAH’s function and output.

Results: An anatomical fit design of the CC was achieved which ensures implantability into the pleural cavity without disturbance of pulmonary function. The CC has a rigid body with a membrane fixed on one side. An air reservoir is situated around the CC. Pressure peaks could be minimized by variation of the frequency and the pressure inside the actively pumping CC. Hence the output was increased by up to 18,2% on the systemic side and 14,8% on the pulmonary side. The impact of gas diffusion through the CC membrane on its function is currently under investigation. Implantation of the CC is being integrated into the chronic animal trials.
Replacement of the HeartMate II Pump Without Cardiopulmonary Bypass

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Study: Replacement of the HeartMate II (HMII) pump has been performed safely through a sternum-sparing subcostal approach, typically on cardiopulmonary bypass (CPB). In this study, we report our experience of HMII pump replacement through a subcostal incision without the use of CPB.

Methods: We conducted a retrospective review of all patients who underwent a HMII pump replacement through a subcostal approach at our institution since December 2012. The patients were divided into those that had the procedure with CPB (ON-CPB) and those without (OFF-CPB). The OFF-CPB approach was adopted by our institution as the technique of choice since August 2013. Data pertaining to patient baseline characteristics and outcomes were collected and analyzed.

Results: 19 subcostal HMII pump replacements were performed on 16 patients. There were 16 ON-CPB and 3 OFF-CPB procedures. There were no significant differences between the groups in age, gender and indication for pump replacement (Table 1). Mean support duration before pump replacement was 522 days, which was not significantly different between the two groups. There were no cerebrovascular accidents or 30-day post-operative deaths with either approach. There were no significant differences in operation times, red cell and plasma transfusions and ICU lengths of stay between the groups. There were no re-operations for bleeding in either group.

Patients in the OFF-CPB group had significantly lower platelet and cryoprecipitate transfusions and significantly shorter hospital lengths of stay (Table 2). Long-term survival after mean follow up of 394 days (ON-CPB group) and 154 days (OFF-CPB group) was 85.7% and 100% respectively (Figure). In conclusion, replacement of the HeartMate II pump can be accomplished with a low morbidity and mortality and excellent long-term outcomes, through a subcostal approach without cardiopulmonary bypass.

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ON-CPB(N=16)</th>
<th>OFF-CPB(n=3)</th>
<th>p</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>59±11</td>
<td>54±13</td>
<td>0.58</td>
</tr>
<tr>
<td>Male</td>
<td>11(69%)</td>
<td>2(66%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Indication for Exchange</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead fracture</td>
<td>6(38%)</td>
<td>0</td>
<td>0.29</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>8(50%)</td>
<td>3 (100%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Infection</td>
<td>2(13%)</td>
<td>0</td>
<td>0.54</td>
</tr>
<tr>
<td>Time to Exchange (days)</td>
<td>578±473</td>
<td>240±184</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Table 2: Operative Data & Outcomes

<table>
<thead>
<tr>
<th></th>
<th>ON-CPB(N=16)</th>
<th>OFF-CPB(n=3)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Operation Time (min)</td>
<td>126±27</td>
<td>129±51</td>
<td>0.93</td>
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<tr>
<td>Red Cell Transfusion (ml)</td>
<td>1004±742</td>
<td>700±1212</td>
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<td>Plasma Transfusion (ml)</td>
<td>669±944</td>
<td>196±183</td>
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<tr>
<td>Cryoprecipitate Transfusion (ml)</td>
<td>54±80</td>
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<tr>
<td>Platelet Transfusion (ml)</td>
<td>223±2340</td>
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<td>0.003</td>
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<tr>
<td>ICU Length of Stay (days)</td>
<td>4.2±4.3</td>
<td>3.3±10.6</td>
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<tr>
<td>Hospital Length of Stay (days)</td>
<td>22.6±21.6</td>
<td>9.3±4.1</td>
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<tr>
<td>Mean Follow Up (days)</td>
<td>394±259</td>
<td>154±157</td>
<td>0.09</td>
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Warfarin Polymorphisms (VKORC1 and CYP2C9) Predict Anticoagulation Variability in a Continuous Flow Left Ventricular Assist Device Population


Study: Polymorphisms of enzymes responsible for metabolizing Vitamin K antagonists may predict variability in dose response and time to therapeutic international normalized ratio (INR). We sought to determine if VKORC1 and CYP2C9 polymorphisms were associated with variation in warfarin dose and INR response in a continuous flow left ventricular assist device (CF-LVAD) population.

Methods: We analyzed VKORC1 and CYP2C9 polymorphisms in 62 (mean age 52±11 years, male 74%) CF-LVAD (HeartMate-II n=31 and HeartWare n=31) patients from 2011 to 2014. Polymorphisms of VKORC1 and CYP2C9 were divided into 3 categories based on clinical phenotype: normal responders (NR), hyper responders (HR), and uncharacterized. Uncharacterized genotypes were included in the HR group for final analysis. Warfarin dose changes, variability of INR response, and days to therapeutic INR (≥2.0) were compared between HR and NR groups.

Results: Polymorphisms of VKORC1 and CYP2C9 were divided into clinical phenotypes (Figure 1). In the overall group, patients took 6.81±2.97 days to achieve a therapeutic INR after CF-LVAD implantation. In these patients, the mean baseline INR was 1.33±0.18 and the average daily warfarin dose was 4.98±1.72 mg. Patients in the NR group took longer (7.92±3.81 days) to achieve a therapeutic INR than patients in the HR group (5.94±1.79 days, p=0.025), despite comparable average daily warfarin doses between groups (5.34±2.06 vs 4.78±1.44mg, p=0.264). Interestingly, NR had greater variability in warfarin dose changes (2.72±2.22mg vs 1.76±0.70mg, p=0.051) and less variability in INR response (0.32±0.15 vs 0.41±0.13, p=0.024) when compared to the HR group. VKORC1 and CYP2C9 polymorphisms are common and associated with significant variation in warfarin dose and INR response. Pharmacogenomics testing may be useful in predicting warfarin's variable response in CF-LVAD patients who are at high risk for both thrombus and bleeding events.

The Effect of Continuous Flow Left Ventricular Assist Device Pump Design on Severity of Acquired von Willebrand Syndrome: Is there a Quantifiable Difference between HeartMate-II and HeartWare?


Study: Densitometric analysis (DA) has previously been used to quantify the loss of high molecular weight (HMW) von Willebrand factor (vWF) multimers in continuous flow left ventricular assist device (CF-LVAD) recipients. We sought to determine whether this method could be used to quantify device specific differences in CF-LVAD patients with acquired von Willebrand syndrome (AVWS).

Methods: We analyzed vWF multimers in 41 patients (HeartMate-II (HM-II) n=14, HeartWare (HW) n=27). Plasma was collected pre CF-LVAD, 1, 3, & 6 months (m) post CF-LVAD and after transplantation. Samples were size-fractionated by SDS-agarose, immunostained, imaged, and subjected to DA. vWF multimer ratios (vMRs) were calculated based on the signal intensity of the 11 lowest bands divided by all remaining higher bands. Ratios less than 20 are considered normal and ratios more than 20 indicate loss of HMW multimers.

Results: In all CF-LVADs, average vMRs at baseline (7.4 ± 2.7), 1m (87.1 ± 83.8), 3m (104.3 ± 93.5), 6m (115.7 ± 105.4) and after transplantation (5.9 ± 0.2) were determined. vMRs indicated early loss of HMW multimers when baseline values were compared to 1, 3, and 6m values (all p<0.001. There was no significant change in vMRs from 1 to 3m or 3 to 6m. Device specific differences in vMRs were identified between HM-II and HW at 1m (153.3 ± 99.5, 45.0 ± 28.1; p=0.0002) and 3m (136.1 ± 90.8, 74.8 ± 89.1; p=0.0163), indicating a greater loss of HMW multimers among HM-II recipients. After transplantation, vMRs indicated HMW multimers had returned to baseline pre CF-LVAD values and were comparable between devices (HM-II 5.7 ± 0.1 vs HW 6.1 ± 0.2, p=0.20). Densitometric analysis can be used to quantify the differential loss of HMW multimers in patients supported with HM-II and HW CF-LVADs. We demonstrated device specific differences in vWF multimers during CF-LVAD support followed by vWF multimer recovery after transplantation.
Rapid Postoperative Recovery of High Molecular Weight von Willebrand Factor Multimers after Cardiac Transplantation in a Patient Bridged with a Continuous Flow Left Ventricular Assist Device

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Study: All patients supported with continuous flow left ventricular assist devices (CF-LVAD) develop acquired von Willebrand syndrome (AVWS) due to the loss of high molecular weight (HMW) multimers. The timing of HMW multimer recovery after CF-LVAD explantation and orthotopic heart transplantation (OHT) is not well characterized. We sought to determine the timing of HMW multimer recovery by serially quantifying von Willebrand factor (vWF) multimer ratios (vMRs) after CF-LVAD explant and OHT.

Methods: We analyzed vMRs from a single patient (age 45 years, non-ischemic) implanted with a HeartWare (HW) CF-LVAD in April 2013 who underwent OHT in December 2013. Plasma samples were size-fractionated by SDS-agarose, immunostained and subjected to densitometric analysis (DA). DA determined the ratio of the signal intensity of the eleven lowest bands divided by all remaining higher bands. Results ≤20 are characterized as normal whereas values >20 indicates loss of HMW multimers.

Results: Densitometric analysis of pre-OHT (Pre-Op) plasma (197.8) indicated an elevated vMR ratio consistent with a CF-LVAD mediated AVWS. Immediately after OHT (within 1 hour of sternal closure), a plasma sample was obtained (time 0), indicating the vMR (4.2) had decreased to a normal ratio consistent with a pooled normal plasma (PNP) control (7.7). Serial samples obtained in the early post-operative (Hours Post-Op) and late postoperative (Days Post-Op) time period consistently demonstrated vMRs in the normal range, indicating stable quantitative recovery of HMW multimers after OHT. DA performed early after CF-LVAD explantation and OHT indicated complete HMW multimer recovery and resolution of AVWS within 1 hour of sternal closure. Additionally, densitometric analysis performed on serial samples obtained after OHT demonstrated stability of HMW multimer recovery throughout the early post-operative time period.

Transient Reversible Inflow Obstruction in Diaphragmatically-Inserted Ventricular Assist Devices

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Study: Two cases of transient reversible inflow obstruction (TRIO) were observed in 2 patients who had Heartware ventricular-assist devices (HVAD) placed via diaphragmatic-surface inflow cannulation. In one patient this affected the left and the other, the right, HVAD.

Methods: Patient 1 received a left HVAD for nonischemic cardiomyopathy (NICMP). The diaphragmatic approach was used due to a very dilated left ventricle and narrow thorax. Patient 2 received bilateral HVAD for NICMP with severe biventricular involvement and ascites. Right HVAD inflow was placed in the diaphragmatic right ventricular surface.

Results: Day 94 post-HVAD patient 1 presented to the emergency room with abdominal pain and decreased HVAD flows (1.3–2.8 l/min, vs 4–5 l/min baseline) and hematocrit (25% from 36%). Computed tomography (CT) revealed a large hemoperitoneum due to splenic rupture, and partial HVAD inflow cannula (arrow) obstruction by the LV anterior wall (Fig. 1).

Intraoperatively, patient 2 had partial inflow obstruction by the ventricular septum requiring intraoperative paracentesis and incisions on the inferior surface of pericardium and diaphragm. Postoperatively, TRIO occurred twice in the first month, heralded by low, labile right HVAD flows and resolved by drainage of ascites. Conclusion: TRIO represents a unique complication of diaphragmatic-surface HVAD inflow cannulation, wherein increased intra-abdominal pressure displaces the device and its inflow cannula upward into the ventricular wall.
Blood Pressure Measurement in Axial Flow Left Ventricular Assist Devices

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Study: Blood pressure (BP) assessment in second generation left ventricular assist devices (LVAD) is challenging because of continuous flow. During the initial post-operative phase, arterial line monitoring is the standard of care for BP assessment. Once the arterial line is discontinued, Doppler ultrasound is used to obtain a mean arterial pressure (MAP). We sought to determine whether Terumo Elemano BP monitor can be reliable in management of these patients after arterial line is removed.

Methods: We measured BP in patients who received axial flow HeartMate II LVAD at our center and had arterial catheter in place. We compared BP measurements using Terumo Elemano BP monitor and Doppler ultrasound to the results obtained in arterial line.

Results: All 3 paired measurements were collected in 72 instances on 10 patients (9 men, 1 woman, mean age of 55±8 years). MAP measurements obtained by Terumo and Doppler were similar, p=0.328. However, both measurements were significantly different in comparison to MAP readings on arterial line, P=0.012 and 0.001 respectively. Systolic BP (SBP) obtained by Terumo was similar to SBP from arterial line, p=0.057.

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>Mean</th>
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<tbody>
<tr>
<td>Arterial line (mm Hg)</td>
<td>96.3 ± 14.5</td>
<td>71.0 ± 12.3</td>
<td>80.7 ± 11.6</td>
</tr>
<tr>
<td>Terumo (mm Hg)</td>
<td>98.2 ± 12.3</td>
<td>75.3 ± 12.3</td>
<td>83.1 ± 12.0</td>
</tr>
<tr>
<td>Doppler (mm Hg)</td>
<td></td>
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<td>84.1 ± 10.2</td>
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The strongest correlation was found between Terumo and arterial line measurements (Pearson r=0.80, P<0.0001 for SBP and r=0.78, P<0.0001 for MBP), followed by Terumo and Doppler measurements (r=0.72, P<0.0001). The weakest correlation was between Doppler MAP measurements and arterial line MAP, r=0.65 and SBP, r=0.60, P<0.0001. Noninvasive and automatic BP measurement obtained with Terumo BP monitor seems to offer acceptable results to be used in patient management.

Extracorporeal Membrane Oxygenator Support as Bridge to Implantation of Continuous Flow Left Ventricular Assist Devices in Patients with Advanced Cardiogenic Shock

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Study: Implantation of continuous flow left ventricular assist devices (CF-LVAD) in the setting of advanced cardiogenic shock (ACS) complicated by multi-organ failure remains controversial because of high procedural mortality and morbidity. We describe our institutional experience of patients bridged with peripheral veno-arterial extracorporeal membrane oxygenation (VA-ECMO) to CF-LVAD.

Methods: Since April 2012, 11 patients with advanced cardiogenic shock were bridged using peripheral VA-ECMO to CF-LVAD. We performed a retrospective chart review to determine preoperative characteristics and outcomes of this group of patients.

Results: All patients were in advanced cardiogenic shock with ≥2 inotropes and multi-organ dysfunction, with mean lactate of 5.56 mmol/l, AST 366 mmol/l, ALT 235 mmol/l and creatinine 1.98 mg/dl, and bilirubin 2.03. The mean age was 60 years (range 39–74). There were 11 males (100%). Etiology of ACS was ischemic in 9 (82%) and non-ischemic in 2 (18%). Mean duration of ECMO support was 11.6 days (range 1–27). Implanted devices were HeartMate II (n=8), Heartware (n=3). Re-operation for bleeding occurred in 4/11 (36%), and right ventricular failure requiring short-term mechanical support occurred in 3/11 (27%). There was one 30-day mortality (9%) and one late death at 66 days. Survival after a mean follow up of 248 days (range 5–622) was 82% (Figure). In conclusion, application of peripheral VA-ECMO to bridge patients with advanced cardiogenic shock to CF-LVADs results in excellent short-term and long-term outcomes.
Hemodynamic Effects of the Impella CP and TandemHeart Temporary Circulatory Support Devices in a Model of Acute Left Heart Injury

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**Study:** Whether directly sourcing blood from the left ventricle (LV) or indirectly via the left atrium (LA) generates a distinct hemodynamic effect is an unresolved issue in the field of percutaneously delivered temporary circulatory support for LV failure. We examined the hemodynamic profile of an axial flow catheter placed directly into the LV (Impella CP) versus a centrifugal flow pump placed into the LA (TandemHeart device: TH) in a bovine model of acute LV injury.

**Methods:** In 3 male (103±8kg) calves, the TH device was placed using a 21-Fr inflow cannula in the LA and a 17-Fr outflow cannula in the left femoral artery. A 14-Fr sheath in the right femoral artery was used to deploy the CP in retrograde fashion across the aortic valve into the LV. Ligation of the left anterior descending artery (LAD) was followed by activation of the CP at a power level of P8. The CP was then removed and the TH activated at 5500 rotations per minute (RPM) followed by 7500 RPM. Conductance and pulmonary artery catheters acquired hemodynamic data at each time point.

**Results:** LAD ligation reduced cardiac output (CO: 3.6±0.5 vs 3.0±0.7, pre- vs post-LAD occlusion, p<0.05) and LV stroke work (LVSW: 3568±876 vs 2464±248, pre- vs post-LAD occlusion, p=0.01). CP activation generated 2.9±0.2LPM of flow and reduced native CO, LV stroke volume (LVSV), LV end-diastolic volume (LVEDV), and LVSW by 32±5%, Off vs On, p<0.01. TH activation at 5500 RPM generated 3.0±0.1LPM of flow and reduced native CO, LVSV, LVEDV, and LVSW by 41±6%, Off vs On, p<0.01. At 7500 RPM, the TH achieved 4.3±0.2 LPM of flow and further reduced native CO, LVSV, LVEDV, and LVSW by 67±2%, Off vs On, p<0.01. Representative pressure-volume loops and percent reduction in LVSW are shown in the Figure. In conclusion, this is the first report directly comparing the hemodynamic effects of the CP and TH devices. These findings may impact clinical decision-making and future device design.

Extracorporeal Membrane Oxygenation as a Bailout Strategy for Transcatheter Aortic Valve Replacement Complications

I. S. Banjac, P. Loyalka, S. Nathan, M. H. Akay, M. Patel, R. Radovancevic, B. Kar, I. D. Gregoric. Center for Advanced Heart Failure, University of Texas Health Science Center at Houston, Houston, TX.

**Study:** Transcatheter aortic valve replacement (TAVR) is an alternative treatment for high-risk patients with symptomatic aortic stenosis. Complications during or after TAVR have been associated with increased mortality, and extracorporeal membrane oxygenation (ECMO) can be used as a procedural rescue option to improve outcomes when a patient experiences reversible respiratory and/or cardiac failure.

**Methods:** We reviewed the records of 118 patients who underwent TAVR and identified 4 patients who developed complications and consequently received ECMO support during or after their TAVR procedure.

**Results:** Two men, 86 and 90 years old, and 2 women, 81 and 91 years old, underwent TAVR using Edwards Sapien valves (26 mm for 3 patients and 23 mm for 1 patient). Two patients had a transfemoral approach, and 2 patients had a transapical approach. Veno-arterial (VA) ECMO was initiated in response to fatal intraprocedural hemodynamic collapse due to a perivalvular leak in 1 patient and ventricular fibrillation in 2 patients. The fourth patient had an aortic root rupture, received VA ECMO, and underwent primary surgical patch repair of the rupture site. Three patients (including the patient with the root rupture) had good preprocedure left ventricular ejection fraction (LVEF) values and received short-term ECMO support for <100 min; they were all discharged home and remain alive. The other patient had poor LVEF before TAVR and received ECMO support for 8167 min (5.6 days) but died 13 days after ECMO weaning. The mean postsurgical hospitalization time for the 3 surviving patients was 18 days. ECMO is a promising rescue therapy for patients who develop TAVR-related complications. Preprocedure LVEF may affect long-term survival despite successful weaning from ECMO.
Pulmonary Function Tests after Left Ventricular Assist Device Placement
G. Yost, D. Jandura, B. Mohamedali, G. Bhat. Center for Heart Transplant and Assist Devices, Advocate Christ Medical Center, Oak Lawn, IL.

Study: Left ventricular assist devices (LVADs) are increasingly being used as life saving bridge to transplant in patients with end stage cardiomyopathy. Little is known about changes in pulmonary function tests (PFTs) after LVAD implantation. We report a case series of bridge to transplant (BTT) patients who underwent baseline PFTs before and after LVAD placement.

Methods: In this retrospective study 24 BTT patients who had performed baseline and post-LVAD PFTs were enrolled. In addition to baseline demographics, PFT data on FVC (L), FVC (% predicted), FEV1 (L), FEV1 (% predicted), FEV1/FVC (%), FEV1/FVC (% predicted), DLCO (mL/min/mmHg), and DLCO (% predicted) was obtained.

Results: 24 patients (16 males and 8 females) with mean age 60±10.45 years were analyzed. 5 (20.8%) had undergone previous sternotomy and 14 (58.3%) were of ischemic etiology. Pre- LVAD PFTs were obtained a median of 7.5 (IQR=19.25) days prior to LVAD implantation, while follow up PFTs were obtained a median of 312.5 (IQR=110.8) days post- LVAD placement. At baseline, PFTs were lower than age and gender matched population controls. All parameters were decreased post-LVAD. FVC, FEV1, and DLCO were statistically significantly decreased after LVAD (Table 1).

Conclusion: Our study demonstrates that PFTs are do not appear to improve after LVAD placement. The significant changes in lung volume and diffusion capacity may be partially explained by compression of left lower lung base by the LVAD or regional pleural constriction after sternotomy. Though the effect of thoracic surgery on lung function is unclear, our study is the first to look at changes in PFT after LVAD placement. Further, larger prospective studies are needed.

Table 1: Pre and Post-LVAD PFTs

<table>
<thead>
<tr>
<th>PFTs</th>
<th>Actual</th>
<th>% Predicted</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
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<tr>
<td>FEV1(L)</td>
<td>1.89±.75</td>
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<tr>
<td>FVC (L)</td>
<td>2.61±.93</td>
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<td>FEV1/FVC (%)</td>
<td>72.17±9.6</td>
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<tr>
<td>DLCO (mL/min/mmHg)</td>
<td>15.21±6.7</td>
<td>10.38±5.23</td>
<td>0.02</td>
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</tbody>
</table>

Pulmonary Function is Decreased After LVAD Placement in Both Obese and Non-Obese Populations
G. Yost, D. Jandura, B. Mohamedali, G. Bhat. Center for Heart Transplant and Assist Devices, Advocate Christ Medical Center, Oak Lawn, IL.

Study: Obesity is a significant risk factor for patients undergoing LVAD placement surgery. Although the influence of obesity on pulmonary function tests (PFT) has been well reported, the effects of LVAD placement on pulmonary function in obese patients are not known. We report a case series of obese patients who underwent PFT prior to and after LVAD placement.

Methods: In this retrospective study 24 patients who had performed baseline and post-LVAD PFTs were enrolled. Patients were divided into two groups based on BMI (BMI≥30 and BMI<30). In addition to baseline demographic data, FVC, FEV1, and DLCO data was obtained. Student’s t-tests were used to compare groups.

Results: The obese group was composed of 15 patients (10 male, mean age 57±11.6 years) whose PFTs were obtained at a median of 8 days pre-LVAD (IQR=19.25) and a median of 295 days post-LVAD (IQR=240). The non-obese group comprised of 9 patients (6 male, mean age 64±6.9 years) whose PFTs were measured at a median of 7 days pre-LVAD (IQR=18) and a median of 422 days post-LVAD (IQR=619). All measurements were decreased following LVAD placement in both groups. However, the decline in FEV1 and FVC was significant only in the obese group (Table 1). Differences in baseline PFTs between the groups were non-significant.

Conclusion: Our study demonstrates a reduction in PFTs in both groups post-LVAD. However, the decline in FEV1 and FVC was statistically significant only in the obese group. DLCO showed a trend towards decrease in both groups. This study is the first to analyze PFTs in obese and non-obese patients after LVAD implantation. Further, larger prospective studies are needed to determine the etiology of such deterioration in PFT and to validate our findings.
Coagulation-Based Hemotherapy Protocol to Decrease Blood Utilization and Need for Reoperation for Bleeding Associated With Left Ventricular Assist Device Implantation

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¹Pathology Department, University of Texas Health Science Center at Houston, Houston, TX, ²Center for Advanced Heart Failure, University of Texas Health Science Center at Houston, Houston, TX.

Study: Left ventricular assist device (LVAD) implantation is associated with a high incidence of bleeding complications, high-volume transfusions, and re-exploration for bleeding, which increase morbidity and mortality rates. We developed an intraoperative algorithm for transfusion support using integrated analysis of hemostatic assay results and transfusion triggers. We sought to determine early results and the effect on bleeding and transfusion rates during and after LVAD implantation.

Methods: We reviewed data from a group of 31 consecutive patients (pts) (30 men and 1 woman; mean age 55±12 years) who received an LVAD at our institution between May 2012 and August 2013 and received intraoperative coagulation-based hemotherapy for transfusion support. Our hemotherapy algorithm included sequential testing during multiple operative and postoperative phases including baseline, after hemoconcentration, at the end of the warming phase, post-heparin reversal, and as necessary for postoperative bleeding. Recommendations for transfusion support were immediately made on the basis of integrated analysis of laboratory data from tests including CBC, a DIC panel, antithrombin, VerifyNow-P2Y12, VerifyNow-ASA, and thromboelastography (TEG).

Results: The mean intraoperative transfusion requirements were 6.4±3.2 RBC units, 6.28±5.75 FFP units, 2.24±0.72 platelet doses, and 0.04±0.2 cryoprecipitate doses. In the 48-hour postoperative period, a mean of less than 3.5 blood products were transfused per pt (1±4.42 RBC units, 3±13 FFP units, 0.4±1.44 platelet doses, and 0.14±0.45 cryoprecipitate doses). The mean cumulative transfusion rate for our pts was 19.2 units; only two pts (6.5%) required reoperation for bleeding. These results for a limited number of pts suggest that integrated hemotherapy support may decrease bleeding and transfusion requirements in a start-up LVAD implantation program.

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Miniaturization of an Implantable Axial-flow Ventricular Assist Device with Non-contacting Levitation System

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Study: Our research group are currently working on development of an axial-flow implantable VAD. The axial flow blood pump has the hydrodynamic bearings that allows non-mechanical contacting levitation of the fast-spinning impeller. We have already developed an implantable VAD for adult patients, and in the present study the blood pump is modified to miniaturise the pump’s dimensions for the system to be applicable to smaller patients with BW of 15–30 kg. The present study deals with the in vitro performance of the first prototype of the miniaturised device.

Methods: The axial flow pump, originally developed as a VAD for adult patients, were modified for smaller patients in the following aspects. The impeller vane was re-designed for the assumed working condition of 2.0 L/min against 100 mmHg considering a use for patients with BW of 20 kg. The design of the driving components and the hydrodynamic bearings were identical to that of the preceding device for adult patients. The hydrodynamic performance and hemolysis testing were carried out for the new vane design. The inlet port was redesigned that attached vertically to the pump casing instead of the conventional 90-degree curved bend.

Results: The blood pump with the new vane impeller demonstrated the equivalent hydrodynamic performance to that of the adult device with higher efficiency at lower flow rates. The hemolytic properties with the new vane was acceptable. The value of N.I.H. after 4 hours of operation at 2.0 L/min, 100 mmHg was 0.00480 (N=3). The newly designed inlet port attached vertically to the pump body contributed to the downsizing of the pump in the axial dimension (from 121 to 81 mm) with a limited extent of losses in its hydrodynamic performance. In conclusion, The re-designed axial flow pump developed for smaller patients demonstrated a sufficient basic performance as a ventricular assist device.
Venoarterial Extracorporeal Membrane Oxygenation with Minimally Invasive Left Ventricular Decompression

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Study: Current limitations to venoarterial extracorporeal membrane oxygenation (VA-ECMO) include pulmonary edema, femoral ischemia, and the inability to ambulate patients. Central cannulation with left ventricular (LV) decompression offers potential to reduce these limitations. At present, there is no established minimally invasive technique for LV decompression.

Methods: This is a case series of patients treated with VA-ECMO and minimally invasive LV decompression (MILVD). VA-ECMO with MILVD

Operative Technique: The arterial limb of the ECMO circuit is connected to an 8 mm graft on the right axillary artery. Through a 6 cm right anterolateral thoracotomy, the right atrium is cannulated with a 40 Fr cannula and the LV is cannulated through the right superior pulmonary vein with a 20 Fr cannula. These cannulas are connected to the venous limb (Figure).

Results: Patient 1: 57 year-old man was placed on VA-ECMO with MILVD for NICM and sepsis from a central line infection. He was extubated on post-operative day (POD) 2, ambulated each day following extubation, and was decannulated on POD 5. He underwent heart transplantation two weeks later. Patient 2: 55 year-old man was placed on VA-ECMO with MILVD for decompensated ICM. He was transitioned to biventricular assist devices on POD5. His course was subsequently complicated by sepsis, resulting in multi-system organ failure. Support was ultimately withdrawn. Patient 3: 39 year-old man was placed on VA-ECMO via femoral access at an outside institution for MI with cardiac arrest. Upon transfer, he was transition to VA-ECMO with MILVD for severe pulmonary edema. The patient demonstrated improvement in cardiopulmonary function. Unfortunately, he did not recover neurologically, and support was withdrawn. In conclusion, MILVD is a novel approach that holds promise for reducing some of the current limitations to VA-ECMO, including the occurrence of pulmonary edema and complications from femoral cannulation.

Lessons Learned from Failed Left Ventricular Assist Device: Inflow Cannula is an Important Source of Device Thrombosis

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Study: Development of LVAD has focused on the biocompatibility and durability of the pump while the biocompatibility of inflow cannula received less attention. VentrAssist LVAD (VA), once considered superior to HeartMate II LVAD (HMII) was terminated in clinical trial due to high incidence of thrombosis. However the source of VA thrombosis was poorly studied. We examined the VA pumps together with explanted hearts to look for the source of preclinical pump thrombosis. We examined the HMII as controls.

Methods: Between July 07 and Sept 09, 18 VA and 21 HMII patients (Pts) received heart transplant in our center. All LVADs functioned properly and there were no clinical pump thromboembolism prior to transplant and LVAD explantation. All Pts received coumadin and aspirin. The explanted hearts and pumps were examined. The severity of thrombosis was graded as follows: Grade 0 = no thrombus, 1 = thrombus size <1cm; 2 = thrombus < 2cm and 3 = >2cm or wrapping >50% of cannula circumference.

Results: There were no differences in age (52 vs 55), length of LVAD support (225 vs 319 days), hemoglobin (11.4 vs 11.8 gms) and platelets (232 vs 195 x1,000) between VA and HMII pts (p>0.05, t-test). VA Pts maintained higher INR than HMII Pts (2.14 vs 1.61, p<0.005, t-test). There were no thrombi inside pumps in either groups. In VA group, thrombi were found around the cannulae in 17 out of 18 Pts (94%, 5 of grade 1, 2 of grade 2 and 10 of grade 3). In the HMII group only 1 out of 21 (4.8%) had grade 1 thrombosis around the cannula. The thrombi in VA group originated from the junction between LV and the cannulae (Fig). There was no pseudointima on VA cannulae, versus well formed one on the HMII.

Conclusions: Despite higher anticoagulation and shorter implantation, the incidence of thrombosis around the inflow cannula in VA Pts was much higher than that in HMII Pts. Future LVAD research should also focus on improving inflow cannula to prevent thrombosis.
Computational Fluid Dynamics Evaluation of Unsteady Flow in a Left Ventricular Assist Device

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Study: Heart failure is still a growing concern worldwide with over half a million patients each year. Ventricular Assist Device (VAD) has been able to provide some form of support in assisting the ventricle to pump blood through the body, thereby reducing workload on the heart while the patients waiting for heart transplantation or cardiac recovery.

Methods: In this study, Computational Fluid Dynamics (CFD) was used in the development of LVAD which was designed based on centrifugal pump with a semi-open impeller structure. Inside the impeller, a small passage was constructed to generate the wash out flow for the region at bottom of the pump chamber which is one of the critical points in most centrifugal LVADs as it has high risk of forming thrombosis. In this research, two designs of passage were evaluated in comparison with the reference design. CFD simulation was adopted to acquire information about hydraulic efficiency, balancing of force on the impeller, and blood damage generated within the pump under the normal operating condition at the rotation speed of 4000 rpm and the flow rate of 0.3m³/h. Transient simulation was used to capture the effect of unsteady force that applied on the impeller due to the unbalanced design of the washout hole during one revolution and totally 120 time steps were specified.

Results: The results from CFD simulation showed that both designs with a hole were able to create the washout flow which eliminate the recirculation and stagnation underneath the impeller with small amount of leakage through the passage compare to the pump flow while it cause slightly loss to the pump efficiency. The hydraulic force analysis displayed fluctuation on the radial force exerted on an impeller caused by the out flow from the washout hole. Hemolysis was analyzed based on the shear stress information; all the design has lower blood damage compare to the recommended clinical limit, with an approximate normalized index of hemolysis (NIH) less than 0.0019g/100l.
Evaluation of Potential Device-related Factors Related to HeartMate II Device Thrombosis

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Study: Device thrombosis is a multifactorial phenomenon, with complex interactions between device, patient, and management related factors. We performed extensive internal investigations to identify potential device and manufacturing related factors that could be contributing to HeartMate II (HMII) device thrombosis.

Methods: A cross-functional internal investigation team comprising of R&D, manufacturing, manufacturing engineering, quality engineering, and scientific affairs was assembled. Focused investigations were prioritized in 2 main areas: 1) device design change from unsealed to sealed grafts; 2) manufacturing consistency during scale-up. Various hypotheses were investigated via theoretical and experimental studies as well as histopathological evaluation of explanted pumps. Manufacturing process variability was evaluated in over 2000 pumps, including the impact of operators, assembly stations, bearing properties, and operational testing.

Results: Evaluation of flow fields, pump function, power consumption and histopathological reports did not reveal any differences between sealed and unsealed grafts. An analysis of customer complaint data demonstrated no difference in the freedom from suspected thrombosis at 6 months between sealed (93.2±0.9%, n=884) and unsealed grafts (94.6±1.0%, n=604, p=0.56). Additionally, all pumps were found to be within established specifications, and no significant differences between critical manufacturing variables in pumps with and without device thrombosis were observed. The table below shows an example of 3 such variables.

<table>
<thead>
<tr>
<th>No Thrombus</th>
<th>Suspected Thrombus</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forward bearing ball surface finish (µIn)</td>
<td>0.89±0.39</td>
<td>0.86±0.37</td>
</tr>
<tr>
<td>Forward cup surface finish (µIn)</td>
<td>0.97±0.55</td>
<td>0.94±0.57</td>
</tr>
<tr>
<td>Operational Testing (hours)</td>
<td>14.4±7.1</td>
<td>14.9±6.9</td>
</tr>
</tbody>
</table>

Conclusions: Extensive evaluation of device related factors potentially related to pump thrombus was undertaken, and no relationship to thrombosis has been found. Additional investigations are ongoing.

Extracorporeal Membrane Oxygenation Support in Refractory Cardiogenic Shock: Treatment Strategies and Analysis of Risk Factors

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Study: The RotaFlow and the Levitronix CentriMag pumps as central or peripheral veno-arterial extracorporeal membrane oxygenation (ECMO) support systems have been investigated, in terms of double-centre experience, as treatment for patients with refractory cardiogenic shock (CS).

Methods: Between January 2006 and December 2012, 228 consecutive adult patients were supported on RotaFlow (n=213) or CentriMag (n=15) ECMO, at our institutions (155 men; age 58.3±10.5 years, range: 19–84 years). Indications for support were: failure to wean from cardiopulmonary bypass in the setting of postcardiotomy (n=118) and primary donor graft failure (n=37); post-acute myocardial infarction CS (n=27); acute myocarditis (n=6); and CS on chronic heart failure (n=40).

Results: A peripheral ECMO setting was established in 126 (55.2%) patients while centrally in 102 (44.7%). Overall mean support time was 10.9±9.7 days (range: 1–43 days). Eighty-four (36.8%) patients died on ECMO. Overall success rate, in terms of survival on ECMO (n=144), weaning from mechanical support (n=107; 46.9%), bridge to mid-long-term ventricular assist device (n=6; 2.6%) and bridge to heart transplantation (n=31; 13.5%), was 63.1%. Hundred-twenty-two (53.5%) patients were successfully discharged. Stepwise logistic regression identified blood lactate level and CK-MB relative index at 72 h after ECMO initiation, and number of PRBCs transfused on ECMO as significant predictors of mortality on ECMO [p=0.010, odds ratio (OR)=2.94; 95% confidence interval (CI)=1.10–3.14; p=0.010, OR=2.28, 95% CI=1.014–3.721; and p=0.011, OR=2.69; 95% CI=1.06–4.16; respectively]. No significant differences were seen by comparing RotaFlow and CentriMag populations in terms of device performance. At follow-up, persistent heart failure with left ventricle ejection fraction (LVEF) ≤ 40% resulted to be a risk factor after hospital discharge.
Evaluation of an Intra-aortic Ventricular Assist Device Concept in a Hybrid Multi-lumped Mock Circulatory Loop
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**Study:** A minimally-invasive intra-aortic ventricular assist device (IntraVAD) has been proposed. It is to be located within the aorta to reduce the afterload while maintaining adequate coronary and vital organ perfusion for heart failure patients. The concept employs a miniature motor within the intraVAD and a deployable impeller around the motor. The optimum position for the IntraVAD in the aorta needs to be established, allowing the design criteria for the miniature motor can be determined, particularly its power consumption.

**Methods:** Therefore, an IntraVAD prototype without the miniature motor was evaluated in a hybrid multi-lumped mock circulatory loop (MCL). The IntraVAD was driven by a standard motor. The MCL was composed of left atrium, left ventricle (LV), ascending/descending aorta, venous reservoir and coronary/vital organ system components, with variable vascular compliance and peripheral resistance. The LV simulator was controlled to accurately reproduce the waveform of the LV in a cardiac cycle. The IntraVAD prototype was inserted at different positions in the aorta in the MCL, and the perfusion of coronary arteries as well as flow rate and pressure in vital organs were monitored. Physiological parameters, such as cardiac output, heart rate, blood pressure in the LV, ascending/descending aorta and vital organs, were obtained from the MCL with the IntraVAD active, and were compared to healthy and pathological conditions.

**Results:** The optimal pump speed and torque generated by the impeller were adjusted to achieve a reasonable afterload reduction and flow augmentation in both coronary system and vital organs. Using this method, the feasibility of the IntraVAD was confirmed for the proposed location in the ascending aorta, and also the design criteria for the miniature motor were established.

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The Influence of a Novel Pulsatile Driving Mode in an Implantable Continuous Flow LVAD (EVAHEART) on Hemolytic Performance
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**Study:** Continuous flow left ventricular assist device (CF-LVAD) has demonstrated increased durability and improved survival of severe heart failure patients. However, we still believe that pulsatile blood flow is necessary, at least in some patients, for adequate organ perfusion, myocardial recovery, and to avoid long-term complications. Thus, we developed a novel driving controller of an implantable centrifugal LVAD (EVAHEART, Sun Medical Technology Research Corp.) which can change pump's rotational speed (RS) in synchronization with patient’s cardiac cycle. We have shown the usefulness of various applications of this system in large animal models, but there remains a concern that the repeated acceleration and deceleration of impeller may induce added hemolysis. In this study, we evaluated the blood trauma of our driving system in a mock circulation to ensure the safety toward clinical application.

**Methods:** We evaluated the EVAHEART in co-pulse mode which increase the RS in systolic phase and decrease in diastolic phase (EVA-P; n = 5). We set the pulse frequency at 60 bpm and set the difference between the lowest RS and the highest RS at 500 rpm. To compare the hemolysis level, the continuous mode of the EVAHEART (EVA-C; n = 4) and the ROTAFLOW (MAQUET; n = 5) were used. The test circuits were filled with fresh bovine blood of 600 ml. The pumps were examined with average flow rate of 5.0 ± 0.2 L/min against average pressure head of 100 ± 3 mmHg. We compared the Normalized index of hemolysis (NIH), calculated by the variance of plasma free hemoglobin during 4 hours.

**Results:** The NIH levels of EVA-P and EVA-C were 0.0030 ± 0.0019 and 0.0026 ± 0.0024 respectively. There were no significant differences between them. In conclusion, when a pulsatile mode is applied to the EVAHEART implantable CF-LVAD, the co-pulse mode with 500rpm rotational speed difference does not affect hemolysis at 60 bpm pulse frequency.
Alternation of Left Ventricular Load by a Continuous-flow Left Ventricular Assist Device with a Native Heart Load Control System in Chronic Awake Phase

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Study: We have previously developed a Native Heart Load Control System for a continuous-flow left ventricular assist device and demonstrated that the rotational speed (RS) in synchronization with the cardiac cycle can alter left ventricular preload and myocardial oxygen consumption under general anesthesia. In this study, we assessed this system in chronic awake phase.

Methods: We implanted EVAHEART via left thoracotomy in three goats (58.7±5.5kg) with a normal heart. 2 weeks after the implantation, we examined the effects of the continuous mode (constant RS), co-pulse mode (increase RS in systolic phase) and counter pulse mode (increase RS in systolic phase) on end-diastolic volume (LVEDV) and stroke work (SW) determined from left ventricular pressure-volume loops in 100%, 75% and 50% bypass. The bypass rate was calculated by dividing pump flow by the sum of pump flow and the ascending aortic flow.

Results: There were decreases in end-diastolic volume (LVEDV) and stroke work (SW) of the counter-pulse mode relative to the values of the continuous mode at every bypass rate. Furthermore, both values increased in the co-pulse mode compared with the values observed in the continuous mode at every bypass rate. In conclusion, the system offers the possibility to control the left ventricular load by changing the rotational speed of a continuous-flow assist device in synchronization with the cardiac cycle. This system may provide the most favorable left ventricular loading conditions for the recovery of the native heart.

The Role of Cardiac Trabeculae on Ventricular Mechanics

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Study: Cardiac trabeculae are cylindrical structures characterized by an axial orientation of myocytes which cover the ventricles endocardium. They represent a significant percentage of ventricular mass (12%-17%) and are preferably oriented along the ventricular apico-basal direction. Aim of the work is to understand the role of trabeculae on heart performances by comparing different finite-element models of the left ventricle (with or without trabeculae).

Methods: The ventricle was simplified as a truncated ellipsoid and the trabeculae as cylindrical strands laying onto the endocardium oriented along the ventricular axis. Different trabeculae diameters and mass were implemented to investigate the influence of these parameters on the model outcomes. The total muscular mass and the intra-ventricular volume were kept constant in all models. The myocardium mechanical behaviour was modelled by an anisotropic hyperelastic law. The material parameters were optimized to fit the physiologic pressure-volume relationship. Cardiac fibres were oriented helically in the ventricular wall and along the axial direction in the trabeculae, according to the literature. The muscular contraction was simulated by increasing the material stiffness according to the contraction curve of a cardiac fibre. Kinematic boundary conditions were applied at the ventricular base, while physiological atrial pressure was set during the diastole. Further, a RCR model was coupled to the ventricle to simulate the systemic circulation.

Results: A significant influence of the trabeculae on ventricular hemodynamics was highlighted. The trabeculated model is characterized by an higher compliance with respect to the “smooth” model (Figure 1). The cardiac output at 75 bpm is 5 l/min for the trabeculated ventricle and 4 l/min for the smooth ventricle. Besides, the end-diastolic and the stroke volume increase with the trabecular mass, while the trabeculae diameter influences the fibre stress.

Fig. 1. Left: trabeculated and smooth geometries. Right: Ventricular PV loop.
ASAIO CARDIAC ABSTRACTS

222

The MVAD® Pump: Suction Detection Initial in-vivo Performance
F. Casas, C. Reyes, J. Wolman, J. LaRose. APD, HeartWare, Inc., Miami Lakes, FL.

Study: The suction detection strategy for the MVAD® pump was tested in an ovine animal model under various suction conditions.

Methods: The suction detection strategy in the MVAD pump is based on the use of the motor’s Back Electromotive Force (BEMF) as an independent predictor of flow. In particular, during low flow pulsatile conditions, the BEMF has the ability to track flow in a quasi-linear fashion. The suction management strategy in the MVAD pump also includes a suction reaction mode. Speed management following a suction condition allows for the collapsed ventricle to recover. An MVAD pump was implanted in a 56 kg sheep via a left thoracotomy. A 10mm Transonic probe was placed on the outflow graft. Hematocrit was measured and entered as a parameter into the Pal™ controller. The creation of suction was attained by using a combination of PA occlusion and inlet cannula positional adjustment. The suction conditions were verified to be present via assessment of ventricular echocardiographic data. The suction response was evaluated at speeds between 14 - 22 kRPM.

Results: The suction management strategy for the MVAD pump was successfully tested in-vivo; suction onset and subsequent resolution after suction detection and reaction were assessed by echocardiographic evaluation. Results from the in-vivo study confirmed the ability of the suction detection and recovery strategies to operate successfully under pulsatile in-vivo conditions. CAUTION: Investigational device. Limited by United States law to investigational use.

223

The MVAD® Pump: Flow Estimation Initial in-vivo Performance
F. Casas, C. Reyes, J. Wolman, J. LaRose. APD, HeartWare, Inc., Miami Lakes, FL.

Study: The flow estimation strategy for the MVAD® pump was tested in an ovine animal model under several hemodynamic conditions. As described previously, the flow estimation theory of operation in the MVAD pump is based on motor current and an additional degree of freedom derived from the impeller’s axial motion and expressed in the motor’s Back Electromotive Force (BEMF).

Methods: Extensive in-vitro characterization data for a range of viscosities, pump speeds, and flows was used to generate a complete performance landscape, which in turn, was embedded in the firmware of the Pal™ controller for the MVAD pump. An MVAD pump was implanted in a 56 kg sheep via a left thoracotomy. A 10mm Transonic probe was placed on the outflow graft. Hematocrit was measured and entered as a parameter into the Pal controller. Average estimated flows from the Pal controller and measured flows from the implanted Transonic probe were captured and compared for pump speeds ranging from 12 kRPM to 22 kRPM.

Results: The average flow estimates calculated by the Pal controller exhibited good correlation when compared to the measured flows obtained during the study. The flow range available was limited by the animal’s physiology. Results suggest that the flow estimation method can perform under physiological conditions. The MVAD pump flow estimation strategy has the potential to allow for average flow estimate tracking during pulsatile in-vivo conditions.

231

EuroSCORE and STS-SCORE in Indicating Vascular Access for Transcatheter Aortic Valve Implantation (TAVI)

Study: Although transcatheter aortic valve implantation (TAVI) has been indicated for patients with a prohibitive surgical risk, indication for TAVI remains illdefined as its vascular access evolves increasingly more invasive and its results having been improved.

Methods: We compared STS scores (STS) and EuroSCORES (EURO) with survival in 194 patients undergoing TAVI during the last 3 years, when the vascular access has been evolved from iliofemoral (Fm), axillo-clavicular, apical and direct aortic approach.

Results: Poorer survival after TAVI in patients with a high-risk in Euro or STS (Fig-1) is natural since these scores portray comorbidities and therefore parallel long-term survival regardless of surgical intervention. It may be more relevant to 30-day survival (open circle), which showed no correlation with these scores among patients undergoing TAVI via Fm access (Fig-2, left). Whereas among patients undergoing TAVI via an access other than Fm (Fig-2, right), a high-risk score, STS>40 or EURO>20, led a significantly high 30-day mortality (closed circle); 5 high-risk patients in both scoring systems had only 20% (1/5) 30-day survival while 26 patients with a low-risk in both systems undergoing TAVI via access other than Fm had 96.2% (25/26) 30-day survival rate.

Conclusion: The result suggest that patients with a low surgical risk may tolerate TAVI through any vascular access with an acceptable risk while patients with a high-risk (Euro>20 and/or STS>40) may better be treated with Fm access without invasive approach.
ASAIO Cardiac Abstracts

232
Enhanced Hemolytic Performance of the MVAD® Pump after CFD-Based Optimization

Study: A primary goal in designing mechanical circulatory support devices is to reduce blood damage due to high shear forces generated within the device by its moving components. We discuss an evaluation of hemolytic performance of the modified HeartWare MVAD Pump during product development.

Methods: Computational Fluid Dynamics (CFD) was utilized as a design tool for identifying candidate pilot devices with minimal estimated blood damage potential. The estimation was based on a critical fluid volume of shear stress above 150 Pa. Pilot devices of low CFD-predicted blood damage were then subjected to in vitro hemolysis testing per ASTM F1841 standard protocol in parallel with reference pumps. Bovine blood was circulated in pump-driven flow loops for 6 hours at 5 liters per min flow rate, 100 mmHg pressure head and 37°C. Furthermore, hemolysis and generation of cellular fragments were quantified in a similar experimental setup for human blood.

Results: Design modifications of the MVAD Pump impeller reduced the CFD-predicted critical shear stress volume by 75% versus the previous generation and led to a significant reduction in in vitro hemolysis. Indicatively, there was an over 2-fold reduction in plasma free hemoglobin levels, corresponding improvement to the normalized and modified indices of hemolysis (NIH, MIH respectively) and a significant reduction in cell debris formation. Conclusion: We are demonstrating a reduction in in vitro blood trauma and enhancement to the hemolytic performance of the modified MVAD Pump following in silico performance optimization.

238
Inferior Left Ventricular Wall Placement of HeartWare Left Ventricular Assist Device
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Study: Implantation of the Heartware ventricular assist device (HVAD) inflow cannula has conventionally been in the left ventricular apex. However, there are circumstances in which apical inflow cannula placement is not feasible. We describe our institutional experience with HVAD inflow cannula placement in the inferior wall of the left ventricle (LV).

Methods: Since May 2013, four patients with refractory cardiogenic shock received an HVAD with the inflow cannula placed in the LV inferior wall. We performed a retrospective chart review to determine the periprocedural characteristics and outcomes of this group of patients.

Results: There were 4 males with mean age of 59 years (range 40–72 years). All patients were in advanced cardiogenic shock with multi-organ dysfunction requiring two or more inotropes and mechanical circulatory support (VA-ECMO = 3, IABP = 1). Etiology of cardiogenic shock was acute coronary syndrome in 3 (2 acute ST-elevation myocardial infarction, 1 ischemic cardiomyopathy) and decompensated dilated cardiomyopathy in 1. Implanted devices were HeartWare HVAD (n = 4) with all cannulas placed inferiorty. Reasons for inferior wall placement were necrotic LV apical myocardium due to acute myocardial infarction (n = 1), subacute anterolateral LV free wall rupture following acute myocardial infarction (n=1) and calcified LV apex due to previous Dor procedure (n = 2). There was 1 early post-operative (<30 day) death due to hemorrhagic complications. 3 patients required a temporary right ventricular assist device. There were no cases of inflow cannula obstruction, hemolysis or pump thrombosis. There were no cerebrovascular accidents. Three patients remain alive after a mean follow up of 247 days (range 56–265 days) including one successful transplant. In conclusion, inferior LV wall placement of the HVAD is a reasonable alternative to conventional apical placement in selected patients in whom the apex is not suitable due to calcification or recent myocardial infarction.

241
Intraoperative Fitting Study of Cleveland Clinic Continuous-Flow Total Artificial Heart
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Study: Implantation of mechanical circulatory support devices in heart failure patients can be challenging, especially in those with a small chest and/or limited space in the mediastinum. The purpose of this study was to evaluate the anatomic fitting of the Cleveland Clinic Continuous-Flow Total Artificial Heart (CFTAH) device in heart transplant recipients.

Methods: A mock pump model of the CFTAH was constructed from biocompatible materials for in vivo fitting evaluation using rapid prototyping. The sterile pump model consists of inflow and outflow ports with adjustable angles and two custom-made outflow conduits with adjustable angles and lengths. After the native heart was explanted, the device was brought to the operative table and the direction, length, and angulation of the inflow ports, outflow ports, and outflow conduits were evaluated. Thoracic cavity measurements were taken from a pre-operative computed tomography (CT) scan in all patients.

Results: The study is ongoing with the device fitting well in all 5 patients (Height: 170 ± 9 cm, Weight: 75 ± 24 kg). The BSA was 1.9 ± 0.3 m² (lowest: 1.6 m²). Based on the initial results, the inflow port orientation of both the left and right housing does not seem to require any modifications from the current version being implanted in calves. The left outflow conduit remained straight but the right outflow direction necessitated a 73 ± 22 degree angulation to prevent potential kinking when placed over the connected left outflow. No other pump features required change (Figure 1).

Conclusions: The pump model fit well in all 5 patients with end-stage heart failure with the lowest BSA of 1.6 m². This data supports the proper anatomical relationship of the CFTAH to the native vessels. Pre-operative CT scans will further confirm the proper fit of the device within the human chest. The lowest BSA has not been determined yet.

Image 232 to 238
The MVAD® Pump: Flow and Impeller Axial Displacement
J. R. Kennington, J. Wolman, H. F. González, S. Castillo, F. Casas.
HeartWare Inc., Miami Lakes, FL.
Study: Measurement of the MVAD® pump impeller axial displacement at multiple pump flow conditions was conducted. Axial location data was compared to hydraulic and electrical measurements to show correlation between electrical signals and impeller location.
Methods: In the MVAD pump the impeller is allowed to move axially, while being centered radially by a contactless passive hydraulic suspension system. The motor’s Back Electromotive Force (BEMF) has shown high correlation with flow, particularly at lower flow operating conditions. Hydraulic performance on the MVAD is a function of the axial location of the impeller; as such the BEMF could be used as a predictor of impeller position. A displacement laser was used to measure the location of the MVAD impeller during nominal operating conditions including fully open and shut-off flow conditions for several pump speeds. A test fixture was used to secure a pump while exposing the inlet through an optically clear port. The laser system was calibrated and incorporated into an automated LabVIEW based data acquisition system. Axial laser measurements were compared with hydraulic HQ curves and electrical BEMF curves.
Results: The measured MVAD impeller axial location showed strong correlation to the BEMF readings provided by the Pal™ controller. This correlation indicates that the BEMF curves could be used to determine the physical location of the impeller. CAUTION: Investigational device. Limited by United States law to investigational use.

Programmed Speed Reduction Enables Aortic Valve Opening and Increased Pulsatility Without Diminishing Aortic Flow
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Study: Aortic valve opening during LVAD support is considered important for preventing valve fusion and possibly aortic incompetence. A speed control algorithm to allow the aortic valve to open intermittently without significantly diminishing the cardiac output was programmed and tested using the HeartMate II and a mock-loop. The programmed low speed algorithm provides a continuous motor speed except for a dwell time, when the motor is decreased to a low speed level. The goal of this study was to measure aortic valve opening and hemodynamics in the LVAD-assisted heart using a mock circulatory loop.
Methods: A HeartMate II continuous flow LVAD with a programmed low speed algorithm (PLSA) controller was integrated into the SDSU cardiac simulator. LV and aortic pressures, LVAD and total aortic flow were measured for experimental conditions which included pre-LVAD, non-PLSA and PLSA combinations of cardiac function and LVAD speed.
Results: The pre-LVAD conditions were recorded to characterize the baseline cardiac function; the low setting corresponded to a cardiac output of 2.5 L/min, stroke volume of 35 ml, and ejection fraction of 20%. The Medium setting accordingly produced 3.2 L/min, 44 ml and 25%. Results showed that with a dwell time of 6s, the PLSA controller with 10krpm speed dropping to 8krpm low speed was insufficient to open the aortic valve during Low cardiac function, whereas the 6krpm low speed produced valve opening continuously during the dwell time for both Low and Medium levels. Total aortic flow was slightly reduced (<10%) compared to non-PLSA conditions and aortic root pulsatility was significantly increased during aortic valve opening. These results suggest that the PLSA controller produces sufficient aortic valve opening without diminishing cardiac output and improves flow mixing.

Position Sensing Development for Pulsatile Blood Pumps
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Study: A fully implantable Total Artificial Heart (TAH) is currently developed and undergoing animal trials at Helmholtz institute Aachen, Germany. The central element of the TAH system is a maintenance-free electrical linear drive unit. It features a low wear design for a high durability. However, for its control a position sensing system (PSS) is needed. Due to the application inside the linearly driven, pulsatile blood pump the PSS has to function under particular constraints: limited mounting space, influence of a magnetic field and a sufficient resolution and speed for a physiological beat rate. In this study we investigated three different concepts for a respective position sensing system (PSS).
Methods: The investigated concepts for a PSS were as follows: 1. Optical distance sensor for absolute position sensing 2. Encoder based PSS, including an optional position reference on the linear scale 3. Optical based PSS for relative position sensing using additional sensors for position reference. These concepts were validated in two different set-ups: a servo-hydraulic testing machine and a mock-circulation loop. The former mimics the moving parts inside the blood pump in order to validate the resolution and speed. The latter was used in order to validate the function of the PSS inside the linearly driven TAH under physiological conditions.
Results: The TAH was fully functional under physiological conditions (120 bpm, AP 120/80 mmHg) with the concepts 2 (encoder based PSS) and 3 (optical based PSS). Concept 3 (optical based PSS) showed limited function for aortic pressures above 160 mmHg. Beat rates beyond 180 bpm resulted in an insufficient resolution of concept 1. In conclusion, concept 2 showed sufficient results for use in the TAH. It could even be combined with concept 1 to a redundant PSS providing higher safety of the blood pump.
ECMO to Cardiopulmonary Bypass via Reservoir Insertion
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Study: The purpose of this evaluation is to look at the efficacy and safety profile of converting from Extracorporeal Membrane Oxygenation (ECMO) to cardiopulmonary bypass (CPB) via cutting in a cardiotomy reservoir. Our rationale for this approach is to limit extra volume and surface area exposure that can occur with changing entire circuits, potentially leading to worsening inflammatory processes. It also allows for a more fluid transition from ECMO to CPB and back to ECMO if needed.
Methods: We performed a retrospective chart review of cardiac ECMO between 2009–2014 at a single institution. Runs were divided into two categories: those where the operative procedure terminated the ECMO run (n=5), and those where the patient was returned to ECMO at the termination of the operative procedure (n=6). We reviewed thromboembolic complications, infection rate and hours on ECMO. Among patients returned to ECMO post CPB, postoperative circuit complications after the reservoir removal were also evaluated.
Results: Among patients whose ECMO run was terminated with the cardiac procedure, there were no bloodstream infections within 72 hours of CPB (0/5,0%), and the incidence of perioperative thromboembolic complications was also 0% (0/5). Among patients who returned to ECMO post CPB, postoperative circuit complications after the reservoir removal were also evaluated.

Outcomes of Left Ventricular Assist Device Patients Requiring a Temporary Right Ventricular Assist Device
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Study: CentriMag is an extracorporeal circulatory support device that has been shown to be a safe and effective method of providing hemodynamic stability. The purpose of this study was to examine survival and quality of life in patients who failed isolated left ventricular assist device (LVAD) support during initial implantation requiring temporary right ventricular support.
Methods: All patients who received a continuous flow LVAD and subsequently required a CentriMag RVAD between March 2005 and December 2013 were examined. Preoperative demographics, days on support, length of stay (LOS), postoperative outcomes, NYHA classification, and survival were analyzed.
Results: A total of 19 patients (13 male, 6 female), average age 54 (range 27–79) required biventricular support at time of implantation (n=10) or postoperatively (n=9, average postoperative day 10, range 1–17). The mean duration of biventricular support was 34 days (range, 4–78) with 79% (n=15) of RVADs successfully explanted. There were no device failures. 6 patients were discharged home or transplanted (n=2) after an average LOS of 65 days (range 30–94), 6 patients were discharged to subacute rehab after an average LOS of 89 days (range 41–182) and 7 patients expired prior to discharge with an average LOS of 48 days (range 4–145). Of the 12 patients alive at 3 months, 1 patient was in class II, 1 patient was in class III, while 83% (n=10) of patients remained in class IV heart failure according to the NYHA classification. At 6 months 63% (n=12) of patients had expired (n=7 MOF, n=3 HCVA, n=1 GI bleeding, n=1 sepsis), 21% (n=4) of patients were transplanted and 16% (n=3) were alive (2 in acute rehab, 1 home) an average of 184 days at study endpoint. Length of stay, quality of life and survival are not favorable for patients who required a CentriMag RVAD after LVAD implant. Patients not transplanted within 1 year have a high mortality.
Development of Gastrointestinal Bleeding During Continuous Flow Left Ventricular Assist Device Support is Associated With Lower Rates of Cardiac Transplantation in Transplant Eligible Patients


Study: Gastrointestinal (GI) bleeding remains a significant concern after continuous flow (CF) Left Ventricular Assist Device (LVAD) implantation. Given the need for red blood cell transfusions, we hypothesized patients with GI bleeds may have reduced rates of cardiac transplantation.

Methods: We retrospectively analyzed patients implanted with HeartMate II LVADs between June 2005 and June 2013. Baseline characteristics were assessed to determine risk factors for GI bleeding and as a predictor of subsequent cardiac transplantation.

Results: 233 patients were analyzed over a total LVAD follow up time of 364 person-years. 60 bleeding episodes occurred in 51 patients (22%), for an event rate of 0.17 GI bleeds/patient year of support. Patients who developed GI bleeds were older (63 vs 55 years, p < 0.001), had lower pre-operative BMIs (26 vs 29 kg/m2, p <0.05) and albumin levels (3.3 vs 3.5 g/dL, p < 0.5). Women made up 15% of the cohort, yet contributed 30% of the GI bleeds (p =0.07). There was no statistical difference in pre-operative bridge to transplant or destination therapy status, INTERMACS profile, or platelet count. There was no statistical difference in 6 month, 1 year, or 2 year survival in patients who developed a GI bleed and those who did not (77% vs 78%, 74% vs 71%, and 61% vs 54%, respectively). In the transplant eligible population, patients with GI bleeding had a 43% lower rate of transplantation (rate ratio 0.57, p <0.05). In this large single center study, GI bleeding rates in CF-LVAD patients were modestly lower than previously published. Risk factors for bleeding were older age, lower pre-operative BMI, albumin, and female gender. In transplant eligible patients with GI bleeding, a significantly lower rate of cardiac transplantation was noted. While the mechanism of this finding is unclear, GI bleeding may be linked to higher transfusion rates and subsequent allosensitzation.

An Improved Method for Triphenyl Tetrazolium Chloride (TTC) Staining of Myocardial Sections in Ischemia-Reperfusion Studies


Study: Myocardial ischemia-reperfusion injury can occur after revascularization treatments for myocardial ischemia, leading to clinically important and sometimes irreversible myocardial damage. Increasing numbers of myocardial ischemia-reperfusion injury studies are being performed to evaluate interventions designed to prevent or mitigate this type of injury. The ability to critically evaluate the extent of myocardial damage, including infarct area and area at risk, and efficacy of the intervention depends on accurate determination of viable tissue. We have developed an improved technique to obtain accurate results in myocardial ischemia-reperfusion studies.

Methods: Our technique modifications include providing structural support for the heart throughout data collection, applying dye (Evans blue) at physiologic perfusion pressures to the non-target tissue and freezing the heart for 20–36 hours post-necropsy before staining with TTC. The frozen heart, including the structural support material, is transected perpendicular to the long axis at 1 cm intervals. Each slice is placed in an approximately 41°C TTC solution until optimal staining is achieved. All slices are subsequently photographed and weighed. High quality photographs of each slice provide the basis for morphometric analysis. We believe that the reported technique modifications provide investigators with a means to more precisely evaluate potential therapeutic interventions for myocardial ischemia-reperfusion injury.
Five-year Durability of the HeartMate II Left Ventricular Assist Device
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Study: The HeartMate II left ventricular assist device (LVAD) is the standard of care for the mechanical support of patients with end-stage congestive heart failure. However, little data exists in the literature regarding long-term durability for this device. We reviewed our institutional experience in order to learn more about the causes of malfunction for patients supported with a HeartMate II LVAD for long-term support.

Methods: All HeartMate II LVADs implanted between December 1, 2008 and December 31, 2013 were retrospectively reviewed. Device malfunction included any LVAD that was explanted for reasons other than transplant or myocardial recovery, or any patient who died due to a primary pump-related cause. Patients who were transplanted or had their devices explanted due to myocardial recovery were censored at the time of LVAD explantation.

Results: Over a five-year period, 115 HeartMate II LVADs were implanted in 102 patients. Patients were 58±14 years old and were 84% male (97/115). Indications for implantation were 44% (51/115) destination therapy and 56% (64/115) bridge to transplant. Median support duration was 280 days (range 1-1831 days). There were 18 device malfunctions resulting in either device replacement or patient death (15 pump thrombus, 1 pump infection, 1 driveline fracture, 1 unknown). Freedom from all-cause device malfunction at 1, 3, and 5 years was 82%, 72%, and 68%, respectively. Survival at the time of LVAD implantation, 7 (3.4%) patients were underweight (< 20 kg/m2), normal (20 to < 25 kg/m2), overweight (25 to < 30 kg/m2), obese (30 to < 35 kg/m2) and morbidly obese (≥ 35 kg/m2). The impact of BMI on survival was assessed with the Kaplan-Meier method and with a competing risks proportional hazard model. Rates of driveline infection, gastrointestinal bleeding and transplantation were also compared.

Results: At the time of LVAD implantation, 7 (3.4%) patients were underweight, 51 (25.0%) were normal weight, 69 (33.8%) were overweight, 45 (22.1%) were obese, and 32 (15.7%) were morbidly obese. BMI was not associated with change in overall survival (p = 0.66). Morbidly obese (BMI ≥ 35) patients had a 61% lower rate of transplantation (rate ratio 0.39, p < 0.01) compared to patients in the BMI 20–30 categories, as well as a trend towards higher rates of driveline infection (rate ratio 1.4, p = 0.11) and lower rates of GI bleeding (rate ratio 0.75, p = 0.18) compared to normal and overweight patients. The survival of patients across BMI categories after LVAD implantation was not statistically different in this single center cohort. Patients in the morbidly obese category had lower rates of cardiac transplantation and a trend toward higher rates of driveline infections. The etiology of the difference in lower rates of transplantation is unknown; however, could be due to high BMI preventing patients from being listed for transplantation.
Chronic Effects of Air Exposure and Suction on Blood Cell Activation and Renal Injury in an Extracorporeal Circuit


Study: Cardiopulmonary bypass (CPB) causes a systemic inflammatory response syndrome (CPB-SIRS), potentially resulting in multiple organ failure (MOF). We developed a porcine model to isolate and quantify the effects of blood exposure to air and negative pressure to characterize the inflammatory response and subsequent organ dysfunction.

Methods: 4 pigs (49 ± 4 kg) were anesthetized and instrumented for hemodynamic monitoring. The animals received 500 U/kg heparin, and the jugular vein was cannulated using an 18 Fr double-lumen cannula connected to an extracorporeal circuit, establishing a veno-venous shunt (10% of cardiac output: 275 ± 25 ml/min) for 2 hours. The control group (n=2) circuit consisted of a simple venous tubing loop and a roller pump. The “air exposure” group (n=2) circuit included infusion of air at 100 ml/min and a venous reservoir, where a negative pressure of -100 mmHg was applied. Animals were recovered at the completion of 2 hours of simulated CPB. Blood samples were collected at baseline and at 2, 6, 24, 48 and 72 hours. Complete blood count with differential, CD 11b expression assessed by flow cytometry and creatinine were performed. Data are expressed as a percentage of baseline (mean ± SEM) or absolute values (mean ± SEM).

Results: The “air exposure” group showed a greater increase in white blood cell count compared to control (157 ± 53% vs 125 ± 34% at 6 hrs, 160 ± 28% vs 126 ± 12% at 24 hrs, 209 ± 31% vs 139 ± 10% at 48 hrs, 147 ± 7% vs 129 ± 30% at 72 hrs). The expression of CD 11b by granulocytes and monocytes increased only in the “air exposure” group (figure 1). Only the “air exposure” group showed a transient increase in creatinine (1.6 ± 0 g/dL vs 1 ± 0.1 g/dL at 6 hrs) (figure 2). Blood exposure to air and negative pressure activates the inflammatory cascade and may cause renal dysfunction. This animal model can be used to develop strategies to minimize the morbidity during CPB.

Development of an LVAD Inlet Cannula Tip With Integrated Volume Sensor

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Study: The lack of direct measurement of left ventricular size is a significant impediment to the development of an automatic pump control system for continuous flow LVADs. We have developed an inlet cannula tip for LVADs with integrated electrodes for volume sensing based on conductance.

Methods: Four platinum ring electrodes were installed into grooves on a cannula body constructed from polyetheretherketone (PEEK). A sinusoidal current excitation waveform (0.1 to 2mA rms; 1 to 50 kHz) was applied across one pair of electrodes, and the conductance-dependent voltage was sensed across the second pair of electrodes. The conductance cannula tip was tested in vitro using a polyurethane mock ventricle and in vivo during acute sheep studies (n=2).

Results: Static in vitro conductance measurements showed a sigmoidal relationship with volume over a 140 ml test range. In vivo conductance measurements were made during pump support with the HeartMate II rotary blood pump. Sonomicrometry crystals were used as a control to measure ventricular dimensions. In the figure below are conductance and dimension recordings during support at 9500 rpm. The conductance measurements correlated linearly with the sonomicrometry measurements over the full range of pump operation from no support to suction. This cannula tip will enable the development of automatic control systems to adjust pump support based on real-time assessment of ventricle size.

Figure 1: The expression of CD11b following blood exposure to air and suction. Data is expressed as a percentage of baseline value.

Figure 2: Plasma creatinine values following blood exposure to air and suction.
Rotary Blood Pump Control Based on Left Ventricle Stroke Work


Study: Although continuous flow circulatory support devices are being used more frequently as therapy for end-stage heart failure, fixed pump speed operation limits preload response, which may be the cause of limited exercise capacity of LVAD patients. A feedback control system was developed to automatically adjust pump speed based on ventricular stroke work (SW).

Methods: The control system was tested in acute sheep studies (n=3) using the HeartMate II rotary blood pump and a custom inlet cannula tip with integrated conductance electrodes to measure LV volume. SW was measured from the integral of the conductance signal and LV pressure measured using a high fidelity pressure sensor in the LV cavity. The feedback control system adjusts pump speed based on the difference between the measured SW and the SW setpoint. The preload response of the control system was evaluated by partially occluding and releasing the caudal vena cava using a vessel loop snare.

Results: The control system increased pump support automatically following step inputs in preload, and reduced pump speed with decreases in preload. Increasing or decreasing the SW setpoint caused the pump speed to be decreased or increased, respectively. The gain of the control system was adjusted to minimize response time and prevent instability. The figure shows an example of the pressure versus conductance curves immediately before and after a preload step, and at steady state. The control system increased pump speed from 8400 rpm to 10800 rpm and pump flow from 3.5 lpm to 4.7 lpm. This study demonstrated the in vivo preload response of an automatic control system based on SW calculated from direct measurement of LV pressure and volume.

Allosensitization after Total Artificial Heart Does Not Affect Short-term Survival

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Study: Total artificial heart (TAH) is being increasingly used in patients with end-stage heart failure as a bridge to transplant. Use of mechanical circulatory support is known to increase allosensitization in transplant patients; however, degree of allosensitization and its effect on post-transplant outcomes is unknown in patients supported with TAH.

Methods: Retrospective review of the United Network of Organ Sharing database for all patients listed for heart transplant and receiving TAH support from 2011–2012 was completed. Sensitization was defined as panel reactive antibodies (PRA) >10%. Short-term post-transplant outcomes were analyzed.

Results: 105 patients [median age: 51y (14-68y)] on the waitlist were supported with TAH. 64 (61%) were transplanted, 33 (31%) died on the waitlist, and 8 (8%) were removed from the waitlist due to clinical deterioration. Sensitization data were available for 52/64 transplanted patients [median PRA 15(0–100)%], of which 28 (54%) were sensitized and 14 (27%) had >50% PRA. Median wait-list time was similar between the sensitized group [162(14–866) days] and the non-sensitized group [112(6–306) days;p=NS]. 36% (10) of the sensitized patients and 12% (3) of the non-sensitized patients had a positive crossmatch (p=0.054). One year post-transplant survival was similar between the sensitized and non-sensitized patients (83% VS. 69% respectively; p=0.177). The degree of sensitization did not effect survival (Figure) 3 patients with a 100% PRA were alive at 1 year followup.

Conclusion: A considerable proportion of patients supported with TAH are sensitized, however, it did not prolong waitlist time. Also, in patients with TAHs, neither sensitization nor the degree of sensitization affected short-term post-transplant survival.
Utilization of Cardiac Tomography Angiography to Assess Predictability of Device Thrombus in Patients with a Left Ventricular Assist Device (LVAD)

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Study: Utilization of cardiac computed tomography angiography (CTA) has been previously described for the use of the diagnosis of LVAD thrombosis. What is not known is if routine utilization of cardiac CTA imaging can predict thrombus in patients with an LVAD that is mal-positioned. We conducted a retrospective cohort study in patients receiving the HeartMate II that additionally underwent cardiac CT post implant.

Methods: Cardiac CTAs were performed on our sample population in “retrospective gating” mode. This retrospective gating provides images of multiple cardiac phases in a cine loop, similar to that of an echocardiogram. This protocol enables the ability to assess wall motion and positions of the LVAD inflow and outflow cannula thus determining mal-positioning. We grouped our sample (N=17) into four groups; those with thrombus and mal-positioned LVADs, those with thrombus and normal positioned LVADs, those without thrombus and mal-positioned LVADs, and those without thrombus and normal positioned LVADs.

Results: Of the 17 patients reviewed, 13 were male and 4 were female. The median age at LVAD implant was 57 years, with the 25th and the 75th percentiles respectively of 42 and 65 years. No statistically significant differences were found in patient characteristics with and without thrombus and cannula position groups. Moreover, no statistically significant association was found between thrombosis in the inflow or outflow cannula of the LVAD.

State of the Art: Virtual Implantation Technique of Mechanical Circulatory Support Devices to Ensure Spatial Compatibility in Small-Size Patients

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Study: The use of mechanical circulatory support (MCS) devices is increasing in children and young adults awaiting heart transplantation. Due to the lack pediatric specific devices on the market and non-specific fitting guidelines, determining eligibility in small patients is challenging. A state of the art method for performing a patient specific virtual fit study of an MCS device is investigated.

Methods: This case study describes a patient in need of an MCS device who did not meet the standard fit criteria for a Syncardia TAH. A previously obtained computed tomography (CT) scan of the patient was used to perform the virtual fit. The Mimics Innovation Suite (Materialise, Leuven, Belgium) was used to segment and create 3D models of important anatomical structures. In addition, each of the Syncardia TAH device pumps were scanned using a 360-slice CT scanner. Virtual implantation of the TAH device was performed and 3D proximity measurements were obtained between the TAH and anatomical structures. The measurements confirmed fit within the chest and no evidence of compression of significant structures.

Results: The patient underwent successful implantation of the Syncardia device despite not meeting the standard criteria. The patient had no compression related postoperative complications. A postoperative CT demonstrated an accurate prediction of the virtually implanted device. After recovering, the patient was transitioned to the portable Freedom Driver and successfully transplanted after 14 months of support. Virtual placement of MCS devices can assess device compatibility and provide quantitative measures of fit. This allows the detection of spatial complications prior to insertion which is imperative given the irreversible nature of the implantation.

Virtual placement of MCS devices in pediatric and small adult patients, similar rigorous virtual compatibility testing will ultimately improve eligibility criteria.
Model for End-Stage Liver Disease Score Predicts Right Ventricular Failure in Left Ventricular Assist Device Patients

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Study: Predicting right heart failure after LVAD implant remains difficult and biventricular support has been associated with increased morbidity and mortality. The Model for End Stage Liver Disease (MELD) Score has been used to identify perioperative bleeding and early mortality in LVAD patients; we evaluated the utility of the MELD score in predicting right ventricular (RV) failure in patients undergoing a LVAD.

Methods: We reviewed a total of 256 patients who received a continuous flow LVAD between March 2005 and September 2013. We excluded device exchanges and patients with a RVAD prior to LVAD implant. Patients were divided retrospectively into three groups: no RV failure (n=174), RV failure (n=67) defined as the use of inotropic agents for >14 days postoperatively and patients requiring a RVAD (n=15) after LVAD implant. Preoperative MELD scores, hemodynamics and survival were evaluated by one-way ANOVA, chi-squared test and logistic regression analysis.

Results: The MELD score (no RV failure 10.3 ± 4.9 vs. RV failure 12.4 ± 5.3 vs. RVAD 14.0 ± 7.1; p<0.001) was strongly associated with RV failure. In logistic regression analysis, MELD score increased the odds of developing RV failure (odds ratio, 1.6 per 5-unit change in MELD score; 95% confidence interval, 1.2–2.1; p 0.001). A similar association was seen between MELD score and RVAD placement (odds ratio, 1.8 per 5-unit change; 95% confidence interval, 1.1–2.9; p.0.02). The other major predictor of RV failure we identified was CVP (no RV failure 11 ± 6 vs. RV failure 12 ± 5 vs. RVAD 16 ± 7; p.003). Survival at 180 days was significantly worse for patients with RV failure or a RVAD (no RV failure 92% vs. RV failure 82% vs. RVAD 36%; p<0.001). The MELD score provides a simple noninvasive tool to predict right ventricular failure which may lead to improved patient selection and help identify patients who will likely need a RVAD.

A Totally Implantable Controller for Use With Rotary LVADs


Study: PennState/3M and Minnetronix developed an implantable motor controller and transcutaneous energy transmission system (TETS) for the total artificial heart (TAH) to eliminate the percutaneous cable. The system was successfully implanted in 66 chronic animal studies. The TAH controller (Fig 1) was designed with hermetic connectors from the military market and was hand assembled. This paper describes updates to the TETS and implantable controller to improve the construction and implantation of the system, for use with the Penn State Tesla left ventricular assist device (LVAD) or any rotary LVAD.

Methods: The implanted controller has improved features. Technology from active implantable devices has been applied to improve the construction of the controller. The TETS coils were resized using simulation and experiments to support easier implantation and a 20W continuous pump instead of an 80W pulsatile pump. A Medical Implant Communication Service (MICS) radio has been incorporated to support telemetry at higher data rates.

Results: The updated implanted controller (Fig 2,3) is a first iteration demonstration design which includes a header with embedded connectors, isolation seals, and a frame. The electronics support motor control for the LVAD, MICS telemetry, TETS power, and battery charging and management for the implanted Li-Ion battery. The battery run time is 3 hours, compared to 1 hour in the TAH system. Further optimization of the electronics package is planned. The MICS radio includes an antenna in the header (Fig 3). The controller supports measured data rates of 4.3 kbps in tandem with continuous motor control and TETS power transfer. The controller is easier to manufacture and to implant. In addition, the subcutaneous TETS coil (Fig 4) was reduced from 29 cm3 to 10 cm3 to improve implant in the infracavicular region.
Continuous Flow Left Ventricular Assist Device Does Not Cause More Aortic Valve Leaflet Fusion Than Pulsatile Left Ventricular Assist Device
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Study: Increased aortic insufficiency (AI) was reported in patients supported with continuous flow left ventricular assist device (C-LVAD) compared with those supported with pulsatile LVAD (P-LVAD). Aortic leaflet fusion was speculated to be one of the main causes. It was unclear if C-LVAD caused more aortic leaflet fusion than P-LVAD. We studied the aortic valves of explanted hearts supported with C-LVAD and P-LVAD and compared them with those from non-LVAD autopsied hearts.

Methods: We performed gross examination of the aortic valves from explanted hearts supported with C-LVAD and P-LVAD. The aortic valves from non-LVAD autopsied hearts were examined as control. A total of 143 aortic valves were studied, 28 from C-LVAD, 16 from P-LVAD and 99 from non-LVAD group separately. Findings of aortic leaflet fusion were documented in each group.

Results: There were no differences in patients’ mean age and length of LVAD support between C-LVAD and P-LVAD group (age 52 ± 12.8 vs 59 ± 9.8 years and 308 ± 261 vs 280 ± 176 days respectively, p> 0.05, t-test for both comparisons). In the C-LVAD group aortic leaflet fusion was present in 6 out of 28 valves (21%) vs 6 out of 16 valves (38%) in the P-LVAD group. There was no difference of leaflet fusion incidence between the two groups (p>0.05, Chi-square). In non-LVAD group the mean age of patients was 46 ± 22.8 years which was significantly younger than that of either C-LVAD or P-LVAD group (p<0.03, t-test) and the aortic leaflet fusion was found in 15 out of 99 non-LVAD hearts (15%), which was not significantly different from other two groups (p>0.05).

Conclusions: There was no difference of the incidence of aortic leaflet fusion among the patients supported with C-LVAD and P-LVAD and the patients without LVAD. Aortic leaflet fusion is not the main cause of aortic insufficiency in patients supported with C-LVAD. The incidence of aortic leaflet fusion appears to increase with age.

Percutaneous Driveline Fracture Following Implantation of the HeartMate II Left Ventricular Assist Device: How Durable is Driveline Repair?
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Study: Durability of the percutaneous driveline is critical for the optimal long-term support of patients after left ventricular assist device (LVAD) implantation. Because there are no data specifically examining the durability of major repair for driveline fracture or its effect on patient outcomes, we review our experience.

Methods: Between May 2004 and January 2014, 518 patients underwent implantation with the HeartMate II LVAD at our respective institutions. Median age at LVAD implantation was 60 years (range, 18–79 years) and 424 patients (82%) were male. The indication for LVAD implantation was bridge to transplant (BTT) in 221 patients (43%). We retrospectively reviewed our prospectively collected institutional databases for patients who underwent percutaneous driveline repair for driveline fracture. We analyzed durability of repair and its effect on patient outcomes.

Results: Follow-up was available in all patients for a total of 808 patient-years of support (median 1.1 years). Percutaneous driveline fracture was identified in 17 patients (3.2%), 8 of whom were implanted as destination therapy. Median time from LVAD implantation to driveline fracture was 1.3 years (range, 4 months to 3.8 years). While 2 of these patients underwent device exchange as primary treatment, 15/17 (88%) underwent repair. Three of these 15 patients required a driveline re-intervention, including device exchange (n=1), re-repair (n=1) and ungrounded cables (n=1). Median time of support after driveline repair was 10 months (range 3 months to 5.4 years). There were no late deaths after driveline repair during the follow-up period with 14/15 patients (93%) active on support and 1 having undergone transplant at last follow-up. These results indicate that driveline repair for driveline fracture is durable and there was no adverse effect on late outcome noted in this series.
Diagnostic Efficacy of Miniaturized TEE in Hemodynamic Management
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Study: A miniaturized TEE probe (ClariTEE(TM), Imacor Inc., Garden City, NY, USA) has now been widely used to guide post-op hemodynamic management (hTEE) of high-risk cardiac surgery and mechanical circulatory support (MCS) patients in the ICU. We assess the diagnostic efficacy of hTEE in post-op hemodynamic management.


Results: Studies reporting diagnostic impact (management change, therapeutic impact) by patient found a diagnostic impact of hTEE in 70%, similar to the 67% reported by Hüttemann. One study (Cioccari L et al., Crit Care 2013;17:R121) reported impact by exam, finding impact in 34% of exams; another study (Cavarocchi NC et al., J Thorac Cardiovasc Surg. 2013;146:1474–9.) described a hTEE-guided protocol for weaning ECMO, finding 100% predictive value albeit in only 21 patients. Although further study is needed, e.g., to determine the effects of hTEE-guided management in critical areas such as RV failure after LVAD implantation, the present meta-analysis shows that the diagnostic efficacy of hTEE in post-op hemodynamic management of high-risk cardiac surgery, mechanical circulatory support, and high-risk acute surgery patients is equivalent to that of conventional TEE in its milieu.
Is Continuous Flow Superior to Pulsatile Flow In Single Ventricle Mechanical Support? Results From a Large Animal Pilot Study.

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Study: Durable mechanical support in situations of physiologic single ventricle has been met with little success so far, particularly in small children. We created an animal model to investigate whether pulsatile or continuous flow would be superior.

Methods: Three 1-month-old sheep (10–16 kg) sheep were instrumented. Via sternotomy and with cardiopulmonary bypass, a large VSD and ASD were created (see the figure). The left ventricle was cannulated using a Berlin Heart inflow cannula. This was connected sequentially to a continuous flow device (Thoratec HeartMate X, Thoratec Corp, Pleasanton, CA; device not in clinical use) and to a pulsatile device (Berlin Heart Excor, Berlin Heart GmbH, The Woodland, TX; 50cc pump chamber, 35% systole). Outflow was via a Y-graft to both aorta and pulmonary artery, striving for equal flow to both. Atrial filling pressures were controlled with volume infusions over a wide range.

Results: Under comparable loading conditions, significantly higher maximum flow was obtained by HeartMate X than by Excor (4.95 ± 1.27 L/min (range, 3.84 to 6.34 L/min) for HeartMate X vs. 1.80 ± 0.85 L/min (range, 1.01 to 2.7 L/min) for Excor, P<0.05). Judging from this limited animal study, in single ventricle scenarios, continuous flow devices may achieve higher pump flows than pulsatile devices when provided with similar filling pressures. More extensive studies are needed. Their clinical use should be investigated.

Computations and Experiments in the Design of Axial Flow Blood Pumps for Patients with Complex Congenital Cardiac Malformations

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Study: Limited treatment options for patients having dysfunctional single ventricle physiology motivate the need for alternative therapies. To address this need, we are developing a collapsible axial flow blood pump. This study investigated the impact of geometric simplicity to facilitate percutaneous placement and maintain optimal performance.

Methods: Three new pump designs were designed and numerically evaluated using ANSYS CFX software for steady and transient flow conditions. In addition, prototypes of the new pump geometries were constructed and tested in an existing flow loop to assess performance.

Results: The Rec design configuration generated the highest pressure rise range of 2–38 mmHg for flow rates of 1–4 L/min at 4000–7000 RPM. This new design outperformed the other two configurations by more than 26%. A transient simulation explored the impact of respiration on blood flow conditions through the Rec pump and revealed a range of pressure generation from 4.5 to 8.5 mmHg over the entire respiratory cycle. Prototype testing of the Rec design confirmed numerical predictions to within an average of approximately 22%. The blood damage indices for the new pump designs were determined to be below 0.5% and predicted low hemolysis levels.
Three-Dimensional Laser Flow Measurements of a Patient-Specific Fontan Physiology with Mechanical Circulatory Assistance

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Study: Mechanical assistance of the Fontan circulation is hypothesized to enhance ventricular preload and improve cardiac output; however, little is known about the fluid dynamics under these conditions. This study is the first to investigate the three-dimensional flow conditions of a blood pump in a patient-specific, anatomic Fontan model.

Methods: Laser flow measurements were conducted on the model having an axial flow impeller in the inferior vena cava (IVC) and for a control case without a pump. Fluid streamlines and velocity profiles were measured. Experiments were performed for a physiologic cardiac output, pulmonary arterial flow splits, and pump speeds of 1000–4000 RPM.

Results: The impeller had a modest effect on the flow conditions entering the TCPC at low pump speeds, but a substantial impact on the rotational velocity at higher speeds. The higher rotational speeds of the pump disrupted the recirculation region in the center of the anastomosis, which could be advantageous for wash-out purposes. A small amount of the rotational force was propagated from the IVC into the TCPC junction. No retrograde velocities in the SVC were measured. These findings further indicate that mechanical cavopulmonary assistance is a viable therapeutic option for patients having dysfunctional single ventricle physiology.

Biventricular Continuous Flow Support in an Adolescent Female

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Study: We report a case of bridging an adolescent to transplantation with biventricular continuous flow devices following failure of the right ventricle (RV).

Methods: A 14 year old female (weight: 36 Kg, BSA: 1.2 m2) with dilated cardiomyopathy (ejection fraction of 15%) in InterMACs profile-1. HeartWare® HVAD was implanted for left ventricle support after 3 days of medical optimization. The patient separated from cardiopulmonary bypass (CPB) on epinephrine, milrinone and nitric oxide for support of the RV. Intraoperative echocardiogram showed low normal RV function with severe tricuspid regurgitation. Within hours following LVAD implantation, device flow decreased to less than 2 L/min with low amplitude and low cardiac output despite increasing inotropic support and fluid administration. Echocardiogram now demonstrated severe tricuspid regurgitation and RV dilation and dysfunction. The patient was urgently returned to the operating room for placement of Centrimag® device without CPB for RV support. This configuration involved right atrial inflow and pulmonary artery outflow cannula tunneled through the upper abdomen. She was extubated 2 days later. At 16 days of support, she was on inotropic medications, ambulating, receiving full enteral nutrition, and was discharged. Discharged on post-op day 9.

Results: We showed that, in an adolescent, biventricular support using continuous flow devices provides excellent rehabilitation. Furthermore, due to the shorter wait list time in this age group BiVAD when needed can be maintained as a bridge to transplantation.

Lung Development in Premature Lambs During Treatment with an Artificial Placenta

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Study: The treatment of prematurity remains an unsolved problem, and is associated with significant mortality and respiratory morbidity. We hypothesized that an artificial placenta (AP) based on venovenous extracorporeal life support (VV-ECLS) without mechanical ventilation (MV) would protect the lungs of premature lambs from barotrauma, and allow for ongoing lung development compared to MV controls.

Methods: Extremely premature lambs of ~110 days gestation (term=145) were delivered by Caesarean section. AP lambs were cannulated for VV-ECLS (jugular drainage, umbilical vein infusion). An endotracheal tube was placed, filled with amniotic fluid, and capped. MV lambs were intubated, ventilated, given exogenous surfactant, and transitioned to high-frequency oscillatory ventilation (HFOV) when gas exchange deteriorated. All lambs received fluids, parenteral nutrition, prophylactic antibiotics, and methylprednisolone. Immunostaining for α-smooth muscle actin and platelet-derived growth factor receptor alpha (PDGFR-α) was performed on 5-micron sections of lung tissue.

Results: See figure: PDGFR-α (green) and α-actin (red) immunofluorescence images for 110 day MV lungs ventilated (MV) for 5.5 hours (A, 200X; B, 400X) and 110 day AP lungs (AP) perfused for 7 days (C, 200X; D, 400X). In A and B, MV lungs show alveolar walls thickened in part by α-actin-positive interstitial myofibroblasts, large airspaces indicative of hypoalveolarization and a loss of PDGFR-α-positive alveolar myofibroblasts which are normally present and required for alveolar development. In C and D, AP lungs show normal alveolar walls and airspaces, as well as ample PDGFR-α + α-actin double-positive cells required for alveolar growth (arrows). These data demonstrate dramatic differences between the AP lungs which are protected and developing normally, and the MV lungs which are severely damaged and underdeveloped. We will further describe the AP’s effects on lung development compared to MV in future studies.
Transvenous Laser Assisted Extraction of Pacing Leads in Pediatric and Complex Congenital Heart Disease

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Study: Transvenous pacemakers and defibrillators are increasing in use in pediatric and congenital heart disease patients. With the finite duration of all leads, transvenous lead extraction with locking stylets and laser energy is a useful technique in pediatric patients. Methods: We report a single center retrospective review of patients from January 2003 to January 2013, that had pacemaker or defibrillator lead extraction at our Children’s Hospital. Results: Seven patients with a variety of diagnoses (Table 1) were treated during this time period. Of these patients, five were female and four had structural heart disease. The median age of the patients was 12 years. All patients have had successful transvenous extraction without any need for open conversion. Four patients required laser assisted extraction and one only required the locking stylet. Early in our experience two patients have also had simple extraction with manual traction. The Excimer laser has given us the ability for lead extraction with complex venous anatomy like in Senning patients and also allowed us to extract leads that have perforated the interventricular septum into the LV in one of our patients.

Surgical Reconstruction of the Head & Neck Vessels Following ECMO Decannulation in Infants

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Study: Due to their large size and easy accessibility, the common carotid artery (CCA) and internal jugular vein (IJV) are commonly used for extracorporeal membrane oxygenation (ECMO) cannulation in infants. Instrumentation of these vessels often results in total or subtotal occlusion following decannulation. We hypothesized that surgical reconstruction of the CCA and IJV would result in restoration of vessel patency.

Methods: Retrospective review of 59 infants <1 year of age who underwent ECMO cannulation between 1/2007 and 11/2013. At the time of decannulation, surgical reconstruction of the CCA and IJV was attempted when appropriate. Vessel patency was then assessed by ultrasound, computed tomography, or catheter angiography.

Results: 59 patients were placed on ECMO during this period. (weight 1.6–9.8 kg) Indications for ECMO included hemodynamic compromise after cardiac surgery (33 pts), respiratory distress (16 pts), and cardiogenic shock secondary to myocarditis or cardiomyopathy (10 pts). 39/59 (66%) patients were cannulated via the CCA and IJV. 35 pts were on VA ECMO, and 4 pts on VV ECMO. Of these, 22/39 (56%) were successfully separated from ECMO. Arterial and/or venous vessel reconstruction by direct closure or patch augmentation was attempted in 20/22 (91%) patients. Follow up data was obtained in 18 pts. Patency was restored in 13/17 (76.4%) reconstructed CCAs, and 9/18 (50.0%) reconstructed IJVs. Neurologic injury occurred in 4 patients, 2 with occluded CCAs and 2 with patent CCAs. One patient with an occluded IV developed apparent head edema, which gradually improved without further intervention. Patency of the carotid artery and internal jugular veins can be restored following ECMO decannulation in infants. Although the risks associated with vessel occlusion on cerebral blood flow and venous drainage are not clear, reconstruction of these vessels should be considered to promote normalization of cerebral circulation and preserve vessel patency for future procedures.
Pre-clinical Evaluation of the PediaFlow® Pediatric VAD and Inflow Cannula


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Study: The PediaFlow® Pediatric VAD is an implantable, magnetically-levitated, turbodynamic, mixed-flow, rotary blood pump designed to support pediatric patients between 3–20 kg for up to six months at 0.3–1.5 L/min. A suction-resistant pediatric inflow cannula has been designed and validated in vitro. Two chronic juvenile ovine studies were performed to assess pump and cannula hemodynamic performance and cellular biocompatibility.

Methods: Two PediaFlow® prototype pumps were implanted off-pump for an intended 30 and 60 day study using the newly developed parabolic-tip inflow cannula and a 6 mm Gelweave™-based outflow graft assembly via left thoracotomy. After anastomosis of the outflow graft to the aorta, the detachable sewing ring was attached to the ventricular apex before insertion of the cannula body through a cruciate incision. After backfilling and pump connection, support was initiated with a target flow of 1.5 L/min.

Results: Both implants were successful with sustained flows between 1.4–2.0 L/min and no observed suction events, hemolysis, or platelet activation throughout the implants. Both animals at necropsy were unremarkable with the pump well-encapsulated, flow paths free of deposition, and no evidence of myocardial bruising or renal infarcts. These implants document the potential of the PediaFlow® Pediatric VAD for chronic cardiac support of infants and newborns with congenital and/or acquired heart disease.

A Porcine Survival Model for the Novel Impella Pediatric Prototype


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Study: Due to a growing need for pediatric circulatory assist devices, Abiomed® has developed a pediatric modification of the Impella percutaneous left ventricular assist device on the current 2.5 L/min platform. The purpose of this porcine study was to show safety and feasibility of this smaller device in a 24 hour survival model.

Methods: Because of requirements to allow free range of motion for the study animal, a spring loaded swivel arm and basket was designed to house the purge cassette, IV pump, and fluids which were tethered to the animal. The console was rewired to allow it to be placed on the outside of the cage. The device was implanted into 1 pig via a tube graft sewn to the carotid artery. The pig was placed in a harness attached to the basket, and the IV tubing and device catheter were secured to the basket and fluid pumps. The animal was awoken from anesthesia and allowed free mobility within the cage during the entire 24 hours of support. Prior to removal, device position within the left ventricle was verified both fluoroscopically and echocardiographically. The device was explanted, and the carotid artery repaired. Euthanasia was performed 24 hours later to evaluate for device complications.

Results: The device position in the left ventricle was maintained despite allowing the pig freedom of movement. At necropsy, there were no significant abnormalities noted in either the carotid artery or left ventricle. The aortic valve was intact. Fibrin deposits were noted on the aortic valve and in the left ventricle, presumably at points of contact with the device. There were no thromboembolic complications. We successfully maintained the Impella pediatric device in an awake and freely moving porcine model for 24 hours without significant complication or device malfunction. This spring loaded swivel arm and basket design may serve as a model for chronic Impella device studies. Further studies are needed prior to providing official insertion and support recommendations.
Development of a Neonatal Index for Complications of ECMO (nICE)
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Study: There are no current risk indices available for stratification and comparison within the ECMO community. Such indices would enable benchmarking and more accurate analyses of techniques and equipment within the ECMO community. We have been developing a Pittsburgh pre-ECMO risk (PIPER) and the Pittsburgh ECMO Risk of Complication (PERC) for the neonatal respiratory ECMO population.

Methods: This study utilized data from the ELSO registry for neonatal respiratory VA ECMO patients from 2000–2010. The Pittsburgh ECMO Risk of Complication (PERC) score was developed using logistical regression techniques targeting survival to discharge on a training set, and then tested on a validation data set. The PIPER and PERC scores were then combined in a single model for hospital survival, the neonatal Index for Complications of ECMO (nICE).

Results: One important finding was a cut point in ECMO hours at 265 hours (~11 days), that had a more negative impact on survival. The PERC score was able to correctly predict the outcome in 73% of the patients in the validation set. The receiver operator curve for this data showed an area under the curve of 0.787 (95% CI 0.773–0.801). Further analysis of the subsets of PERC categories with the PIPER scores revealed that certain types of complications were more likely to occur with increasing PIPER scores. These included hours on ECMO, bleeding, clotting, and renal complications. A combined PIPER and PERC score resulted in a neonatal Index for Complex ECMO (nICE) that was able to predict 74% of the outcomes, with an ROC area under the curve of 0.82 (95% CI 0.801–0.839). Future work will include additional parameters for older pediatric patients.

Figure 1: Exponential increase in mortality (LEFT) and ROC curve (RIGHT) demonstrate reasonable sensitivity and specificity for the model.

Optimal Insertion of HVAD in Children

Study: Although the HVAD (HeartWare Inc) can be placed in the pericardial space as recommended by the manufacturer (Fig A), if the rotor housing conforms to the chest wall laterally the inlet cannula will become malpositioned and directed toward the septum. This is particularly concerning in children whose LV cavity is small. Ideally, the inflow should be aligned with the LV long axis (Fig B). We report a technique that ensures optimal position of the inflow cannula.

Methods: Prior to administration of heparin a left preperitoneal pocket is created by dividing the diaphragm anteriorly. With cardiopulmonary bypass support, the HVAD inflow is inserted into the LV apex through the sewing cuff. The LV apex is then reoriented caudally and medially by securing the pump below the diaphragm. With this maneuver, the axis of the inflow cannula becomes parallel with the interventricular septum. Upon completion of outflow graft anastomosis, HVAD support is initiated as bypass is weaned.

Results: Five children underwent HVAD placement with this technique. Median age and BSA (range) were 9 (6 - 14) years old and 0.9 (0.8 and 1.4) m², respectively. Preoperative LV end-diastolic dimensions were 57 (53 - 61) mm. All patients had an uneventful early postoperative recovery. Median time to extubation was 1 (0 - 3) days. Median pump speed at ICU admission was 2100 (2000 - 2400) RPMs. One was successfully transplanted after 4 months of support, whereas the other 4 are receiving ongoing support. One with LV noncompaction developed extremity weakness 3 weeks after implantation despite therapeutic anticoagulation and normal pump function. During 324 total days of support, none had spikes of pump power consumption associated with low pump flow or laboratory evidence of pump hemolysis. The technique described is reproducible and provides favorable inflow configuration even in small children with a BSA as low as 0.8 m².
Sixty-day in vivo Performance of Infant Jarvik 2000® Ventricular Assist Device in a Juvenile Sheep Model

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Study: The Infant Jarvik 2000® Ventricular Assist Device (VAD) is based on an intraventricular axial-flow pump designed for circulatory support to neonates and infants. In present study, the 60-day in-vivo performance of this device was investigated in the juvenile sheep model.

Methods: Twenty-one juvenile sheep (21.2 to 30.2kg) were divided into three cohorts to investigate configurations of the outflow graft and blade profile (tall blade with 6 mm Dacron graft, short blade with 8 mm PTFE graft, tall blade with 8 mm PTFE graft). The Infant VAD was placed surgically in the left ventricle through the apex of each animal. The outflow graft was anastomosed to the descending aorta. Anticoagulation was maintained with continuous heparin infusion (ACT 150–200). The device function and biocompatibility was evaluated for 60 days.

Results: All other animals recovered from surgery uneventfully. The average duration in three cohorts are 48.7±14.5 days (n=6), 43.9±16.7 days (n=7) and 46.9±19.3 days (n=8) respectively. Plasma free hemoglobin averaged at 10.62 ± 5.54 mg/dL, 15.43 ± 9.37 mg/dL and 9.42 ± 6.67 mg/dL respectively. Mild hemolysis was noticed in the animals in the cohort 2. The clotting was noticed in the 6 mm Dacron graft from the cohort 1. No apparently visible thrombus was found in the grafts or explanted devices during the necropsy after the 8 mm PTFE graft was used. The animals had normal organ chemistries except for surgery-related transient alterations in kidney function and liver function. No device failure and mechanical complication were noted during the study in the cohort 3. Complications include weight loss, leg injury, graft infection, IV line disconnection and pulmonary failure. Conclusion The Infant Jarvik 2000 VAD has acceptable performance with mid-term reliability and good biocompatibility. This in vivo study demonstrates the future feasibility of this device for clinical use.

Peritoneal Dialysis in Infants With Acute Kidney Injury Following Open Heart Surgery: A Single-institution Experience

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Study: Acute kidney injury following open heart surgery is associated with high mortality rate in infant patients requiring renal replacement therapy. The purpose of this study was to investigate the risk factors associated with mortality of the infant patients underwent peritoneal dialysis after open heart surgery based on a single-institution experience.

Methods: From July 2009 to May 2012, a total 116 infants underwent open heart surgery for congenital heart disease in Xijing hospital. 29 patients (2.5%) experienced acute kidney injury and required peritoneal dialysis as renal replacement therapy. A chart review of these patients was performed. Then the clinical and laboratory variables were compared between the survivors and non-survivors groups.

Results: No significant difference was noticed about preoperative characters between two groups. However, the non-survivors (n=15,51.7%) had a longer cardiopulmonary bypass time (141±45vs. 107±39minutes, p=0.0403), longer duration of mechanical ventilation (8.9±3.3vs.4.4±2.1days, p=0.0002), higher volume of blood transfusion (655±137vs.792±174mL, p=0.0269), and higher Postoperative Inotropic Score (7.13±2.33vs. 5.07±1.98, p=0.0163) than survivors (n=14, 48.3%). During peritoneal dialysis, the PH of the arterial blood gas analysis in non-survivors was lower than survivors (7.29±0.09 vs. 7.37±0.11for PD day 1, 7.30±0.06vs.7.38±0.06 for PD day 4, 7.27±0.05vs.7.33±0.04 for PD day 7, respectively,p<0.05). Furthermore, the non-survivors had a longer interval between the onset of acute kidney injury and the peritoneal dialysis initialed (4.7±2.3vs.3.0±1.7days, p=0.0415) than survivors.The longer cardiopulmonary bypass time, circulatory arrest, higher volume of blood transfusion, delayed peritoneal dialysis initiating, and continued and irreversible metabolic acidosis might be associated with the high mortality in infant patients with peritoneal dialysis after open heart surgery.
Development of Mechanical Circulatory Assist Device for Failed Fontan Circulation


Study: The purpose of the study is to develop a permanent right heart assist pump called the Fontan Circulation Assist Device (FCAD) for failing Fontan circulation patients by applying the basic principal of the Penn State developed Tesla Left Ventricular Assist Device (LVAD). Although the LVADs continue to expand in use for bridge-to-transplant and destination therapy for isolated left heart failure, these devices are not suitable for Fontan support because of the anatomy of the total cavopulmonary connection, as well as concerns with off-design point operation of LVADs.

Methods: Two prototype FCADs have been designed and built; one with the rotor from our Tesla LVAD having 11 discs and the other having 3 discs. The FCAD has two inlets to receive blood from the superior vena cava (SVC) and inferior vena cava (IVC). There are two outlets on a common volute supplying blood to the left and right pulmonary arteries. Both the 11 and 3 disc FCADs were modeled in computational fluid dynamics (CFD) with Autodesk® Simulation CFD to estimate H-Q (pressure head, H, and flow rate, Q, relationship) performance. They were tested on a mock circulatory loop. For optimal hemodynamic performance, the range of H was designed to be 12 - 15 mmHg at high and low cardiac outputs, respectively. The forward flow pressure drop was also measured with the 3-disc rotor FCAD to measure a patient sustainability if the motor stopped.

Results: There was good agreement between the experimental and computational H-Q curves (see Figure). We found the 3-disc rotor at 3500 RPM to be optimal for pulmonic pressure and flow while ensuring the bearing remains hydrodynamic. The forward pressure drop testing was also measured with the 3-disc rotor FCAD to measure a patient sustainability if the motor stopped.

Anticoagulation and Hematological Measurements In Surgical Shams and in Animals Implanted With the Penn State Pediatric VAD

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Study: As part of the continued development of the infant-sized Penn State Pediatric Ventricular Assist Device (PVAD), 2 surgical shams and 2 chronic PVAD implantation studies were performed.

Methods: Surgical sham procedures simulating PVAD implantation were performed in 2 lambs (20 and 23.5 kg). PVAD implantation was performed in 2 animals (27 and 23 kg). An improved ePTFE cannula system was used to cannulate the left ventricular apex and descending thoracic aorta. A minimal anticoagulation protocol was used in both groups using unfractionated heparin to attain TEG R-times of 2x normal. Platelet inhibitors were not used.

Results: The studies were terminated electively at 54 and 56 days for the shams, and 27 and 50 days for the PVAD studies. Pre-op and post-op aPTT values (Fig 1.) demonstrate minimal anticoagulation; pre-op and post-op ACT were not significantly different in the PVAD animals. Antifactor Xa levels were 0.045 +/- 0.093 for the shams and 0.064 +/- 0.126 for the PVAD group, well below the normal therapeutic range of 0.3–0.7 for heparin anticoagulation in similar devices. Excluding the first 2 weeks after surgery, there was no significant difference between pre-operative and post-operative platelet aggregation by 10 uM ADP for the sham or pump animals. There was no clinical evidence of thromboembolism. At necropsy, PVAD1 had 3 small (< 5mm) chronic cortical infarcts in both kidneys (< 1% of kidney volume) and clean pump surfaces, while PVAD2 had normal kidneys and a 1 mm diameter white deposit on the sac surface. Interestingly, there were multiple grossly observed and histologically confirmed cortical infarcts in both kidneys in Sham1.

Conclusions: Minimal TEG-based anticoagulation is adequate for successful outcomes of the Penn State PVAD in lambs. Sham animals show similar responses to the heparin protocol. Additionally, renal infarcts do occur in non-device (sham) animals, which may affect the interpretation of infarct findings in device animals.
A Fluid Dynamic Study of the Effect of Hematocrit in the 12cc Penn State Pediatric Ventricular Assist Device

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Study: Viscoelasticity has been shown to influence the fluid mechanics through medical devices. As such, changes in hematocrit (HCT), which alter the viscoelasticity of blood, can have a profound effect on flow within ventricular assist devices. Many in vitro studies have used Newtonian fluid approximations, when in reality, pediatric (especially neonatal) blood HCT can vary from 20–60%. Specific flow characteristics like high shear rates are correlated to diminished instances of thrombosis so it is extremely important to understand the fluid dynamic influence of hematocrit for pediatric devices. As part of the ongoing development of the Penn State 12cc pediatric ventricular assist device (PVAD), this study focused on how changes in fluid analog HCT alter the fluid mechanics within the device.

Methods: An acrylic model of the PVAD was placed in a mock circulatory loop with an average flow rate of 1.5 L/min and an arterial pressure of 90/60 mmHg. Two-dimensional planar particle image velocimetry was used to develop whole field velocity and wall shear rate profiles. Pediatric blood analogs with HCTs of 20%, 40%, and 60% were used in the flow loop.

Results: While the general flow pattern within the PVAD was similar, the varying blood analogs created distinct inlet/outlet jets and rotational flow patterns. Based on these findings, variations in blood HCT between pediatric patients can lead to altered flow fields within the PVAD.

Mid-term Results of a Novel Valved Polytetrafluoroethylene Conduit for the Right Ventricular Outflow Tract

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Study: Development of a competent, valved polytetrafluoroethylene (PTFE) conduit for the right ventricular outflow tract (RVOT) with the hope to reduce reoperations. After careful in vitro in-silico testing and mock loop studies, our conduit had been modified (1st - 3rd generation) to obtain optimal valve mechanics. In this study we report the midterm results of this novel designed valved-PTFE conduit and assess the efficacy of modification and comparisons to the homograft conduit.

Methods: Since 2008, we have implanted valved-PTFE RVOT conduits in 81 patients, aged 6.7±6.5 yrs (5d-21y). 1st-generation (bicuspid valved-PTFE conduit) was implanted in 34 patients (Group-1), 2nd-generation (11% smaller leaflets than the 1st-g) was used in 36 (Group-2), 3rd-generation (tricuspid valved-PTFE conduit) was implanted in 11 (Group-3).

Follow-up periods were 4.1±2.0, 1.7±0.9 and 0.6±0.4 yrs, respectively. For comparison, 67 patients (12.6±7.5 yrs, follow up 4.5±1.5 yrs) who underwent RVOT reconstruction using homograft were also evaluated. Incidence of re-intervention, and conduit function using echocardiography were reviewed. Conduit failure was defined as the presence of more than moderate regurgitation, or stenosis > 0.5mmHg peak pressure gradient.

Results: Seven patients in Group-1 required re-intervention; stent(1), Melody valve(2) and replacement(4). Four patients in Group-2 required re-intervention; stent(1) and replacement(3). No re-interventions or conduit failure was seen in Group-3. Freedom from conduit dysfunction was 69% in Group-1, 83% in Group-2 and 100% in Group-3. At 3 yrs follow-up, freedom from re-intervention among patients > 2 yrs old were 100% in Group-3 and 93% in the homograft group. Among patients < 2 yrs old, it was 86% in PTFE, 46% in homograft at two yrs and 49% and 23% at five yrs, respectively (p=0.0077). The evolution of our valved-PTFE conduit has promising midterm results with improved leaflet mechanics and decreased conduit dysfunction.
Continuous Flow Support in Children Using the Heartware HVAD: Lessons Learned From a Single Center Experience

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Study: Continuous flow ventricular assist devices (CFVAD) are an established means of mechanical support in adults with medically refractory heart failure. CFVADs have not been utilized frequently in pediatric patients, leading to limited data about this population. Here in, we provide our initial experience with the Heartware HVAD adolescents.

Methods: We evaluated 6 adolescents aged ≤18 years old supported on HVAD. HVAD implantation began after FDA approval in Nov 2012 in which clinical outcome data including INTERMACS adverse events were collected prospectively to Jan 2014. Outcomes were compared to a group of young adults (AG) with dilated cardiomyopathy during the same time period.

Results: The adolescents mean age: 12.9 years [range 10.8–15.7] and BSA: 1.45m² [range: 1.19–1.82]. Diagnosis included dilated cardiomyopathy [n=5] and autoimmune myocarditis [n=1]. Two patients were INTERMACS profile (IP)-1 and 4 were IP-2. Total patient days of support for all adolescents are currently at 880 days with 2 still on device. Range of HVAD support is 14–406 days at present. Adverse events occurred at a rate of 1.36 per 100 days support compared to 1.31 in the AG (p=0.7). Adolescents had no neurological events or deaths while on HVAD versus one each in the AG. Four adolescents were discharged home on device in NYHA class I and four have undergone successful transplantation. In comparison to the AG there was no statistical differences in patient days of support [AG:830days], operative mortality and 6 month survival post implant.

Conclusions: CFVAD such as HVAD provides excellent mechanical circulatory support in adolescents with outcomes that appear similar to adults. It allows the adolescent to be discharged home, participate in rehabilitation and normal adolescent activities. Challenges of device morbidity for active adolescents will require continued study.
Oxygenator With Integrated Pulsatile Pump And Heat Exchanger: In Vitro and In Vivo Results

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Study: To reduce priming volume and surface area of ECMO circuits, a heat exchanger and a pulsatile pump are integrated into an oxygenator.

Methods: Flexible silicone tubes (Øi 2 mm, Øo 2.6 mm) within an oxygenator, collapse and expand due to tempered water pulsed through them. Combined with active valves at the oxygenator’s in- and outlet, these tubes allow a pulsatile blood flow, while heat is exchanged by the tempered water. The oxygenator’s priming volume is 27 ml, gas exchange area is 0.24 m² (PMP, OXYPLUS® fibers) and heat exchange area is 0.016 m². In-vitro tests regarding gas and heat exchange were performed following ISO 7199. Four in-vivo tests using VV-ECMO circuits in sheep were performed to proof feasibility of this novel device. Six further in-vivo tests using Carmeda® coated VA-ECMO circuits in pigs were performed to investigate the range of applications and the possibilities of low ACT levels.

Results: During in-vitro tests, O2 exchange was 33±0.7 ml/min, CO2 exchange was 25±0.7 ml/min, and heat exchange efficiency was 18±0.8 %, at 500 mlblood/min. In-vivo, 500 mlblood/min were achieved for all tests (VV & VA). The ACT level was <200 s in the VA-ECMO circuit, without thrombus related complications. The aimed test duration of 6 h was achieved without complications in all ten in-vivo tests. These studies demonstrate the feasibility of this novel concept to use flexible silicone tubes as a pulsatile pump and heat exchanger within an oxygenator. The compact design allows using ECMO circuits with low priming volume and surface area. The promising results indicate that a combination of oxygenator, pump and heat exchanger into one device could potentially expand the range of future applications.

Efficacy of a Parallelized Oxygenator Circuit in a Pumpless Artificial Placenta

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Study: Premature infants require mechanical ventilation after birth. This treatment frequently exposes them to critical respiratory insufficiencies. Development of an artificial placenta may provide a potential alternative therapy to mechanical ventilation. Previous studies suggest that minimizing placental circuit resistance is essential to the development of this technology. To achieve these requirements, we developed the parallelized oxygenator circuit system. The aim of this study was to compare the efficacy of a parallel circuit with a single oxygenator circuit using perterm lambs.

Methods: Pregnant sheep underwent surgical delivery at 109–135 d gestation. Fetuses were exteriorized and umbilical vessels were cannulated. In the parallelized circuit group (n=6), each arterial catheter was connected to one oxygenator separately. In the single circuit group (n=5), both arterial catheters were connected to one single oxygenator. Lambs were then delivered, submerged in a saline bath. Physiological parameters and blood chemical and gas data were compared for statistically significant differences between groups.

Results: Gestational age at delivery was significantly lower (130±1.6 vs. 113±1.1 d), survival time was longer (18.2±3.2 vs. 53.7±4.4 h), arterial pH was higher (7.24±0.02 vs. 7.45±0.04), and minimum lactate level was lower (120.5±33.5 vs. 36.4±11.0 mg/dL) in the parallel group, compared with that in the single group. Fetuses maintained on a parallelized oxygenator circuit showed remarkable improvements in essential physiological parameters. These data suggest that a parallelized oxygenator circuit improves the performance of a pumpless artificial placenta.
Particle Image Velocimetry for the Validation of Computational Fluid Dynamic Simulations of a Cross Layered Oxygenator


Study: CFD simulations in oxygenators are commonly used to investigate the flow field. Helpful conclusions can be drawn from these simulations, but the experimental validation is commonly done only by the comparison of the total pressure drop. We performed Particle Image Velocimetry (PIV) measurements on an up scaled transparent model of an oxygenator with cross layer fiber arrangement for the experimentally validation of the CFD simulations of the oxygenator.

Methods: The oxygenator is designated to be used as an artificial placenta with flows from 30 -- 120 mL/min. The similitude theory was used to calculate a factor of 5.8 for the up scaled PIV model. Fully transparent PMMA material was used for fibers and the housing of the PIV model. The refraction index of the PIV fluid was adapted to the one of PMMA. Three component PIV measurements of two flows were performed, corresponding to the flow range of the original oxygenator. The CFD model was generated and meshed unstructured in the original size of the oxygenator. The fiber bundle was modeled as isotropic porous media. According to the experiment, the corresponding flow rates were simulated.

Results: The comparison of results from PIV measurements and CFD simulations leads to a similar macroscopic flow field distribution, areas of high flow and stagnation areas. The view on the (microscopic) flow between the fibers shows differences. The meandering flow of the fluid around the fibers in PIV (Fig. 1 - sequence of PIV pictures) cannot be represented by the CFD results of the isotropic porous model. This effect of the tortuosity can be quantified by the comparison of the path length of stream lines. The quality of validation between PIV and CFD is in progress and will be presented at the ASAIO conference 2014. These first PIV measurements of an up scaled model of a cross layer oxygenator show promising results to be used as a validation methodology for CFD simulations of oxygenators in the future.

Immune-mediator Regulation From Donor Lungs Using the Organ Care System® - A Potential Mechanism For Improved Outcome

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Study: Release of donor-derived immune mediators (IM), triggering allorecognition and inflammation after transplantation (Tx), may impinge on clinical outcome using warm perfusion of donor lungs (Organ Care System®, OCS) or standard cold preservation (SOC). IM were analysed in preservation solutions (PS) and peripheral blood (PB), also clinical outcomes monitored.

Methods: IM were quantified in PS and plasma by multiplex-technology at the end of warm (n=12) or cold preservation (n=9) and in PB. Midterm outcomes, donor and recipient demographics were evaluated.

Results: In PS, concentrations of IL-6, IL-10, IL-16, IFN-g CXCL8, CCL4, Ang-2, PECAM-1 and PDGF-b were significantly higher in OCS (p<0.0001). Inverse distribution was observed for FGF-b (p=0.005). High concentrations in PS following OCS correlated with lower concentrations of IM in recipient plasma after Tx. OCS vs. SOC median donor age was 45 vs. 46 years, median recipient age 55 vs. 56 years. Underlying diagnoses: IPF (n=6 vs. n=5), CF (n=3 vs. n=2), IPAH (n=0 vs. n=1) and emphysema (n=3 vs. n=1). No significant differences of median cross clamp times (minutes) for right (430 vs. 505) and left lung (569 vs. 641) were seen. Shorter median mechanical ventilation time (MVT) (795 vs. 1051 min) and ICU-stay (3585 vs. 3750 min) were observed in OCS group. PGD-scores were lower at T24 in OCS group (p=0.28). Significantly higher %predicted FEV1 at discharge (FEV1) was seen in OCS group (71% vs. 55%, p=0.04). Six-month-survival was not different. Correlations between Ang-2 or IL-6 concentrations and FEV1, MVT, paO2/FiO2 and ICU-stay were identified. Summarising, IM remained low in PS using SOC probably due to reduced metabolic activity in lung tissue during cold ischemia. During OCS preservation, significantly higher amounts of IM were released into PS which may potentially represent depletion from the organ by accumulation in PS. This ‘dialysis’ effect was associated with an improved clinical outcome in OCS group.
Development of a Ventilator System for Total Liquid Ventilation Using Silicone Membrane Oxygenator
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Study: Total liquid ventilation (TLV) is an effective treatment for severe respiratory failure such as acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD). TLV has been investigated since 1970's with various systems. However, there still remains the problem about CO2 removal from the living body. The CO2 removal performance depends on an oxygenator. We developed a ventilator system for TLV using silicone membrane oxygenator to improve these problems. The ventilator system is composed of a controller unit, a quantitative pump, a pressure sensor, a heat exchanger, a PFC reservoir, a roller pump and an oxygenator. The oxygenator equips a flow distributor. Flow distributor produces high gas exchange performance. Moreover, we designed the oxygenator by using computational fluid dynamics (CFD). The ventilator system controls the adjustment of tidal volume, inspiration and expiration times by airway pressure.

Methods: We conducted in-vitro experiment to measure the performance of the ventilator system by using a mock circuit. The mock circuit was simulated with O2 consumption of 40 mL/min and CO2 production of 30 mL/min, which are the standard values of newborn infants. We constructed the mock circuit with a roller pump, an oxygenator and a PFC reservoir. Experimental conditions of the ventilator system were as follows: tidal volume of 39 mL, respiratory rate of 8 breath/min, O2 gas flow rate of 3.5 L/min and N2 gas flow rate of 2.5 L/min.

Results: PaO2 and PaCO2 of PFC in the mock circuit were maintained in the normal value (PaO2>100±25 mmHg, PaCO2<40±5 mmHg) during experiments. These results show that the gas exchange performance of the ventilator system has feasibility as a TLV system for newborn infants.

Definition of an Ultra-compact Membrane Oxygenator for New Born Infant
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Study: Extra-corposreal Membrane Oxygenation (ECMO) is an important method to support newborns with respiratory failure. However, the ECMO gives excessive physical burden to newborn infant as to blood volume in high. Therefore, using Computational Fluid Dynamics (CFD) analysis, we developed ultra-compact membrane oxygenator (UC-MO) with lower priming volume, high gas exchange performance.

Methods: The UC-MO was designed to equalize blood flow using a CFD analysis. The hollow fiber bundle was treated as a porous medium. The membrane surface area was 0.15 m2; the membrane filling rate was approximately 35% for housing, and the priming volume was 21 mL. We examined gas exchange performance and pressure drop in vitro experiment. Gas exchange performance was evaluated Blood flow rate of Q = 200, 400, 600 mL/min and V/Q = 1, 2.

Results: CFD analysis showed that blood flow was equalized in the UC-MO. Oxygen and carbon dioxide transfer rates were 21.63 mL/min and 21.56 mL/min, at a blood flow rate 400 mL/min, V/Q = 2. Pressure drop was 12 mmHg, at a blood flow rate 600 mL/min (Max flow rate). We could develop the UC-MO that allows low priming volume, high gas exchange performance and low pressure drop. The novel UC-MO developed in this study can be effectively not only ECMO for newborn infants but also artificial placenta.

A New Software Control with Safety Feedback on Airway Pressure for a Total Liquid Ventilation Prototype
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Study: A new software was implemented to manage the ventilator prototype developed by our research group to perform neonatal Total Liquid Ventilation (TLV) in a pressure-controlled lung-protective strategy. The software comprises a safety feedback control limiting airway pressure to avoid barotrauma.

Methods: The software, implemented in LabView (National Instruments), is interfaced with our TLV prototype (Pro-Li-Ve) integrating the liquid perfluorocarbon pumping and oxygenation functions in a non-volumetric pulsatile device. The control software comprises 3 main functions:
- Acquisition: to real-time acquire, visualize and record flow rate and airway pressure signals.
- Ventilation: to control the device and set the ventilation parameters (i.e. tidal volume, respiratory rate, inspiration to expiration ratio, end-inspiratory or expiratory pause, etc.).
- Feedback: to limit airway pressure in a clinically safe range by acting on the solenoid valve regulating the inflow and outflow pumping-gas.

A user-friendly graphic interface allows the user to manage the ventilator, monitor the signals and set the feedback thresholds. The Pro-Li-Ve software was widely tested first in vitro, applying different ventilation settings, then in vivo during TLV trials on animals.

Results: Both in vitro and in vivo tests proved the software reliability and safety. It controls the ventilator, always limiting pressure in the desired range (e.g. -10 to 20 cmH2O), and allows tidal volume and airway pressure monitoring and recording. Conclusions: The new software allows the Pro-Li-Ve to meet the requirements for a safe neonatal TLV treatment.
Evaluation of a Long-term Durability and Antithrombogenicity for a Novel ECMO System Consisting of BIOCUBE 6000 and SOFTLINE Coated ROTAFLOW

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Study: ECMO is used to treat the patients with severe respiratory and/or circulatory failure. To provide good antithrombogenicity, heparin coating is usually applied to ECMO system. Some of ECMO systems with heparin coating have outcomes of a long-term use for more than a few weeks. On the other hand, biogenous substance such as heparin requires high cost and complicated handling process. To avoid this issue, SOFTLINE® coating was developed as a polymer surface treatment. In this study, we developed an ECMO system by combining SOFTLINE coated centrifugal pump (ROTAFLOW®) with a durable heparin coated ECMO circuit, and its durability and antithrombogenicity were evaluated by long-term chronic animal experiments.

Methods: Our developed durable ECMO circuit was consisted of a compact oxygenator (BIOCUBE™ 6000) made of polymethylpentene membrane to prevent plasma leakage, and was coated its entire blood-contacting surface with a heparin bonding material (T-NCVC®). Veno-arterial bypass ECMO was conducted for 5 weeks using 2 goats. Systemic anticoagulation was not conducted, except for one-shot heparin injection at cannulation. Bypass flow rate was set at 2.5 L/min by adjusting rotational speed of the pump.

Results: As a result, heparin-free ECMO could run for 5 weeks without device exchange in all cases. Bypass flow rate could be maintained stably in the range of 3097–3376 rpm. O2 and CO2 transfer rates were kept at sufficient levels (142 ± 28 and 101 ± 31 mL/min, respectively). After the experiments, a small amount of thrombi was found around the pivot of impeller and the bifurcation of the outlet port in the 1st pump, while no thrombi were observed in the 2nd pump. Pieces of thrombi were stuck on the inlet side of the bundle of hollow fiber membranes in each oxygenator. In conclusion, the ECMO system has sufficient durability and thrombo-resistant property for 5 weeks heparin-free cardiopulmonary support.

Investigating Effects of Internal Pulsation on Gas & Heat Exchange in an Oxygenator


Study: Shunt flows and low concentration gradients between fibers and blood reduce gas exchange within oxygenators. This also applies to heat exchange. This study investigates, if internal pulsation in oxygenators can improve gas and heat exchange, by equalizing negative effects of shunt flows and low gradients.

Methods: 62 flexible silicone tubes were placed within two oxygenator-geometries (with & without shunt flows). Tempered water inside the tubes facilitates heat exchange. In-vitro tests were done following ISO7199, using porcine blood. Four operating points for constant flows, using a DP2 blood pump, were compared with corresponding pulsatile flows. The latter were generated by periodically pumping water through the tubes to collapse and expand them. Combined with valves at the oxygenator’s inlet and outlet, blood flows pulsatile through the oxygenator.

Results: Heat exchange efficiency was improved by 19±4% for pulsatile flows compared to constant flows. For the geometry with shunt flows, CO2 and O2 exchange could be improved by 24±10% and 20±11% respectively by pumping with the silicone tubes compared to continuous flow from the DP2, with higher influence at low blood flows. Internal pulsation did not have a significant effect on gas exchange in oxygenators without shunt flows. The results prove that pulsation caused by pumping tubes inside an oxygenator improves gas and heat exchange in geometries with shunt flows. This can be explained by an improved flow distribution in the device, which could also reduce risks of recirculation areas. This principle of improving gas and heat exchange by inducing pulses inside a heat exchanging oxygenator, could potentially improve flow fields in future cardiopulmonary devices.
Percutaneous Double Lumen Cannula for Right Ventricular Assist: A Computational Fluid Dynamics Study with Experimental Validation

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Study: Objective: We are developing a percutaneous right ventricular assist device (pRVAD) based on a double lumen cannula (DLC), eliminating two open chest surgeries for installation and removal. The objectives of this study were to evaluate the DLC performance/flow pattern and the potential for blood hemolysis/thrombosis.

Methods: The DLC is inserted from the right jugular vein into the superior vena cava, right atrium (RA), right ventricle and curved to the pulmonary artery (PA) (Fig). Blood is withdrawn from RA through drainage lumen and perfuses PA through infusion lumen. Computational fluid dynamics (CFD) was performed on the pRVAD DLC 3D geometry at 1–5 l/min flow rates. The Reynolds number (Re) calculation defined DLC flow patterns. Numerical steady-state computations were performed using Navier-Stokes equations for laminar and transitional flow. Shear-stress transport (SST) k-ω steady solution was implemented for turbulent flow. Blood was assumed to be a Newtonian fluid. Finite volume method was used for governing equations discretization. Bench testing with a 27 Fr prototype was used to validate CFD model.

Results: The pressure-flow data from the CFD simulation was very close to experimental data with only 7% error. This CFD study predicted that our 27 Fr pRVAD DLC can handle up to 5 l/min blood flow. The Re indicated laminar flow at 1–2 l/min flow, transitional flow at 2–4 l/min, and turbulent flow at 4–5 l/min. At 5 l/min blood flow, the highest wall shear stress was 409 Pa, but hemolysis is unlikely due to the very short exposure time (0.00007 sec). Blood stagnancy at low blood flows and recirculation at high blood flows were indicative of thrombogenicity.

Conclusion: Our experimental data validated the CFD simulation very well. The 27 Fr pRVAD DLC has very limited potential hemolysis at 5 l/min blood flow. However, blood stagnancy and recirculation may cause thrombosis.

Development of a high efficiency Passive exchange Paracorporeal Ambulatory Assist Lung (P-PAAL) Through Bundle Geometry Variation

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Study: The University of Pittsburgh is developing the Paracorporeal Ambulatory Assist Lung (PAAL) device, intended to provide 70% to 100% lung support through two approaches, a Passive exchange PAAL (P-PAAL) and an Active mixing PAAL (A-PAAL). The P-PAAL approach focuses on improving efficiency through hollow fiber membrane (HFM) bundle design, whereas the A-PAAL focuses on improving efficiency through impeller design. We previously demonstrated that the oxygenation performance of a cross flow HFM device can be predicted by a dimensionless mass transfer correlation. Therefore, in this study we hypothesized this analysis can be used to predict oxygenation in bundles of multiple geometric configurations and various surface areas. This would allow engineering the P-PAAL device to achieve 175 ml/min oxygenation at 3.5 L/min blood flowrate with 0.65 m2 surface area.

Methods: The P-PAAL features a cylindrical HFM bundle of stacked sheets, which allows a range of Re to be achieved by varying bundle diameter. First, the correlation was validated against two devices of 0.85m2 surface area between Reynold’s numbers (Re’s) of 10 - 100. Then, the HFM bundle geometry was designed to meet the desired performance by reducing surface area and increasing Re, to maintain oxygenation.

Results: Experimental oxygenation results for two devices of varied geometry were predicted within 5%, validating the design approach. We then fabricated a device with a diameter of 1.75 inch and Re of 135 to meet the 175 ml/min oxygenation and 0.65 m2 surface area requirement. This P-PAAL device has a calculated shear stress of 127 dyne/cm2 and 1.9 sec blood residence time, which suggests low potential for shear induced hemolysis. Further work will be done experimentally validate these oxygenation and hemolysis predictions.
Superior RV Unloading of a Transseptal Right-Atrium-to-Left-Atrium Artificial Lung: A Simulation Study

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Study: We are developing a transseptal right-atrium-to-left-atrium (RA-LA) artificial lung for end-stage lung disease. This RA-LA artificial lung is inserted percutaneously from the right jugular vein. Blood is withdrawn from RA and then delivered to LA, providing not only lung assistance but also right ventricular (RV) unloading by reducing both pre- and after-loads. This simulation study was used to demonstrate the superior RV unloading of the proposed device compared to a traditional RA-to-pulmonary-artery (RA-PA) RVAD.

Methods: A numerical lumped-parameter model of human circulatory system was employed to simulate right heart failure (RHF), characterized by an impaired cardiac output (CO) (3.1 lpm); elevated mean RA pressure (mRAP) (14 mmHg) and mean PA pressure (mPAP) (49 mmHg). RVAD flow (Q_{RVAD}) of the RA-LA artificial lung and the RA-PA RVAD were varied from 1 to 5 lpm to simulate different levels of RV assistance. CO, RV total work, mRAP, and mPAP were calculated to compare the effectiveness of RV unloading between the RA-LA artificial lung and the RA-PA RVAD.

Results: The RA-LA artificial lung augmented CO more significantly, where CO increased from 3.1 lpm to 5.9 lpm vs 3.9 lpm in the RA-PA RVAD at Q_{RVAD} = 3 lpm (Fig.1C). The RA-PA RVAD decreased the RV stroke work but increased the RV internal work. As a result, overall RV unloading only occurred at Q_{RVAD} higher than 4 lpm (Fig.1B). In contrast, the RA-LA artificial lung decreased two folds more than that in the RA-PA RVAD. This study successfully delivers comprehensive investigation on hemodynamic behaviors of two types of RV assistance. The results demonstrate that the transseptal RA-LA artificial lung is superior in ventricular unloading and CO augmentation to traditional RA-PA RVADs.

Use of Double Lumen Veno-Venous Extracorporeal Membranous Oxygenation Cannula for Patients with Acute Pulmonary Failure as a Bridge to Decision or Lung Transplantation

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Study: Double lumen veno-venous extracorporeal membranous oxygenation (VV ECMO) may be used for patients with acute pulmonary failure as a bridge to decision or lung transplantation to avoid ventilator associated lung injury. Indications and survival benefit of this treatment strategy has not been clearly delineated.

Methods: All patients with irreversible lung disease who required double lumen VV ECMO cannula as a bridge to decision or lung transplant at our institution were included in the study. Survival of the ECMO patients was compared with patients who did not require ECMO with lung allocation score (LAS) in the highest 20% for the same period.

Results: From January 2011 to December 2013, 15 patients (9 male, 46 ± 17 years old) received double lumen VV ECMO. Etiology of pulmonary failure included pulmonary fibrosis in 6 patients, cystic fibrosis in 3, pulmonary veno-occlusive disease in 2, coal workers pneumoconiosis in 2, eosinophilic pneumonia in 1 and chronic obstructive pulmonary disease in 1. Mean length of ECMO support was 18.2 (ranged 1 to 60) days. Of these, 7 (47%) patients were bridged to lung transplant, 6 (40%) died on ECMO and 2 (13%) weaned to recovery. Three patients (20%) were converted to veno-arterial ECMO due to insufficient oxygenation. Of the 7 patients listed for lung transplant at onset of ECMO, 5 transplanted and 2 died on ECMO. Of the 8 patients not listed at the time of ECMO insertion, 2 transplanted, 4 died on ECMO and 2 weaned. Overall survival to hospital discharge was 60%. Causes of death were oxygenation failure in 2 patients, bleeding in 2, sepsis in 1 and right ventricular failure in 1. Survival of patients with LAS in the highest 20% (average LAS of 69.7) in the same period was 75%. Double lumen VV ECMO cannula is a reasonable option to bridge patients with acute pulmonary failure to decision or lung transplantation. Survival rate may be higher in the patients who are listed at the time of cannulation.
Evaluation of a Test Circuit for Oxygenators: Required Gas Exchange Area and Parallel or Serial Setup of Deoxygenators


Study: Normative in-vitro testing of oxygenators for gas exchange efficiency can be done with one simple circuit containing one oxygenator for both, testing and deoxygenation. Advanced in-vitro testing in a clinical setup requires a test setup including two parallel, cross-linked circuits. One circuit for each, test oxygenator and deoxygenator, allows simultaneous testing and deoxygenation. Such a circuit would serve three main purposes: (1) ensure venous blood at the inlet of the test oxygenator at all times, (2) simulation of the blood gases of critically ill patients, and (3) investigation of the dynamics of a test oxygenator confronted with different O2 and CO2 levels in the blood. Such a test circuit would improve scientific findings prior to in-vivo testing and could help to reduce the number of in-vivo tests.

Methods: Our circuit contains a custom-made reservoir with two chambers, one blood line for testing and one blood line to mimic the patient. Fig. 1 shows a schematic drawing of the test circuit. Initial tests were performed to investigate the required proportion between test device and “patient device” in terms of gas exchange area. Additionally, a parallel (1) and a serial (2) setup for deoxygenators were investigated. Different blood flows within the test oxygenator and the deoxygenators (all Medos Hilite 7000; 1.9 m² of gas exchange area) were investigated. Different flows and mixtures of N2, CO2 and O2 for deoxygenators were tested.

Results: Results show that one deoxygenator is able to remove the O2 (to a venous value) in ~1 L/min oxygenated blood, two deoxygenators in ~2 L/min, respectively. There were no differences between the parallel and the serial setup of the deoxygenators. We found the removal of O2 is only related to the gas exchange area of the deoxygenators. The loading with CO2 is independent from the gas exchange area. An advanced test circuit is possible, but requires ~2 m² gas exchange area in the deoxygenators for one liter per minute test flow of blood.

Evaluation of Current Trends in Research on Oxygenators


Study: Reviewing the publications of the last decade regarding oxygenator research, we found that we had no simple way to compare the different designs to one another. The aim was to assess the design with respect to the gas exchange efficiency, which is the main purpose of an oxygenator. Focusing on hollow fiber membranes, we found three groups: oxygenators with integrated pump, intravascular, and paracorporeal devices. Micro capillary approaches were included, supposing this technology may further increase the surface-to-volume ratio and thereby the efficiency compared to hollow fiber membranes.

Methods: All research prototypes of oxygenators are different, e.g. in size and blood flow path. These three parameters were available for all reviewed devices and were chosen for a comparison: (1) membrane surface area, (2) maximum blood flow, and (3) gas exchange rate. As a parameter to evaluate the efficiency of the gas exchange in a design, the gas exchange rate standardized per blood flow and per membrane surface area (mL Gas/L Blood/m²) can be used. As a second parameter, the market-readiness of the published data was estimated. Based on the assumption that a new design has to match the efficiency of the current technology to make it to the market, a benchmark can be calculated by comparing to commercial oxygenators. The healthy lung was included as a reference as well.

Results: Fifteen research approaches for oxygenators were compared, see Table 1 (Supers: (1) in-vivo, (2) ex-vivo, (3) in-vitro, (4) for 1 layer, (5) from graph). Results show that the efficiency can be improved by optimizing the design regarding the flow path, independent of the group. Applying an evenly flow distribution through the fibers as well as inducing secondary flows show the still idle potential of the hollow fibers. Paracorporeal devices are a promising development struggling with long-term durability. Micro capillary devices were found to be very efficient, but flows would have to increase 300-fold for a practical relevance.

<table>
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<th>Lung</th>
<th>Membrane Surface Area (m²)</th>
<th>Blood Flow [L/min]</th>
<th>CO2 Exchange Rate [mL CO2/L Blood/m²]</th>
<th>O2 Exchange Rate [mL O2/L Blood/m²]</th>
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Table 1
The Pediatric Artificial Lung: Development of a Model of Pediatric Chronic Lung Disease
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Study: Pediatric chronic lung disease (CLD) remains a significant clinical challenge with a relatively poor prognosis. Extracorporeal membrane oxygenation (ECMO) has been effective at treating acute lung disease in children but is poorly suited to treat CLD. The purpose of this study was to develop a model of pediatric CLD for upcoming assessment of a pediatric artificial lung (PAL), specifically a model of large alveolar dead space and pulmonary hypertension.

Methods: Lambs weighing 20-30kg were anesthetized and underwent left thoracotomy. The right pulmonary artery (PA) was ligated and changes in deadspace were measured. Lambs were then recovered and monitored for cardiopulmonary failure.

Results: Three of 7 (43%) lambs included with this study could not be weaned from the ventilator post-operatively due to cardiorespiratory failure. Of the 4 lambs successfully weaned, average survival was 44.5h (range 11-93h). Following right PA ligation, deadspace fraction increased in all animals (n=7) from 46.6% ± 7% (SD) to 61.1% ± 10.2%. In survivors (n=4), mean PA pressure increased over the course of the experiment from 17±2.2 mmHg to 29±4.3 mmHg, pCO2 from 40.6±10.0 mmHg to 54.9±18.8 mmHg and 3/4 (75%) required supplemental oxygen to maintain PaO2 > 70mmHg. Surgical ligation of the right PA creates a model of pediatric lung disease with mild pulmonary hypertension, increased deadspace, and hypoxemia requiring supplemental oxygen therapy. Pediatric CLD is a heterogeneous group of pathologies and ligation of the right PA acutely creates a reasonable model of pediatric CLD that can serve as a model to demonstrate the efficacy of the PAL.

An Ovine Animal Model for Long Term Evaluation of Artificial Pump Lungs
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Study: Animal models appropriate to evaluate artificial lungs for long term respiratory and/or cardiopulmonary support are critical to success of development of these devices. Two artificial lung devices (artificial pump-lung (APL) for respiratory support, pediatric pump-lung (PediPL) for cardiopulmonary support) were tested in an ovine animal model. 40 in vivo long term experiments were retrospectively studied to evaluate the reliability of the animal model.

Methods: Dorset hybrid sheep (16.2 to 31.2 kg and 45.0 to 69.0 kg) were used for evaluation of these artificial pump lung devices. Anesthesia was maintained with 1–4% isoflurane. A left lateral thoracotomy was performed through the forth intercostal space. The PediPL device was placed from the right atrium to descending aorta while the APL device was placed from the right atrium to pulmonary artery. The animals all recovered after surgery and were placed in a stanchion for the study evaluation. Heparin was continuously infused for anticoagulation therapy.

Results: 52.5% (21/40) experiments were completed as intended for 7 days or 30 days. Support duration averaged 6.8±1.5 days in the 7-day PediPL study, 22.0±9.9 (1–32) days in the 30-day PediPL study and 19.3±14.3 (1–37) days in the 30-day APL study. Complications included internal bleeding, IV line disconnection, weight loss, device failure, diarrhea, blood transfusion related events, device related mechanical events, and surgical complications. Heparin was increased 100–200 IU/day and reached to 1800–2500 IU/hour in the first week to achieve the targeted activated clotting time (ACT) 150–200 second. The reliable oxygenation function and biocompatibility data were collected for evaluate the device performance in the animal model. Conclusion The long term sheep model is a reliable, reproducible animal model for testing artificial pump lungs. With this animal model and appropriate post-care management, long term in vivo performance of PediPL and APL devices were evaluated reliably.
An in vitro System to Replicate Thrombosis in ECMO

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Study: Extracorporeal membrane oxygenation (ECMO) is a form of life support that is associated with many complications. A major challenge is to balance anticoagulation to prevent clot formation within the circuit, while simultaneously preventing bleeding complications in the patient. Clotting in ECMO is poorly understood and is often limited to ad hoc treatment. We have developed an in vitro system to recreate the clinical clotting problems with a recirculating, high-volume, whole blood system that can run for >24 hours. Our previous characterization of ECMO thrombosis has allowed us to recreate the problem spots in ECMO and mimic ECMO clotting in a repeatable manner.

Methods: The system incorporated tubing and connectors (Medtronic) and a bypass pump (Century). Whole heparinized porcine blood was collected fresh and perfused for long durations (24–72 hrs). Circuit volumes were in the range of 150 - 300 mL and flow rates were 500 - 600 mL/min. Simplified circuits were constructed with three connectors. After perfusion, the circuit was drained of blood and inspected. Carstairs’ stain was used to determine the fibrin or platelet dominance in the clots.

Results: Clots consistently formed at the junctions formed by the tubing and connectors in our in vitro circuit (27/18) matching the location and incidence of clots in the patient ECMO circuits (42/45). The in vitro clots were adherent to the connector edge and grew in the direction of flow, consistent with patient circuits (Fig 1). The in vitro clots were fibrin rich with few platelets, as were the patient clots (Fig 2). Thus, the in vitro model of circulating porcine blood can be used to explore the mechanisms of ECMO clotting and develop potential preventative methods via modifications to connector geometry, surface, and blood composition.

Utility Operating Method to Achieve Effective Veno-venous Extracorporeal Membrane Oxygenation

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Study: Veno-venous extracorporeal membrane oxygenation (VVECMO) is increasingly used for adult respiratory failure patients. However, recirculation which blood oxygenated by ECMO returns into the ECMO circuit may occur in VVECMO. Some factors such as cannula position and bypass flow rate affect recirculation. Therefore these factors influence gas exchange. The aim of this study is to investigate utility operating method of VVECMO for effective oxygenation.

Methods: We performed VVECMO to 5 goats (mean body weight, 58.6 ± 1.9 kg). We changed the bypass flow from 1 to 4 L/min and the position of return cannula in the inferior vena cava (IVC), the right atrium (RA) or the superior vena cava (SVC), whereas the position of drainage cannula was fixed in the IVC. We investigated the recirculation rate and whether oxygen delivery and carbon dioxide removal by ECMO could cover the demand of the systemic organs by measuring of arterial oxygen saturation (SaO₂), arterial oxygen pressure (PaO₂) and arterial carbon dioxide pressure (PaCO₂).

Results: The recirculation rates increased as the bypass flow rates increased, and it was lowest at the SVC position. All goats whose bypass flow exceeded 3 L/min had SaO₂ > 80 %. In the group of SVC return cannula, PaO₂ was the highest among three positions. PaCO₂ was approximated normal range when the bypass flow was more than 2 L/ min. The recirculation rate in VVECMO is influenced by both cannula position and the bypass flow rate. Most desirable return cannula position is in the SVC, and both the cannula position and the bypass flow rate are important for effective oxygenation and carbon dioxide removal.

Fig 1. Clot formation in the in vitro circuit (A) forms in the same area and grows similarly to clots formed in the ECMO circuits (B).

Fig 2. Histological analysis (A) in vitro clot reveals a fibrin-rich composition, which is similar to (B) an ECMO patient clot.
Propofol Use in Patients Supported with Extracorporeal Membrane Oxygenation is Associated with an Increased Risk of Adverse Events.


Study: Sedative agents are commonly used in critically ill patients requiring ECMO support. Sedation practices vary widely and a recent international survey reported that up to 35% of ECMO centers use propofol during ECMO therapy. The purpose of this study is to investigate if the use of propofol is associated with an increased risk of adverse events in patients receiving ECMO.

Methods: Retrospective chart review of all adult patients supported with ECMO at the University of Alabama at Birmingham between January 2013 and December 2013.

Results: A total of 50 patients underwent ECMO during the study period. Demographics were: Age 44.3±16.9 years, Gender (Male 56%), Weight 86.6±27.8 kg, BMI 29.7 ± 9.5. Indications were: Respiratory (n=26), Cardiac (n=18), Bridge to Transplant (n=6). Configuration was: Veno-Venous (VV) 55%, Veno-Arterial (VA) 41%, Other 4%. Mean duration of ECMO was 9.2 ± 9.7 days (Median 7). Propofol was used in the majority of patients (n=40, 80%). Cumulative propofol dose was 19,352±31,046 mg, and mean dose was 14.8±18.8 mcg/kg/min. Patients receiving propofol had higher levels of triglycerides (TG) (645.5 vs. 154.2 mg/dL, p=0.007). Similarly, peak plasma free hemoglobin (PFHb) was higher among patients receiving propofol (303 vs. 166 mg/dL, p=0.09). Five patients that received propofol had triglyceride levels of ≥ 1,000 mg/dL and required multiple oxygenator membrane changes, with three patients requiring plasmapheresis. Propofol use was not associated with increased bleeding complications (p=0.5) or an increased risk of mortality (p=0.3).

Conclusions: Propofol use in patients supported with ECMO is associated with increased levels of TG and PFHb, and may be associated with an increased risk of oxygenator failure.

Computational Study of Blood Damage Potential in Three Types of Hollow Fiber Membrane Bundles

J. Zhang, J. Ding, B. P. Griffith, Z. J. Wu. Surgery, University of Maryland School of Medicine, Baltimore, MD.

Study: Blood damage in hollow fiber membrane based medical devices is still a significant problem, which can affect devices’ performance and cause clinical complications. Computational fluid dynamics (CFD) has been used to understand hemodynamics, estimate and help to reduce or eventually eliminate blood trauma in these devices. In this study, blood flow through three representative types of arrays, square, diagonal and random, with the porosity of 0.55, were simulated, and blood damage potential were estimated.

Methods: Computational domains were meshed with Ansys, and Fluent 14.0 was used to solve the flow fields. Interstitial shear stress fields between hollow fibers were derived from the interstitial flow velocity fields; hemolysis and platelet activation were then estimated by solving a set of convection-diffusion-reaction equations with shear stress as a source term.

Results: For simulated flow rates, hemolysis is negligible since the maximum shear stresses in these arrays are well below 150 Pa, which is considered the threshold causing hemolysis. On the other hand, shear induced platelet activation and deposition are essential. Specifically, significant amounts of platelets were activated by shear. Although the diagonal array had higher shear stress than the square array, fewer platelets were activated in the diagonal array than in the square array. Areas with high activated platelet concentration coincide with recirculation areas, which indicated that longer exposure time in recirculation areas caused more shear induced platelet activation. Since flow velocities were low in recirculation areas, more platelet adhesion and aggregation were expected in the square array. In conclusion, exposure time plays an important role in platelet activation in hollow fiber bundles; the square array has the highest blood damage potential.
Optimizing the Shape of Hemodialysis Puncture Needles Based on Measurement of Pressure Distribution Inside the Needle

S. Takahashi, S. Yamauchi, Y. Motohashi, T. Sato, T. Agishi. Clinical Engineering, Toin University of Yokohama, Yokohama, JAPAN.

Study: In hemodialysis, a large difference arises between the set and the actual flow rate as puncture needles become thinner. Side holes have been added at the tip of the needle in an attempt to overcome this problem; however, almost no theoretical or experimental studies have been conducted concerning the optimum number and shape of these holes. For this research, we modified commercial hemodialysis puncture needles by adding 0–3 side holes, and experimentally investigated the effect of the number of side holes on the difference between the set and actual flow rates.

Methods: Using a commercial 16-G puncture needle without side holes, we prepared needles with 1–3 side holes (diameter, 0.6 mm). A model blood vessel made from polyvinyl chloride (internal diameter, 12 mm) was fixed to a metal table, and water was circulated through the vessel at a flow rate of 700 ml/min using an artificial cardiopulmonary roller pump. A needle with side holes was placed in the model blood vessel and connected to the blood circuit. The blood removal volume was then set using a dialyzer roller pump, and the difference between set and actual flow rates was measured. We then attempted to measure the pressure distribution inside the needle using a guidewire fitted with a pressure sensor. Pressure distribution inside the puncture needle was measured at 5-mm intervals as the guidewire was pulled from the base toward the tip of the needle.

Results: As the number of side holes increased from 0 to 3, the difference between set and actual flow rates tended to decrease. When measuring the pressure distribution inside the needle, we found that the blood removal volume from the tip was dramatically reduced as a result of the provision of side holes. These results suggest that, by optimizing the number and position of side holes so that the blood removal volume from the tip is increased, it may be possible to produce a fine-gauge puncture needle capable of adequately removing blood at the set flow rate.

Acetaminophen Attenuates High Glucose-induced Oxidative Stress and Fibrogenesis in the Human Renal Mesangial Cells

M. Wu1, C. Wang1, R. Arvapalli1, X. Dai2, W. E. Triest3, J. W. Leidy3, Y. Masannat4, E. Blough5. 1Center for Diagnostic Nanosystems, Marshall University, Huntington, WV, 2Department of Physiology, Medical School of Southeast University, Nanjing, CHINA, 3Huntington VA Medical Center, Huntington, WV, 4Department of Internal Medicine, Joan C. Edwards School of Medicine, Huntington, WV, 5School of Pharmacy, Marshall University, Huntington, WV.

Study: Kidney disease affects over 20 million people in the United States alone. Hyperglycemia is thought to count prominently among the contributing factors, while effective prevention strategies remain limited. Recent data from our laboratory have suggested that acetaminophen (30mg/kg/d) can attenuate the incidence of renal injuries (Free Radic Biol Med 2013;65:1417–26). Here we hypothesize that the renoprotective effects of acetaminophen are mediated, at least in part, by attenuating hyperglycemia-induced oxidative stress and renal fibrogenesis.

Methods: Human renal mesangial cells (HRMC) exposed to high glucose (25 mM) or H2O2 (10 µM, to mimic direct oxidative stress) were treated with acetaminophen (10 µM). Cellular oxidative damage, the activation of p38 MAPK signaling, and the expression and secretion of profibrotic factors were examined. Treatment effects were analyzed using the SAS GLM procedure and the Tukey post hoc test was used to determine to differences between groups.

Results: Exposure to elevated glucose levels and H2O2 activated the profibrotic pathway in HRMCs, including the increased expression and secretion of transforming growth factor beta, connective tissue growth factor, and fibronectin, while acetaminophen treatment significantly decreased the secretion of these factors and extracellular deposition of fibronectin. The protective effects of acetaminophen were associated with decreases in cellular ROS and the activation of p38 MAPK. Taken together, these data suggest that a low therapeutic dose of acetaminophen can attenuate high glucose-induced fibrogenesis by decreasing cellular oxidative stress levels and p38 MAPK overactivation. Our findings support further translational research and clinical application of acetaminophen in reducing renal damage risk in diabetic patients.
Hemocompatibility Enhancement of Silicon Nanopore Membranes (SNM) using Optimized Deposition of Thin-Film Poly(Sulfobetaine Methacrylate) (pSBMA)

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1Department of Bioengineering and Therapeutic Sciences, University of California - San Francisco, San Francisco, CA, 2Division of Nephrology, University of California - San Francisco, San Francisco, CA, 3Division of Nephrology, Vanderbilt University, Nashville, TN.

Study: The precision geometry and manufacturability of SNM is fundamentally enabling for the development of an implantable bioartificial kidney. To enhance long-term hemocompatibility, we optimized the deposition of sub-5nm thick pSBMA, a zwitterionic polymer to provide an anti-thrombogenic non-pore-occluding surface coating on SNM. This work details the optimization parameters for pSBMA deposition and presents hemocompatibility results under static and flow conditions.

Methods: By varying the starting reagent concentrations, 2,2'-bipyridyl (BPY) and copper (II) bromide (CuBr₂) from 0 to 0.3 M, and 0 to 0.4 M, respectively, and polymerization time (PT) from 10 to 60 min, we optimized for sub-5 nm pSBMA coating and minimal protein adsorption (fibrinogen and albumin). Coating thickness was determined by ellipsometry. Hydraulic permeability was measured for SNMs before and after coating. Fibrinogen adsorption was determined by enzyme-linked immunosorbent assays after 2 hour incubation and FITC-labeled bovine serum albumin adsorption after 1 hour incubation. pSBMA-coated silicon (Si) was compared to bare-Si after 2 hour fresh heparinized human blood flow (20 ml/min and 73.3/s wall shear rate). Platelet activation (CD62) (immunohistochemistry) and cell attachment (scanning electron microscopy) on surface were analyzed.

Results: The optimized protocol (0.3 M BPY and 0.01 M CuBr₂ with 15 min PT) produces a ~4.6 nm thin-film pSBMA coating that significantly reduced protein adsorption compared to bare-Si. For static conditions and relative to bare-Si, albumin adsorption was reduced by 52%, while fibrinogen adsorption was reduced by 64%. Under flow conditions, there was a qualitative decrease in both platelet activation and cell adhesion. This study shows that pSBMA performance can enhance SNM hemocompatibility in both static protein solutions and under blood flow conditions.

Particle Image Velocimetry (PIV) of the Venous Needle Jet During Haemodialysis

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Study: During haemodialysis, the jet exiting the venous needle (VN) has been shown to produce turbulence and high wall shear stresses in arteriovenous fistula. The effects of recirculating flows produced by these forces have received little attention and could contribute to the high incidence of thrombosis and intimal hyperplasia. This study used particle image velocimetry (PIV) to determine the effect of the VN jet on the core flow for a range of flow rates.

Methods: Constant flow was established through a twice scaled idealised model under standard haemodialysis conditions. A mixture of sodium iodide (76.5%) and glycerol (23.5%) provided a viscosity similar to blood and was seeded with 5μm polyamide particles. A range of flow rates was investigated (200ml/min, 300ml/min and 400ml/min) with corresponding trigger rates of 1750Hz, 2500Hz and 3250Hz. The flow field was imaged from 10-200mm downstream from the needle tip to measure the range of flow disturbances in the core flow caused by the impinging jet.

Results: A distinct recirculation zone formed under all flow rates as depicted in Figure 1. The risk of coagulation is potentially increased due to the higher particle residence within this recirculation zone. Aside from the high forces produced by the impinging jet on the floor of the vein, the roof of the vein may also be susceptible to intimal hyperplasia due to the reverse flow component of the recirculation zone. More complex flows developed with higher needle flow rates and the recirculation was found to become very transient at 400ml/min due to the higher degree of dissipation and jet instability.
Synthetic Ligand-coated Magnetic Nanoparticles for Microfluidic Bacterial Separation From Blood

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Study: Bacterial sepsis is a serious clinical condition that can lead to multiple organ dysfunction and death despite timely treatment with antibiotics and fluid resuscitation. We have developed an approach to clearing bacteria and endotoxin from the bloodstream, using magnetic nanoparticles (MNPs) modified with bis-Zn-DPA, a synthetic ligand that binds to both Gram-positive and Gram-negative bacteria. Magnetic microfluidic devices were used to remove MNPs bound to E. coli, a Gram-negative bacterium commonly implicated in bacterial sepsis, from bovine whole blood at flows as high as 60 mL/h, resulting in almost 100 % clearance. Such devices could be adapted to clear bacteria from septicemic patients.

Methods: N/A

Results: N/A

On-line Dialysate Infusion to Estimate Absolute Blood Volume in Dialysis Patients

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Study: It was the aim to study the distribution and elimination of ultra-pure dialysate as volume indicator in stable hemodialysis patients during on-line hemodiafiltration (HDF).

Methods: Dialysate was automatically infused as a volume indicator at a constant rate using standard on-line HDF equipment (Fig. 1, left panel). Indicator concentration was non-invasively measured in the arterial blood-line (BVM, Fresenius Medical Care) and its time course was analyzed to obtain the elimination rate as well as the distribution volume Vt at the time of dilution (Fig. 1, right panel).

Blood volume at treatment start (V0) was calculated accounting for the degree of intra-dialytic hemoconcentration.

Results: Five patients (two females) were studied during 15 treatments. Two to six measurements using indicator volumes ranging from 60 to 210 mL were done in each treatment. V0 was 4.59±1.15 L and larger than the volume of 4.08±0.48 L estimated from anthropometric relationships. The mean half-life of infused volume was 17.2±29.7 min. Conclusion: Given pre-dialysis volume expansion V0 was consistent with volume determined from anthropometric measurements. Information on intravascular volume could substantially improve volume management in hemodialysis patients and fluid therapy in intensive care patients undergoing extracorporeal blood treatment. The system has the potential for complete automation using proper control inputs for BVM and HDF modules of the dialysis machine.
ASAIO RENAL ABSTRACTS

70

Quantitation of Transfer of Dissolved Oxygen in Extracorporeal Hemodialysis Circuits
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Study: Using Redy 2000 single bath hemodialysis machine, we saturate the dialysate with dissolved oxygen then we measure the amount of dissolved oxygen that crosses from the dialysate compartment to the blood compartment. Dissolved oxygen in the dialysate compartment readily crosses the dialysis membrane and it equilibrates with the blood in the blood compartment in a single run. The amount of the dissolved oxygen in the dialysate is small. This problem can be solved by increasing dialysate flow relative to blood flow. When dialysate and blood flows run at a ratio of 5:1 or higher, the blood can be fully oxygenated in a single pass. Therapeutic uses of this property can be exploited.

Methods: Redy 2000 Hemodialysis machine was hooked to sheep blood using standard techniques. Oxygen is dissolved by bubbling it in the dialysate compartment. Dialysate to blood flow were varied until a ratio that allows full oxygenation of the circulating blood is reached.

Results: At a ratio of 5:1, oxygenated dialysate can fully oxygenate the blood in a single pass. At blood flow of 250 ml/min, about 10 ml/min of dissolved oxygen is transferred to the patient.

110

Absolute Blood Volume and Hepato-splanchnic Blood Flow Measured by Indocyanine Green Kinetics During Hemodialysis
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Study: A non-invasive technique to measure absolute blood volume and hepato-splanchnic blood flow (QH) during hemodialysis (HD) was examined.

Methods: The dispersion and elimination of indocyanine-green (ICG) was measured by optical means originally developed for on-line hematocrit monitoring (CritLineIII, Hemametrics, UT) and compared to transcutaneous measurements using pulse dye densitometry (DDG-2001A/K, Nihon Kohden, Tokyo, Japan). Distribution volumes (V) and elimination rate constants (k) were determined from arterial indicator concentrations assuming a single-compartment model. Cardiac output (Qc) and access flow (Qa) were measured by saline dilution technique (Transonic Systems Inc., Ithaca, New York).

Results: Duplicate dilutions were available in 7 subjects (78.0±9.66 kg dry weight; 2 female subjects). k was not different between measuring techniques (0.246±0.07 vs. 0.249±0.06 min⁻¹, p=n.s.) (Fig. 1, left panel). V was 4.71±0.75 L (60.86±10.21 ml/kg dry body weight) and not different from anthropometric blood volume Vₐ (p=n.s.) (Fig. 1, right panel). ICG half-life was 3.05±0.89 min in the range of normal liver function. Therefore, ICG clearance (K=kV, 1.14±0.32 L/min) was assumed to correspond to QH. Systemic blood flow (Qs) calculated as difference between Qc (7.11±1.47 L/min) and Qa (1.56±0.88 L/min) was 5.55±1.33 L/min. Thus, during HD 21±5% of Qs were consumed by the hepato-splanchnic circulation.

Conclusion: The analysis of ICG distribution and elimination using available on-line hematocrit technology developed for routine HD provides plausible bedside information regarding absolute blood volume (Vₐ) and hepato-splanchnic perfusion (QH) which could be of clinical interest in chronic and acute modes of extracorporeal blood purification.
Fluid and Solid Mechanics Modeling of Arteriovenous Fistula Biomechanics

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Study: After the surgical creation of an arteriovenous fistula, the vein undergoes a rapid remodeling process whereby it can double in diameter. Hemodynamic forces have long been thought to constitute the primary external influence on the tissue remodeling. It is thought that the vein dilates in order to return the viscous wall shear stress to some preferred value in what has traditionally been called the hypothesis of mechanical homeostasis. However, recent numerical simulations of AV fistulae flow have shown that very large wall shear stresses (>150 dyn/cm²) can persist in mature and functioning access sites, thus challenging the traditional view of mechanical homeostasis. However, these previous studies have assumed that the fistula lumen is rigid. Here, we perform fluid-structure interaction numerical simulations of a single patient-specific model of a functioning end-to-side arteriovenous fistula used for dialysis access in order to assess the sensitivity of the wall shear stress results.

Methods: Three-dimensional reconstructions of a fistula are obtained with a custom 3D ultrasound imaging system. The vessel wall is treated as an elastic membrane structure. An in-house finite-element code is used to compute the structural motion and a finite-volume code is used to solve the fluid flow. Fluid-structure simulation results are compared to a corresponding rigid wall case.

Results: Large differences are computed between the distensible and rigid vessel simulations with respect to the spatial distribution of the viscous wall shear stress, as high as 50% and a mean of about 20%. The distensible wall simulations predict systematically lower values. Nevertheless, very high wall shear stress, 100–150 dyn/cm², persist at the anastomosis in the distensible vessel simulations. These results do not modify the conclusions of previous studies, namely that very high wall shear stresses exist in normal, functioning access arteriovenous fistulae.

Comparison of Outflow Vein Wall Shear Stress (WSS) with the Arteriovenous Fistula Eligibility (AFE) System and Traditional Arteriovenous Fistula (AVF) Using Mock Loop In Vitro Models

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Study: Prior work suggests that WSS is the key stimulus for dilation of outflow veins from AVF vascular access sites, and that poor control of WSS is a contributing factor in AVF maturation failure. Flow Forward Medical’s AFE System™ is designed to rapidly dilate peripheral veins over a 10 - 14 day period prior to AVF creation, thereby improving eligibility and reducing maturation failure. The device pumps blood from the central venous circulation into peripheral veins at a steady WSS of 4 Pa, promoting dilation and maturation. A mock circulatory loop was used to study WSS levels in outflow veins after AVF or AFE System placement in the human forearm.

Methods: For the AVF configuration, a VAD and air-charged compliance chamber simulated pulsatile arterial pressures and flows using a blood analog solution of 35% w/w glycerin at 22 °C. An open reservoir modeled the central venous circulation. Flexible PVC tubing simulated AVF inflow arteries and outflow veins of various diameters. For the AFE configuration, a centrifugal blood pump moved blood from the central venous reservoir into the outflow vein. WSS values were calculated from flows measured at points around the loop.

Results: AVF outflow vein WSS varied across the entire range of outflow vein diameters, whereas the AFE System maintained an optimal WSS dose. By adjusting AFE System speed, optimal outflow vein WSS was possible across a range of diameters, correcting a problem with conventional AVF vein maturation. These findings align with a pilot porcine study showing AFE System treatment at a WSS dose of 4 Pa caused 1.2 mm / day of outflow vein dilation with minimal intimal hyperplasia while an AVF made using the same vein had 0.06 mm / day of outflow vein dilation and severe intimal hyperplasia. Use of the AFE System to rapidly dilate peripheral veins prior to AVF creation could enable routine use of smaller veins in making AVFs and reduce AVF failure rates.
Comparison of Outflow Vein Pulse Pressure with the Arteriovenous Fistula Eligibility (AFE) System and Traditional Arteriovenous Fistula (AVF) Using Mock Loop in Vitro Models


**Study:** Cyclic vein stretching by cardiac pulsation has been implicated in AVF outflow vein intimal hyperplasia and maturation failure. Flow Forward Medical’s AFE System™ is designed to pump non-pulsatile blood into peripheral veins for 10 - 14 days, promoting rapid outflow vein dilation and maturation. A mock circulatory loop was used to study pressure in outflow veins after AVF or AFE System placement in the human forearm.

**Methods:** For the AVF configuration, an open reservoir modeled the central venous circulation while a VAD and an air-charged compliance chamber simulated pulsatile arterial pressures and flows using a 35% w/w glycerine blood analog solution at 22 °C. Flexible PVC tubing simulated various diameters of AVF inflow arteries and outflow veins. For the AFE configuration, a centrifugal blood pump moved blood into the outflow vein from the central venous reservoir. Pressure waveforms were collected at points around the loop.

**Results:** AVF outflow vein pressure was pulsatile and that pulsatility varied with outflow vein diameter, showing higher pulse pressures with smaller veins. In contrast, AFE System outflow vein pressure was non-pulsatile.

All AVF outflow veins had substantial pulsatility with larger pulse pressures in smaller veins. This effect is a likely stimulus for AVF outflow vein intimal hyperplasia and may contribute to the higher rates of AVF failure seen when smaller veins are used. These results correlate with pilot porcine studies showing that AVF outflow veins rapidly developed severe intimal hyperplasia and stenosis, with declining outflow vein blood flow. In contrast, AFE System outflow veins showed minimal intimal hyperplasia, rapid dilation, and increasing blood flow. Use of the AFE System to rapidly dilate peripheral veins prior to AVF creation could reduce the time and number of procedures required to establish a usable AVF, and reduce catheter use.

Prediction of Single Patient Response During Dialysis: Bayesian Estimation of Patient-specific Parameters and Latent State Variables

G. Casagrande, C. Bianchi, E. Lanzarone, M. L. Costantino.

**Study:** Health conditions and quality of life of uremic patients undergoing dialysis could be improved by a patient specific tailoring of the treatment. Several mathematical models can be found in the literature describing body fluids and solutes kinetics during standard or alternative Hemodialysis in reference uremic subjects. The models developed by our group can be adapted to the single patient characteristics once a suitable set of parameters is identified. This work aims to compare two methodologies to identify these patient-dependent parameters.

**Methods:** Data from 338 dialysis sessions of 13 patients were used to estimate the patient-specific parameters of our latest kinetic model with two different approaches: a constrained nonlinear optimization algorithm (CNLO) and a Bayesian method (BM). The latter allows the parameters estimation in terms of probability density function, and also the description of the patient’s conditions over time by generating values of latent state variables that cannot be acquired. Finally, estimates were used to investigate the effects of different treatment settings on each patient.

**Results:** BM results in better and more stable parameters estimations than classical CNLO. Solutes concentrations and volume profiles show to better fit clinical data when considering parameter densities estimated via BM. Moreover, the effects of different parameter settings are highlighted in terms of different molecules removal efficiency. Summarizing, our kinetic model, coupled with a more robust method to identify patient-specific parameters, allows a better prediction of electrolytes and fluid transfer during dialysis, and the evaluation of different therapy settings effects. These results will be beneficial to improve dialysis therapy planning. This study is funded by the INTERREG IT-CH EU Program: DialysIS (Dialysis therapy between Italy and Switzerland)-ID 33570710.
A Nanofibrous Bioactive Hemodialysis Access Graft
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Study: Complications of hemodialysis access remain a significant issue for patients receiving renal auxiliary therapy. In patients unable to receive primary fistulas, expanded polytetrafluoroethylene (ePTFE) arteriovenous (AV) grafts are the prostheses of choice. Yet, a third of these grafts fail within the first year, primarily due to thrombosis secondary to stenosis at the venous anastomosis or within the graft itself. Recurrent needle punctures can also provide a route for infection, transmural cellular migration/proliferation and pseudo-aneurysm (hematoma) formation.

Methods: A novel nanofibrous hemodialysis graft with inherent self-sealing properties and a drug-loaded (antithrombin, antiproliferative and antimicrobial) microstructure was synthesized and characterized (Bio-Access Graft™ or BAG). BAG and ePTFE AV grafts were then implanted into a canine common carotid artery (CCA) to jugular vein (JV) AV grafting model followed by biweekly needle punctures to assess patency and evaluate the luminal and capsular healing characteristics over 30 and 60 day periods.

Results: There were no differences in patency at 30 and 60 days between the two grafts. However, striking differences in healing patterns were evident. The BAG had no capsular formation and no transmural cellular migration through puncture sites. Additionally, the CCA and JV anastomosis showed minimal intimal proliferation. In contrast, ePTFE grafts exhibited gross capsular formation, significant transmural cellular migration and increased intimal proliferation at the CCA and JV anastomosis, all of which are precursors to graft failure. Longer implantation time periods are needed to fully assess healing and patency rates for the BAG upon subjection to recurrent needle punctures.

8-Day Implantation of Silicon Nanopore Hemofilter
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Study: End-stage renal disease (ESRD) patients face a severely limited supply of donor organs and disappointing mortality and morbidity on maintenance dialysis. Existing hollow-fiber membranes are thrombogenic, foul quickly, and require high driving pressures. An implantable artificial kidney could improve outcomes and quality of life in ESRD. Our work is focused on development of new ultrathin, uniform pore size, silicon membrane technology. We report the first implant of the high efficiency filtration membrane.

Methods: Parallel plate hemofiltration cartridges were designed using computational fluid dynamics to guide geometry. A silicon nanopore membrane (SNM) with porous surface area of 0.36 cm² and critical pore dimension of 5.6 nm was surface-modified with polyethylene glycol (PEG) and mounted in a cartridge. We fully implanted the cartridge and collection reservoir in an adult purpose bred dog. All experiments were approved by the Institutional Animal Care and Use Committee. 6 mm PTFE grafts were anastomosed to the aorta and common iliac as inflow and outflow conduits to the device. Low-molecular weight heparin (1.0 mg/kg) was administered perioperatively. Graft patency was serially assessed by Doppler ultrasound. On postoperative day 8 the animal was euthanized by protocol and the cartridge explanted.

Results: We report the first successful prolonged implantation of a SNM hemofilter. The animal displayed no signs of distress during the postoperative period. Evidence of graft patency was noted on each postoperative observation. At explant, brisk flow was noted through the grafts and 27.5 mL of ultrafiltrate were collected. There were no signs of thrombus within the device. These findings demonstrate meticulous attention to surface chemistry and conduit geometry can permit implementation of this novel technology.
Shear Stress Enhanced Proximal Tubule Cell Bioreactor Systems

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Study: A compact parallel-plate system based on silicon nanopore membranes (SNM) is under development for an implantable bioartificial kidney. This study investigates two parallel-plate flow system bioreactors and resulting enhancement of cellular reabsorption by microenvironmental shear stress manipulation.

Methods: The two systems were developed to characterize proximal tubule cell function in a planar flow geometry as shown in figures 1 and 2. Both systems utilized a 400 μm thick gasket defined flow path. System A is compatible with commercially available Corning Snapwell inserts and System B utilized a polycarbonate porous membrane incorporated into the device at the time of assembly. System B allows for SNM to be embedded in the flow cell. For both systems Lewis Lung Cancer Porcine Kidney Cells (LLC-PK1) were statically cultured on the porous membranes before assembly into the devices and exposing cells to physiological shear stress levels.

Results: System A maintained LLC-PK1 barrier function with 3.5 fold increase in reabsorption performance with increasing shear stress rates, as shown in the figure 3. System B maintained LLC-PK1 viability on SNM for up to 1 week with sustained creatinine and urea barrier performance, as shown in figure 4. Barrier performance is calculated by normalizing concentration difference between apical and basal sides using (C_{apical} - C_{basal})/ C_{apical}. In summation, the two bioreactor systems have been developed and demonstrated potential for long-term cell viability, toxin barrier performance and enhanced reabsorption by LLC-PK1 cells under shear stress in a parallel-plate flow system geometry.

Effects of Anastomotic Angle and Boundary Conditions on Disturbed Flow in Radiocephalic Fistulae for Hemodialysis

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Study: Even if the radiocephalic arteriovenous fistula (AVF) for hemodialysis (HD) is a high blood flow conduit, we have recently shown that disturbed flow occurs in focal points that locate well the sites of future stenosis [1]. In the present study, we investigated the influence of anastomosis angle and flow division ratio on the localization of disturbed flow in radial-cephalic end-to-side AVF.

Methods: By means of a parametric AVF model, we created 4 equivalent meshes, having respectively the anastomotic angle of 30°, 45°, 60° and 90°. We performed transient, non-Newtonian blood, computational fluid dynamics (CFD) simulations using measured blood flows and division in subjects requiring primary access [2] as boundary conditions and an implicit time integration scheme to solve the time-dependent Navier-Stokes equations. Time averaged WSS (TAWSS) and relative residence time (RRT) [3] were calculated as indicators of disturbed flow. Disturbed flow was localized by the wall surface area exposed to low and oscillating WSS below objectively defined thresholds.

Results: Low and oscillating WSS was located in zones where flow recirculation and stagnation occurs, on the inner wall of the swing segment and on the artery floor of the AVF. Regarding the anastomotic angle, we have found that smaller angles AVF have lower RRT areas and absolutes values. Different flow distribution ratio between the proximal and distal arteries had great impact on RRT distribution on the artery floor, but not on the venous limb. Conclusions: We have shown that in AVF for HD the anastomosis angle does impact on the local disturbed flow patterns. The clinicians should consider this at the time of AVF creation because anastomosis angle is in part amenable to surgical manipulation. An acute angle (30° - 40°) would be the preferred choice. References: 1. Ene-Iordache B and Remuzzi A, NDT 27(1):358–68, 2012. 2. Sivanesan S et al., NDT 13(12):3108–10, 1998. 3. Himburg HA et al., AJP 286(5 55-5):H1916-H192, 2014.
The Self-locating Catheter is Preferable to a Straight Tenckhoff for Acute Onset of Peritoneal Dialysis

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ASAIO, Renal Abstracts

Methods: The study included 106 operations. Three operations were excluded from analysis due to inability to insert a catheter due to extensive intraabdominal adherences. Of the remaining 103 insertions a straight Tenckhoff catheter was inserted in 62 and a self-locating catheter in 44 patients. During the first 41 insertions it was decided to start with a double cuffed straight Tenckhoff catheter. If reoperation was necessary, the first option was to change the catheter into a self-locating wolfram catheter. If this catheter did not function crossover was planned into a straight Tenckhoff catheter. Thereafter first choice of catheter was randomized into either a straight Tenckhoff or a self-locating wolfram catheter. If this catheter did not function crossover was planned into a straight Tenckhoff catheter. A previously described operation technique allowed immediate postoperative start of dialysis.

Results: We found that significantly more straight Tenckhoff catheters had to be re-operated due to flow problems (p=0.010). Catheter survival devoid of outflow problems was superior using the self-locating catheter (95% versus 75% at 70 months). In conclusion the study showed that when using the self-locating wolfram catheter fewer outflow problems occurred. This type of catheter therefore can be recommended for acute start of peritoneal dialysis using our insertion technique.

Manipulating the Microenvironment of Primary Renal Tubular Epithelial Cells Alters Cell Phenotype

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Methods: Cells were isolated from human donor kidneys not suitable for transplantation and were maintained in serum free, hormonally defined media. Cells were analyzed by western blotting for proximal tubule markers N-Cadherin and Claudin-2. Cells were grown to confluence on culture plastic, Transwell inserts, and inserts coated with Matrigel. A subset of Transwell culture inserts was exposed to fluid shear stress of 1 dyn/cm² for 5 days in a custom perfusion system. Cells were fixed and sectioned for TEM analysis of morphology and mitochondria counts.

Results: Cells showed expression of N-Cadherin and Claudin-2 on all growth substrates. Cell growth substrate had the most significant impact on overall cell morphology. Cells grown on Matrigel exhibited a more columnar morphology that is characteristic of tubular epithelial cells. Cells grown on plastic substrates showed a more flattened morphology. Perfusion and fluid shear stress increased mitochondria content compared to cells grown in static conditions. In summary, cell culture microenvironment plays a significant role in determining cell phenotype, and optimizing culture parameters may provide a means of maintaining long-term differentiated phenotype of cells in a tissue engineered bioartificial kidney.
272

The World Apheresis Association Apheresis Registry Enables You to Perform Own Report


Study: The apheresis activities have been prospectively collected in few national registries and in an open access WAA apheresis registry. The WAA registry has been updated in several steps. The aim of the latest update has been to enable each centre to analyse their data more frequently.

Methods: The software has been updated by the ICT Services and System Development (ITS) by economical support by the Swedish Association of Local Authorities and Regions. The registry is part of the Swedish quality assessment system. The registry now contains more than 48 000 apheresis procedures from 27 centres in 12 countries.

Results: The latest update enables each participating centre to download their own data whenever they want in an excel version. This version can be used for statistical analyses. In addition the registry now allows each centre to perform reports using a dynamic system that allows analyses of data in a cross sectional way but also aggregating longitudinal data.

Conclusions: In conclusion the new version of the WAA apheresis registry allow each centre to perform their own reports and data analyses independent of central administration. Comparison can be made with the own country and with the aggregated data from the whole registry. This allow i.e., the centre to make helpful comparisons.
ASAIO Author Index

Aaronson, Keith ......................................................... 86
Abdel-Sayed, Saad ...................................................... 44
Achamyel, Firehiwot ................................................... 59
Achneck, Hardean E .................................................. 9
Acosta-Lara, Pilar ...................................................... 106
Adachi, Ikki ................................................................. 92
Adamson, Robert .................................................. 10, 10, 10
Adamson, Robert .................................................. M, 56
Agishi, Tetsuzo .......................................................... 2, 3, 3
Agypaong, George .................................................. 111, 112
Ahmed, Sara ............................................................... 26
Aiello, Salvatore R ..................................................... 82
Aikawa, Masayasu .................................................... 5
Akay, Mehmet H ...................................................... 68
Akhdar, Ali ................................................................... 98
Akhter, Shahab .......................................................... 49
Akimoto, Naoko ........................................................ 5
Akikawa, Masatoshi .................................................. 44
Akuta, Masatake ........................................................ 35
Aghanem, Fares ....................................................... 104
Alharethi, Rami A .................................................... 12
Alhusseini, Aala ......................................................... 38
Aliseda, Alberto ....................................................... 115, 15, 5
Allada, Vivekananda .................................................. 95
Álvarez, Oskar A ........................................................ 25
Amacher, Rafael ........................................................ 58
Amatya, Dev .............................................................. 86
Amirriazi, Saleh ........................................................ 88
Amiya, Eiwaoka ........................................................ 41
Anand, Jatin ................................................................. 51
Anderson, Allen S .................................................... 49
Anderson, Jill D ....................................................... 7
Ando, Masahiko ....................................................... 75
Andressova, Saltana .................................................. 60
Andrade, Aron ........................................................... 23, 24, 4
Andrade, Gustavo ..................................................... 23
Annich, Gail ................................................................. 11, 5
Antaki, James F ....................................................... 16, 22, 26, 61, 91
Antoun, David ........................................................... 51
Arafune, Tatsuko ..................................................... 10, 99, 99
Araiwa, Mamoru ........................................................ 74, 75
Araque, Juan C .......................................................... 19, 31
Arens, Jutta ............................................................... 100, 60, 97, 98
Arnerlöv, Conny ...................................................... 115
Arvapalli, Ravikumar ................................................. 107, 109
Atsuta, Yuichi ............................................................ 110
Audzijoniene, J .......................................................... 7
Avsar, Murat .............................................................. 98
Axdorph Nygell ........................................................ 9
Axelson, C.G .............................................................. 5
Aycock, Kenneth L ................................................... 13
Bagnoli, Paola ........................................................... 99
Bai, Yu ................................................................. 07, 10, 102
Bajwa, Iyer G ............................................................. 111, 112
Baker, Alex ................................................................. 38
Baldwin, Andrew C ................................................... 51
Ballard-Croft, Cherry .............................................. 101, 102
Baltagi, Sirine ........................................................... 96
Banayosy, Aly E ........................................................ 42
Banjac, Igor S ........................................................... 68
Barber, Tracie ............................................................ 108
Barbour, Michael ..................................................... 15
Bartlett, Robert ...................................................... 104, 11, 5
Bartlett, Robert H .................................................... 82, 89
Bartz, Raquel ............................................................ 71
Beach, Kirk ............................................................... 111
Bealle, Corinne ........................................................ 68
Beaty, Christopher D ................................................ 79
Bekassinsky, Serik ..................................................... 60
Bekassinskyova, Makhabbat ..................................... 60
Bellot, Scott C ........................................................... 106
Benner, Brooke 108 .................................................. 15
Bennett, Jami ............................................................. 62, 67
Bentley, Kelley ........................................................... 89
Benza, Raymond L .................................................. 61
Berlin, G ................................................................. 116
Bhardwaj, Chetan ..................................................... 77
Bhat, Geetha ............................................................. 47, 50, 52, 56, 69, 79, 85
Bhatti, Saad ............................................................. 110
Bhuiyan-Ludvikova, Z ............................................... 20
Bichl, Camilla ........................................................... 112
Bick, Julian S ............................................................ 54
Bimal, Tia ................................................................. 26
Bini, Fabiano A ........................................................ 1
Biscegli, Franco ....................................................... 24
Biscegli, José F .......................................................... 23
Bixler, Heidi .............................................................. 83
Blaha, Charles ........................................................... 15
Blaha, M ................................................................. 111
Blaszczyn, Yvonne ................................................... 78
Blough, Eric .............................................................. 107, 109
Bock, Eduardo .......................................................... 4
Bogar, Linda J ........................................................... 53
Bonadonna, Desiree ................................................... 71
Bonde, Pramodi ........................................................ 61
Bonfanti, Mirko ........................................................ 99
Bonugli, Katherine ................................................... 25, 63
Boord, Jeffrey ........................................................... 65
Borchardt, Ralf ........................................................ 100, 97
Borovetz, Harvey S ................................................... 91
Boston, Umar ........................................................... 89
Boston, Umar S ........................................................ 96
Bourque, Kevin ........................................................ 63
Boutet, Bruno G ........................................................ 80
Bouwmeester, James C ............................................. 61
Brakenman, Paul ..................................................... 114
Brannstrom, Thomas ............................................... 115
Brehm, Christoph .................................................... 42
Briana, Stephen ........................................................ 73
Briceno, Juan C ...................................................... 19, 24
Briceño, Juan C ...................................................... 21, 25, 31, 34
Brown, Michael C ................................................... 41
Brunisholz, Kimberly ............................................... 12
Brusen, Robin M ....................................................... 44
Bruzzi, Mark ............................................................. 28
Bryner, Benjamin ................................................... 104
Bryner, Benjamin S ................................................... 89
Budge, Deborah ........................................................ 12
Buesen, Martin ........................................................... 18
Bumrungpetch, Jeerasit ............................................. 72
ASAIO Author Index

<table>
<thead>
<tr>
<th>Name</th>
<th>Page Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burton, Nelson A.</td>
<td>53</td>
</tr>
<tr>
<td>Cabrales, Pedro</td>
<td>34</td>
</tr>
<tr>
<td>Cabrera, Antonio G.</td>
<td>92</td>
</tr>
<tr>
<td>Cabrera, Santos E.</td>
<td>44</td>
</tr>
<tr>
<td>Caine, William T.</td>
<td>12</td>
</tr>
<tr>
<td>Campbell, Robert L.</td>
<td>13</td>
</tr>
<tr>
<td>Candela, Xavi J.</td>
<td>33</td>
</tr>
<tr>
<td>Canter, Charles E.</td>
<td>89, 96</td>
</tr>
<tr>
<td>Cardoso, Jose R.</td>
<td>4</td>
</tr>
<tr>
<td>Carey, Sandra</td>
<td>84</td>
</tr>
<tr>
<td>Carlon, Tim A.</td>
<td>9</td>
</tr>
<tr>
<td>Carrasquilla, Jennifer</td>
<td>32, 41</td>
</tr>
<tr>
<td>Carter, Annicka</td>
<td>12</td>
</tr>
<tr>
<td>Casagrande, Giustina</td>
<td>112</td>
</tr>
<tr>
<td>Casanova, Holly</td>
<td>66</td>
</tr>
<tr>
<td>Casanova, Holly C.</td>
<td>65</td>
</tr>
<tr>
<td>Casas, Fernando</td>
<td>16, 76, 76, 78</td>
</tr>
<tr>
<td>Casas, Juan C.</td>
<td>21</td>
</tr>
<tr>
<td>Castillo, Brian</td>
<td>70</td>
</tr>
<tr>
<td>Castillo, Samir</td>
<td>78</td>
</tr>
<tr>
<td>Castleberry, Chesney</td>
<td>83</td>
</tr>
<tr>
<td>Castro, Camila I.</td>
<td>21</td>
</tr>
<tr>
<td>Castro, Mario</td>
<td>95</td>
</tr>
<tr>
<td>Castro, Nathaniel</td>
<td>71</td>
</tr>
<tr>
<td>Cavaipeiro, Andre C. M.</td>
<td>4</td>
</tr>
<tr>
<td>Cedano, Francisco J.</td>
<td>21</td>
</tr>
<tr>
<td>Centola, Luca</td>
<td>4, 88</td>
</tr>
<tr>
<td>Centoni, P.</td>
<td>8</td>
</tr>
<tr>
<td>Cestari, Idagene A.</td>
<td>17</td>
</tr>
<tr>
<td>Cestari, Idagene A.</td>
<td>28</td>
</tr>
<tr>
<td>Cestari, Ismar N.</td>
<td>17</td>
</tr>
<tr>
<td>Chammas, Joseph</td>
<td>56</td>
</tr>
<tr>
<td>Chan, Chris H. H.</td>
<td>11</td>
</tr>
<tr>
<td>Chan, Chris H. Houng</td>
<td>21</td>
</tr>
<tr>
<td>Chen, Tzu-Ping</td>
<td>45</td>
</tr>
<tr>
<td>Cheng, Bin</td>
<td>44</td>
</tr>
<tr>
<td>Cheng, Jin</td>
<td>115</td>
</tr>
<tr>
<td>Cheng, Wen-Jin</td>
<td>45</td>
</tr>
<tr>
<td>Chin, Clifford</td>
<td>83</td>
</tr>
<tr>
<td>Chopski, Steven</td>
<td>88, 89</td>
</tr>
<tr>
<td>Chorpenning, Katherine</td>
<td>25, 5</td>
</tr>
<tr>
<td>Chou, Chau-Chang</td>
<td>45</td>
</tr>
<tr>
<td>Christensen, Kenneth T.</td>
<td>28</td>
</tr>
<tr>
<td>Chrysostomou, Constantinos</td>
<td>95</td>
</tr>
<tr>
<td>Chung, Ben</td>
<td>49</td>
</tr>
<tr>
<td>Civitello, Andrew</td>
<td>51</td>
</tr>
<tr>
<td>Clark, J. Brian</td>
<td>94</td>
</tr>
<tr>
<td>Clayson, Stephen E.</td>
<td>12</td>
</tr>
<tr>
<td>Clifton, Will.</td>
<td>48</td>
</tr>
<tr>
<td>Clubb, Fred J.</td>
<td>27, 53, 80</td>
</tr>
<tr>
<td>Cluzel, Philippe</td>
<td>76</td>
</tr>
<tr>
<td>Cognswell, Rebecca</td>
<td>80, 81</td>
</tr>
<tr>
<td>Cohn, William</td>
<td>63</td>
</tr>
<tr>
<td>Cohn, William E.</td>
<td>48, 51</td>
</tr>
<tr>
<td>Colarusso, Jennifer</td>
<td>55</td>
</tr>
<tr>
<td>Cole, Adam</td>
<td>55</td>
</tr>
<tr>
<td>Collet, Jean Philippe</td>
<td>76</td>
</tr>
<tr>
<td>Colvin-Adams, Monica</td>
<td>71, 80</td>
</tr>
<tr>
<td>Condemi, Francesca</td>
<td>101</td>
</tr>
<tr>
<td>Conger, Jeff L.</td>
<td>48</td>
</tr>
<tr>
<td>Contreras, Mauricio A.</td>
<td>113</td>
</tr>
<tr>
<td>Cooper, Timothy</td>
<td>94</td>
</tr>
<tr>
<td>Corbett, Scott C.</td>
<td>91</td>
</tr>
<tr>
<td>Cornell, Marie</td>
<td>104</td>
</tr>
<tr>
<td>Cortella, Lucas R. X.</td>
<td>17</td>
</tr>
<tr>
<td>Costantino, Maria L.</td>
<td>112, 75</td>
</tr>
<tr>
<td>Costantino, Maria Laura</td>
<td>99</td>
</tr>
<tr>
<td>Costas, Gil G.</td>
<td>48</td>
</tr>
<tr>
<td>Costello, William</td>
<td>54</td>
</tr>
<tr>
<td>Cotter, Christopher</td>
<td>63</td>
</tr>
<tr>
<td>Coyle, Laura</td>
<td>79, 85</td>
</tr>
<tr>
<td>Craven, Brent A.</td>
<td>13</td>
</tr>
<tr>
<td>Crump, Julian</td>
<td>34</td>
</tr>
<tr>
<td>Cruz, Vincent</td>
<td>77</td>
</tr>
<tr>
<td>Cruz, Vincent B.</td>
<td>43, 43</td>
</tr>
<tr>
<td>Cyr, Kevin</td>
<td>115</td>
</tr>
<tr>
<td>Cysyk, Joshua</td>
<td>30, 32, 59, 82, 83, 94</td>
</tr>
<tr>
<td>Dague, Charles</td>
<td>63</td>
</tr>
<tr>
<td>Dahibawkar, Manasi</td>
<td>6</td>
</tr>
<tr>
<td>Dai, Xiaoyui</td>
<td>107, 109</td>
</tr>
<tr>
<td>Daly, Richard D.</td>
<td>86</td>
</tr>
<tr>
<td>Daneshmand, Mani</td>
<td>71</td>
</tr>
<tr>
<td>Date, Kazuma</td>
<td>7, 74, 75</td>
</tr>
<tr>
<td>Dave, Jaydev</td>
<td>6</td>
</tr>
<tr>
<td>Davies, Ryan</td>
<td>79</td>
</tr>
<tr>
<td>Davis, Erin S.</td>
<td>55, 81</td>
</tr>
<tr>
<td>Davis, Mary E.</td>
<td>54, 65, 65, 66, 86</td>
</tr>
<tr>
<td>Davis, Ryan</td>
<td>89</td>
</tr>
<tr>
<td>Davis, Ryan P.</td>
<td>104</td>
</tr>
<tr>
<td>Day, Steven W.</td>
<td>52</td>
</tr>
<tr>
<td>DeFrance, Carinne</td>
<td>76</td>
</tr>
<tr>
<td>Degerman, Christina</td>
<td>115</td>
</tr>
<tr>
<td>del Alamo, Juan Carlos</td>
<td>10</td>
</tr>
<tr>
<td>Delgado, Reynolds</td>
<td>48</td>
</tr>
<tr>
<td>Delorme, Yann T.</td>
<td>22</td>
</tr>
<tr>
<td>del Rio, J. M.</td>
<td>71</td>
</tr>
<tr>
<td>Dembtsky, Walter</td>
<td>10, 10, 10, 56</td>
</tr>
<tr>
<td>Demou, Zoe N.</td>
<td>16, 77</td>
</tr>
<tr>
<td>Denfield, Susan W.</td>
<td>92</td>
</tr>
<tr>
<td>Derfler, K.</td>
<td>12, 116</td>
</tr>
<tr>
<td>de Sá, Eduarto F.</td>
<td>17</td>
</tr>
<tr>
<td>Desai, Shashank S.</td>
<td>53</td>
</tr>
<tr>
<td>Deshpande, Shripasad</td>
<td>105</td>
</tr>
<tr>
<td>Deutsch, Steve</td>
<td>33, 33</td>
</tr>
<tr>
<td>Deutsch, Steven</td>
<td>95, 95</td>
</tr>
<tr>
<td>Dhital, Kumud</td>
<td>57</td>
</tr>
<tr>
<td>Dhondt, A.</td>
<td>16</td>
</tr>
<tr>
<td>Diaz-Guzman, Enrique</td>
<td>106</td>
</tr>
<tr>
<td>Di Bartolomeo, Roberto</td>
<td>73</td>
</tr>
<tr>
<td>Dimas, V.V.</td>
<td>91</td>
</tr>
<tr>
<td>Ding, Jun</td>
<td>106, 23</td>
</tr>
<tr>
<td>Di Prima, Matthew</td>
<td>6</td>
</tr>
<tr>
<td>Dockery, W. Dee</td>
<td>84</td>
</tr>
<tr>
<td>Dolor, Aaron</td>
<td>108</td>
</tr>
<tr>
<td>Dongaonkar, Ranjeet M.</td>
<td>34</td>
</tr>
<tr>
<td>Doxtater, Bradley</td>
<td>94</td>
</tr>
<tr>
<td>Drakos, Stavros G.</td>
<td>49, 55, 81</td>
</tr>
<tr>
<td>Dreyer, William J.</td>
<td>92</td>
</tr>
<tr>
<td>Drigo, Evandro</td>
<td>23</td>
</tr>
<tr>
<td>Driscoll, Henry</td>
<td>109</td>
</tr>
<tr>
<td>Dulin, Kelly</td>
<td>6</td>
</tr>
<tr>
<td>Duncan, Daniel</td>
<td>79</td>
</tr>
<tr>
<td>Name</td>
<td>Pages</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Dzhetybayeva, Saltanat</td>
<td>60</td>
</tr>
<tr>
<td>Eckman, Peter</td>
<td>80, 81</td>
</tr>
<tr>
<td>Efvergren, M.</td>
<td>13</td>
</tr>
<tr>
<td>Eghtesady, Pirooz</td>
<td>89, 96</td>
</tr>
<tr>
<td>El-Banayosy, Aly</td>
<td>42, 64, 77</td>
</tr>
<tr>
<td>Elmer, Ashley</td>
<td>55, 81</td>
</tr>
<tr>
<td>Elnachef, Mohamed W.</td>
<td>110</td>
</tr>
<tr>
<td>Eloot, S.</td>
<td>16</td>
</tr>
<tr>
<td>Emoto, Takahiro</td>
<td>35</td>
</tr>
<tr>
<td>Endo, Katsuaki</td>
<td>36</td>
</tr>
<tr>
<td>Ene-Jordache, Bogdan</td>
<td>114</td>
</tr>
<tr>
<td>Epstein, Deirdre</td>
<td>96</td>
</tr>
<tr>
<td>Esposito, Michele</td>
<td>68</td>
</tr>
<tr>
<td>Falk, Christine</td>
<td>98</td>
</tr>
<tr>
<td>Farrar, David</td>
<td>78</td>
</tr>
<tr>
<td>Farrar, David, J.</td>
<td>43, 73</td>
</tr>
<tr>
<td>Favre, Julien</td>
<td>44</td>
</tr>
<tr>
<td>Federspiel, William J.</td>
<td>101</td>
</tr>
<tr>
<td>Fedson, Savitri</td>
<td>49</td>
</tr>
<tr>
<td>Feller, Erika D.</td>
<td>62, 66</td>
</tr>
<tr>
<td>Ferrara, Eduardo</td>
<td>28</td>
</tr>
<tr>
<td>Ferrell, Nicholas</td>
<td>114, 115</td>
</tr>
<tr>
<td>Ferrier, William T.</td>
<td>4, 88</td>
</tr>
<tr>
<td>Ferro, Giuseppe</td>
<td>4, 88</td>
</tr>
<tr>
<td>Finocchiaro, Thomas</td>
<td>78</td>
</tr>
<tr>
<td>Fisher, Brad</td>
<td>10, 10</td>
</tr>
<tr>
<td>Fissell, William</td>
<td>113, 114</td>
</tr>
<tr>
<td>Fissell, William H.</td>
<td>108, 115, 15</td>
</tr>
<tr>
<td>Fitzgerald, Keif</td>
<td>2</td>
</tr>
<tr>
<td>Folesani, Gianluca</td>
<td>73</td>
</tr>
<tr>
<td>Fonseca, Jeison</td>
<td>23, 24</td>
</tr>
<tr>
<td>Forsberg, Anya</td>
<td>6</td>
</tr>
<tr>
<td>Forsberg, Flemming</td>
<td>6</td>
</tr>
<tr>
<td>Forsberg, Mark</td>
<td>6</td>
</tr>
<tr>
<td>Forsberg, Ulf</td>
<td>115</td>
</tr>
<tr>
<td>Foster, Graham D.</td>
<td>11, 21, 23</td>
</tr>
<tr>
<td>Fox, Carson</td>
<td>89</td>
</tr>
<tr>
<td>Fox, Traci</td>
<td>6</td>
</tr>
<tr>
<td>Fragomeni, Gionata</td>
<td>101</td>
</tr>
<tr>
<td>Franano, F. N.</td>
<td>111, 112</td>
</tr>
<tr>
<td>Frankel, Steven H.</td>
<td>22</td>
</tr>
<tr>
<td>Frankowski, Brian</td>
<td>101</td>
</tr>
<tr>
<td>Fraser, Katharine H.</td>
<td>11</td>
</tr>
<tr>
<td>Fraser, Jr., Charles D.</td>
<td>92</td>
</tr>
<tr>
<td>Frazier, O H.</td>
<td>51</td>
</tr>
<tr>
<td>Frazier, O.H.</td>
<td>63</td>
</tr>
<tr>
<td>Fujii, Yasuhiro</td>
<td>4, 88</td>
</tr>
<tr>
<td>Fujii, Yutaka</td>
<td>105, 46</td>
</tr>
<tr>
<td>Fujino, Takeo</td>
<td>41</td>
</tr>
<tr>
<td>Fukamachi, Kiyotaka</td>
<td>43, 43, 77</td>
</tr>
<tr>
<td>Fukui, Tsuyoshi</td>
<td>18</td>
</tr>
<tr>
<td>Fukui, Yasuhiro</td>
<td>10, 46, 99, 99</td>
</tr>
<tr>
<td>Fulker, David</td>
<td>108</td>
</tr>
<tr>
<td>Fumero, Roberto</td>
<td>75</td>
</tr>
<tr>
<td>Funakubo, Akio</td>
<td>10, 97, 99, 99</td>
</tr>
<tr>
<td>Gailani, David</td>
<td>65, 66</td>
</tr>
<tr>
<td>Gallagher, Colleen</td>
<td>79, 85</td>
</tr>
<tr>
<td>Galyanov, Gregory</td>
<td>90</td>
</tr>
<tr>
<td>Gandini, Alberto</td>
<td>16, 22</td>
</tr>
<tr>
<td>Gasova, Z.</td>
<td>20</td>
</tr>
<tr>
<td>Gazit, Avihu Z.</td>
<td>96</td>
</tr>
<tr>
<td>Gerberich, Brandon G.</td>
<td>37</td>
</tr>
<tr>
<td>Gilbert, Edward M.</td>
<td>55</td>
</tr>
<tr>
<td>Giridharan, Guruprasad A.</td>
<td>13, 36, 39</td>
</tr>
<tr>
<td>Golding, Leonard A.</td>
<td>77</td>
</tr>
<tr>
<td>Gollapudi, Raghava</td>
<td>56</td>
</tr>
<tr>
<td>Gomez, Ramiro</td>
<td>5</td>
</tr>
<tr>
<td>González, Hernán F.</td>
<td>78</td>
</tr>
<tr>
<td>Gonzalez-Stawinski, Gonzalo</td>
<td>84</td>
</tr>
<tr>
<td>Good, Bryan</td>
<td>95</td>
</tr>
<tr>
<td>Gow, Kenneth</td>
<td>15, 5</td>
</tr>
<tr>
<td>Gowen, Marie Alice</td>
<td>90</td>
</tr>
<tr>
<td>Grace, Brian W.</td>
<td>48</td>
</tr>
<tr>
<td>Graef, Felix</td>
<td>63</td>
</tr>
<tr>
<td>Graham, Joel</td>
<td>32</td>
</tr>
<tr>
<td>Granegger, Marcus</td>
<td>58</td>
</tr>
<tr>
<td>Gray, Brian W.</td>
<td>89</td>
</tr>
<tr>
<td>Gregoric, Igor</td>
<td>62</td>
</tr>
<tr>
<td>Gregoric, Igor D.</td>
<td>67, 68, 70</td>
</tr>
<tr>
<td>Grenet, Justin E.</td>
<td>9</td>
</tr>
<tr>
<td>Griffith, Bartley P.</td>
<td>104, 106, 62, 66, 93</td>
</tr>
<tr>
<td>Griffith, Bartley P.</td>
<td>23</td>
</tr>
<tr>
<td>Grigioni, Francesco</td>
<td>73</td>
</tr>
<tr>
<td>Griskevicius, A.</td>
<td>7</td>
</tr>
<tr>
<td>Groot, Helena</td>
<td>33</td>
</tr>
<tr>
<td>Groszek, Joseph J.</td>
<td>113</td>
</tr>
<tr>
<td>Guerrero, Albert</td>
<td>19</td>
</tr>
<tr>
<td>Guerrero, Alvaro F.</td>
<td>31</td>
</tr>
<tr>
<td>Guglielmo, Nicola I.</td>
<td>1</td>
</tr>
<tr>
<td>Guleserian, Kristine J.</td>
<td>90, 91</td>
</tr>
<tr>
<td>Guorong, Li</td>
<td>45</td>
</tr>
<tr>
<td>Gupta, Aditi</td>
<td>6</td>
</tr>
<tr>
<td>Gutierrez, Erick</td>
<td>6</td>
</tr>
<tr>
<td>Guzman-Prueneda, Francisco A.</td>
<td>92</td>
</tr>
<tr>
<td>Haditsch, Bernd</td>
<td>109, 110</td>
</tr>
<tr>
<td>Haft, Jonathan W.</td>
<td>55, 82</td>
</tr>
<tr>
<td>Haglund, Nicholas A.</td>
<td>54, 65, 65, 66, 86</td>
</tr>
<tr>
<td>Haida, Munetaka</td>
<td>19</td>
</tr>
<tr>
<td>Halaweish, Ihab</td>
<td>55</td>
</tr>
<tr>
<td>Hall, Shelley</td>
<td>84</td>
</tr>
<tr>
<td>Halldorsdottir, Valgerdur</td>
<td>6</td>
</tr>
<tr>
<td>Hamaji, Masatsugu</td>
<td>36</td>
</tr>
<tr>
<td>Hambly, Rebecca J.</td>
<td>11, 21</td>
</tr>
<tr>
<td>Hambright, Claire</td>
<td>6</td>
</tr>
<tr>
<td>Hanna, Hitesh</td>
<td>5</td>
</tr>
<tr>
<td>Handy, Kelly</td>
<td>63</td>
</tr>
<tr>
<td>Hanita, Takushi</td>
<td>97</td>
</tr>
<tr>
<td>Haq, Zeeshan</td>
<td>49</td>
</tr>
<tr>
<td>Hara, Michael</td>
<td>10, 10</td>
</tr>
<tr>
<td>Haridas, Balakrishna</td>
<td>20</td>
</tr>
<tr>
<td>Hartanto, James</td>
<td>37</td>
</tr>
<tr>
<td>Harvey, Laura</td>
<td>80, 81</td>
</tr>
<tr>
<td>Hashimoto, Issei</td>
<td>57, 59</td>
</tr>
<tr>
<td>Hastings, Harold M.</td>
<td>87</td>
</tr>
<tr>
<td>Hastings, Susan M.</td>
<td>105</td>
</tr>
<tr>
<td>Hata, Norihiiko</td>
<td>10, 99, 99</td>
</tr>
<tr>
<td>Hatano, Masaru</td>
<td>41</td>
</tr>
<tr>
<td>Haverich, Axel</td>
<td>98</td>
</tr>
<tr>
<td>Hawkins, Karl M.</td>
<td>11, 21</td>
</tr>
<tr>
<td>Healy, Aaron H.</td>
<td>49, 55, 81</td>
</tr>
</tbody>
</table>
ASAIO Author Index

Heinle, Jeffrey S......................................................... 92
Hellmuth, Rudolf......................................................... 28
Hernandez, Ruben ...................................................... 51
Hershenson, Marc ........................................................ 89
Hertzog, Ben ................................................................. 48
Heshmat, Hooshang ........................................................ 54
Hesselmann, Felix .......................................................... 60, 98
Hearing, Jace ................................................................. 48
High, Kane ................................................................. 59
Hiivala, Nicholas J .......................................................... 66
Hirschl, Ronald .............................................................. 104
Hodges, Bill ................................................................. 88
Hoffman, Haley ............................................................. 104
Hollander, Seth A ......................................................... 90
Holley, Christopher ..................................................... 81
Holley, Christopher T ..................................................... 80
Homma, Akihiko .........................................................10, 46, 99, 99
Hoopes, Charles W ......................................................102
Horne, Benjamin D ......................................................12
Horvath, David ............................................................. 77
Houzelle, Alexandre ..................................................... 29, 31
Hrdlickova, R ................................................................. 19
Hsu, Po-Lin ................................................................. 102
Huff, Nidhi ................................................................. 71
Hultdin, Johan .............................................................. 115
Humes, H. D ................................................................. 115
Hunsberger, Andrew .................................................... 54
Imamura, Teruhiko ...................................................... 41
Inaba, Toshiro .............................................................. 41
Inada, Yuji ................................................................. 36
Iqbal, Zohora ...............................................................108, 15
Iram, Nazia ................................................................. 84
Iyer, Arjun ................................................................. 57
Izer, Jenelle ................................................................. 94
Jaffe, Samantha ............................................................. 6
Jafarencosco, Giuliano ................................................ 73
Jahanmir, Said ............................................................. 54
Jamiolekowksi, Megan ................................................. 28
Jamiolekowiski, Megan A ............................................. 26
Jamiolekowiski, Ryan M .............................................. 9
Jandura, David ............................................................69, 69
Jansen, Sebastian ......................................................... 18
Jansen, Sebastian V ...................................................... 60, 98
Jantscher, Andreas ......................................................110
Jantzen, Alexandra E .................................................. 9
Jarvik, Robert .............................................................. 93
Jask, Brian ................................................................. 56
Jayawardene, Ishanth D ................................................ 57
Jeewanandam, Valluvan ................................................ 49
Jeewa, Aamir .............................................................. 92
Jefferies, John L .......................................................... 83
Jessen, Michael E ......................................................... 90
Jessen, Staci L ............................................................ 53, 80
Jhun, Choon-Sik ..........................................................30, 32, 82, 83, 94
Jin, Zhenxiao .............................................................. 93
John, Ranjit ................................................................. 71, 80, 81, 86
Johns, Laura ............................................................... 30
Jones, Alyssa K ........................................................... 11, 21
Jones, Anna ............................................................... 11, 5
Jones, Anna M ............................................................ 82
Jonsson, Per .............................................................. 115
Josephy, Noam ........................................................... 91
Joyce, Lyle D .............................................................. 86
Kafezy, Dhyaa ............................................................. 88
Kagawa, Hiroshi .......................................................... 4, 88
Kakuta, Nobuaki .......................................................... 74
Kalle, Faouzi ............................................................... 78
Kamashima, Rei .......................................................... 10
Kameneva, Marina ...................................................... 28
Kameneva, Marina V ..................................................14, 22, 26, 7, 91
Kamiyko, Akemi ........................................................ 19
Kanda, Keiichi ............................................................. 7
Kanemaru, Shin-ichi .................................................... 36
Kant, Rishi ................................................................. 113
Kanwar, Manreet K ..................................................... 61
Kapur, Navin K ........................................................... 68
Kar, Biswajit ..............................................................62, 67, 68, 70
Karas, Richard ........................................................... 68
Karimov, Jamshid H .................................................... 77
Karp, Seth J ................................................................. 113
Katagiri, Nobumasa ...................................................100, 105, 74
Katahira, Shintaro ......................................................... 44
Katano, Kazuo ............................................................ 46
Katayama, Masato ....................................................... 35
Kato, Yoshihisa ...........................................................100
Kaufmann, Beth ........................................................ 90
Kaufmann, Tim ..........................................................18
Kaufmann, Tim A. S .................................................... 8
Kawaguchi, Akira T .....................................................18, 19, 76
Kawaguchi, Fumio ...................................................... 19
Kawaguchi, Gen ......................................................... 18
Kawaguchi, Yasu ......................................................... 8
Kawahito, Koji ............................................................ 50
Kawamoto, Shunsuke .................................................. 44
Kawamura, Shintaro .................................................... 99
Kawats, Satoshi .......................................................... 44
Keebler, Mary ........................................................... 65, 86
Keebler, Mary E .......................................................... 54
Keenan, Jeffrey E ....................................................... 71
Kennington, Jeffrey R .................................................. 78
Kensinger, Clark D ..................................................... 113
Kerins, Paul ............................................................... 79
Kerlo, Anna-Eldie M .................................................... 22
Kfoury, Abdallah G ..................................................... 12
Khan, Muhammad S ................................................... 83
Kim, Eun Jung ...........................................................108, 15
Kim, Gene ................................................................. 49
Kim, Steven ............................................................. 108, 15
Kinoshita, Osamu ....................................................... 41
Kinouchi, Katsushi ....................................................... 4
Kinouchi, Yosuke ........................................................ 35
Kinizawa, Koichi ........................................................ 41
Kishimoto, Satoru .......................................................7, 74, 75
Kitanishi, Ryuta .......................................................... 97
Kitano, Tomoya .......................................................... 40
Klein, Kimberly L ....................................................... 70
Kline, Christina D ....................................................... 42
Knezek, Sarah F ........................................................ 26, 34
Knutson, F ................................................................. 3
Kobayashi, Yoshiyasu ................................................... 97
Kocharian, Richard ..................................................... 30
Kocyildirim, Ergin ....................................................... 91
ASAIO Author Index

Koenig, Steven C. .................................................. 13, 36, 39
Koepsel, Richard R. .................................................. 7
Koerler, Reiner ...................................................... 63
Kojima, Fumitsugu .................................................. 36
Kojima, Kouichi .................................................... 46
Koliopoulos, Antigone ............................................. 49
Komatsu, Hideshi ................................................... 36
Komuro, Issei ........................................................ 41
Kon, Zach ............................................................... 66
Körner, Reiner ........................................................ 78
Kosaka, Ryo ............................................................ 8, 9
Koyama, Isamu ........................................................ 5
Kreutzer, Jacqueline ............................................... 95
Krisper, Peter ......................................................... 109, 110
Krivitski, Nikolai .................................................... 90
Kron, Joachim ........................................................ 109
Kroschwitz, Robert ................................................. 88
Ku, David N. ........................................................... 105
Kuch, Bradley .......................................................... 92
Kühn, Christian ...................................................... 98
Kuipers, Kristin ........................................................ 63
Kumar, Robert ........................................................ 56
Kurita, Daisaku ........................................................ 19
Kyo, Shunei ............................................................ 41
Laali, Mojgan .......................................................... 76
Lai, Christine .......................................................... 65
Lai, K. .......................................................... 17
Lancron, Trevor ....................................................... 27
Lande, Arnold J. ...................................................... 115
Landervan, L. .......................................................... 6
Langheinrich, Denise .............................................. 17
Lansk, M. ............................................................... 11
Lanzarone, Ettore ..................................................... 112
LaRose, Jeffrey ....................................................... 76, 76
LaRose, Jeffrey A. ................................................... 16, 5, 77
Lasagni, Andris F. ................................................... 17
Lassen, E. ............................................................... 1
Leão, Tarcisio ........................................................... 23
Leao, Tarcisio ........................................................... 4
Lee, Eric ................................................................. 88
Lee, Jung-Jae ........................................................... 109
Lee, Sangjin ........................................................... 43, 43
Lee, Sara L. ............................................................. 80
Lee, Yeunju ............................................................ 51
Leibich, Patrick ........................................................ 30, 94
Leidy, John W. ........................................................ 107
Leithner, G. ............................................................. 12
Leone, Julianna ........................................................ 23
Leotta, Daniel .......................................................... 111
Leprince, Pacal ........................................................ 76
Letzen, Brian S. ....................................................... 61
Leu, Wayne ............................................................ 37
Lewis, Christopher S. .............................................. 29, 31
Li, Tie-Luo ............................................................. 104
Liao, Kenneth ......................................................... 71, 80, 81, 86
Liepmann, Dorian .................................................. 114
Lilla Della Monica, Paola ........................................ 73
Limmer, Karl .......................................................... 56
Lin, Fu-Hsiung ........................................................ 9
Lin, Qiuyu .............................................................. 9
Liu, Ji-bin ............................................................... 6
Liu, Yang ............................................................... 104, 93, 93
Liubomirov, G. ......................................................... 116
Loforte, Antonio ..................................................... 73
Logan, Thomas G. ................................................... 74
LoGerfo, Frank W. ................................................... 113
Loghmanpour, Natasha A. ...................................... 61
López, Rocio ........................................................... 19
Lopez, Rocio .......................................................... 33
Loree, Howard M. .................................................. 111, 112
Lorts, Angela .......................................................... 83
Lorts, Angie ........................................................... 84
Loyalka, Pranav ....................................................... 62, 67, 68, 70
Lucchi, Julio ........................................................... 24
Luc, Lora ............................................................... 85
Lukic, Branka .......................................................... 29, 94
Lutts, Eddie R. ........................................................ 91
Lutz, Patrick ........................................................... 47
Lyon, L. A. .............................................................. 105
Machado, Priscilla .................................................. 6
Madhani, Shalv P. ................................................... 101
Madueke, Peace ....................................................... 84
Maeda, Katsuhide .................................................... 88, 90
Mager, Ilona ........................................................... 100, 97
Maher, Kevin O. ..................................................... 105
Mahmood, Muhammad ........................................... 109
Major, Terry ........................................................... 11, 5
Maki, Hisakata ......................................................... 41
Makri, Ralouka ........................................................ 76
Mallidi, Hari R ........................................................ 48, 51
Maltais, Simon ....................................................... 54, 65, 66, 86
Manning, Keefe ..................................................... 33, 33, 95, 95
Manning, Keefe B. ................................................... 13, 33
Mariani, Massimiliano ............................................. 75
Marinelli, Giuseppe ................................................ 73
Marous, John .......................................................... 47
Marr, Dennis ........................................................... 73
Marshall, Andrew .................................................... 6
Martin, Andrea ........................................................ 16
Martin, Andrea S. ................................................... 22
Martin, Cara E. ....................................................... 53
Martin, Peter J. ........................................................ 91
Martin Suarez, Sofia ................................................ 73
Marushima, Yoichi ................................................... 3
Maruyama, Osamu ................................................... 8, 9
Masannah, Yanzal .................................................... 107
Masetti, Marco ........................................................ 58
Masse, Andrew M. ................................................... 53
Massey, H.T. ........................................................... 52
Matafonov, Anton ................................................... 65, 66
Matonick, John ........................................................ 30
Matsuda, Tadashi .................................................... 97, 99
Maul, Timothy M. ................................................... 91, 92
May, Judith ............................................................ 88
May, Robert ............................................................ 88
May-Newman, Karen .............................................. 10, 10, 78
Mayo, Caroline V. ................................................... 20
McCandless, Sean P. ................................................ 12
McGah, Patrick ....................................................... 111, 5
McGah, Patrick M. ................................................... 15
McKellar, Stephen H. ............................................... 49, 55, 81
McKenna, Kelll ....................................................... 88
ASAIO Author Index

McKenzie, E. D................................................................. 92
McMahon, Richard A....................................................... 74
Medressova, Assel ........................................................................ 60
Mehegan, Mary ........................................................................ 89, 96
Mehta, Nicole A........................................................................ 53
Merchel, Renee A.................................................................. 12
Mery, Carlos M........................................................................ 92
Meyer, Richard S................................................................. 33
Mielke, Nicole........................................................................... 77
Milano, Camelo ........................................................................ 71
Milano, Carmelo A.................................................................. 9
Miller, Matthew W............................................................... 80
Miller, P B............................................................................... 65
Ming Tan, Zhi ......................................................................... 108
Misawa, Yoshio........................................................................ 50
Missov, Emil ............................................................................ 71
Miura, Hidekazu...................................................................... 40
Miura, Yuichiro ....................................................................... 99, 99
Miyagi, Norihiro....................................................................... 18
Miyamoto, Yuji ......................................................................... 105
Miyasaka, Munehiro .................................................................. 9
Miyazawa, Mitsuo..................................................................... 5
Mizuno, Tosihide ...................................................................... 100, 46, 70, 74, 75
Moazami, Nader .................................................................... 43, 43, 77
Moeller, John F......................................................................... 35
Mohamedali, Burhan.............................................................. 47, 50, 52, 56, 69, 69
Mohiuddin, Mohammad W.................................................. 26, 34
Mokvist, K .............................................................................. 3
Mondal, Nandan K................................................................. 62
Mondry, Jack .......................................................................... 85
Monreal, Gretel........................................................................ 36, 39
Montalto, Andrea .................................................................... 73
Mooney, Ryan J........................................................................ 7
Moore, Ryan........................................................................... 84
Moore, Theodore...................................................................... 30, 94
Morabito, Vincenzo E.............................................................. 1
Morales, David.......................................................................... 84
Morales, David L. S.................................................................. 83
Morales Serrano, Francisco J.................................................. 52
Morrill, Victor .......................................................................... 95
Moreno, Constanza L............................................................. 21
Möttzel, M ............................................................................... 116
Mosadegh, Bobak ..................................................................... 37
Moscatos, Francesco .................................................................. 58
Moskowitz, William .................................................................. 88, 89
Motohashi, Yuka ...................................................................... 1, 107, 2, 3, 3, 3
Motoyoshi, Naotaka.................................................................. 44
Moutis, Maria.......................................................................... 43
Mukaibayashi, Hiroshi ............................................................. 46
Müller, Bernadette.................................................................. 98
Muller, Paul.............................................................................. 2
Murali, Srinivas........................................................................ 61
Muramatsu, Mikiya................................................................... 28
Murase, Tomohiro................................................................. 89, 9
Murata, Masashi...................................................................... 25
Murata, Tatsuo.......................................................................... 36
Nakamura, Yasuhide.................................................................. 7
Nakanjo, Juan D........................................................................ 19
Narvaez, Diana M.................................................................. 33
Nasirov, Teimour.................................................................... 4, 88
Nathan, Sirmal ........................................................................ 51, 62, 67, 68, 70
Nativi, Josef N........................................................................... 55
Navarrete, Sandra C............................................................. 25
Navarro, Javier ........................................................................ 19, 34
Navarro Rueda, Javier ........................................................... 31, 33
Nawata, Kan............................................................................ 41
Nedelcu, Elena........................................................................... 70
Neidlin, Michael ....................................................................... 8
Nelson, David W................................................................. 113
Neudörfl, Christine............................................................... 98
Newman, E............................................................................. 15
Newswanger, Raymond........................................................... 29, 30, 82, 83, 94
Ngai, Gwendolyn A................................................................ 111, 112
Nguyen, Katrina ...................................................................... 38
Nguyen, Nghia D..................................................................... 70
Nguyen, Phuc H....................................................................... 26
Nguyen, Quoc .......................................................................... 20
Nicolosi, Denys........................................................................ 24
Nilsson, Christina H............................................................. 115
Nilsson, T................................................................................ 116
Nishida, Masahiro..................................................................... 8, 9
Nishimura, Motonobu............................................................. 74
Nishimura, Takashi................................................................. 74, 75
Niu, Shuqiong.......................................................................... 23, 93
Noguchi, Hiroo ......................................................................... 10, 99, 99
Nouaga, Kazuhiro.................................................................... 10, 99
Norman, Vanjah...................................................................... 56
Novelli, Gilmaro P..................................................................... 1
Novelli, Simone I...................................................................... 1
Noviani, Maria.......................................................................... 9
Novikova, Svetlana.................................................................... 60
Nukii, Shohei ........................................................................... 99
Nunez, Nathalie J..................................................................... 32
O'Brien, Maureen T............................................................... 80
Ochsner, Gregor....................................................................... 58
Ogawa, Daisuke......................................................................... 74
Ohnuma, Kentaro...................................................................... 46
Okada, Katsuya ......................................................................... 5
Okaifusa, Toshio....................................................................... 35
Okamoto, Kojun........................................................................ 5
Okambara, Marcos.................................................................... 4
Olia, Salim E........................................................................... 14, 91
Ono, Minoru........................................................................... 41, 75
O’Rear, Edgar A........................................................................ 20
O’Rear III, Edgar A................................................................... 27
Orosco, Jose............................................................................. 73
Oyama, Helena T....................................................................... 17
Ozturk, Mesude....................................................................... 27
Paden, Dave B.......................................................................... 91
Pae, Walter ............................................................................ 64, 67, 77, 83
Pae, Walter E........................................................................... 42, 42
Pagani, Francis D.................................................................... 86
Palacios, Anthony.................................................................... 41
Papavassiliou, Dimitrios V....................................................... 20, 27
Pappas, Pat............................................................................... 52, 56
<table>
<thead>
<tr>
<th>Name</th>
<th>Page(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park, Jaehyun</td>
<td>15</td>
</tr>
<tr>
<td>Parker, Chris</td>
<td>2</td>
</tr>
<tr>
<td>Parnis, Steven</td>
<td>63</td>
</tr>
<tr>
<td>Parnis, Steven M.</td>
<td>48</td>
</tr>
<tr>
<td>Paruchuri, Vikram</td>
<td>68</td>
</tr>
<tr>
<td>Patel, Bababhai</td>
<td>30</td>
</tr>
<tr>
<td>Patel, Manish</td>
<td>51, 62, 67, 68, 70</td>
</tr>
<tr>
<td>Patel, Roshan</td>
<td>110</td>
</tr>
<tr>
<td>Pathan, Saif G.</td>
<td>113</td>
</tr>
<tr>
<td>Pelletier, Benedikt A.</td>
<td>78</td>
</tr>
<tr>
<td>Pereira, Travis</td>
<td>37</td>
</tr>
<tr>
<td>Peri, Laxmi</td>
<td>73</td>
</tr>
<tr>
<td>Perides, George</td>
<td>68</td>
</tr>
<tr>
<td>Persson, Sven E.</td>
<td>115</td>
</tr>
<tr>
<td>Pfeifferkorn, Matthew</td>
<td>30</td>
</tr>
<tr>
<td>Pham, Duc Thinh</td>
<td>68</td>
</tr>
<tr>
<td>Pham, Si</td>
<td>62</td>
</tr>
<tr>
<td>Pham, Si M.</td>
<td>66</td>
</tr>
<tr>
<td>Phaneuf, Matthew D.</td>
<td>113</td>
</tr>
<tr>
<td>Phaneuf, Tina M.</td>
<td>113</td>
</tr>
<tr>
<td>Phillips, Stephanie M.</td>
<td>20</td>
</tr>
<tr>
<td>Picone, Michael</td>
<td>30</td>
</tr>
<tr>
<td>Pieper, Ina L.</td>
<td>11, 21</td>
</tr>
<tr>
<td>Pietila, Todd</td>
<td>84</td>
</tr>
<tr>
<td>Pietras, Colleen</td>
<td>64, 67</td>
</tr>
<tr>
<td>Pilato, Emanuele</td>
<td>73</td>
</tr>
<tr>
<td>Pitsillides, Koullis</td>
<td>4</td>
</tr>
<tr>
<td>Pizarro, Christian</td>
<td>79</td>
</tr>
<tr>
<td>Poelma, Christian</td>
<td>11</td>
</tr>
<tr>
<td>Poli, Luca U.</td>
<td>1</td>
</tr>
<tr>
<td>Price, David T.</td>
<td>91</td>
</tr>
<tr>
<td>Price, Jack F.</td>
<td>92</td>
</tr>
<tr>
<td>Price, Lauren</td>
<td>64, 67</td>
</tr>
<tr>
<td>Price, Lauren C.</td>
<td>42</td>
</tr>
<tr>
<td>Priest, Marc A.</td>
<td>79</td>
</tr>
<tr>
<td>Privitera, Mary Beth</td>
<td>20</td>
</tr>
<tr>
<td>Prophet, H.</td>
<td>10</td>
</tr>
<tr>
<td>Ptak, J.</td>
<td>116</td>
</tr>
<tr>
<td>Pya, Yuriy</td>
<td>60</td>
</tr>
<tr>
<td>Pye, Roger</td>
<td>57</td>
</tr>
<tr>
<td>Qi, Le</td>
<td>9</td>
</tr>
<tr>
<td>Quick, Christopher M.</td>
<td>26, 34</td>
</tr>
<tr>
<td>Quijano, Lina M.</td>
<td>31</td>
</tr>
<tr>
<td>Quinlan, Nathan</td>
<td>28</td>
</tr>
<tr>
<td>Quinn, T A.</td>
<td>44</td>
</tr>
<tr>
<td>Radley, Gemma N.</td>
<td>11, 21</td>
</tr>
<tr>
<td>Radovanovic, Rajko</td>
<td>62, 67, 68, 70</td>
</tr>
<tr>
<td>Rajagopal, Keshava</td>
<td>62, 66</td>
</tr>
<tr>
<td>Ramlow, W.</td>
<td>10</td>
</tr>
<tr>
<td>Ramsauer, B.</td>
<td>116</td>
</tr>
<tr>
<td>Rasmusson, Brad</td>
<td>12</td>
</tr>
<tr>
<td>Ravikumar, Anuraug</td>
<td>38</td>
</tr>
<tr>
<td>Reese, Robert W.</td>
<td>80</td>
</tr>
<tr>
<td>Reibson, John</td>
<td>30, 83, 94</td>
</tr>
<tr>
<td>Reid, Bruce B.</td>
<td>12</td>
</tr>
<tr>
<td>Reinhardt, Olaf</td>
<td>4, 88, 90</td>
</tr>
<tr>
<td>Remuzzi, Andrea</td>
<td>114</td>
</tr>
<tr>
<td>Reuser Kaasenbrood, E.</td>
<td>23, 116</td>
</tr>
<tr>
<td>Reyes, Carlos</td>
<td>41, 5, 76, 76</td>
</tr>
<tr>
<td>Ribbitsch, Werner</td>
<td>109, 110</td>
</tr>
<tr>
<td>Rice, Kevin</td>
<td>109</td>
</tr>
<tr>
<td>Rich, Jonathan D.</td>
<td>49</td>
</tr>
<tr>
<td>Richmond, Marc E.</td>
<td>44</td>
</tr>
<tr>
<td>Ridge, Alex N.</td>
<td>74</td>
</tr>
<tr>
<td>Riebman, Jerry</td>
<td>30</td>
</tr>
<tr>
<td>Riemer, Robert K.</td>
<td>4, 88</td>
</tr>
<tr>
<td>Robbins, Constance M.</td>
<td>22</td>
</tr>
<tr>
<td>Rodefeld, Mark D.</td>
<td>22</td>
</tr>
<tr>
<td>Rodriguez-Sierra, Carlos A.</td>
<td>48</td>
</tr>
<tr>
<td>Rojas-Pena, Alvaro</td>
<td>89</td>
</tr>
<tr>
<td>Rojas-Pena, Alvaro</td>
<td>104</td>
</tr>
<tr>
<td>Rojas-Peña, Alvaro</td>
<td>82</td>
</tr>
<tr>
<td>Rosenberg, Gerson</td>
<td>29, 30, 32, 82, 83, 94</td>
</tr>
<tr>
<td>Rosenthal, David</td>
<td>90</td>
</tr>
<tr>
<td>Rosner, Carolyn M.</td>
<td>53</td>
</tr>
<tr>
<td>Roth, Scott L.</td>
<td>87</td>
</tr>
<tr>
<td>Roy, Shuvo</td>
<td>108, 113, 114, 15</td>
</tr>
<tr>
<td>Rubiano, Andres</td>
<td>24</td>
</tr>
<tr>
<td>Rusanov, Alexander</td>
<td>44</td>
</tr>
<tr>
<td>Russell, Alan J.</td>
<td>7</td>
</tr>
<tr>
<td>Ryan, Thomas D.</td>
<td>83</td>
</tr>
<tr>
<td>Sá, Rosa</td>
<td>23</td>
</tr>
<tr>
<td>Saiki, Yoshikatsu</td>
<td>44</td>
</tr>
<tr>
<td>Saito, Masatoshi</td>
<td>97</td>
</tr>
<tr>
<td>Saito, Nobumichi</td>
<td>18</td>
</tr>
<tr>
<td>Sakota, Daisuke</td>
<td>8, 9</td>
</tr>
<tr>
<td>Salcedo, Felipe</td>
<td>21</td>
</tr>
<tr>
<td>Salov, Roman</td>
<td>60</td>
</tr>
<tr>
<td>Sanchez, Diana M.</td>
<td>31</td>
</tr>
<tr>
<td>Sanchez, Pablo G.</td>
<td>104, 93</td>
</tr>
<tr>
<td>Sanchez-Palencia, Diana</td>
<td>19</td>
</tr>
<tr>
<td>Sandoval, Nestor</td>
<td>19</td>
</tr>
<tr>
<td>Sandoval, Nestor F.</td>
<td>31</td>
</tr>
<tr>
<td>Sandoval-Martinez, Elena</td>
<td>51</td>
</tr>
<tr>
<td>Sano, Kyosuke</td>
<td>40</td>
</tr>
<tr>
<td>Santos Filho, Diolino J.</td>
<td>4</td>
</tr>
<tr>
<td>Saracino, Giovanna</td>
<td>84</td>
</tr>
<tr>
<td>Sarolia, Amita</td>
<td>62, 67</td>
</tr>
<tr>
<td>Sasaki, Kazuma</td>
<td>1, 2</td>
</tr>
<tr>
<td>Sato, Hiroshi</td>
<td>5</td>
</tr>
<tr>
<td>Sato, Toshio</td>
<td>1, 107, 2, 3, 3, 3</td>
</tr>
<tr>
<td>Sayer, Gabriel</td>
<td>47, 52, 56, 79, 85</td>
</tr>
<tr>
<td>Scaparra, Andrew H.</td>
<td>80</td>
</tr>
<tr>
<td>Schettle, Sarah</td>
<td>86</td>
</tr>
<tr>
<td>Schilcher, Gernot</td>
<td>109</td>
</tr>
<tr>
<td>Schima, Heinrich</td>
<td>58</td>
</tr>
<tr>
<td>Schirger, John A.</td>
<td>86</td>
</tr>
<tr>
<td>Schlanstein, Peter</td>
<td>100, 97</td>
</tr>
<tr>
<td>Schlanstein, Peter C.</td>
<td>60, 98</td>
</tr>
<tr>
<td>Schmid Daners, Marianne</td>
<td>58</td>
</tr>
<tr>
<td>Schmidtke, David W.</td>
<td>20, 27, 29, 31</td>
</tr>
<tr>
<td>Schmitz, Stephanie</td>
<td>63</td>
</tr>
<tr>
<td>Schmitz-Rode, Thomas</td>
<td>100, 60, 97, 98</td>
</tr>
<tr>
<td>Schneditz, Daniel</td>
<td>109, 110</td>
</tr>
<tr>
<td>Schroder, Jacob</td>
<td>71</td>
</tr>
<tr>
<td>Schultz, Michael</td>
<td>84</td>
</tr>
<tr>
<td>Scott, Steven</td>
<td>85</td>
</tr>
<tr>
<td>Sebastian, Vinod</td>
<td>90</td>
</tr>
<tr>
<td>Selazek, Marc</td>
<td>63</td>
</tr>
<tr>
<td>Seetharamuji, Harish</td>
<td>102</td>
</tr>
<tr>
<td>Seiden, Allen</td>
<td>20</td>
</tr>
<tr>
<td>Selzman, Craig H.</td>
<td>49, 55, 81</td>
</tr>
</tbody>
</table>
ASAIO Author Index

Serrani, Marta ........................................................................... 75
Shaheen, Palak ........................................................................ 53
Shah, Sapna ............................................................................. 110
Shankaran, Venkat ................................................................... 91
Shef, Donald ........................................................................... 88
Sheth, Neerav .......................................................................... 77
Shiba, Kenji ..........................................................57, 59, 71, 76
Shigeno, Keiji .......................................................................... 36
Shirai, Mikiyasu ....................................................................... 46
Shiraishi, Yasuyuki ................................................................... 40
Shumway, Sara .......................................................... 71, 76, 86
Shuttleworth, Paul ................................................................... 90
Sikole, A. .................................................................................. 18
Silva, Bruno .............................................................................. 24
Silver, Jeremy ........................................................................... 95
Silvestry, Scott............................................................................ 96
Simmons, Anne ....................................................................... 108
Simo, Grace ............................................................................. 35
Simoni, Jan ............................................................................... 35
Simpson, Kathleen ........................................................... 89, 96
Singh, Steve K. .......................................................................... 51
Sisneros, Andres ..................................................................... 84
Slattery, Margaret .................................................................... 33, 33
Slaughter, Mark S. ...........................................................13, 36, 39
Smith, Harrison R. ................................................................... 80
Snyder, Shaun T. ...................................................................... 91
Snyder, Trevor .......................................................................... 20, 27
Snyder, Trevor A. ..................................................................... 29, 31
Sobieski, Michael A. .............................................................. 36, 39
Sogabe, Masahiro ..................................................................... 35
Soleimanlou, Behzad ..........................................................42, 59, 64, 67, 77
Soleimanlou, Behzad B. ..................................................... 42
Soler, Peter ................................................................................ 114
Soltesz, Edward G. ................................................................... 43, 43
Sonntag, Simon J. ..................................................................... 8
Sorensen, Erik N. ..................................................................... 62, 66
Soucy, Kevin G. ......................................................................... 36, 39
Spangler, Taylor ....................................................................... 63
Sparks, Joshua D. ...................................................................... 89, 96
Sperker, Wolfgang ..................................................................... 115
Spiliopoulos, Sotirios ................................................................ 63
Spinelli, Elena ........................................................................... 82
Spotnitz, Henry M. ..................................................................... 44
Spotnitz, Matthew E. ............................................................... 44
Starling, Randall ......................................................................... 43
Stauffer, Megan ......................................................................... 29
Stefen, Robert ........................................................................... 77
Steffen, Robert J. ....................................................................... 43, 43
Steinmayr, Bernd ....................................................................... 115, 115, 116
Steinmayr, Christofer .................................................................. 115
Stehlik, Josef .............................................................................. 49, 55, 81
Steinseifer, Ulrich ..........................................................100, 18, 60, 63, 78, 8, 97, 98
Stenbaek, Jan ............................................................................. 115
Stephenson, Edward .................................................................. 64, 67
Stephenson, Edward R. ........................................................... 42
Stoker, Sandi ............................................................................. 12
Stoloff, David ............................................................................. 30
Strinholm, V. .......................................................................... 116
Stulak, John .............................................................................. 65
Stulak, John M. ......................................................................... 86
Sumikura, Hirohito ..................................................................... 46, 7
Sun, Benjamin ........................................................................... 63
Sun, Guocheng .......................................................................... 93
Sunagawa, Gengo ....................................................................... 77
Sundararajan, Sakthi.................................................................... 56
Sundareswaran, Kartik S. ..................................................... 43, 73
Svitek, Robert ............................................................................ 47
Taban, Diana M. ....................................................................... 21, 33, 34
Takakaw, Yoshiyuki .................................................................... 100, 46, 46, 7, 70
Takakeshi, Satomi ..................................................................... 107
Takase, Kenichiro ....................................................................... 5
Takahara, Ippei ........................................................................... 50
Takenaka, Masato ....................................................................... 3
Takekawa, Yoshiaki ................................................................... 105
Takekawa, Yoshitaka .................................................................. 100, 46, 46, 7, 70, 74, 75
Talero, Vivian A. ....................................................................... 34
Talken, Linda ............................................................................... 4, 88
Tamez, Dan .................................................................................. 77
Tamez, Daniel ............................................................................. 25, 5
Tan, Andy .................................................................................... 72
Tanaka, Rica ................................................................................. 18
Tanaka, Takaharu ....................................................................... 7
Tanaka, Zenji ............................................................................... 35
Tang, Meng-Xing ...................................................................... 11
Tansley, Geoff D. ....................................................................... 111, 112
Taskin, M. Ertan ......................................................................... 77
Taskin, Mustafa E. ..................................................................... 16
Tatrooles, Antone ....................................................................... 47, 52, 56, 79, 85
Tatrooles, Antone J. .................................................................... 50
Tatsumi, Ei-Suke .................................................................. 100, 105, 46, 46, 7, 70, 74, 75
Taylor, Joshua .............................................................................. 33
Taylor, Joshua O. ....................................................................... 33
Taylor, Michael ............................................................................ 84
Tchantchailievili, Vakhantak ...................................................... 52
Teal, John .................................................................................... 93
Thornton, Cathy A. .................................................................... 11, 21
Throckmorton, Amy ................................................................... 88, 89
Thuramalla, Naveen ................................................................... 90
Togo, Konori ............................................................................... 105
Tolpen, Sam ................................................................................. 10, 78
Tomaz, J. .................................................................................... 116
Tomaszewski, Mike .................................................................... 54
Toms, H. ....................................................................................... 19
Toomasian, John M. .................................................................... 82
Treadway, Joshua B. .................................................................... 80
Trejo, Alejandro ........................................................................... 48
Tricarico, Nicole M. ................................................................... 54, 65, 65, 66, 86
Triest, William E. ....................................................................... 107
Truong, Wanda ............................................................................. 44
Truskey, George A. ..................................................................... 9
Tsukuba, Yosuke ......................................................................... 40
Tsukiyama, Tonomori ..............................................................100, 46, 70, 74, 75
Tudorache, Igor ......................................................................... 98
Tuluca, Alexandra ...................................................................... 51
Tuzun, Eghem ............................................................................. 25, 63
Tuzun, Eghem ............................................................................. 26
Umaña, Juan B. ............................................................................ 31
Umeki, Akihide ........................................................................... 75
Usuda, Haruo ............................................................................... 97
Utah, Bruno ................................................................................. 23
Valerioso, Tracy B. ...................................................................... 49
<table>
<thead>
<tr>
<th>Name</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varghese, Rony</td>
<td>48, 51</td>
</tr>
<tr>
<td>Venado, Aida</td>
<td>106</td>
</tr>
<tr>
<td>von Segesser, Ludwig-Karl</td>
<td>44</td>
</tr>
<tr>
<td>Voskoboynikov, Neil</td>
<td>32, 41</td>
</tr>
<tr>
<td>Vrielink, H.</td>
<td>22</td>
</tr>
<tr>
<td>Wagner, Chad E.</td>
<td>54</td>
</tr>
<tr>
<td>Wagner, William R.</td>
<td>26, 91</td>
</tr>
<tr>
<td>Wagoner, Scott</td>
<td>105</td>
</tr>
<tr>
<td>Wakatsuki, Mariko</td>
<td>36</td>
</tr>
<tr>
<td>Walsh, Kelly M.</td>
<td>63</td>
</tr>
<tr>
<td>Wang, Cuiuen</td>
<td>107, 109</td>
</tr>
<tr>
<td>Wang, Daniel Y.</td>
<td>44</td>
</tr>
<tr>
<td>Wang, Dongfang</td>
<td>101, 102</td>
</tr>
<tr>
<td>Wang, Jian</td>
<td>91</td>
</tr>
<tr>
<td>Wang, Yao-Chang</td>
<td>45</td>
</tr>
<tr>
<td>Wang, Yaxin</td>
<td>74</td>
</tr>
<tr>
<td>Wang, Yu</td>
<td>13</td>
</tr>
<tr>
<td>Warnecke, Gregor</td>
<td>98</td>
</tr>
<tr>
<td>Watanabe, Yukihiro</td>
<td>5</td>
</tr>
<tr>
<td>Watkins, A C.</td>
<td>104, 93</td>
</tr>
<tr>
<td>Wearden, Andrew P.</td>
<td>14</td>
</tr>
<tr>
<td>Wearden, Peter D.</td>
<td>91, 92</td>
</tr>
<tr>
<td>Weaver, Jason D.</td>
<td>6</td>
</tr>
<tr>
<td>Webb, Melissa K.</td>
<td>91</td>
</tr>
<tr>
<td>Weeks, Brad R.</td>
<td>53, 80</td>
</tr>
<tr>
<td>Weeks, Phillip</td>
<td>51</td>
</tr>
<tr>
<td>Weinberg, Peter D.</td>
<td>11</td>
</tr>
<tr>
<td>Weiner, Daniel</td>
<td>68</td>
</tr>
<tr>
<td>Weiss, William</td>
<td>30, 59, 82, 83, 85, 94, 94</td>
</tr>
<tr>
<td>Weiss, William J.</td>
<td>29</td>
</tr>
<tr>
<td>Welsh, Kerry</td>
<td>70</td>
</tr>
<tr>
<td>Whitesides, George</td>
<td>37</td>
</tr>
<tr>
<td>Wiegmann, Bettina</td>
<td>98</td>
</tr>
<tr>
<td>Wieloch, Rudi</td>
<td>7</td>
</tr>
<tr>
<td>Wigger, Mark</td>
<td>65</td>
</tr>
<tr>
<td>Wille, Keith</td>
<td>106</td>
</tr>
<tr>
<td>Williams, Phil</td>
<td>113</td>
</tr>
<tr>
<td>Wilmot, Ivan</td>
<td>83</td>
</tr>
<tr>
<td>Witer, Lucas J.</td>
<td>82</td>
</tr>
<tr>
<td>Wittmer, Kory P.</td>
<td>33, 33</td>
</tr>
<tr>
<td>Witt, V.</td>
<td>121</td>
</tr>
<tr>
<td>Wolman, Justin</td>
<td>76, 76, 78</td>
</tr>
<tr>
<td>Wong, Kin</td>
<td>10</td>
</tr>
<tr>
<td>Woolley, Joshua R.</td>
<td>26</td>
</tr>
<tr>
<td>Wright, G A.</td>
<td>12</td>
</tr>
<tr>
<td>Wu, Miaozong</td>
<td>107, 109</td>
</tr>
<tr>
<td>Wu, Te-Chiu</td>
<td>45</td>
</tr>
<tr>
<td>Wu, Zhongjun</td>
<td>23</td>
</tr>
<tr>
<td>Wu, Zhongjun J.</td>
<td>104, 106, 62, 93</td>
</tr>
<tr>
<td>Xiaodong, Zhu</td>
<td>45</td>
</tr>
<tr>
<td>Yaegashi, Nobuo</td>
<td>97</td>
</tr>
<tr>
<td>Yamada, Akihiro</td>
<td>40</td>
</tr>
<tr>
<td>Yamaji, Satoru</td>
<td>35</td>
</tr>
<tr>
<td>Yamane, Takashi</td>
<td>8</td>
</tr>
<tr>
<td>Yamauchi, Shinobu</td>
<td>1, 107, 2, 3, 3, 3</td>
</tr>
<tr>
<td>Yambe, Tomoyuki</td>
<td>40</td>
</tr>
<tr>
<td>Yanagida, Roh</td>
<td>102</td>
</tr>
<tr>
<td>Yang, Fuqian</td>
<td>101</td>
</tr>
<tr>
<td>Yao, Atsushi</td>
<td>41</td>
</tr>
<tr>
<td>Yeager, Eric</td>
<td>30</td>
</tr>
<tr>
<td>Yeager, Torin</td>
<td>113</td>
</tr>
<tr>
<td>Yee, Brian</td>
<td>37</td>
</tr>
<tr>
<td>Yeh, Chi-Hsiao</td>
<td>45</td>
</tr>
<tr>
<td>Yeh, Justin</td>
<td>90</td>
</tr>
<tr>
<td>Yokoi, Ryo</td>
<td>99, 99</td>
</tr>
<tr>
<td>Yorizumi, Keiichi</td>
<td>3</td>
</tr>
<tr>
<td>Yoshida, Masahiro</td>
<td>95</td>
</tr>
<tr>
<td>Yost, Gardner</td>
<td>50, 56, 69, 69</td>
</tr>
<tr>
<td>Yu, Jane</td>
<td>11</td>
</tr>
<tr>
<td>Yu, Shiqiang</td>
<td>93</td>
</tr>
<tr>
<td>Zafar, Farhan</td>
<td>83</td>
</tr>
<tr>
<td>Zanetti, Margaux</td>
<td>5</td>
</tr>
<tr>
<td>Zellers, Thomas M.</td>
<td>91</td>
</tr>
<tr>
<td>Zeng, Zijing</td>
<td>2</td>
</tr>
<tr>
<td>Zhang, Jiafeng</td>
<td>106</td>
</tr>
<tr>
<td>Zhang, Tao</td>
<td>23</td>
</tr>
<tr>
<td>Zhao, Guangfeng</td>
<td>101</td>
</tr>
<tr>
<td>Zhao, Rong</td>
<td>93</td>
</tr>
<tr>
<td>Zhou, Bin</td>
<td>11</td>
</tr>
<tr>
<td>Zhu, Liqun</td>
<td>4, 88</td>
</tr>
<tr>
<td>Ziegler, Luke A.</td>
<td>14</td>
</tr>
<tr>
<td>Zifir, Jeffrey B.</td>
<td>47</td>
</tr>
<tr>
<td>Zimpieter, Daniel</td>
<td>58</td>
</tr>
<tr>
<td>Zulkefli, Nur E. Binti</td>
<td>57</td>
</tr>
<tr>
<td>Zwischenberger, Joseph</td>
<td>101, 102</td>
</tr>
<tr>
<td>Zwischenberger, Joseph B.</td>
<td>102</td>
</tr>
</tbody>
</table>