A NOVEL NEUROVASCULAR STENT COVERED IN STRETCHABLE THIN FILM NiTi SIGNIFICANTLY DECREASES FLOW INTO A WIDE-NECK ANEURYSM *IN VITRO*

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Objective: To evaluate the *in vitro* hemodynamic changes that occur after deployment of a novel, stretchable, thin film NiTi microstent in a cerebral aneurysm model. **Methods:** Low profile neurovascular thin film stents were constructed by covering commercially available Boston Scientific Neuroform stents with the highly stretchable (> 400% elongation) thin film NiTi (S-TFN), manufactured by patterning thin film NiTi. Stents were deployed in an *in vitro* wide-neck aneurysm model which was constructed by PDMS molding methods, commonly used for rapid prototyping. 5 and 10μm polystyrene particles suspended Glycerol and DI water (58.5:42.5) mixture was used for flow pattern and velocity analysis. Continuous and pulsatile flow was applied at arterial velocities (i.e., 0.5 – 1.0 m/sec) seen in a CNS artery, 4mm in diameter. Florescent and high speed microscopic images were used to visualize the changes in flow patterns and to trace the particle velocities in the aneurysm sac. **Results:** Deployment of a bare Neuroform stent reduced the neck flow velocity to 67.25±0.8% and intra-aneurysmal flow velocity to 22.3±0.3%. However, the intra-aneurysmal flow velocities were reduced approximately 88±3.6% after placement of the S-TFN microstents. Specifically, flow velocities in the upper planes of the neck showed 96.9±0.9% reduction compared to the model without S-TFN microstents. **Conclusion:** S-TFN microstents significantly reduce flow velocity and alter flow patterns in wide neck aneurysm sacs after deployment. This significant reduction has great potential to promote thrombosis in the aneurysm sac and may represent a more effective way to treat cerebral aneurysms.

CHITOSAN/GELATIN MODIFIED FILM FOR USE IN PREVENTION OF POSTOPERATIVE PERITONEAL ADHESIONS

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Postoperative adhesions remain a significant complication of abdominal surgery and can result in pain, infertility, and potentially lethal bowel obstruction. Pharmacotherapy and barrier devices have reduced adhesion formation to varying degrees in preclinical studies or clinical trials; However complete prevention of adhesions remains to be accomplished. As a part of our ongoing effort to develop a biodegradable film for use as an anti adhesion barrier based on gelatin/chitosan. We produced Blends between chitosan (CS) and gelatin (G) with various compositions (CS/G 20/80, 40/60, 60/40, 80/20 w/w), as candidate materials for prevention of postoperative abdominal adhesion. Different amounts of glutaraldehyde were used to crosslink CS/G blends. Several methods such as infrared analysis, Scanning Electron Microscopy (SEM), XRD, dissolution and swelling tests were used to evaluate the effects of composition and crosslinking on the samples physico-chemical properties. Mechanical properties of the crosslinked samples were also determined by stress–strain and creep tests. The in vitro degradation in PBS (pH 7.4) in the presence of 1.5 mg/ml lysozyme and in vitro cytotoxity test on human fibroblasts cells were determined. Finally, *In vivo*evaluation test in Rats showed that modified films can remain during the critical period of peritoneal healing and do not provoke any inflammation or adverse tissue reaction and can significantly reduce adhesion.

DEVELOPMENT OF A NEW ANTI-THROMBOGENIC CEREBRAL STENT USING ION BEAM SURFACE MODIFICATION – A FIVE YEAR ANIMAL STUDY

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Background: Recently cerebral stents have been reported excellent outcomes in patients with acute intracranial occlusions in whom other recanalization methods have failed. However several problems (rethrombosis, cerebral hemorrhage, long-term durability etc.) exist after stent implantation. Purpose of this study is to develop a new anti-thrombogenic cerebral stent using ion beam surface modification. **Method:** Thirty self-expanding mesh stents were fabricated from Ti-Ni metal wire with a dimention of 4mm(D) × 25mm(L) × 0.15mm(T). Twenty stents were coated with type-1 collagen and irradiated with a He^+ion beam(ion stent group). Ten stents had no treatment(non-ion stent group). The stents were implanted into the right and left femoral arteries of 15 beagle dogs. Heparin(100units/kg) was administered intravenously before implantation. Following stents implantation, no antiplatelet or anticoagulant drugs were administered. **Results:** The 1-month patency rate for the non-ion stent group was 10%(1/10) and for the ion stent group was 80%(16/20). P=0.0004 by Fisher's exact test. Six ion stents ware extracted to make histopathologic examination with thin neointima formation. Ten ion stents remain patent after 5 years with no antiplatelet or anticoagulant drugs. Scanning electron microscopy showed that the neointima surface was covered with a compleate confluent layer of endothelial-like cells. **Conclusion:** A He^+ion-implanted collagen coated Ti-Ni self-expanding stents provides excellent antithrombogenisity and biocompatibility. This "next-generation" ion stent offers a promising new cerebral stent.

EVALUATION OF CELL PROLIFERATION POTENTIAL ON A FIBROUS SCAFFOLD STRUCTURE

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Stereoscopic design of artificial scaffolds is required for evaluating the construction of microscopic extracellular environments and complex three-dimensional structures. Electrospinning is an effective method for fabricating nano- to microscale fibers that correspond to the structure and function of the extracellular matrix. This study demonstrates the great potential of cellular adhesion and proliferation for fabricating nano- to microscale segmented polyurethane scaffolds. Nanofiber (nF), microfiber (mF), and mixed nano/microfiber (nmF) scaffolds were prepared using an electrospinning method. The fiber diameters of the electrospun scaffolds were 0.82±0.16 μm, 5.07±0.65 μm, and 0.79±0.15 μm or 5.65±0.78 μm for nF, mF and nmF, respectively, which were measured using scanning electron microscopy. Porosity of the electrospun scaffolds was 48.1%, 77.1%, and 61.6% for nF, mF, and nmF scaffolds, respectively. Mouse fibroblasts (NIH3T3) were used for cell affinity studies. The NIH3T3 cells proliferated on the mF scaffold with high porosity as determined by 3-(4,5-dimethyl-thiazoyl) −2,5-diphenyl-SH-tetrazolium bromide (MTT) assay. In addition, the cells infiltrated into the mF fibrous scaffold. However, cell productivity was improved significantly in the nF scaffold. In conclusion, nano/microfibers have the potential to perform effective cell proliferation by controlling the mixing ratio of the fibers.

BLOOD DISPERSION IN CAPILLARIES

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Purpose: The aim of our theoretical study is to asses pulsatile and nonpulsatile flows and explain why pulsatile flow is better than nonpulsatile one. One experimental study demonstrated very clearly that pulsatile flow perfused larger account of capillaries and caused an increase in the erythrocyte velocity in capillaries. So we could claim that physiological pulsatile flow creates *larger blood dispersion in capillaries* than nonpulsatile flow. **Methods:**

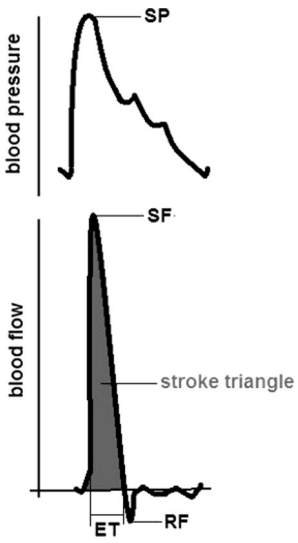

Fig. Blood pressure and blood flow in the ascending aorta. SP – systolic pressure, SF – systolic flow, ET – ejection time, RF – retrograde flow (coronary circulation).

The systolic flow (SF) determinates systolic pressure (SP). The systolic flow is variable and its value depends on the resistance of the vascular bed (on "vascular bed size"). The area of the stroke triangle is stroke volume (SV). The nonpulsatile flow represents smaller dispersion blood flow in capillaries, decrease in count of perfunded capillaries, and increase in capillary shunting. **Summary of Results:** The pulsatile flow causes larger tissue perfusion due to larger blood dispersion in capillaries. The creation of sufficient blood dispersion, hence sufficient flow throughout all capillaries depends not only on adequate total flow but also on generation of peak flow in the systemic vascular bed, which generates non hypotensive pressure maximum with characteristic pressure wave pattern.

VA ECMO SETTING OPTIMALIZATION IN PATIENTS SUFFERING FROM CARDIOGENIC SHOCK

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Purpose of Study: VA ECMO for children has been used as a treatment of last resort with relatively positive outcomes. The results of VA ECMO therapy for adult patients are less satisfactory. The negative outcomes for adult may be explained by insufficient microcirculation (blood dispersion) caused by a low hybrid flow generated by the nonpulsatile pump and a failing heart. Our theoretical study proposes solutions - increasing hybrid systemic overall flow using more ECMO componnents. **Methods:** The pump flow for pediatric patients is generally calculated in ml/kg/min and the recommended rate is 100–120ml/kg/min for children. The pump flow for adult patients calculated in ml/kg/min or ml/min/m2 and recommended rate is 70–80ml/kg/min. The recommended hybrid flow for adults is lower than recommended hybrid flow for children. Cannulation of a single groin is a impediment for a achievement of a higher nonpulsatile pump flow for reason of the limiting pressure in the lines. **Summary of Results:** Changes in the method of implanting the ECMO should aim to maximize hybrid flow. Cannulation of both groins and the introduction of two arterial and two venous cannulas in the femoral vessels should achieve a higher flow rate under the same limiting pressure in the lines as cannulation of a single groin.

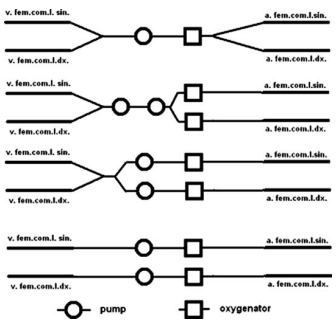

Fig. Possible connection of ECMO componnents (schematic views).

LIVER REGENERATION BY PORTAL CELL THERAPY: TRANSPLANTED HUMAN CORD BLOOD DERIVED UNRESTRICTED SOMATIC STEM CELLS GENERATE HEPATOCYTE-LIKE CELLS THROUGH TRANSDIFFERENTIATION BUT NOT CELL FUSION

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Liver resectability in patients with liver tumors is often limited by low future remnant liver volume (FRLV). Partial portal vein embolizattion (PVE) is an established method for induction of compensatory liver expansion in untreated segments prior to partial hepatectomy due to tumor disease. In a clinical setting it has been demonstrated that transplantation of adult stem cells promotes liver regeneration. Aim of our preclinical study was to evaluate the impact of transplanted human pluripotent cord blood derived unrestricted somatic stem cells (USSC) on liver regeneration and identify the underlying mechanisms in an ovine model. We performed partial PVE of the right liver lobe and grafted USSC in the portal venous system of the left liver lobe. After four weeks livers were explanted and analysed for transdifferentiation of USSC into hepaocytes by histopathological examination and for fusion of USSC with recipient hepatocytes by single-cell-PCR) and Western blotting. These studies revealed that transplanted human USSC differentiate into hepatocytes and produce human Albumin. No ovine DNA was found in the hepatocytes with a human phenotype. Transplantation of USSC enhances the number of viable hepatocytes in liver disease by transdifferentiation and opens new perspectives for the therapy of loss of hepatocytes.

OPTIMAL IDENTIFICATION OF NEED FOR RIGHT VENTRICULAR SUPPORT USING COST-SENSITIVE DECISION TREE

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Purpose: Right ventricular support (RVAD) following left ventricular assist device (LVAD) implantation increases morbidity and mortality, however predicting the need for RVAD prior to surgery remains difficult. Predictive models such as the Right Ventricular Failure Risk Score (RVFRS) can stratify RV failure risk, but identify only 35% patients with RV failure. We develop a misclassification cost-sensitive decision tree to optimally predict the need for RVAD. **Methods:** A retrospectively collected dataset was used, including clinical, laboratory, echocardiographic and hemodynamic variables for 81 LVAD alone patients and 12 LVAD patients receiving an RVAD. Support vector machine (SVM) with recursive feature elimination (RFE) facilitates variable selection. A decision tree was built according to the highest information gain ratio. It also considers differential costs of two types of misclassification – failing to initially implant an RVAD when needed is twice as expensive as implanting an RVAD unnecessarily. **Results:** Based on 10-fold cross validation, the performance of this model was evaluated. The detailed prediction is summarized in Table 1.

Table 1.

	Prediction	
Cost-Sensitive Decision Tree	LVAD Alone	Post-RVAD in LVAD
Reality		
LVAD alone	72 (88.9%)	9 (11.1%)
Post-RVAD in LVAD	3 (25%)	9 (75%)

Conclusion: We establish a cost-sensitive decision tree using 5 variables. It correctly predicts *88.9% of patients who only needed LVAD support and 75% of those who needed RVAD support after LVAD* by 10-fold cross validation, which outperforms the recent RVFRS. This model may provide better triage of patients preoperatively to LVAD alone or planned biventricular support.

AUXILIARY ARTIFICIAL HEART ENDURANCE TEST WITH A MOCK CIRCULATION LOOP SYSTEM

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We are performing an endurance test with a mock circulation loop system to obtain data about durability and reliability analysis on the Auxiliary Total Artificial Heart (ATAH). In this study, three mock circulation loop systems with two chambers were built. The systems consists of a two chamber acrylic box, where arterial pressure, system compliance, temperature are simulated and a flow sensor and a pressure transducer are coupled for obtaining data. Corrosive properties of blood are also simulated. Fluid viscosity was not considered. Endurance test duration will be registered for durability analysis and preliminary reliability data for risk management tools. So far, none of the devices used in this study have registered any failure occurrences and no problem with the mock loop systems was noticed.

SUSTAINED RELEASE NITRIC OXIDE FROM LONG LIVED CIRCULATING NANOPARTICLES

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Given the critical importance of nitric oxide (NO) in regulating pathophysiologic states involving the vasculature, controlled and sustained intravascular NO delivery could profoundly impact current treatment of cardiovascular disease states. This work presents physiological responses to circulating NO releasing hybrid hydrogel/glass nanoparticles (NO-np). In this system, hydration controls the release of NO generated through thermal reduction of nitrite trapped within the dry particles.[1] In the current work, we present data showing that, in a dose-dependent manner, circulating NO-np increased exhaled NO, decreased blood pressure, and induced microvascular dilatation over several hours, all without inflammatory response. Conversely, control nanoparticles (made without nitrite and therefore lacking NO release) did not produce hemodynamic changes. The sole observed adverse event from circulating NO-np was methemoglobin (metHb) formation inherent to intravascular release of NO. Hypertension and vasoconstriction induced by NO synthase inhibition was reduced by intravenous administration of NO-np. NO-np physiological responses clearly suggest their potential as a therapeutic agent for cardiovascular, inflammatory, and thrombotic disorders, and as a promising tool to promote understanding of NO signaling mechanisms.

NITRIC OXIDE (NO) GENERATING SILICONE HOLLOW FIBERS

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The artificial surfaces of oxygenators clot blood and subsequently increase blood flow resistance, decrease gas transfer, and generate thromboemboli. Oxygenator fibers represent the majority of the surface area of artificial lungs and are thus the primary source of clot generation. To prevent clotting, oxygenator fibers were created that generate and release nitric oxide (NO) from endogenous nitrosothiols in blood. Three μm Cu particles (Sigma Aldrich, St Louis, MO) at 10 weight percent were blended into silicone (Nusil Silicone Tech, CA) and extruded into hollow fibers (n=6) and then oxidized. Structural and surface characterization was performed using energy-dispersive X-ray spectroscopy (EDS) by means of SEM (Phillips XL30FEG) and Image J. Sectioned fibers' (SA= 0.139 cm^2) NO flux rate was also measured *in vitro* by chemiluminescence (Sievers 280i NOA GE, Boulder, CO) using 1μM S-nitrosoglutathione as the NO-donor.

Final fibers had an outer diameter of 350$\pm$17 μm, a wall thickness of100$\pm$5 μm, and the exposed Cu was 8.41$\pm$0.48% of the total surface area. Peak NO flux generated from the fibers was $1.01\pm0.28 \times 10^{-10}$ mol/cm^2/min, within the published range of human endothelial NO flux ($0.5–4.0 \times 10^{-10}$ mol/cm^2/min). However, previous clotting assays with these surfaces suggests a greater surface exposure of Cu is necessary to significantly reduce coagulation. Thus, future work will examine a means of focusing the copper content on the fiber surface.

COMPUTATIONAL ASSESSMENT OF TWISTED CAGE FILAMENTS FOR AN INTRAVASCULAR AXIAL FLOW BLOOD PUMP FOR CAVOPULMONARY ASSISTANCE

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Purpose: We are developing an intravascular blood pump to support the cavopulmonary circulation in patients with a failing single ventricle physiology. To support the pump in the vessel, an outer protective cage was designed with radially arranged filaments as touchdown surfaces to protect the vessel wall. This study examined the geometry of the protective cage of filaments and blood pump. **Methods**: Three models of the protective cage, including fully twisted filaments, straight filaments, and partially twisted filaments, were created. Computational fluid dynamics (CFD) analyses were performed on each model to numerically predict the hydraulic performance of the pump and filaments. We then compared the performance of each filament design. A blood damage analysis was also performed on the models to assess the probability of blood trauma. **Results**: The partially twisted and straight filament configuration demonstrated an acceptable hydraulic performance by delivering 1 to 4 L/min at rotational speeds of 7,000 to 10,000 RPM and generating pressure rises of 2 to 20 *mmHg* with low blood damage indices. Expected trends in the hydraulic performance of the pump models were found. **Conclusions**: This study represents another design phase of the pump and protective cage of filaments. Validation of these flow and performance predictions will be completed in the next round of experimental testing with blood bag evaluation.

ADVANCES IN ARTIFICIAL HEARING

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Aim: A brief introduction into implantable hearing systems is given. A pilot clinical study a novel implantable hearing system for combined hearing loss (DACS: Direct acoustical cochlear stimulator) is presented in detail. **Methods:** DACS is based on the principle of a power-driven stapes prosthesis. It consists of an implantable electromagnetic transducer, which transfers acoustic energy directly to the inner ear, and an audio processor worn externally behind the implanted ear. The device is implanted using a specially developed retromeatal microsurgical approach. After removal of the stapes, a conventional stapes prosthesis is attached to the transducer and placed in the open window to allow direct acoustical coupling to the inner ear fluid. **Results:** Four patients were implanted with an investigational DACS device. The hearing threshold of the implanted ears before implantation ranged from 78 to 101 dB (Air conduction, pure tone average PTA, 0.5 – 4 kHz) with air-bone-gaps of 33 to 44 dB in the same frequency range. Postoperatively, substantial improvements in sound field thresholds, speech intelligibility as well as in the subjective assessment of everyday situations were found in all patients. Two years after the implantations, monosyllabic word recognition scores in quiet at 75 dB improved by 45% to 100% when using the DACS. Because of a second stapes prosthesis which was implanted in parallel to the DACS, Patients already had some improvement when the DACS was switched off. No device related serious medical complications occurred and all patients have continued to use their device on a daily basis for over two years.

ASSESSING SHEAR-INDUCED PLATELET ACTIVATION: IN VITRO COMPARISON BETWEEN HUMAN AND BOVINE BLOOD

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Purpose: To develop potential test procedures for the in vitro evaluation of platelet activation during exposure of flowing blood to medical devices, this study compared platelet responses to shear stress between human and bovine blood. **Methods:** Fresh whole blood samples (human and bovine) anticoagulated with heparin or ACDA (Anticoagulant Citrate Dextrose, solution A) were exposed to a series of shear stresses ranging from 0 to 40 Pa for 120 sec using a cone-plate rheometer. Following stimulation, platelet activation was characterized using multiple markers including platelet counts, flow cytometry measurement of platelet P-selectin expression, and ELISA analysis of serotonin and thromboxane B2 concentration in blood plasma. **Results:** All of the platelet markers increased in magnitude with increasing shear stress, except for the platelet counts which decreased. A summary of the sensitivity of each platelet activation marker to shear stress stimulation is shown in the table below. In general, human blood platelet markers were more responsive to shear stress than bovine platelet markers. ACDA anticoagulation was preferred over heparin for human blood, but heparin was preferred for bovine blood. While bovine blood is often used during comparative in vitro hemolysis testing of medical devices, its use for platelet activation studies may be limited.

Comparison of platelet activation marker sensitivity to shear stress stimulation for human and bovine blood. Key: (+++) very sensitive, (-) minimally responsive.

Table 1.

	Human Blood		Bovine Blood	
Markers	ACDA	Heparin	ACDA	Heparin
Platelet count	+++	++	−	−
p-Selectin	+++	++	−	+
Thromboxane	++	−	+	+
Serotonin	+	+	−	++

APPARATUS FOR MEASURING THE EFFECT OF APICAL TORSION ON FUNCTIONING ISOLATED HEARTS

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The aim of this project is to test the feasibility of using mechanical apical torsion as a means to support the failing heart. We hypothesize that actively turning the apex of the heart will restore a significant portion of the pumping action lost to congestive heart failure by directly wringing blood from the heart while simultaneously lowering wall stress. To test this hypothesis we have designed a custom isolated heart apparatus comprising an in vitro perfusate circuit, cardiac pacing unit, rotary stepper-motor, and apical interface device (AID). The protocol for testing live hearts is as follows. First, hearts harvested from 50–60 kg pigs are cannulated and positioned vertically on the AID so that the apex is free to rotate. The cardiac base is then secured to a fixed mounting ring via cannulae attached to the aorta, pulmonary artery, superior vena cava and left atrium to simulate in vivo attachment to the great vessels. Hearts are perfused in Langendorff mode until normal sinus rhythm is restored. The circuit is then reconfigured to allow the heart to function normally in four-chamber working mode in preparation for torsion experiments. During testing the motor is triggered by the cardiac pacing signal (80 bpm) and the twist parameters adjusted so that applied torsion is completed during systole. Tests performed using anatomically accurate silicone heart models (human, dilated) indicate that rotational volume displacement varies linearly with twist angle, with LV/RV stroke volumes reaching 16.3±1.5 and 13.8±2.0 mL respectively with 30° rotation of the apex. These values may be even greater in working hearts due to reduced myocardial wall stress leading to improved myofibrillar shortening.

NOVEL PERCUTANEOUS IMPLANT MODEL FOR PRECLINICAL TESTING

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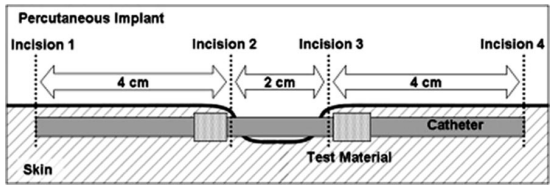
Animal models used to evaluate the skin interface of percutaneous devices typically result in significant implant loss due to automutilation. We have developed a novel percutaneous implantation scheme that uses a double-sided implant. The percutaneous implant (PI) consisted of a section of polyurethane catheter 10 cm long, with a test (titanium (Ti) mesh) or control material (Dacron) affixed to each end of the catheter.



Ten rabbits were implanted with 2 sets of PIs (40 total) for 3 or 6 wks and 30 rats were implanted (60 implants) for 6 wks. Endpoints were histological evaluation and mechanical analysis of the tissue-implant interface, respectively. All devices were stable at explant, with no signs of infection. Automutilation of the implant was limited in the rat study, and eliminated in the rabbits, and all implants were recovered in both studies. The explants provided histological evidence that there was greater connective tissue ingrowth into the Ti mesh compared to Dacron at both 3 and 6 wks. The modulus and tensile load at primary and ultimate failure were greater for a "deep" configuration of Ti mesh compared to both a "shallow" Ti mesh as well as the Dacron. This novel implantation method provides excellent device recovery in both models for evaluating percutaneous devices, with the ability to detect differences in tissue reaction and mechanical fixation between the percutaneous biomaterials.

EVALUATION OF OXYGEN EXCHANGE IN TOTAL LIQUID VENTILATION WITH A BUBBLE GAS EXCHANGER

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Total liquid ventilation (TLV) using perfluorochemicals (PFC) with a dedicated liquid ventilator consist to ventilate completely filled lungs with a tidal volume of oxygenated PFC. A gas exchanger must be used to remove CO_2 from the PFC by saturating it with O_2 and medical air. The objective of this study is to validate the efficiency of a bubble oxygenator during TLV.

Five healthy newborn lambs (<4 days old, 2.5–3.6 kg) were intubated, anaesthetized and paralysed. Our own liquid ventilator, Inolivent-4, was used to perform TLV with a dedicated bubble oxygenator using Perfluorodecalin (F2-Chemicals, UK) as PFC. Various fraction of oxygen in air bubbles (FO_2) and minute ventilation (Vmin) were assessed. Thirty minutes after reaching each new setting, the partial pressure of oxygen was measured with a dedicated sensor (Fibox 3 LCD, Presens, Germany) in the PFC coming from the lungs (PeO_2) and the PFC sent to the lungs (PiO_2). A blood sample was also drawn for PaO_2 and $PaCO_2$ analysis. The experimental protocol was approved by our institutional Ethics Committee for Animal Care and Experimentation.

When Vmin varied from 120 to 180 ml/min/kg (FO_2 of 100%), PiO_2 values were up to 713±7 mmHg while PeO_2 averaged 574±29 mmHg; measured PaO_2 raised from an average of 163±46 to 262±45 mmHg while $PaCO_2$ decreased from 50±4 to 40±4 mmHg. Increasing FO_2 from 65 to 100% (Vmin of 180 ml/min/kg) increased PiO_2 from 478±7 to 707±13 mmHg, PeO_2 from 345±31 to 587±23 mmHg, PaO_2 from 99±47 to 185±60 mmHg while $PaCO_2$ averaged 44±4 mmHg.

To conclude, the PFC can be saturated in oxygen (FO_2=100%) and PaO2 can be modulated as needed by varying FO_2, without altering $PaCO_2$ significantly.

3-D RECONSTRUCTED PATIENT-SPECIFIC CAVOPULMONARY CONNECTION WITH MECHANICAL ASSISTANCE IN THE INFERIOR VENA CAVA

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Purpose: This study numerically evaluated the performance of an intravascular, axial flow, blood pump for Fontan patients. A patient-specific total cavopulmonary connection (TCPC) was reconstructed from magnetic resonance imaging data, and the intravascular pump model was placed into the inferior vena cava (IVC) to simulate mechanical support. **Methods:** Computational fluid dynamics (CFD) analyses were performed to predict the hydraulic performance of the pump under varying physiologic flow rates and pulmonary arterial pressures. Pressure-flow characteristics, energy generation calculations, and fluid streamlines were also carefully evaluated. **Results:** Simulations indicated that the pump produces pressure rises of 1–10 mmHg for rotational speeds of 2000–5000 RPM and flow rates of 1–4 L/min, which are acceptable for Fontan patients. A rotational velocity component was noted at the outlet of the pump at the TCPC. The pump was to able to augment the energy of the fluid, and, as anticipated, energy losses in the patient-specific TCPC without a pump in IVC increased at higher flow rates. All trends for the pressure and flow conditions met expectations. **Conclusions:** These results support the continued development of this blood pump to produce a new therapeutic alternative for the clinical treatment of patients with failing Fontan physiology.

EFFECTS OF STORAGE TIME AND ABO GROUP ON MALE AND FEMALE DONOR RED BLOOD CELL SUSPENSION VISCOELASTICITY

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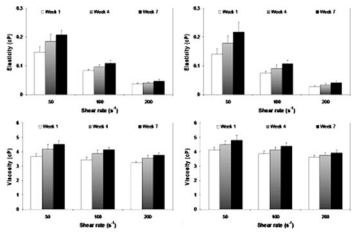
For several decades it has been known that red blood cell (RBC) deformability progressively decreases during storage. Yet, the potential effects of blood type and gender on the deformability of stored donor RBCs are not well known. The objective of this study was to determine the effects of storage time and ABO group on male and female donor RBC deformability through measurement of RBC suspension viscoelasticity (VE). Leukoreduced RBC units from 12 male and 12 premenopausal female donors (three from each ABO group) were obtained from the local FDA licensed blood center and tested at 1, 4 and 7 weeks of storage at 1–6°C. Hematocrit of each RBC suspension was adjusted to 40% using Dulbecco's PBS and VE was measured using a Vilastic-3 Viscoelasticity Analyzer (Vilastic Scientific, Inc.). Both male and female donor RBCs demonstrated statistically significant increases ($p<0.05$) in viscosity and elasticity at equivalent shear rates during 7 weeks of storage (Figure 1). An increase in RBC suspension elasticity calculated for all shear rates was ~15% (female) and ~25% (male) at Week 4 and ~30% (female) and ~55% (male) at Week 7 compared to Week 1. An increase in elasticity signifies a proportional decrease in RBC deformability. No statistically significant differences in viscosity or elasticity were observed between the ABO groups for both genders.



TWO-POOL PHYSICAL SIMULATOR OF THE INTER-COMPARTMENTAL MASS TRANSFER DURING DIALYSIS

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A two-pool simulator of fluid and mass transfer among patient body compartments during hemodialysis (HD) was developed to characterize commercial dialyzers taking into account dynamic mass transfer effects. **Materials and Methods:** The two-pool simulator replicates intra- and extra-vascular compartments: the former by means of a rigid reservoir and a set of semi permeable hollow fibers, the latter by means of a compliant reservoir. The simulator design was optimized (in terms of fiber number, reservoir dimensions, etc.) by an *ad hoc* developed computational model. The set-up was then tested by simulating HD procedures with commercial filters. Blood samples were withdrawn from the simulator to evaluate urea and electrolytes (Na^+, Ca^{++}, Cl^-, Mg^{++}, K^+) concentration. Intra- and extra-vascular volumes were directly monitored on the set-up. The experimental results were compared with clinically measured data. **Results:** All electrolytes (except K^+) and urea concentrations showed good agreement with the clinical data (maximum shift 11%). K^+ concentration instead showed shifts of nearly 22%, probably due to the non replicated active mass transfer through the cellular membrane. Plasmatic volume profile showed good correlation with clinical patterns (0,24% shift) despite the tangled ultrafiltration rate setting on the simulator. **Conclusions:** The patient simulator satisfactorily reproduced electrolytes and volume profiles during a simulated HD thus showing reliability in testing dialyzers dynamic response. The device accuracy can be improved by reproducing active mass transfer through the cellular membrane as well as defining easier procedures to set ultrafiltration rate.

COMPLIANT THORACIC ARTIFICIAL LUNG DESIGN USING FLUID-STRUCTURE INTERACTION MODELING

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Thoracic artificial lungs (TALs) are being developed as a bridge to lung transplantation. Current TALs possess blood flow impedances greater than the natural lungs, which can result in abnormal pulmonary hemodynamics. Compliant TAL (cTAL) designs utilize a compliant housing to reduce TAL impedance. This study examined the effects of different inlet and outlet housing designs on cTAL impedance. SolidWorks computer aided design software was used to create models with varying housing geometries using inlet and outlet expansion angles, θ, of 15°, 45° and 90°; manifold heights, h, of ¼ and 1 in; and Biospan housing thicknesses, t, of 0.02 and 0.04 in. The expansion into and contraction out of the device becomes more gradual with a smaller θ and larger h. These models were imported into the ADINA computational fluid dynamics program and used for fluid-structure interaction analysis. Pulsatile blood flow was simulated for flow rates of 2, 4, and 6 L/min, heart rates of 60, 80, and 100 beats/min, and pulsatilities of 3.75 and 2. Inlet and outlet pressure and flow data were obtained and used to calculate model impedance. Results indicate device impedance increases as flow rate and pulsatility increases and heart rate decreases. At 4 L/min, 100 beats/min, and $t = 0.02$ in, zeroth harmonic impedance modulus, Z_0, for the 15°, 45°, and 90° device was 1.07, 1.16, and 1.38 mmHg/(L/min), respectively. First harmonic impedance modulus, Z_1, was 0.57, 0.71, and 1.11 mmHg/(L/min), respectively. Device impedance was reduced with smaller θ and t and larger h. Optimizing compliant housing geometry allows for reductions in cTAL impedance over previous TAL designs which had Z_0=1.8 mmHg/(L/min).

LEFT VENTRICULAR MECHANOENERGETIC COST OF BLOOD AND PLASMA VISCOSITY DURING HEMODILUTION

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This study investigates how changes in blood oxygen carrying capacity affect cardiac function, and how left ventricular energy is determined by the plasma expander viscosity. Experiments were performed in hamsters. Exchange volumes were defined as a fraction of blood volume (BV). **Moderate hemodilution** (n=5), exchanging 40% of BV with dextran 2 MDa (6.3 cp). **Severe hemodilution** (n=5), accomplished by two exchanges, first 25% of BV with dextran 70 kDa (3.0 cp), followed by 40% the BV with dextran 2 MDa. Left ventricular cardiac function was assessed with a miniaturized pressure-volume conductance catheter. Moderate hemodilution reduced hematocrit from 53±2% to 27+2%, and severe hemodilution from 50±3% to 17±2%, respectively. Cardiac output significantly increased from 10.4±1.8 to 13.34±3.20 ml/min after moderate hemodilution ($P<0.01$), and slightly increased from 10.0±1.7 to 10.8±1.1 ml/min after severe hemodilution. Moderate hemodilution decreased oxygen delivery by 24%, and severe hemodilution by 49%. Blood and plasma viscosities decreased to 3.6 cp and 2.1 cp after moderate hemodilution and to 3.0 cp and 2.0 cp after severe hemodilution, respectively. Mean arterial pressure (MAP) and heart rate (HR) decreased in both groups compared to baseline ($P<0.01$). However, there was no significant difference between groups for MAP and HR. Stroke work increased by 29% after moderate hemodilution compared to baseline ($P<0.05$), while it was not different from baseline after severe hemodilution. dP/dt_{max} after severe hemodilution was between 9–13% lower than after moderate hemodilution ($P<0.05$). Cardiac function was limited by blood oxygen content, and oxygen demand was determined by blood viscosity.

ROBUST SIMULATION OF CFD-PREDICTED HEMOLYSIS

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Numerical simulations excel at predicting the single-point performance characteristics of fluid handling devices. However, real world situations complicate the simulation process by introducing environmental variability and physical uncertainty, such as phenomenological models of turbulence, radiation, or blood damage. Such stochastic variability may be quantitatively addressed via error bars in experimental measurements. All flow simulations performed today are deterministic (or single-point) in nature and therefore do not handle this type of variability and physical uncertainty. Robust simulation is a new methodology designed to accept stochastic inputs and can compute the associated error/performance bounds on device simulation analogous to error bars associated with experimental testing. We applied robust simulation to a highly nonlinear biomedical problem of current interest, namely, CFD-predicted hemolysis. Using a stenotic nozzle geometry, we performed CFD analyses at various throat Reynolds numbers. Utilizing the Optimal hemolysis model, robust simulation predicted error bounds associated with uncertainties of shear stress, time exposure, blood viscosity, hematocrit, and three key parameters unique to our model. Robust simulation computed realistic bounds, instead of a single deterministic values, of device-induced hemolysis. Furthermore, cause-and-effect relationships were automatically discovered in the forensically quantified model input parameters that most contributed to hemolysis generation.

NUMERICAL AND EXPERIMENTAL INVESTIGATION OF THE FLOW THROUGH THE LVAD OUTLET CONDUIT-AORTA ANASTOMOSIS

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Purpose: Artificial assist devices offer a promising treatment option for patients with congestive heart failure, especially when the patient is not eligible for heart transplantation. New clinical evidence shows that in order to achieve clinical success, uniform flow fields at the inlet and at the outlet of a left ventricular assist device (LVAD) are as important as the flow through the LVAD. Due to the high rotational speeds of the rotary blood pumps, blood cells pass through the pump rapidly, without undergoing any deformation. However, even with optimized heart pumps fatal complications can occur because of the deformations around the inflow cannula or through outlet conduit-aorta anastomosis. This study investigates the blood flow through the LVAD outlet conduit-aorta anastomosis. **Method:** Numerical and experimental studies are performed. A patient-specific aorta geometry, which is scanned via computer tomography, is used to generate the CAD model for the numerical analysis. Effect of the anastomosis location and angle is investigated via flow simulations. Experiments are performed via 3-dimensional particle image velocimetry with simplified aorta geometry. **Results:** If the axes of the aorta and the outlet conduit make up a high angle, than large wall shear stresses occur on the aortic wall. Variation in the anastomosis location changes the extent of the reverse flow towards the aortic valve.

DELAYING BLOOD TRANSFUSION DURING EXTREME ANEMIA WITH PERFLUOROCARBON EMULSION

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To avoid unnecessary blood transfusions, physiologic transfusion triggers rather than exclusively hemoglobin-based transfusion triggers have been suggested. The objective of this study was to determine systemic and microvascular effects of using a perfluorocarbon-based oxygen carrier (PFCOC) in maintaining perfusion and oxygenation during extreme anemia. The hamster (55–65 g) dorsal skinfold window chamber model was used. Two isovolemic hemodilution steps were performed using 10% hydroxyethyl starch (HES) at normoxic conditions to hematocrit (Hct) of 19% (5.5 g_{Hb}/dl), point where the transfusion trigger was reached. Two additional hemodilution exchanges using the PFCOC Oxycyte™ and increasing FiO_2 to 1.0 were performed to reduce Hct to 11% (3.8 g_{Hb}/dl) and 6% (2.0 g_{Hb}/dl), respectively. No control group was used as this level of hemodilution with conventional plasma expanders is lethal. Systemic parameters, microvascular perfusion, functional capillary density (FCD) and oxygen tensions across the microvascular network were measured. At 6% Hct, the PFCOC maintained mean arterial pressure, cardiac output, systemic oxygen delivery (DO_2) and consumption (VO_2). As hematocrit was lowered from 11% to 6%, FCD, calculated microvascular DO_2 and VO_2 decreased, and extraction ratio (DO_2/VO_2) was close to 100%. Peripheral tissue oxygenation was not predicted by systemic oxygenation. PFCOC and hyperoxia were able to sustain life and partially provide systemic oxygenation during extreme anemia over the observation period. The PFCOC can work as a bridge until red cells are available for transfusion, or where additional oxygen required. However, there may be possible limitations in peripheral tissue oxygenation.

NONINVASIVE DIAGNOSIS OF DYSPHAGIA USING VIDEO IMAGES OF THROAT SURFACE MOVEMENT AND SWALLOWING SOUNDS

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As a new screening test method for dysphagia that is both quantitative and objective, we are studying a method of analyzing swallowing sounds based on time-frequency analysis. In our research to date, we have been collaborating with a company in the development of a device that records and plays back both videofluorography (VF) images and audio recordings of swallowing, and custom software that displays as well as analyzes the captured data. We have discovered from the analysis results that we can identify the causes for the generation of swallowing sounds, of which there are generally three sounds. However, patients who have difficulty swallowing tend to ingest food and drink by means of repeated, multiple, small swallowing actions. So, in addition to the swallowing sounds of direct interest in the present study, acceleration sensors placed on the surface of the throat also detect additional signals resulting from the movement of the throat surface and respiration both before and after swallowing. It is therefore difficult to identify swallowing sound signals from among all these signals. So, we examined to identify swallowing sounds by using video images of throat surface movement. Using a video camera, video of the throat surface movements was captured along with synchronized audio of swallowing sounds. Analysis of these images and sounds revealed that typical three swallowing sounds are coincided with the throat surface movements. We concluded from these results that it was possible to make a diagnosis of dysphagia noninvasively by analyzing the video images and the swallowing sounds.

NUMERICAL MODEL OF THROMBOSIS AND THROMBOEMBOLIZATION: MICROFLUID EFFECTS

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Objective: Microscopic phenomena associated with thrombus growth, consolidation, and embolization were described in a numerical model of blood flow in medical devices. Previously, commercial computational fluid dynamics (CFD) codes were utilized to predict flow characteristics in realistic devices using supercomputers. User-defined subroutines (UDSs) were added to predict the behavior of blood platelets and platelet-related agonists along with the flows. In this work, a UDS strategy that addresses the microfluidity of newly-forming thrombi and the embolism of consolidated thrombi, as suggested by experimental observations, was developed. **Methods:** Numerical descriptions of individual thrombi were added to existing thrombosis computer code. The microfluidity of forming thrombi was described in terms of shear-dependent adhesion and consolidation kinetics, with thrombus microtranslation accounted for using a pseudo-Lagrangian approach. Computational models of hemodialysis catheters (Mahurkar and Ash designs) and prototype flow cells were constructed. The geometries were drawn in SolidWorks® or Autocad® and were automeshed into tetrathedral meshes using StarDesign® software on a workstation with grid resolutions consistent with previous grid-independence studies. The transient CFD/thrombosis code was run for these models using Star-CD® software and a Portland Group fortran compiler on a Dell Linux Cluster. Convergence was confirmed at each time step for pressure, velocities, and chemical/cellular parameters. **Results:** The effects of the programmed phenomena will be illustrated with movies of the predicted thrombus growth and embolization.

ANALYSIS OF PULSATILE FLOW IN A QUASI-ANGIOSTENOSIS MODEL USING THE FINITE ELEMENT METHOD

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At anastomosis of AVF and AVG, hardening of blood vessels and stenosis occurs due to intravascular membrane thickening, resulting from the impact of jet-like blood flow on vein walls. As a result, when a shunt function is favorable a continuous "low pitch" shunt murmur changes into an intermittent "high pitch" shunt murmur. However, there are few examples that theoretically explain the relationship between the frequency characteristics of these kinds of shunt murmurs and the degree of angiostenosis. From this perspective, we used finite element method (FEM) analysis in an attempt to clarify the mechanism by which shunt murmurs are generated, and to theoretically describe how the characteristics of shunt murmurs vary in accordance with the degree of angiostenosis. We have developed an analysis model for angiostenosis that simulates AVF, and subsequentry applied a flow resistance model so that the pressure loss from the constriction of the quasi-angiostenosis model due to clamping could be incorporated into the FEM analysis. In addition, we attempted to analyze flow as a pulsatile flow, simulating blood pressure changes of an actual hemodialysis patient, is applied to the quasi-angiostenosis model. We found that the values of pressure and flow rate determined by FEM analysis at two outflow points, when there is pulsatile flow from inflow points on the artery side, agree very well with experimental values obtained by using a custom-desinged pulsatile flow system.

DIFFERENT FLOW CONDITIONS DO NOT ADVERSELY AFFECT INTEGRITY AND ACTIVATION OF THE ENDOTHELIAL SURFACE OF A NOVEL ARTIFICIAL GAS EXCHANGE MEMBRANE

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Purpose: Aiming towards the engineering of a bioartificial lung, the influence of different flow conditions on the integrity and activation of a confluent endothelial monolayer seeded onto a heparin/albumin coated hollow fiber gas exchange membrane (PMP) was investigated. **Methods:** Human cord blood derived endothelial cells (HCBEC) were seeded onto PMP membranes. The endothelialized PMP membranes were perfused for different time periods in flow chambers with different flowrates. The integrity of the monolayer before and after perfusion was qualitative verified by fluorescence microscopy and quantified by measuring the calcein-stained HCBEC with a multiplate reader. Endothelial phenotype verification and expression levels of activation state markers were quantified by qRT-PCR. **Results:** Different flow rates did not adversely affect the integrity of an intact monolayer on the PMP membranes. A stable endothelial phenotype (e. g. CD31, vWF, VECad) was verified. Expression levels of adhesions molecules (e. g. ICAM-1, VCAM-1, E-Selectin) were slightly elevated, though not comparable to an induction by using TNFα. **Conclusions:** The integrity and inactivity of the seeded endothelial monolayer on the PMP membranes under different flow rates is a promising step in the development of a bioartificial lung, particularly for long-term use.

EVALUATION OF SMALL INTESTINE SUBMUCOSA VASCULAR GRAFTS FOR SMALL-DIAMETER VEINS REPLACEMENT: METHODOLOGY AND EARLY RESULTS IN AN ANIMAL MODEL

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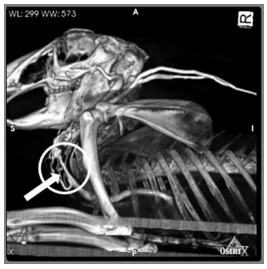
Materials used in arterial grafts have not been satisfactory in venous grafts. Currently only autologous saphenous vein is used for vein replacement, but with limited availability. Porcine small intestine submucosa (SIS) is an acellular collagen matrix that allows tissue regeneration and has been found promising as a large-diameter vascular graft. The aim of this study is to evaluate the suitability of small-diameter SIS grafts for vein replacement and to determine if immobilizing heparin on SIS improves graft permeability.

Porcine SIS grafts are manufactured and sterilized by our group. Tubular grafts (3.2–4.7 mm diameter, 20 mm long) are implanted in the left external jugular vein of New Zealand rabbits (4.0–5.0 kg) by an end-to-end anastomosis, in two groups: A) untreated grafts (n=6); B) grafts with chemically immobilized heparin on inner surface (n=6). Doppler examinations are performed one week after implantation and then monthly; a CT scan is performed after 15 days (see figure). For each group grafts are explanted with adjacent segments of native vessel after 45 (n=2), 90 (n=2) and 180 days (n=2) for patency evaluation, mechanical biaxial characterization and histological studies.

Up to date, all three implanted grafts remain patent (30, 40 and 90 days), bearing a satisfactory patency rate for vein grafts.



PRESSURE VERSUS VOLUME LOOP ASSESSMENT FOR A PHYSICAL CARDIOVASCULAR SIMULATOR SYSTEM

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A physical cardiovascular simulator was developed to study Ventricular Assist Devices (VADs). The use of cardiovascular simulators reduces the amount of "in vivo" experiments and specifics variables become possible to be controlled and evaluated.

This physical simulator, a mock loop automatically controlled by computer in a Virtual Instrument, is able to model the human cardiovascular system and is composed basically by four modules: an electromechanical pump; two prosthetic valves; an adjustable compliance chamber; and an adjustable clamp. In order to pump the working fluid, a Brushless Direct Current Motor (BLDCM) has been used, driving a planetary roller screw that changes motor rotation into linear displacement of a diaphragm. Pumping chamber has passive filling that happens according to reverse venous pressure. Once pumping chamber is completely full, the electronic controller driver the BLDCM to eject fluid. Since roller screw displacement can be modulated, the internal chamber volume can be adjusted changing the "heart elastance". As result, changes in shape and position of Pressure versus Volume loop (figure 1) can be performed. Therefore, several pathologic conditions can be simulated, making possible to evaluate the assistance provided by VADs.

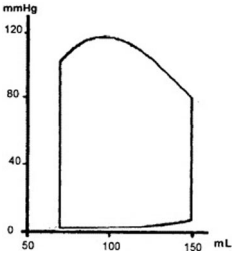

Figure 1. Intraventricular pressure versus volume loop.

LIPOSOME-ENCAPSULATED HEMOGLOBIN ALLEVIATES HEARING LOSS AFTER TRANSIENT COCHLEAR ISCHEMIA AND REPERFUSION

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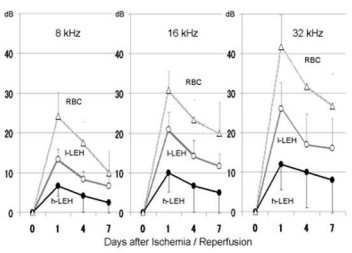
Introduction: Liposome-encapsulated hemoglobin (LEH), an artificial oxygen carrier, was tested in transient cochlear ischemia and reperfusion as an experimental model of sudden deafness. **Methods:** Mongolian gerbils were randomly assigned to receive 2 ml/kg of either high-affinity LEH (h-LEH, $P_{50}O_2$=45mmHg), low-affinity LEH (l-LEH, $P_{50}O_2$=10 mmHg), homologous red blood cells (RBCs), or saline (each n=6) 30 min before 15-min occlusion of the bilateral vertebral arteries and reperfusion. Sequential change in hearing were assessed by auditory brain response at 1, 4, and 7 days after ischemia/reperfusion, when the animals were sacrificed for pathological studies. **Results:** h-LEH was significantly more effective than l-LEH in suppressing hearing loss over a wide range of auditory frequencies (8, 16, 32 kHz) in contrast to RBCs and saline, which were associated with significant hearing loss and inner hair cell loss in the same order. **Conclusion:** The results suggest that pretreatment with h-LEH (2 ml/kg) is significantly more effective than l-LEH in mitigating hearing loss and inner hair cell loss following transient cochlear ischemia and reperfusion.



BIOENGINEERED SKIN ALLOGRAFTS – A NEW METHOD TO PREVENT HUMORAL RESPONSE

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We previously reported that a bioengineered membrane as an artificial interface between skin allograft and wound surface prolonged graft survival in the absence of immunosuppression. We now evaluated whether incorporation of FGF-1 leads to prolonged graft survival and prevents the development of donor-specific antibody. **Methods:** Full thickness skin grafts (8mm) were cross-transplanted between Balb-C and C57BL/6 mice (n=15 per group): Group 1- skin allografts transplanted without treatment; Group 2- wound surfaces of skin allograft and recipient wound treated with the bioengineered membrane; Group 3- incorporation of FGF-1 into the membrane prior to application. Mice were followed by visual inspection, biopsy, and flow cytometry. **Results:** Rejection of untreated grafts resulted in open wounds that formed scabs. Allograft survival in Group 2 and Group 3 was significantly prolonged ($p<0.05$). Once the skin graft was sloughed off, it left an intact pseudo-dermis. Untreated skin grafts stimulated a shift in the number of circulating CD4 positive cells and the development of donor-specific antibody. Group 2 exhibited a substantially reduced shift in CD4 positive cells, although donor- specific antibody developed. Group 3 mice did not develop donor-specific antibody.

Table 1.

	Rejection Onset	Cellular Response	Humoral Response
Group 1	7 days	10 fold shift	Detected at day 14
Group 2	28 days	4 fold shift	Detected at day 45
Group 3	27 days	4 fold shift	Negative

Conclusion: Treatment with a bioengineered membrane delays the onset of allograft rejection in the absence of systemic immunosuppression. FGF-1 prevents development of humoral response suggesting that rejection is mediated by cellular mechanisms.

A FONTAN-TYPE MOCK CIRCUIT WITH HETEROMETRIC AUTOREGULATION

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In Turkey, 3000 patients needed heart transplantation; but donor shortage and poor coordination allowed only 12 transplants in 2008. A nationwide mechanical circulatory assistance R&D program is unavailable for lack of finances, organization and facilities. Remedial efforts are underway, which include development of engineering infrastructure, large animal labs and training programs. We describe the design of a Mock Circuit as the first part of this endeavor.

A piston-in-cylinder, actuated with a compact electro-mechanical driver, functions as the LV ejecting into an afterload reservoir/compliance chamber. Unidirectional flow is secured with electronic valves. Two gravity-filled cylinders serve as pulmonary and left atrial reservoirs/compliances. Pressure transducers, flow probes & meters, amplifiers, low-pass filters, microcontrollers with PIC are built in-house. Instantaneous reservoir heights, pressures, flows and compliances are modeled using Continuity, Energy/Force Balance, Pressure Loss and Gay-Lussac equations separately for diastole, isovolumic contraction & relaxation and systolic rapid ejection & deceleration phases. Using Laplace transform, numeric solutions for first order initial value water level systems are computed in Matlab, which then compares physiologic measurements with Fourier transforms of empirical time-varying elastance data and corrects for piston force. Heart rate, cardiac output, pre & afterload, vascular & valvular impedances are varied to obtain normal and pathological cardiac physiologies.

The single-ventricle mock circuit simulates myocardial function with nearly perfect load independence for given elastance. System is ready for performance testing of original LVAD designs.

EARLY UNLOADING OF INFARCTED HEARTS PREVENTS CARDIAC REMODELING AND PRESERVES CALCIUM HOMEOSTASIS

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Post-infarction remodeling is characterized by geometric changes of the left ventricle that severely affect cardiac global function. Early unloading with ventricular assistance devices provide an effective decrease in wall stress, oxygen consumption, and adequate cardiac support. Fifteen sheep were used: one group (n=8) underwent 25% myocardial infarction, one group (n=5) underwent 25% myocardial infarction plus implantation of Impella pump after 2 hours and the third group (n=2) was used as control. The pump was operating for up to two weeks and then removed. All animals survived the 12-week protocol and were terminated. Echocardiographic data was collected at baseline, post-MI and termination. Regional tissues (infarct, adjacent and remote zones) were collected at termination for analysis. Unloaded hearts had significant reductions in increase of end-diastolic volume (78 to 87 ml vs. 76 to 110 ml; $p=0.02$), infarct expansion (44 % vs. 93%) and decrease of global cardiac function (LVEF: 54 to 45 vs. 52 to 37; $p=0.01$). Morphologic analysis of myocytes revealed decreased hypertrophic changes in the adjacent zone of unloaded hearts (2046 pixels vs. 3887 pixels; $p=0.045$). Normal expression of SERCA2a and NCX-1 and increased expression of phospholamban were found in the adjacent zone of the unloaded hearts while altered calcium-regulatory proteins were observed in the adjacent zone of the infracted hearts compared to those of the normal control. Early unloading of the infarcted hearts with a heart assist device as Impella is effective and beneficial, preventing cardiac remodeling, reducing infarct expansion and preserving the calcium homeostasis and global cardiac function.

CONSTRUCTION OF A SYSTEM FOR ANALYSIS OF CELL POPULATION BEHAVIOR ON A FIBROUS SCAFFOLD

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The construction of a system for analysis of cell population behavior during real-time monitoring is necessary to evaluate normal cellular function noninvasively and quantitatively on scaffolds. This report presents the construction of a cell visualization system in real-time and reports measurement of cellular singular nature on the scaffolds. Two types of segmented polyurethane (SPU) scaffolds, including nanofiber (0.76 ± 0.12 μm) and microfiber (5.79 ± 0.46 μm) scaffolds with fiber orientation were fabricated using an electrospinning method. Mouse fibroblasts (NIH3T3) with a cell area of 25 mm^2 were disseminated to SPU fibrous scaffolds in a culture well. The relations of the scaffold structure to the direction and speed of movement of the cell population were investigated to analyze cell population behavior over the period of a week using particle image velocimetry (PIV) in real-time. The PIV analysis results demonstrated the ability to perform vector analysis at the same time for plural numbers of cells. The movement of individual cells in the population was analogized using fibers designed with a diameter of 0.76 ± 0.12 to 5.79 ± 0.46 μm. Individual cells in the cell population moved approximately 30 μm/h on the fibrous scaffolds. In conclusion, the system developed using PIV was effective for the analysis of cell population behavior.

INTRODUCTORY TESTS TO IN VIVO EVALUATION: MAGNETIC COUPLING INFLUENCE IN MOTOR CONTROLLER

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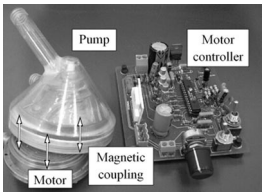
An implantable centrifugal blood pump is been developed with original features for a ventricle assist device (VAD). This pump is part of a multicenter and international study with objective to offer simple, affordable and reliable devices to developing countries. Previous computational fluid dynamics investigations were performed followed by prototyping and in vitro tests. Also, previous blood tests for assessment of Hemolysis shown mean NIH results of $0.0054 \pm 2.46 \times 10^{-3}$ mg/100 L (at 5 L/min and 100 mmHg). In order to precede in vivo evaluation, measurements of magnetic coupling interference and enhancements of actuator control were necessary.



Methodology was based in study of two different work situations (1 and 2) studied with two different types of motor (A and B). Situation 1 is when the rotor of pump is closest to the motor and Situation 2 its opposite. Torque and mechanical power were collected with a dynamometer (80 g.cm) then plotted and compared for two situations and both motors. The results showed that motor A has better mechanical behavior and less influence of coupling. Results for Situation 1 showed that it is more often under magnetic coupling influence than Situation 2. The studies lead the conclusion that motor A is the best option for in vivo studies since it has less influence of magnetic coupling in both situations.

HUMAN FACTORS AND WHEN TO EVALUATE THE DEVICE

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Active implantable medical devices such as left ventricular assist systems (LVAS) require significant user interaction to achieve the intended therapeutic benefit. Human Factors Engineering (HFE) is a blended science of human behavior and product interaction to facilitate ease of use and minimize detrimental effects related to incorrect use. HFE efforts feature strongly at the beginning of the project lifecycle for "ease of use" type product specifications but are critical throughout the product lifecycle.

Identification of users and the use environment depends upon the system's intended use and human interaction. This process begins prior to the formal product development phases to ensure that the product is technically feasible and usable for the target market. User focus groups, prototype demonstrations, and expert reviews are common methods to obtain necessary feedback and validation throughout the design process.

Risk mitigation of misuse is the second critical process in HFE. Mistakes can occur in complex systems such as a LVAS and must be anticipated as best as possible to minimize potential ill effects. A Hazard and Operability Study (HAZOP) is a useful tool to systematically identify unintended system use issues and its associated consequences. Unintended interactions that result in high severity events are candidates for redesign or other mitigation methods.

HFE is an integral part of the product development process beginning in the feasibility phase and continuing through commercialization. A well thought out and planned design can enhance safe use, reduce user anxiety, and maximize the intended therapeutic benefit. In addition, avoiding post market enhancements to correct HFE issues greatly reduces cost.

PLASMAPHERESIS THROUGH A MICROFABRICATED SILICON NANOFILTER

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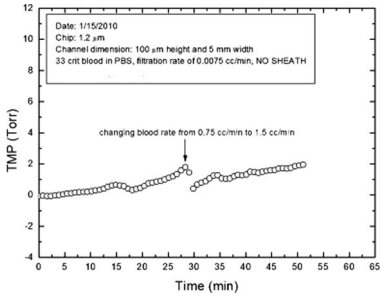
Microfabricated silicon nanofilters are chips about 700 μm thick supporting a very thin (~1um) silicon nitride layer perforated by micron-sized apertures. The silicon support has low-resistance drainage paths. The chips themselves offer near zero resistance to plasma flow and perfect rejection of cells at reasonable pressures. The system requires special handling of a flowing blood layer for significant plasma extraction. The layer must be microfluidic and sheared to prevent cell adhesion and facilitate back-transport of cells off the filter, all with a low pressure gradient in the flow direction.

We built a precision flat-channel cell for blood flow, 3 mm wide and 100 μm high o hold a small 3mm sq test filter. Blood was drawn from a stirred reservoir through the channel by a syringe pump with a fraction drawn through the filter by a second pump, while recording filter flow and trans-filter pressure. Results depended on blood flowrate, filtration fraction, hematocrit, pore size and surface treatment of the filters. Two modes were investigated: 1) ultrafiltration with $1/15^{th}$ of the blood flow removed, and 2) dialysis with unmixed sheathing layers between the blood layer and each wall, and with the sheath plus $1/15^{th}$ of the blood layer removed. Results for both modes will be reported in terms of a filtration model and relative to a prospective clinical device. A typical pressure profile is shown.



DESIGN OF A NEW MAG-LEV HEMOLYZER USING CFD

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Purpose: Blood damage is a problem in cardiovascular devices. There have been many attempts to determine the relationship between shear stress, exposure time and blood damage under constant uniform shear conditions for device design and development. However, these attempts have been plagued with problems associated with the imperfect devices used. The aim of this work was to design a flow-through shearing device based on a magnetically levitated rotor to eliminate heat damage and to generate a large uniform shear region in which the shear stress value is the maximum for the whole fluid domain. **Methods:** Computational Fluid Dynamics (CFD) was used to perform a parametric analysis on two different original designs: angled and rounded. The study parameters included the dimensions of the narrow, hemolyzing gap, the angles in the angled design and the radius of curvature for the rounded design. Commercial software (Ansys) was used to build the geometry (DesignModeler), mesh (Meshing), and calculate the flow (Fluent). A combination of steady and unsteady, laminar, 2nd-order calculations were used. **Results:** The angled design produced a high shear spot at the inlet to the narrow gap. The strain rate magnitude in this spot was reduced by increasing the angle of entry but was still 1.8 times the strain in the gap. The diffusing section after the gap in the rounded design produced flow separation and vortices with associated high shear regions (strain rate = 1.4 x gap strain rate). Combining the good parts of both versions produced a design with the desired properties. This combined design has now been optimized by means of further parametric studies and is currently being manufactured. The next step will be to use it in hemolysis experiments.

PRELIMINARY EXPERIMENTAL VALIDATION OF A PRESSURE-REGULATED, VOLUME-CONTROLLED LIQUID VENTILATION MODE

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Total liquid ventilation (TLV) requires the insertion and removal of a tidal volume (Vt) of perfluorochemicals (PFC) in the lungs with a liquid ventilator. Recent results with our prototype, Inolivent-4, have demonstrated that expiration pressure-regulated and volume-controlled was efficient. The objective was to test the hypothesis that pressure-regulated ventilation mode can be both used for expiration and inspiration.

One healthy term lamb (< 4 days old, 2.4 kg) was anaesthetized and paralyzed. TLV (Vmin=140 ml/kg, PEEP=5.5 cmH2O) was performed with perfluorodecalin (F2-Chemicals, UK) saturated in oxygen. The expiratory and inspiratory pressures were closed-loop controlled at the mouth. The pressure references, Pref,i for the inspiration and Pref,e for the expiration, were adjusted in an attempt to achieve Vt of 25 and 30 ml/kg. The mean tracheal pressure was computed over each inspiration (MTP,i) and expiration (MTP,e). Thirty minutes after reaching each new setting, a blood sample was drawn for analysis. The experimental protocol was approved by our institutional Ethics Committee for Animal Care and Experimentation. The measured Vt (averaged over 30 minutes) were respectively 24.7±1.3 and 29.8±1.7 ml/kg. The averaged PEEP and PEIP were 5.7±0.7 and 14. ±1.4 cmH_2O. During the inspiration, Pref,i value was adjusted at +140cmH_2O and this value was adequately reached at the mouth; but, the averaged MTP,i was 14.3±3.5 and 7.4±0.8 cmH_2O. During the expiration, Pref,e were −11.0 and −15.0 cmH_2O, and the averaged MTP,e was 0.7±0.9 and 0.6±0.2 cmH_2O. Blood gases were maintained in an acceptable range (PaO_2 of 275 and 255 mmHg, $PaCO_2$ of 46 and 39 mmHg, pH of 7.367 and 7,384).

PLATELET ADHESION TO POLYURETHANE UREA UNDER CARDIAC IMPULSE

Katherine A Chorpenning, Margaret J Slattery, Steven Deutsch, Christopher A Siedlecki, Keefe B Manning. *Bioengineering, The Pennsylvania State University, University Park, PA.*

Platelet adhesion to an artificial surface is one of the key events in thrombus development for cardiovascular devices. Polyurethane urea (PUU), one of the most used biomaterials in medical devices today, posses many desirable mechanical properties and numerous studies have documented its blood compatibility. This work focuses on testing the platelet adhesion properties of this material under simulated physiologic conditions by first, coating the surface with platelets and then applying an impulse. This impulse represents the acceleration typically seen at the inlet of a left ventricular assist device at the start of diastole at 75 bpm. The surface is coated with platelets by incubating the disk and material in platelet rich plasma (PRP) obtained from bovine blood. A rotating disk system (RDS) is used to deliver the impulse, and the number of remaining adhered platelets are quantified by immunofluorescent labeling using CAPP2A mouse anti-bovine $\alpha IIb\beta 3$ antibody and Alexa-Flur 488 donkey anti-mouse IgG. A RDS was used so platelet adhesion over a range of shear stresses could be determined based on the cells' radial distance. This work will characterize the effect of a "cardiac" impulse on platelet adhesion to the PUU surface, identifying shear stress regions that could potentially lead to high levels of platelet adhesion and subsequent thrombus development.

***IN VITRO* OBSERVATIONS OF THE FLUID MECHANICS INSIDE THE PENN STATE PVAD USING BLOOD ANALOGS OF VARYING HEMATOCRITS**

Breigh N Roszelle, Steven Deutsch, Keefe B Manning. *Department of Bioengineering, The Pennsylvania State University, University Park, PA.*

Children have a large range of blood hematocrit (HCT), which corresponds to a variation in their blood's viscoelasticity. Because of its influence on fluid mechanics, the viscoelasticity is of interest for medical devices involving blood flow. Blood viscosity in the animal models used to test these devices may also be different than that of a patient. As Penn State continues development on our 12cc pulsatile pediatric ventricular assist device (PVAD), it is desirable to observe the fluid mechanics inside the device as a function of HCT. In order to accomplish this, three blood analogs were prepared that mimic 40% and 60% HCT pediatric blood and 26% HCT goat blood. An acrylic model of the PVAD was placed in a mock circulatory loop, and 2D particle image velocimetry was performed throughout the cardiac cycle to produce whole flow field and wall shear maps.

Comparisons between the blood analogs show that while the general flow pattern was retained, there were differences between the fluids including differences in the profiles of the inlet and outlet jets, the penetration of flow into the bottom of the device, and the overall coherence of the rotational flow field. These differences were extensive when comparing the goat analog, a nearly Newtonian fluid, to the two pediatric analogs. Overall, we found that variations in HCT could lead to unique flow profiles for different patients and, perhaps more importantly, the study highlighted the effect of differences in viscoelasticity between animal models and clinical patients.

AN IMPROVED EXPERIMENTAL WALL SHEAR ESTIMATION WITHIN A 50cc PENN STATE BLOOD PUMP

Jason C Nanna, Ning Yang, Breigh N Roszelle, Steven Deutsch, Keefe B Manning. *Department of Bioengineering, The Pennsylvania State University, University Park, PA.*

Although VAD therapy has had success in assisting the failing heart, thrombus formation within these devices is one of various complications that still limit their long term use. Research has shown that thrombus deposition in VADs is largely a function of the underlying fluid mechanics within these devices. Wall shear rates below 500 s^{-1}act as a marker for thrombus formation for the Penn State pulsatile VAD. In order to more accurately measure wall shear rates within a Penn State 50cc device, high magnification particle image velocimetry (PIV) and a post-processing wall shear algorithm are used at resolutions of 12 and 35 μm/pixel. In determining an optimal PIV magnification, the accuracy of the wall shear rate measurement is considered. As the wall shear rate calculation is based off of particle velocity and particle to wall distance, any error in wall shear rate lies in the uncertainty of these measurements. For a given distance from the wall, shear rate errors are reduced by roughly a factor of 1.8 from 460 s^{-1} to 255 s^{-1} at 35 μm/pixel compared to 12 μm/pixel. The accuracy of the wall shear rate measurement is therefore significantly improved at the 12 μm/pixel magnification.

A comprehensive VAD flow study along with wall shear contour maps will act as a guide for identifying areas susceptible to thrombus formation in order to advance the design of the 50cc Penn State VAD by comparing *in vivo, in vitro,* and computational data.

A FLOW ANALYSIS OF A POLYMERIC TRILEAFLET HEART VALVE

Dylan L Frank, Joseph J Pearson, Breigh N Roszelle, Jason C Nanna, Steven Deutsch, Keefe B Manning. *Department of Bioengineering, The Pennsylvania State University, University Park, PA.*

Nearly a million people died in 2005 due to cardiovascular disease, which represents over 35% of all fatalities that year. One of the leading contributors is valvular insufficiency, particularly the aortic valve. Penn State has been, and continues to conduct fluid dynamics research on the Abiomed polymeric trileaflet heart valve. In order to fully analyze this valve, one needs to study not only the flow through the valve, but that in the sinuses as well. To do this, the valve was placed in an acrylic model mimicking the Sinuses of Valsalva and embedded in a mock circulatory loop of the systemic circulation. A 40% hematocrit blood analog was used in this loop, which was run at physiological conditions. Two dimensional particle image velocimetry was performed at 100 ms intervals in diastole and at 25 ms intervals in systole over the cardiac cycle to produce flow maps of the desired regions. Initial tests with this study have been performed with a twisting and normal valve. The difference between these two is that the twisting valve opens and closes with a twisting motion, while the normal valve does not. The initial results showed that the twisting valve performs better than the normal valve, causing more regurgitant flow within the sinuses and a wider jet downstream of the valve. This is due to the leaflets opening further into the sinuses with the twisting valve, producing a larger effective orifice area. A study is currently being run on the twisting valve, to determine if thinner leaflets will improve flow within the sinuses.

AORTIC OUTLET EXTENSION IN THE 12CC PENN STATE PEDIATRIC VENTRICULAR ASSIST DEVICE

Michael G Fickes, Breigh N Roszelle, Steven Deutsch, Keefe B Manning. *Bioengineering, The Pennsylvania State University, University Park, PA.*

Approximately 36,000 children are born each year with a heart defect, the most common birth defect in the U.S. Due to the low availability of donor hearts, pediatric ventricular assist devices (PVADs) are a possible solution to sustain the life of pediatric patients until a donor heart can be transplanted. Penn State is currently developing a 12cc PVAD, which is a scaled down model of the successful 70cc Pierce-Donachy VAD. The reduction in volume necessary to accommodate smaller patients led to various changes in the functional fluid mechanics. One of these changes was a blockage region upstream of the aortic outlet, a characteristic that increases the probability of blood damage and can lead to emboli and other adverse effects within blood. In an attempt to eliminate this region, the outlet port was extended 2 inches away from the model through the use of an acrylic extension. The PVAD was connected to a mock circulatory loop that models the systemic circulation using normal physiological conditions with a 40% hematocrit blood analog as the fluid. Two dimensional particle image velocimetry was used to produce flow maps throughout the entire cardiac cycle. Preliminary results have shown that the flow patterns in the body of the device remain similar to previous experiments, including the area of blockage upstream of the aortic valve. However, the extension of the aortic valves has reduced the fluid velocity around the blockage, leading to a reduction in possible blood damage.

THE SCALING EFFECTS IN COMPARING PEDIATRIC AND ADULT MECHANICAL HEART VALVES

Stephen R Topper, Jason C Nanna, Richard S Meyer, Steven Deutsch, Keefe B Manning. *Bioengineering, The Pennyslvania State University, University Park, PA.*

Past studies of fluid flow in ventricular assist devices have shown that flow dynamics are not constant in geometrically similar devices. Scaling an adult mechanical heart valve (MHV) down to the size of a pediatric MHV may also change the dynamics of the fluid flow through the valve. The purpose of this study is to determine the effects from scaling an adult valve to a pediatric valve by measuring the closing velocity and cavitation of adult and pediatric TTK Chitra and Bjork-Shiley Monostrut (BSM) MHVs.

Experiments are conducted in a single-shot chamber under loads of 2000 and 3500 mmHg/s with degassed water (6 ppm). Two valve sizes (19 mm and 29 mm) are tested for BSM pyrolytic carbon MHVs and ultrahigh molecular weight polyethylene TTK Chitra MHVs. A hydrophone acoustically measures the amount of cavitation caused by closure and rebound. A laser sweeping technique measures the occluder closing velocity upon impact and is used with the hydrophone data to assess the scaling differences between the adult and pediatric MHVs.

We conclude that both valve material and closing velocity directly affect the degree of cavitation upon closure. The denser BSM valves cause more cavitation than the less dense TTK Chitra valves. Under higher loading conditions, the valves show greater closing velocities correlating well with more cavitation production. Contrary to expectations, the closing velocity does not vary with different valve sizes, only with valve materials.

EFFECT OF LIPOSOME-ENCAPSULATED HEMOGLOBIN ON ANTIGEN-PRESENTING ACTIVITY

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Background: Liposome-encapsulated hemoglobin (LEH), an artificial oxygen carrier, at large dose may lead to impaired immunity against pathogens or tumors by overloading the antigen-presenting function of the reticuloendothelial system. **Methods:** Changes in cellularity and surface markers of dendritic cells (DCs) and macrophages (MCs) were monitored serially up to 4 weeks in wild-type mice receiving 20 mL/Kg of LEH, murine RBC or saline by flow-cytometry. Next, DCs were collected from spleen of wild-type mice 1, 7 and 28 days after receiving one of the above solutions. These cells were then co-cultured with CD4 T cells derived from T cell receptor transgenic mice specific to ovalbumin or Toxic Shock Syndrome-1 in the presence of either one of the antigens. **Results:** After 20 ml/kg of LEH administration, the cellularity of DCs and MCs in recipient mice did not differ from that in saline-treated mice. IL-2 productivity shortly after LEH administration was not affected despite a small increase in the expression of co-stimulatory molecules. We found that DCs and MCs from LEH-administered mice expressed high levels of co-stimulatory proteins and supported IL-2 production in response to third-party antigens as in the DCs in mice treated with RBC or saline. **Conclusion:** The results suggest that LEH at putative transfusion dose (20 ml/kg) does not suppress host's antigen-presenting activity to third-party antigens.

REGULATED DELIVERY OF IGF-1 USING LOCALIZABLE MICROENCAPSULATED GENETICALLY MODIFIED CELLS

Roshni S Patel, Amy Chang, Jeffrey R Morgan, Michael J Lysaght. *Center for Biomedical Engineering, Brown University, Providence, RI.*

Localized delivery of growth factors is recognized as an essential component of *in situ* tissue regeneration. Such processes can require delivery in a delayed or interrupted manner, giving rise to the need for localizable systems capable of controllable delivery. The goal of this study was to develop and characterize a microencapsulated cell-based system for the regulated delivery of human insulin-like growth factor 1 (IGF-1), a cytokine widely employed in orthopedic tissue development, using a tetracycline controlled transcriptional activation gene expression system. This system was adapted to stably express the IGF-1 gene in CHO-K1 cells in the presence of doxycycline (Dox, a tetracycline derivative) in a dose-dependent manner. In the absence of Dox, cells did not express the gene. Stable expression of IGF-1 in the presence of Dox (1 mg/mL) was confirmed 6 hours post-induction in unencapsulated modified cells. For encapsulated culture studies, genetically modified and unmodified cells were suspended in a 1.8% alginate solution, extruded as droplets through a vibrating (5000 Hz) nozzle (100-μm), and cross-linked in 1.7% calcium chloride. Dox (1 μg/mL) was introduced to the cultures for Day 0–3 and then removed from Day 3–10. IGF-1 concentration was measured by ELISA daily. Preliminary findings indicate an increase in IGF-1 release during Dox exposure, with a peak at Day 4 (one day post-Dox), and then steady decrease daily post-day 4, demonstrating that encapsulated genetically modified CHO-K1 cells are capable of regulated release of IGF-1 using a tetracycline-inducible gene switch system and at a concentration consistent with the requirements for orthopedic tissue regeneration.

DRINKING MECHANISM FOR AN ARTIFICIAL ESOPHAGUS AND SUPER STENT SYSTEM

Tomoyuki Yambe, Yasuyuki Shiraishi. *MEC, Tohoku University, Sendai, Miyagi, JP.*

Surgical resection of the esophageal cancer is one of the most difficult procedures in the Surgery, because of the reconstruction of the esophagus. Invasion to the patients may become smaller when the realization of an artificial esophagus will become possible. Simple tube is not enough when we consider the peristalsis function of an esophagus. Various kinds of peristalsis mechanism were proposed until now. However, total occlusion of an esophagus for peristalsis motion is difficult, when we consider the mechanism of a smaller implantable actuator. In this study, see saw game motion actuator was developed, and animal experiments using healthy goats weighting almost same with average Japanese people was carried out in this study. Silicone tube (outer diameter 20mm, internal diameter 18mm) with cover components and shape memory alloy (SMA) actuator was developed and peristalsis motion was embodied in this system. Animal experiments using healthy adult goats were carried out after anesthesia inhalation with ethical committee allowance.

As the results, the peristalsis motion became possible in the animal experiments. Super esophagus stent system with healing hyperthermia effect and peristalsis motion is now under planning. So, actuation mechanism for the implantable artificial esophagus and Stent system may be useful mechanism in near future.

EXPANDING CAPSULE FOR DIET CONTROL

Tomoyuki Yambe, Yasuyuki Shiraishi, Hidekazu Miura. *Medical Engineering and Cardiology, Tohoku University, Sendai, Miyagi, JP.*

Obesity and metabolic syndrome are the most important problem in all over the world when we consider the economical situation of medical fee. Almost patients with severe obesity failed to control their weight by only the diet. Surgical operation must be considered for the severe cases of obesity. By the use of the technology of micro-machining and nano-technology, mechanical expanding capsule for diet control had been started to be developed in our University. The technology for the transcutaneous energy transmission system (TETS) with nano technology for the energy support was used in the development for the energy transmission to the expanding capsule in the stomach.

When the patients will feel hungry, then, just drink the newly developed expanding capsule. The capsule will go into the stomach, and then the patients attach the first coil of TETS from outside of the human body surface. Energy will transmit to the capsule to expand. After the expansion of the drinking capsule, sensor in the internal surface of the stomach will be stimulated so the patients will feel full stomach. After the finishing of the session, if the patients take of the first coil of TETS. The capsule will shrink and the reduction will enable the capsule go into the intestine and go out by defecation form anus. Animal experiment were carried out using healthy adault goats and the results showed us the expanding power need over 10 mmHg, so, basic concept was embodied. Linear actuator will be enabled us the expanding mechanism. Double blind animal experiments using healthy adult goats with expanding capsule and pseudo non-expanding capsule will be under planning. If the diet effect is satisfactory in animal experiments, we want go into the clinical application.

FUNCTIONALIZATION OF POLYMERIC MEMBRANES FOR TISSUE ENGINEERING OF HEART VALVES

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Purpose of Study: We evaluated methods of obtaining polymeric membranes with distinct porosities and surface properties for their use in tissue engineering of heart valves. **Methods:** Polycaprolactone (PCL) membranes were prepared with or w/o the addition of NaCl or PVA as porogens. Functionalization of polyetherurethane (PEU) membranes was achieved with the insertion of hydroxyl groups and chitosan deposition. Membranes were seeded with ovine aortic valve cells and cultured under static conditions. Porosity and cell distribution of PCL and PEU membranes were evaluated by scanning confocal microscopy. Functionalization of PEU membranes was evaluated with infrared spectroscopy (IR-FT) and by contact-angle measurements. **Results:** Porosity of PCL membranes (figure 1A) varied in accord with type and concentration of porogen. Cell growth was dependent on the presence of pores and occurred preferentially at around 30μM of the membrane surface (figure 1B). Cell density and localization varied from control (figure 2A) and PEU membranes after hydroxyl and chitosan deposition (figure 2B).

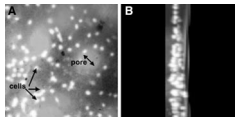

Figure 1.

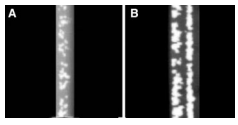

Figure 2.

IN-VITRO HEMODYNAMIC EVALUATION OF VENTRICULAR SUCTION CONDITIONS OF THE EVAHEART ASSIST PUMP

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Purpose: Since rotary blood pumps are preload insensitive, ventricular suction may occur when there is a mismatch between pump flow output and venous return. This research describes an in-vitro study to characterize the operating conditions under which the EVAHEART System can be operated with minimal concern of LV suction. **Methods:** The Evaheart VAD was interposed into a mock circulatory system (MCS) that incorporated an apically-cannulated, pneumatically driven pulsatile pump representing the left ventricle. The pump speed was increased step-wise for each test condition until suction was observed: identified based on pump inlet pressure. Experiments were repeated for varying conditions of preload, afterload and ventricular contractility. **Results:** Suction was found to be sensitive to both preload and afterload. With reduced preload (< 10mmHg) and afterload (<= 60mmHg), suction was observed for speeds >= 2200 rpm with both normal and dysfunctional LV contractilty. Suction was not found to occur at any speed (up to max speed, 2400 rpm) when preload remained within 10–14mmHg and afterload >= 80mmHg. **Conclusion:** The experimental results indicated that ventricular suction can be avoided if sufficient preload and afterload are maintained. Conditions of hypovolemia and/or hypotension however introduce risk of suction at the highest speeds irrespective of native ventricular contractility. Guidelines for pump speed should account for the likelihood of these conditions in a patient-by-patient basis - which could be aided by ultrasonography at various points in the course of support.

DIFFERENCES IN HYDRODYNAMIC PERFORMANCE AND FLOW ESTIMATION BETWEEN AXIAL AND CENTRIFUGAL LVAD

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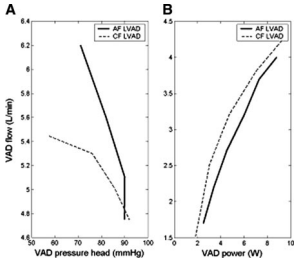
Purpose: The purpose of this study was to compare the hydrodynamic performance and flow estimator (FE) accuracy between implantable axial flow (AF) and centrifugal flow (CF) LVADs. **Methods:** Static and dynamic mock circulatory systems were used to assess the hydrodynamic performance and the FE accuracy of the AF (Heartmate II) and CF (HeartWare HVAD) LVADs. Hydrodynamic performance and FE accuracy was evaluated by collecting hemodynamic and pump data at three viscosities (2.7–3.7 cP), five different pump speeds (2000–3600 rpm for HVAD, 7000–11000 rpm for HM II), and four afterload conditions. **Results:** AF LVAD had a flatter HQ curve and consumed more power (Figure 1). The estimated flow for the AF LVAD was non-linearly related to the actual flow, while the CF LVAD estimated flow had a linear relationship to the actual flow. Once calibrated to the actual flow, the FE error was higher with the AF (±0.9 L/min at 2.7 cP, ±0.7 L/min at 3.2 cP, ±0.8 L/min at 3.7 cP) compared to the CF LVAD (±0.5 L/min at 2.7 cP, ±0.2 L/min at 3.2 cP, ±0.5 L/min at 3.7 cP). **Conclusions:** Overall pump performance was similar between the AF and CF LVADs with some potential advantages for the CF pump. The CF LVAD consumed less power which may allow for a smaller and lighter battery pack and the FE in CF LVAD provides better accuracy but requires periodic input of the patient's blood viscosity.



PLATELET INHIBITION BY ANTIBIOTICS AND IMPLICATIONS IN CIRCULATORY SUPPORT DEVICE DEVELOPMENT

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Circulatory support devices remain an important therapy for cardiovascular disease. However, these devices are still plagued by thrombus formation resulting from platelet activation/interactions with the device. Measurement of activated platelets in animal models before, during and after circulatory support provides valuable information for further development of these devices. We routinely make measurements of activated platelets in animal models using flow cytometric immunochemistry, principally targeted against CD63 on activated platelets. Our results were found to be largely as expected and reported by others, with numbers of circulating activated platelets rising, and susceptibility to activation by biochemical agonists also increasing. However, our results also demonstrate that clinical treatment of the animals, principally in the area of infection and antibiotic treatments, can lead to drastic changes in platelet activation. Upon receiving antibiotics, platelet activation levels drop precipitously, and activation by ADP and collagen is drastically reduced. Platelet activation levels and susceptibility to activation return shortly after antibiotic treatment is halted. In summary, the clinical treatment of animals affects measured platelet parameters and needs to be considered in analysis of platelet activation by implanted devices.

BRAIN BASED ELECTROSPUN TISSUE SCAFFOLDS: A PARAMETRIC STUDY

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Purpose of Study: Electrospinning has proven to be an effective method of producing nano- and microscale sized fibers for use in tissue engineering. In order to create a functional electrospun scaffold, the parameters of fabrication must be controlled to produce effective, repeatable results. The specific set of requirements for an electrospun scaffold can vary based upon the intended target in the body. This study focused on analyzing and optimizing the parameters of electrospun fiber fabrication for scaffolds intended for direct implantation in the brain. **Methods Used:** An electrospinning chamber was used to fabricate electrospun fiber scaffolds composed of PLGA with varying parameters, including I: Polymer Concentration, II: Polymer Solution Flow Rate, III: Electric Field Strength, IV: Separation Distance, and V: Polymer Type. The set of nonwoven mat scaffolds were then analyzed with the following methods: scanning electron microscopy to measure average fiber diameter and standard deviation; tensile testing to measure scaffold strength; in vitro degradation testing to determine the scaffold's response to the unique conditions of the CNS; and in vivo testing using a rat based brain injury model. **Results:** Solution flow rate, concentration and field strength are influential in the outcome of fibers created through electrospinning. Maintaining constant conditions throughout the fabrication process requires fine tuning of the flow rate with electric field strength. The unique setting of the brain may limit the utility of some synthetic biodegradable materials due to hydrolytic degradation. **Conclusion:** Electrospun tissue scaffolds are a promising platform in furthering regenerative medicine within the brain.

MODELING AND DIAGNOSTICS OF TOTAL ARTIFICIAL HEART

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Presented are online adaptive models for a total artificial heart (TAH) which consists of two axial flow pumps. Using orthogonal least squares method (OLS), steady state models are developed to estimate the cardiac output (CO) and the power consumption of the two devices. These parameters are critical to physicians during patient care as well as in diagnosing TAH operation. The online adaptive nature of these models will be used to estimate effective blood viscosity in real-time and to create a mechanism whereby specific TAH diagnostics, important to robust CO delivery, can be identified, isolated and estimated. The experiments conducted were ex-vivo in a mock circulation loop in which the precise nature of the working fluid properties can be controlled and measured.

DEVELOPMENT OF A 2ND GEN. DATA ACQUISITION PLATFORM FOR THE PEDIAFLOW VAD

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The PediaFlow VAD is a magnetically levitated, turbodynamic, continuous flow pediatric heart pump. Previous testing of the pump utilized WinDAQ to log key pump and system parameters. This method did not allow for the real-time calculation of an estimated flow (EF) or pulsatility index (PI), clinically relevant parameters. Therefore, the PediaFlow data acquisition platform (PDAP) was developed to provide an intuitive interface, the required estimated parameters, and the data logging ability needed for adequate testing and future clinical use. The first iteration (PDAP1.1) met this goal by utilizing a parallel two-loop state machine structure, separating the event handler from all other activity to maximize efficiency. The PDAP1.1 allowed for user-defined filenames, linear scaling of volts to pressure, setting of rotor position limits for alarming, and file generation on the hour to minimize corruption. While successful, the PDAP1.1 required acquisition stoppage during setting changes and had a fixed number of channels.

The second build (PDAP2.1) aimed to improve and extend the functionality of the initial program using a parallel, three-loop state machine architecture. Acquisition is now a dedicated process, running alongside of the event handler and any user activity. Setting changes are passed using queues between read cycles to prevent any loss of data. Built-in scalability allows for user-defined inputs and outputs, EF equations, linear calibration curves and alarm generation across all channels. Analysis of *in vitro* data from the 2nd Gen. PediaFlow with the PDAP2.1 indicates that we have developed an all-inclusive program to measure, analyze, and log system parameters during pump evaluation.

SIMULATION OF BREATHING EFFECTS AND MOVEMENT ARTEFACTS IN MOCK CIRCUITS

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For in vitro testing of diagnostic and therapeutic cardiovascular equipment, mock circulations usually mimic only the heart-beat. For enhanced evaluation and testing of the device software, additional simulation of breathing effects and random movement artifacts can be necessary. In this study, for the evaluation of a coronary interventional device, a mock circulation was modified to include such asynchronous effects. **Methods:** A mock circulation using a pulsatile pneumatic ventricle, a windkessel and a tubing system was established to mimic the pressure and flow conditions particularly in the coronary venous circulation. To add effects of breathing and accidential patient movement, two prototypes for mini-manipulators were added using Lego-Mindstorm™ components. Based on LabView™, pseudo-randomized sequences for motor cantilever movement and gradual tubing occlusion were programmed. **Results:** The modified mock circulation could reproduce exactly the artifacts seen from pressure transducers, from regular breathing and from breathing irregularities, required for the testing of the controller software of the interventional device. Ranges of artifact repetition could be easily modified by using pseudo-randomized program sequences.

In conclusion, with the used components an extremely rapid and cheap installment of enhanced functions of the mock circulation could be successfully performed.

FIBRONECTIN INFLUENCES *STAPHYLOCOCCUS EPIDEMIDIS* RP62A ADHESION AND INTERACTION WITH PLATELETS ON POLYURETHANE BIOMATERIAL SURFACES

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Microbial infection is one of the major problems associated with the use of blood-contacting devices. The initial bacterial adhesion is influenced by interactions with adsorbed proteins and platelets, however, the mechanism behind these interactions is still not clear. We assessed the protein adsorption on polyurethane (PU) surface by immuno-AFM technique and measured the *Staphylococcus Epidemidis* RP62A adhesion on surfaces following preadsorption of proteins. Results showed that fibronectin (Fn) adsorption lead to increased bacterial adhesion compared to fibrinogen (Fg) and human serum albumin (HSA). The good correlation between molecular scale measurements of protein (Fn) adsorption on PU surfaces and macroscale bacterial adhesion suggests that Fn is a principal protein in bacterial adhesion. The interaction forces between proteins and bacterial cell surfaces were measured by protein modified AFM probes. The force mapping showed a heterogeneous distribution of protein receptors on cell surface and Fn displayed a larger adhesion force than Fg. The interaction of platelets and bacteria was measured by fluorescent microscopy. The images showed that bacteria aggregated on surface with platelets adherent. The presence of Fn was found to increase the formation of bacterial aggregates.

Although the interior structures of the aggregates are not clear, the results suggest that Fn may serve as a linker for bacteria-platelet aggregation. Taken together, results suggest that fibronectin is an important protein influencing *Staphylococcus Epidemidis* RP62A adhesion and interaction with platelets on polyurethane surfaces.

DEVELOPMENT OF A CELL POUCH TO FORM AN ARTIFICIAL PANCREAS

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Carbohydrate control is routinely achieved by allotransplantation of islets of Langerhans. However the current clinical technique of islet infusion via the portal vein requires large numbers of islets (10,000IEQ/Kg). Here we describe a novel subcutaneous artificial pancreas which provides carbohydrate control with minimal doses of islets. The artificial pancreas comprises a proprietary polymeric cell pouch (CP), ergonomically designed with multiple chambers, maximal surface area to volume ratio, and a contoured design for cellular implantation following removal of polymeric rods which maintain the space for cells as the artificial pancreas develops. The CP is implanted subcutaneously where it stimulates a foreign body response resulting in an extensively vascularised collagen deposition internally between the device and the polymeric rods. After 4–8 weeks the rods are withdrawn and islets implanted into the resulting void volume of 1.57ml. In preliminary studies CP's were pre-implanted subcutaneously in the abdominal region of 12–16 week old pigs who received islet autografts following a 90% pancreatectomy and induction of diabetes with IV streptozotocin (150mg/Kg). Five days post pancreatectomy and following confirmation of diabetes (blood glucose ~20mMol/L) pigs receiving a mean of 4,581±881 immature islet equivalents/Kg became normoglycaemic on average 22±5days post transplant, with mean blood glucose of 6.6±1.1mMol/L. No adverse events occurred from either the implanting the CP or transplantation of the islets. These data indicate that this technique provides a suitable environment for the survival, development and function of immature islets and may be of value for the implantation of other cell types.

FIBRINOGEN BIOACTIVITY AND PLATELET ADHESION ON BIOMATERIAL SURFACES

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Biomaterial-induced thrombosis arises from interactions between plasma proteins, biomaterial surfaces, and platelets. We utilized immuno-atomic force microscopy techniques to measure the activity of fibrinogen on surfaces and correlated to platelet adhesion. Protein solutions ranging from binary mixtures of human fibrinogen/albumin to platelet poor plasma were adsorbed onto different model surfaces including muscovite mica, highly ordered pyrolytic graphite, and a series of polyurethane materials. A monoclonal antibody recognizing the platelet binding site in the fibrinogen γ-chain dodecapeptide showed that the post-adsorption fibrinogen activity exhibits time-dependent behavior, with peak times depending on surface properties and protein concentration. The presence of albumin affects the activity of fibrinogen as increased platelet-binding sites in fibrinogen. Fibrinogen activity data show good correlation with platelet adhesion. The molecular measures were applied to a series of polyurethanes having different soft segment chemistries (PDMS-, PC-, and PTMO-) and hard segment content (30%–52%). Results show that platelet adhesion does not necessarily correlate with the amount of fibrinogen present, but rather is related to the activity of fibrinogen. Analysis of the fibrinogen activity and the number of adherent platelets shows a sigmoidal rise in platelets with fibrinogen activity for the mica and HOPG surfaces, but this is altered by the nanoscale chemistry present in PUU materials. Results suggest that platelet adhesion is affected by a series of factors including the activity of adsorbed fibrinogen as well as the distribution of surface chemistries on the polymer substrates.

BIODEGRADABLE AND THERMORESPONSIVE HYDROGELS DESIGNED FOR INJECTION THERAPY TO IMPROVE FUNCTION IN ISCHEMIC CARDIOMYOPATHY

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Objective(s): In an effort to alter adverse remodeling and preserve cardiac function post-infarction we developed a novel biodegradable, thermoresponsive hydrogel for cardiac wall injection and temporary mechanical protection. **Methods:** A family of hydrogels was synthesized by copolymerizing N-isopropylacrylamide, hydroxyethylmethacrylate and polylactide-methacrylate at monomer feed ratios of 80/10/10, 82/10/8 and 84/10/6. The polymers were characterized in terms of phase change from fluid to gel below body temperature, mechanical behaviour, biodegradation and cytocompatibility. The optimal design (80/10/10) was evaluated in a rat myocardial infarction model by peri- and central infarct injections 2 wk post-infarction (n=9 rats), followed by echocardiography over 16 wk. Buffered saline (PBS) was injected in control rats (n=9). **Results:** The hydrogels were cytocompatible with thermoresponsive behavior providing injectable fluid below room temperature and strong hydrogels at 37°C (tensile strength 100 kPa). In vivo, the left ventricle continued to dilate and contractile function decreased ($p<0.05$ vs pre-injection) with PBS injection, while in the hydrogel group dilatation was blocked and function preserved over 16 wk. **Conclusions:** Thermoresponsive hydrogel injection into the infarcted ventricular wall followed by gelation and slow degradation was associated with improved functional outcome in treated rats and may offer a relatively simple approach to alter adverse myocardial remodeling.

SENSITIVITY OF HEMODYNAMICS AND WALL STRESS TO THE SPEED OF CONTINUOUS FLOW PUMP

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Continuous flow left ventricular assist devices (LVAD) are increasingly used to treat end stage heart failure (HF). However, there is yet a quantitative study of ventricular unloading on hemodynamics and mechanics as a result of different pump speed (ω). This study is to elucidate the effect of ω on LV hemodynamics and mechanics.

A Tesla type pump was extracorporeally placed in a 94 kg calf. Sonomicrometry crystals and a Millar pressure transducer were used to measure LV volume and pressure, respectively. Acute heart failure was induced using esmolol. Baseline (BL) data was acquired before esmolol was administered. The ω varied from ~5500 rpm to ~8000 rpm. Hemodynamic parameters, pressure-volume (P-V) relationship, and wall stress (WS) were examined at different ω.

The ω was linearly related to hemodynamics and mechanics for BL and HF. For BL, as ω increased by 2500 rpm, LV pressure (LVP) and WS at end-diastole (ED) were reduced by 130 % while reduced by 10 % at peak-systole (PS). LVP and WS at ED were the most sensitive to ω. For HF, unloading over ω showed the similar trend to BL, however, rate of unloading on the LVP and WS at ED was about 2.4 times greater than that of BL. P-V loop showed a reduction of stroke work with increasing ω for both BL and HF.

Unloading is systematically related to ω that is mainly effective on the diastolic phase. This study provides insight on the mechanics of unloading with a continuous flow LVAD that may be beneficial to studies of reverse remodeling and recovery with LVAD support.

NEUROMORPHIC VLSI-BASED ECHOLOCATION CIRCUITS OF THE BIG BROWN BAT

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Echolocating bats are excellent examples of agile aerial hunters capable of navigating in complicated, dynamic 3D environments. Evolved from the basic mammalian auditory system, echolocation appears to utilize signal processing concepts typical of both auditory and visual processing.

Inspired by the neural circuitry of the bat auditory system, we are developing a low-power mixed analog/digital VLSI-based sonar system that mimics the neural computational principles and tracking behavior found in the bat.

Towards this goal, we design circuits in silicon to emulate the spiking neurons found in the bat brain that estimate echo time-of-flight and echo azimuth and elevation based on binaural cues.

Beyond just sensing, we are also pursuing biologically-plausible models of short-range navigation and collision avoidance.

I will discuss a variety of projects in our laboratory, describe a few of the specific neural systems that we investigate, and describe the neuromorphic VLSI circuits and performance they provide in our closed-loop sensorimotor testbeds.

CONTACT ACTIVATION OF BLOOD COAGULATION BY MIXED THIOL SELF-ASSEMBLED MONOLAYERS

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Blood plasma coagulation arising from blood-materials remains a challenge to the development of cardiovascular medical devices. The classical view of contact activation imparts coagulation factor XII (FXII) activating properties to anionic hydrophilic surfaces. However, this group has previously shown that surface-mediated autoactivation of FXII in buffer occurs at nearly equal levels for hydrophilic and hydrophobic surfaces, while FXIIa generation in plasma appears to be attenuated at hydrophobic surfaces rather than accentuated at hydrophilic surfaces. In this work, we utilized mixed carboxyl/methyl-, hydroxyl/methyl-, and amine/methyl-terminated thiol modified surfaces as the activating materials for in vitro plasma coagulation assays or, alternatively, placed these materials into purified FXII solutions and measured enzyme activation. While plasma coagulation studies support a role for anionic surfaces in contact activation, studies of FXII activation in neat buffer solution suggest FXII activation is related simply to surface wettability. In neat buffer studies, a minimum level of FXII activation is seen for materials having mid-level wetting, and there is no statistically distinguishable difference between the pure carboxyl- and hydroxyl-terminated hydrophilic surfaces. These findings suggest that surface-mediated FXII activation is dependant on the surface wettability of the activating material.

DEVELOPMENT OF A NOVEL MATERIAL TESTING METHOD FOR SIMULATION OF BIOMEDICAL MATERIALS

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Purpose: Minimizing the patients risk during cardiac surgery is one of the main goals of medical research. This includes minimal invasive surgery, e.g. self-expanding heart valve prostheses. These stent structures are based on a material behavior called shape memory (SM) effect. Thus, in the development of stent structures, the specific material data is needed. This data is often not precisely specified in simulation models. In this study a novel material testing method and analysis based on experimentally obtained material properties for FEA simulation with SM alloys is introduced according to ASTM F2516. **Methods:** The test material is a nickel-titanium alloy used for heart valves. The material data is obtained from tension tests performed with specially designed micro specimens which are laser-cut out of a nickel-titanium tube. To determine the temperature dependent behavior of the alloy, an electric tempering unit is developed and 5 specimens are analyzed for 4, 22 and 37°C. The analysis is based on linearization of tension strain charts (TSC) and strain temperature relation. 14 parameters are determined and a cross-validation is performed by simulation of tensions tests at all temperatures and transitions. The simulation is compared to experimental data, including failure investigation. **Results:** The parameters are able to represent the material model for 22 and 37 °C. At 4 °C the data set can be completed by assumptions only due to a missing lower plateau in the TSC. However, the simulations are in good agreement with the experiments. Thus, a precise testing method and analysis routine for SM alloys was successfully developed. It can be applied to further SM alloys used in biomedical engineering.

A METHODOLOGY TO STUDY THE HEMODYNAMICS IN PATIENTS WITH BIDIRECTIONAL GLENN SHUNT

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Bi-directional Glenn Shunt (BDG) is one of three important procedures from a staged surgery, called Total Cavopulmonary Connection (TCPC). TCPC is the preferred palliative repair for single ventricle heart disease. The BDG anastomoses the superior vena cava to the pulmonary artery assuring blood flow thru lungs to be oxygenated. If the patient's adaptation is adequate, TCPC is performed to establish a circulation similar to normal. The aim of this work is to establish a methodology for the study of the hemodynamics in patients with BDG.

Hemodynamic data are taken from pre surgical catheterism. A fluids analysis is performed to determine changes in pulmonary vascular resistance (PVR). Variations in PVR with systemic and pulmonary outputs are obtained to find changes in the system regarding stagnation zones and patient's adaptation. From diagnostic images, real geometry is now obtained to run a computational fluid dynamics (CFD) simulation in order to identify stagnation zones. Particle image velocimetry (PIV) analysisis is performed to compare results with the CFD simulation.

At the time, two lumped-parameter models have been implemented. The first compares variations in PVR with pulmonary output and systemic outputs. Diminish in the pulmonary output due to augmentation of the PVR was detected. The second model, a circuit with fluxes and resistances make the same comparisons of the first model varying PVR. One patient's geometry reconstruction has been performed. Using CFD simulation, fluid velocity could be calculated. With geometry reconstruction taken to PIV analysis, the model could be correctly adjusted. This methodology is being use to study the effect of altitude on the hemodynamics of BDG.

PREDICTORS OF LATE EXIT SITE INFECTIONS ASSOCIATED WITH VENTRICULAR ASSIST DEVICE (VAD) THERAPY

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Purpose: Late onset exit site infections (LESI) leads to repeated sepsis, interventions and re-admissions for VAD recipients. In spite of advances in miniaturization of pump technology, driveline and cannula infections remains a continuing cause for morbidity. LESI may have a profound effect on late survival but risk factors for development have not been examined. **Methods:** All patients (n=233) receiving VAD therapy were analyzed for LESI(onset after 60 days). Demographics, pre & post procedural and device specific variables were collected and analyzed by univariate and multivariate methods (SPSS 17.0). **Results:** There were 163 patients from 1996–2008 on VAD support. The incidence of total ESI was 36.6%, with LESI in 22.7%(n=37). There was no statistical difference in terms of demographics and risk factors between those who had LESI and the one's without. Seven patients had early ESI who went on to develop LESI. Antibiotic administration unrelated to ESI occurred in 73 (45%) out of which only 12 patients developed LESI. Multivariate analysis showed early ESI and need for BiVAD support to be the significant predictors. Patients who received antibiotics in the 60 days prior (unrelated to ESI) negatively co-related with development of LESI. Outcomes with LESI were:bridged to transplant (n=23), died on device (n=12) and weaned successfully (n=2). Three patients with LESI died of sepsis. **Conclusions:** Late onset ESI continues to be a significant cause for morbidity in VAD patients. Development of early ESI and need for BiVAD support resulted in a higher rate of LESI. Influence of antibiotic administration in the first 60 days conferred some protective effect on the development of LESI.

STUDY OF THE INFLUENCE OF LECITHIN CONCENTRATION ON THE STABILITY OF PERFLUOROCTYL BROMIDE EMULSIONS

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The properties of perfluorocarbon emulsions used as oxygen carriers (PFCOCs) are challenged by biocompatibility and stability issues. The purpose of this work was study the influence of lecithin's concentration on the different structures and on the emulsion stability.

Emulsions with high, medium and low concentration of lecithin (3, 2 and 1 % w/v) were prepared and stored at 5°C. Due to sedimentation observed within the first two hours after preparation, the supernatant and the sediment were studied separately. The characterization was done by following pH, osmolality, particle size, phase separation and near infrared spectroscopy (NIRS) over 21 days. An approximation to the relationship between particle size and the NIRS spectrum of a lecithin/water system was determined to help interpreting the data.

Lecithin concentration turned out not to be significant regarding pH, osmolality, particle size and phase separation. However, a rupture of the emulsions with 2% w/v, and 1% w/v of lecithin was observed 7 days after the preparation. pH showed a decreasing tendency due to the oxidation of lecithin. Osmolality and average particle size showed a fluctuating tendency. Sedimentation stopped after the 7 the day. The NIRS spectrum of the supernatant and sediment differed from each other in two zones (between 1200–1350 nm and at 2200 nm).

In summary, the emulsion with 3% w/v lecithin was found to be the most stable. The study of specific zones of the NIRS spectrum would allow the association with the presence of different particle types (as liposomes and droplets) and different unstability phenomena in the supernatant and the sediment.

IMPELLA LVAD EFFECTIVELY DECREASES STRAIN IN THE LEFT VENTRICLE AFTER MYOCARDIAL INFARCTION

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In order to compensate for the loss in pumping function after myocardial infarction (MI), the heart undergoes changes meant to maintain homeostasis. This leads to a remodeling process that is initially compensatory, but later becomes maladaptive. Progression of the remodeling process can eventually lead to left ventricular (LV) dysfunction and heart failure as the heart becomes more spherical and loses its ability to effectively contract. The present in-vivo study investigates if implantation of a left ventricular assist device (LVAD) affects the strain distribution in the LV free wall. Twelve adult sheep underwent surgery to implant sonomicrometry transducers and induce a 25% MI. Five of the sheep were also implanted with an Impella LVAD post-MI. LV contractile motion and deformation were studied by calculating distances between the transducers and creating a 3D model at end-diastole. From this, contractile and remodeling strains were calculated to assess changes in contractility and LV geometry. Results were grouped into regions based on proximity to the infarct: remote, adjacent, and infarct zones. Average remodeling strains reduced from 13.5, 34.7, and 66.5% for the group without circulatory support to 3.1, 14.1, and 33.5% for the group implanted with the Impella device (for the remote, adjacent, and infarct zones respectively). Contractile strain was decreased from −17.0, −10.6, and −4.6% without LVAD support to −23.0, −17.0, and −16.1% with support. These significant differences in strain between the two groups indicate effective unloading with the Impella LVAD. Furthermore, this study provides strong support for the use of LVADs to slow and possibly stop the remodeling process.

SURGICAL CORRECTION OF PTOSIS BY IONIC POLYACRYLONITRILE ARTIFICIAL MUSCLES

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Presented is a methodology and a microsurgical procedure to employ pH-activated contractile fibrous polyacrylonitrile (PAN) gel muscles as sutured implants for the restoration of eyelid function and correction of ptosis or upper eyelid droop syndrome. The muscle controlling lid opening is the levator palpebrae superioris and it is innervated by the third cranial nerve (oculomotor nerve).

Fibrous PAN gel muscles present a unique solution for surgical correction of ptosis. The surgical procedure includes implantation and suturing of eye drop (pH) activated and actuated fibrous contractile and expansive artificial muscles such as pH active hydrogels of polyacrylonitrile (PAN) artificial muscles that are surgically implanted and sutured under the superior palpebral conjunctiva in a serpentine parallel configuration with respect to the tarsal (meibomian) glands of the upper eyelid and anchored to the tissues of superior fornix. Upon using an eye drop of pH=4, such as Ciloxan, and upon penetration through the palpebral conjunctiva, the PAN muscles contract and draw the eyelid open by providing the necessary resilient contraction force in tension to overcome the weight of the eyelid and draw the eyelid open. The natural muscles of eye closure or the orbicularis muscles are, however, sufficiently strong to overcome the artificial muscle tension and resiliency thereby stretching the highly resilient and compliant PAN muscle fibers and closing the eye so as to provide normal blinking function. An eye drop with a pH of 8 such as Timolol will in turn enable the PAN muscle fibers to expand and relax to allow the eye to blink or remain closed for sleep or at other desired times.

MOLECULAR SURGERY FOR THE TREATMENT OF MALIGNANT TUMORS

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Introduction: It is well known that malignant tumors are produced when the patient is under immunosuppressed condiditon. In order to treat malignant tumors, extracorporeal apheresis filters were developed to induce an autoimmunological active state to patients.

The immunoactivation status included not only cellular modulation but also humoral modulation. Such immunological status is introduced by extracorporeal circulation of bioincompatible apheresis filters and it is necessary to introduce safe and reproducible immunological shock to the patients. We have named this procedure the BIC-MAC (Bioincompatible Material Apheresis for Cancer) therapy. In order to secure patients safety against any side effects of immunological shock, it is essential to perform apheresis under general anesthesia with intratracheal intubation. Blood pressures and blood gases were properly maintained by such procedures. This procedure can be called molecular surgery. **Method and Results:** Two synthetic and two non-synthetic polymers were subjected as BIC-MAC columns. Substantial cellular and humoral immune activation were generated in dogs after one hour apheresis at the rate of 100 ml/min by one non-synthetic apheresis column. General anesthesia was maintained for six hours. In spite of blood pressures droped at 50 mm Hg levels at 30 minutes, it became normal within sixty minutes. Luecocytes dropped its counts inside the circulatory blood approximately to the level of 20% in thirty minutes, but returned to normal in six hours. **Conclusion:** Safe and effective immunoactivation to experimental animals was introduced by this Bic-MAC therapy. It is hoped this method could be effective for the treatment of malignant tumors or severe infection.

DEVELOPMENT OF A HIGHLY EFFICIENT NON-VIRAL VECTOR FOR CARDIAC GENE THERAPY

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Effective cardiac gene therapy requires safe and effective gene delivery into the myocardium. Previously, we developed a series of star-shaped cationic polymers, termed star vectors (SVs), and found that the 6-branched SVs was the most efficient in terms of numbers of branches. Usually, the SVs are synthesized as mixture of polymers which have various molecular weights, however, it is not clear how much molecular weights are the most effective in the SVs. In this study we separated the 6-branched SVs into several fractions, compared the transfer efficiency in vitro and evaluated in vivo gene transfer efficiency of the SVs to the heart. We used a 6-branched poly(N,N-dimethylaminoethly methacrylate) with mean molecular weight of 100 kDa and separated into seven fractions (Mn32~643kDa) using size exclusion chromatography, and examined their gene transfer efficiency. Among these fractions, the fraction of 643 kDa indicated the highest luciferase gene expression. We thus adopted the 643-kDa fraction of the 6-branched SVs and examined the charge ratio and cytotoxicity (polymer/pDNA) of the pDNA complexes in detail. It is found that the transfection efficiency was enhanced with an increase in the charge ratio of polymer/DNA up to 30 within permissible cellular cytotoxicity. In vivo transfection activity of the system was investigated in rat. The polymer/DNA complexes were injected directly into myocardium of rat and a higher level of Lac Z gene expression was obtained as well. These results demonstrated the development of a highly efficient novel non-viral vector for myocardium of rat, suggesting that further development may provide new useful agents for gene therapy for the cardiovascular disease.

COATING POLYMERS WITH A HUMAN EXTRACELLULAR MATRIX (hECM) SIGNIFICANTLY IMPROVES IMPLANT BIOCOMPATIBILITY

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Polymers, that could be used to create implants, fail due to inflammatory responses. Here we present the methods and assessments of coating an engineered family of human extracellular matrix (ECM) proteins, to various polymers.

hECM, generated by neonatal dermal fibroblasts grown on dextran microspheres grown in a stirred bioreactor, was to used to coat: nylon, PPE, and PET nonwoven scaffolds using: Glutaraldehyde, “dip & dry”, UVA, Acetic acid etch, PVA. hECM-coated samples were characterized using: FTIRS and immunoflouressence. The best ECM-coated and uncoated scaffolds were then surgically implanted subcutaneously in SCID mice. Histological samples of excised implants were assessed for inflammatory response, cellular infiltration, foreign body giant cell and capsule formation.

The FTIR results suggest highest ECM coverage via the PVA and UVA techniques from ECM solution of 0.6mg/ml. This trend was confirmed by the SEM and fluorescence micrographs where homogenous and dense ECM coverage was seen. Human aortic endothelial cells (HAoEC) seeded to ECM-coated and uncoated scaffolds were assayed for cellular proliferation with the Alamar Blue assay. Typically the materials that demonstrated the highest ECM coverage (under FTIR and SEM) also bound cells more efficiently and supported two-fold increase in cellular proliferation.Subcutaneously implanted ECM-coated (PET, PPE and nylon polymeric scaffolds) demonstrated a significant reduction in immune cell infiltration and foreign body giant cell formation, improved collagen capsule formation and tissue integration was observed with the ECM coated polymers compared to their uncoated controls.

FLOW PATTERNS OF THE LVAD-ASSISTED LEFT VENTRICLE STUDIED IN A MOCK CIRCULATORY LOOP

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The fluid mechanics of the blood are altered in patients with left ventricular assist devices (LVADs). During periods of high LVAD support, blood flow occurs entirely through the LVAD, the aortic valve is continuously closed and the heart operates *in series* with the pump. When the heart contracts strongly enough, it can provide partial support with some of the blood flowing through the aortic valve, and the two pumps operate *in parallel*. In order to better understand the fluid dynamics in the left ventricle of LVAD users, a mock circulatory lop was interfaced with a particle image velocimetry (PIV) system. Flow visualization of a transparent rubber left ventricle attached to a Micromed Debakey LVAD was performed for a variety of normal, series and parallel flow conditions. PIV results show a stable vortex in the center of the ventricle during LVAD-only conditions, throughout which the mitral valve is continuously open. The difference in average velocity across the vortex was directly proportional to the net bulk flow rate as measured in the LVAD outflow conduit. While the velocity difference was in the range of .7–1 m/s, as would be calculated from the bulk flow measurements, the forward and reverse vortex velocities were 3–6 m/s. This observation indicates that the blood is exposed to much higher velocities in a LVAD-supported heart than would be predicted from the bulk flow rate. These findings have important implications for clinicians who must set the LVAD pump speed based on clinical variables that do not reflect differences in the flow fields or level of myocardial contractility that exist in some patients.

HEMOTECH-BLOOD SUBSTITUTE ROLE IN THE PREVENTION OF PLATELET ACTIVATION IN PERCUTANEOUS CORONARY INTERVENTION (PCI) PATIENTS

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HemoTech, a second-generation free Hb-based blood substitute, developed at Texas Tech University, utilizes a novel concept of "pharmacologic cross-linking." This blood substitute consists of bovine Hb cross-linked intramolecularly with *o*-ATP and intermolecularly with *o*-adenosine and conjugated with reduced glutathione (GSH). HemoTech is in the pre-clinical stage of commercial development with the intent to be used as a perfusion fluid in PCI patients. Since platelets play a pivotal role in the pathogenesis of PCI-related thrombotic complications, the aim of this study was to assess the impact of HemoTech on platelet aggregation, as well as platelet serotonin (5-HT) release, a significant mediator of restenotic events. Platelets, from nineteen patients with acute coronary syndrome who underwent PCI with stent(s), obtained before, during and 6 hours after the procedure, were incubated *EX VIVO* with HemoTech and challenged with platelet aggregation agonists; arachidonic acid, ADP, epinephrine and collagen. Thirty healthy individuals served as controls. All procedures were done according to the guidelines of the TTUHSC IRB (#L07–010 & L07–065). Results indicate that HemoTech markedly inhibited the pro-aggregatory effect of all agonists ($p<0.05$). The release of platelet 5-HT in the presence of HemoTech was significantly reduced ($p<0.01$). This data suggests that adenosine, which provides HemoTech with pharmacological properties, inhibits platelet aggregation, and together with GSH diminishes the release of 5-HT. HemoTech could be an effective perfusion fluid for PCI.

DELIVERING PHYSIOLOGIC PULSE PRESSURES WITH CONTINUOUS FLOW VENTRICULAR ASSIST DEVICES

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Background: Continuous flow (CF) ventricular assist device (VAD) support diminishes vascular pressure pulsatility. Despite its recent clinical success CF VAD support has been associated with a higher incidence of gastrointestinal bleeding, fusion of aortic valve leaflets and hemorrhagic strokes. To overcome this limitation, we are developing algorithms to provide vascular pulsatility using a CF VAD. **Methods:** A total of 174 different control algorithms to modulate CF VAD flow were tested using a computer model of the human circulatory system simulating heart failure. All control algorithms maintained a CFVAD flow of 5.0±0.1 L/min (full support) or 2.5±0.1 L/min (partial support). **Results:** These control algorithms increased vascular pulsatility by up to 400 %, reduced left ventricular external work (LVEW) by 10% to 75%, and allowed for periodic opening of the aortic valve. Importantly, reduction in LVEW and increase in pulsatility can be adjusted to user-defined values, while maintaining the same average CF VAD flow rate. **Conclusions:** These control algorithms enable tailored unloading of the native ventricle to provide rest and rehabilitation (maximal unloading to rest followed by gradual reloading to wean), which may promote sustainable myocardial recovery. Further, these algorithms may reduce the incidence of adverse events associated with CF VAD therapy by increasing vascular pulsatility.

SURVEILLANCE AND MANAGEMENT OF HEARTMATE II PERCUTANEOUS DRIVELINES

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Percutaneous drivelines present a potential durability problem in the long-term use of ventricular assist devices (VADs). We have supported 49 patients implanted with Heartmate II VADs, 5 of whom experienced significant driveline related issues.

One patient had external driveline damage which was repaired by Thoratec personnel without pump replacement,. Three patients experienced internal driveline fractures resulting in pump failure. Two of those patients survived pump replacement, while the remaining patient was not a candidate for surgery due to multiple risk factors.

In one additional patient implanted at another center, excessive early activity and trauma resulted in poor driveline incorporation and subsequent infection. After extensive, but unsuccessful efforts to eliminate the infection and develop improved driveline adhesion, pump replacement with a new percutanous lead exit site became necessary.

To mitigate these issues, we have: 1) developed a percutaneous driveline risk assessment protocol with regular driveline x-rays based on suspected risk factors for driveline fracture including patient size, patient post-operative weight gain, and internal percutaneous lead motion; 2) Revised the placement of the percutaneous lead internally; and 3) adopted aggressive wound management techniques, including the use of vacuum-assisted closure devices to manage slow healing or traumatized exit sites.

These techniques may reduce the frequency of percutaneous driveline-related adverse events; however, the chronic management and care of the driveline remains a significant concern for long-term support of VAD patients.