American Society for Artificial Internal Organs (ASAIO) & International Society for Artificial Organs (ISAO) 2003 Annual Meetings
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Introduction and General Comments

This was my third ASAIO annual meeting. ASAIO is a relatively small society with a aging membership. However, they still seem to have some cutting edge but accessible presentations. I was not disappointed this year. I attended a blood substitutes workshop that was very timely. Tissue engineering of organs with complex microstructures (like kidneys) appears to be advancing more rapidly that I would have expected. Several talks involved *in situ* repair of MI damage using "cellular engineering" techniques (stem cells, growth factors and growth factor genes). There have been some interesting advances on implanted artificial lungs that were news to me. A group in Japan has a heparin coated ECMO circuit that they've used on a goat continuously for over 5 months. All the usual suspects (gene array chips, stem cells, nanotech, reperfusion injury, the shortage of organs for transplant, tissue engineering, numerical modeling, etc.) were mentioned in one presentation or another. Below are summaries of most of the presentations I attended. I've tried to keep them short and concise. I've stressed topics that related to classes that I teach. They have not been edited all that carefully. I've included some of my own comments (generally at the end of the summaries for each session). If you have any questions, don't hesitate to contact me.

Blood Substitutes Present & Future (Workshop)

T. M. S. Chang from McGill University made the opening remarks. He noted that nitric oxide (NO) absorption by hemoglobin based oxygen carriers (HBOC's) is still a problem (this process is generally believed to be the cause of the hypertension associated with the administration of many of HBOC's). He noted that much is his work is available online at www.artcell.mcgill.ca.

A. G. Grennburg from Brown University spoke about civilian applications of blood substitutes. He noted that last winter's nightclub fire in Rhode Island overwhelmed the state's blood supply. He mentioned problems with System Inflammatory Response Syndrome with some blood substitutes. He made a distinction between first generation substitutes as those that expand volume and carry oxygen for hours or days as opposed to third generation substitutes that will replace most or all the functions blood for long periods (week or months).

T. Reid of Walter Reed Army Institute of Research spoke about military applications of blood substitutes. In addition to stressing the need for improved resuscitation fluids for battlefield casualties, he described a new "iceless" storage system under development for blood transport and storage.

T. Silverman from the FDA talked about the FDA's expectations clinical trails of blood substitutes (oxygen therapeutics as they're calling them) clinical trials. She stated that the results from a single clinical study can be sufficient for approval (but the study would have to be very well designed and executed and the results definitive). She implied that generally more than one study will be required. For biologics (like HBOC's) the FDA requires demonstration of maintained safety, purity and potency (effectiveness). She spoke of a guidance document for blood substitutes that is being developed to replace the current one that was issued in 1997. She noted surrogate markers for clinical endpoints can be used in some cases if required by circumstances and correlation is proven. She mentioned a 1999 workshop on trauma trials in which short term survival does not correlate with long term survival. She stated that the FDA suggests that HBOC's be tested for both trauma and elective surgical uses (this policy is based on current usage of blood products and the realization that once approved, HBOC's will be used for both applications). She also noted that trauma trials may be eligible for exemption form ordinary informed consent requirements. She also mentioned the existence of a Blood Products Advisory Committee and the Baxter clinical trial (that I believe was suspended due to poor results).

S. A. Gould from Northfield Labs, Inc. provided an update on the status of their glutaraldehyde crosslinked human polyhemoglobin (PolyHeme) product. He presented impressive results of a study involving historical control group and Jehovah's Witnesses (JW's). See J. Am. Coll. Surg. (1999). He indicated that a trauma study versus saline (the current standard of care) is being planned. See Transfusion (July 2002).

M. S. Gawryl of Biopure Corp. provided an update on the status of their glutaraldehyde crosslinked bovine polyhemoglobin (Hemopure). She stated that Biopure has raised $500 million to fund the development of their product. It is currently being used in South Africa. She noted that oxygen binding by bovine hemoglobin is not 2,3-DPG dependent. She noted that their product interferes with pulse oxymetry and other colormetric clinical tests. Patients receiving large amounts of Hemopure have exhibited jaundice like skin discoloration, but not clinical jaundice.

P. E. Keipert of Alliance Parm Corp. provided an update on their Oxygent perfluorochemical oxygen carrier. They have currently suspended development of their product due to lack of funding. They have investigated the CVA's that lead to the suspension of their cardiovascular surgery clinical trial (rates of 5% for the experimental group versus 1% for the control group). Keipert feels they traced the problem to their protocol, the way in which some investigators were executing the protocol and some inadvertent over/under reporting by investigators. Gut tonometry done at one center as part of their study indicated possible reduced intestinal ischemia with their product during CABG. Unfortunately, due to the suspension of their clinical trails, it now appears they will run out of funding before getting their produce approved. They are currently in licensing discussions with overseas companies.

T. M. S. Chang returned to talk about the next generation of blood substitutes and their possible applications. He asked (and answered) the question, "where might blood

substitutes be better than real blood." I described experiments that indicate that combining super oxide demurase (SOD) and catalase (CAT) with polyhemoglobin (polyHb) might provide protection from reperfusion injury. He also described nano-dimension PEG-polylactic acid (PLA) spheres containing hemoglobin and enzymes.

A. I. Alayash a research from the FDA's Center for Biolgics describe his latest work. He mentioned the FDA's Office of Blood Research and Review (OBRR). He described in some details the way in which Fe^{2+} can act as an oxidant in the body (becoming Fe^{3+} and even Fe^{4+}) thereby destroying NO and causing cellular damage. See Biochem. 41:7407 (2002). He noted that in intact RBC's there are enzymes to prevent these reactions. He is looking into the chemistry of HBOC's other than simply their ability to carry oxygen. He is particularly interested in DBBF-Hb (described latter by Winslow). It appears to be important in preventing oxidative damage. He also mentioned Trolox, a vitamin E analog.

D. Freilich of the Naval Medical Research Center described a series of animal experiment intended to compare HBOC's with hetastarch solutions (the current standard of care for resuscitation of hemorrhagic shock casualties). In general, the HBOC seemed to out perform the hetastarch. He reported plasma base excess and lactic acid concentration as indicators of hypoxia (ischemia). He noted that transcutaneous oxygen monitoring (TCOM) can be used in the presence of HBOC's.

E. Tsuchida from Waseda University described his work with hemoglobin vesicles and albumin-hemes. The hemoblogin vesicles are about 250 nm in diameter and have PEG modified membranes. They have a 2-year shelf life at room temperature. He also described the production of albumin-heme molecules using recombinant technology. Each of these molecules contains 16 heme groups. See Macromolecules 32:8388 (1999).

R. Winslow of Sangart Company described MP4, a new non-vasoactive polyethylene clycol (PEG) hemoglobin conjugate. This product appears to be a refinement of αα-Hb (a.k.a., DCL-Hb and DBBF-Hb which were crosslinked with bis(3,5-dibromogalicyl) fumarate) and related to Baxter's HemAssist). See J. Int. Med 253(5):508-17 (2003). MP4 has 6 PEG-5000 molecules attached to each Hb tetramer. It has a P_{50} of 5 to 6 mm Hg. In studies in hemodiluted hamsters, both MP4 and bovine polyHb delivered oxygen, but MP4 delivered more to the capillaries while bovine polyHb delivered most of its oxygen to the precapillaries. Winslow suggested that this behavior has to do with a P_{O2} dependent autoregulation mechanism involving oxygen transport to the vessel surface. He thinks it may be independent of the NO mechanism.

C. Hsia of SynZyme Technologies described their HemoZyne product for battlefield hemorrhagic trauma. He referred to HemoZyne as a "Golden Hour Extender" and presented animal data support his claim. This HBOC incorporates antioxidant functionally in the form of dextran and an NO compound. These molecular structures mimic SOD and CAT. It is in the pre-IND stage.

Y. Hasegawa provided the most novel presentation of the session. He described his work on synthetic platelets. He described the brief history of synthetic platelets including infusible platelet membrane (IPM) – Cyplex and Plateletsome. His work involves 1000 nm diameter vesicles containing recombinant GP-Ib α – albumin. The half-life of the vesicles is only 3 minutes but they did show some effectiveness in enhancing coagulation in animal studies.

My Comments

In spite of some recent setbacks, practical blood substitutes (for short volume expansion and oxygen delivery) will soon be available in the U.S. (in years not decades).

A better understanding of mass transfer (of O_2, NO, etc.) and the physiological effects of these process is still needed. This understanding might explain the observation that oxygen carriers with low P_{50}'s seem to "work better" than those with normal P_{50}'s.

Many current HBOC's may contribute to reperfusion injury. In fact, free hemoglobin is a pretty toxic molecule.

Inclusion of anti-oxidant materials and enzymes may reduce this problem and could even make blood substitutes better than real blood in some situations (treatment of hemorrhagic shock and stroke).

The military still has the most interest in blood substitutes.

Alliance Parm's perfluorocarbon oxygen carrier Oxygent may have worked out, if the company hadn't had problems in the design of their clinical trial protocol.

ASAIO President's Address

S. J. Philips talked about the past, present a future of artificial organs. He compared the current state of axial flow VAD's to the state of pacemakers 30 years ago. He described a magneto-hydrodynamic (MHD) blood pump design he was involved with about 10 years ago. He noted that it required some flow to "jump start it" but when operating provided 4 l/min at 100 mm Hg. He also noted that he has used cobra venom to inhibit complement activation. He sees the future of artificial organs to be driven by nano and molecular scale technologies (he show a fun image of a nano guitar).

Vascular Grafts and Heart Valves (Slide Session)

Note: I didn't attend them, but noticed the Cardiopulmonary Session A presentations on clinical experiences with particular VAD's were standing room only.

I. Vesely of the Cleveland Clinic described tissue engineered heart valves. He mentioned Cryolife's SynerGraft (a devitalized porcine valve) and MIT's preformed PLA/PGA matrix as alternatives to his approach. Both of these approaches involve *in vivo* in growth

and formation of tissue. Vesel's approach involves basic research to produce a functional tissue valve *in vitro*. He noted that natural heart valves are complex structures composed of collagen fiber bundles, elastin tubes and sheets and GAG's. He stated that remolding does not occur in natural valve tissue. He uses directed gel shrinkage (cells trapped with collagen fibers in constrained 3-D gel blocks) to form collagen bundles with cells and an elastin sheath. He showed a picture dynamic bioreactor made using SLA (rapid prototyping) technology. He grows cells on textured hylan (hyaluronan of HA) surfaces to form elastin sheets. The size scale of his structures is on the order of that of the largest bundles in natural valves. They take about a month to form (complete apotosis occurs over about 8 weeks). He envisions a multi-step process for forming functional tissue valves.

D. Vorp of the University of Pittsburg described his work on producing tissue engineered blood vessels for small diameter vascular grafts. He studied the use of autologous adult Bone Marrow Derived Progenitor Cells (BMPC's) in his basic research work. He noted that the factors involved in the differentiation of BMPC's into usable cell types are not yet understood. Some of these factors are time, chemical and mechanical stimuli. He uses a FlexerCell™ device for cell culture under repeated mechanical strain. Repetitive strain appears to cause the cells to differentiate into smooth muscle cell (SMC) like cells but inhibits proliferation. He entraps cells in tubular gel structures and cultures them under repetitive mechanical strain to produce a vessel like structure in a process that takes weeks.

H. Harasaki from the Cleveland Clinic described his work with mechanical heart valves. He showed some data for bi-leaflet St. Jude Medical valves (SJV's). His most interesting data involved experimentally determined velocity profiles obtained using Digital Particle Image Velocimetry (DPIV) and a three leaflet mechanical valve that is under development by Triflo Medical.

Tissue Engineering and Novel Approaches to Organ Replacement (Slide Session)

D. Falkenhagen described the current state of artificial liver research in Europe. He described the Molecular Adsorption Recirculation System (MARS). It involves a dialyzer, activated carbon and ion exchange resin. In clinical trials with about 3000 patients, the MARS system has shown a survival benefit over current standards of care. However, removal of unconjugated bilirubin (that is carried on albumin) by the MARS device is poor. The Prometheus system replaces the carbon with a neutral adsorption resin and the dialyzer with an ultrafiltration device that passes albumin. The Prometheus system had coagulation problems when used with heparin so a citrate infusion system is now being used. He also described two bioreactor systems: the Modular Extracorporeal Liver System (MELS) and the AMC-BAL system. The MELS system involves a large 3 fiber system bioreactor. It initially used porcine hepatocytes but now uses human cells from organs not suitable for transplantation. The AMC-BAL system involves a 3-D non-woven bioreactor. Both the MELS and AMC-BAL systems are in clinical trials in Europe.

H. D. Humes of the University of Michigan Medical School and Nephros Therapeutics described his work on the development of a bioartifical kidney. He began his talk by describing the unmet medical need of acute renal failure (ARF) and end-stage renal failure (ESRF) patients. ARF patients have a 50% mortality rate (with the cause of death typically being sepsis or SIRS leading to shock with ischemic damage to and ultimate failure of multiple organs) and ESRF patients have a 5 year life expectancy with 10% of patients withdrawing themselves from treatment. He noted the chances of a full recovery by ARF patients are good if they can survive 5 to 10 days post injury. His approach is based on the hypothesis that renal tubule cells play an important role in maintaining the normal inflammatory, immune and vasomotor state. He noted that progenitor tubule cells exist in human kidney tissue and can be isolated. His process involves two hollow fiber devices. The first device ultrafilters the blood while the second exposes the filtrate to living renal tubule cells. The system has completed phase I clinical trails and phase II trails will be starting soon. Rapid, but often only temporary, improvement in intrinsic renal function was generally observed in the phase I trails. He also mentioned the use of gene chip arrays in the evaluation of phase I patient status. He is currently obtaining cells from donated, but unusable kidneys. He acknowledged there could be issues with using donated tissue cells in a commercial medical device under current U.S. law, but is working to address this problem. He also noted that while the current cell supply would be adequate for ARF patients it would not be enough for all ESRF patients. Treatment of ESRF patients would require other cell sources (differentiated stem cells being the most likely). His systems have a self life (literally in this case) of 4 to 5 months at 37°C.

Cardiopulmonary Tissue (Slide Session)

R. Snyder of LVAD Technology described his experience with the Viaderm™ percutaneous access device (PAD) used with the Kantrowitz CardioVAD System (KCV). This device is based on autologous fibroblast seeding of a polycarbonate surface having 1 μm pores.

Y. Huang of the Royal North Shore Hospital in Sydney described his work with the HeartPatch direct cardiac compression (DCC) device in sheep with acute heart failure. This device consists of two gas bladders attached to the outer surface of the ventricles. The inflation of these bladders is timed to support the ventricles and provide additional pumping power. His results showed the device can effectively augment hemodynamics during heart failure.

Y. Shirakawa from the National Cardiovascular Center Research Institute in Japan described a study on heart cell gene transfection with hepatocyte growth factor (HGF) cDNA. He described a hierarchy of VAD outcomes including long term support, bridge to transplant and bridge to recovery. The transfection study was an attempt to enhence the recovery of the heart after myocardial infarct (MI). The results of this proof of concept study were impressive, if somewhat limited. The study involved goats with MI's caused by ligation of the LAD coronary artery and placed on BVAD support with and without HGF transfection. The HGF treated animals were shown to have better hemodynamic

function when weaned from the VAD's, grater factional shortening of the heart and less cardiac fibrosis than those in the control group.

Stopped Here…

H. Naito from the National Cardiovascular Center Research Institute in Japan described a very interesting study involving 3-D cardiac tissue engineering using a thermoresponsive matrix. The matrix solution consisted of poly (N-isopopylacrylamide)-grafted gelatin (PNIPAM-gelatin) with added hyaluronic acid. This material gels when warmed to body temperature. Fetal rat cardiac cells entrapped in this matrix survived and began to contract spontaneously after a week.

My Comments

Functional (as opposed to space filling) bioartificial tissues and organ devices are coming but will not be available any time soon.

Cell sources for these devices (and the processing time for autologous cells) will be a major problem.

Host Response to Artificial Organs & Materials (General Session)

J. Anderson of Case Western Reserve spoke about the current understanding of apoptosis (programmed cell death) on biomaterials. He stated that shear and surface adherence are known to contribute to cell compromise and apoptosis. He noted that apoptosis is an orderly process involving nuclear degeneration, cytoplasmic breakdown and finally cellular breakup into smaller membrane enclosed elements and that the contents of the cells to not leak out during this process. He described some of the factors involved in macrophage fusion to form foreign body giant cells (FBGC's) and that fusion seems to protect the cells from apoptosis. He showed slide indicating that cells undergo less apoptosis on cationic surfaces than on neutral hydrophilic or anionic surfaces. He speculated that micro-motion might be involved in some of the cellular response to stents.
R. Virmani of the Armed Forces Institute of Pathology described her work on the host response to stents. She began by noting that most stents are tested on healthy animals with no arterial disease. She indicated at the very least, neointimal formation and restenosis in humans occurs much more slowly than in animal models. She showed data from human subjects showing correlation between inflammation and fibrin deposition with restenosis and that these conditions are often the result of vascular injury. With regard to drug eluting stents, she noted that outcomes are very depend on the design of the stent with some drug eluding stents performing no better than control (non-drug eluding) stents of a different design. He also noted the criticality of the selection of the material eluded and expressed doubts about the long term benefit of some drug eluding designs. Her presentation also included of number of very interesting images (both photomicrographs and drawings).

H. P. Greisler from the Loyola University Medical Center summarized the current understanding of the host response to small diameter vascular grafts. He began by noting that his talk was really about the failure modes of vascular grafts because no artificial materials exhibit acceptable long term performance *in vivo* due to intimal hyperplasia. He noted that cells continually to proliferate and die in and around artificial grafts. His opinion is that complete endothelialization is the only approach that will address all currently observed failure mechanisms. In particular he noted that heparin coating only address thrombotic problems not hyperplasia and delayed occlusion. He feels that neovascularization of the graft is critical to achieving a stable endothelial lining. He suggested and is investing a number of approaches intended to encourage neovascularization. These include elution of specific angiogenic growth factors or modified growth factors and rDNA technologies. The rDNA approach he described involves immobilization of genetically modified viruses onto graft surfaces. During the question and answer period someone asked about circulating endothelial progenitor cells. He indicated that he is still skeptical about these. His show included a number of very interesting tabular summary slides.

Tissue Engineering: Organ Repair and Regeneration (Slide Session)

S. Nigam from USCD described his work in understanding the factors involved in normal kidney development with the objective of applying the knowledge to tissue engineering. He started by describing the normal development of the kidney involving an uregenic bud (UB) of epithelial cells and adjacent mesenchymal cells that ultimately form the kidneys. He described an extensive series of cell culture experiments in which he identified some of the key soluble factors that control the development and differentiation of these cells. He used antibodies and gene chips to identify what surface receptors and genes that are expressed in these cells during their development. He concluded by describing a general scheme by which multiple kidneys could be grown from a single fetal UB sample. He also plugged his fiction books “The Snake Charmer” and “Transplanted Man” that I want to find out more about.

S. Itescu from Columbia-Presbyterian Medical Center described his work on using bone marrow derived angioblasts to reduce and possibly repair the myocardial damaged caused by MI’s. He stated that while conventional wisdom is that cardiomyocytes (CMC’s) seem to irreversibly withdraw from the cell cycle and don’t reproduce, it now appears that here is a population of CMC’s that can reenter the cell cycle under some conditions. These conditions seem dependent on the angiogenesis which is consistent with the observation that vascular network formation precedes organogensis during normal development. He noted that treatment with VEGF does not appear to result in the formation of persistent vascular network. In his work he sorted bone marrow cells to find cells that express a certain marker (CD34). When he infused these cells into a rat MI model, he found significant vascular network formation, reduce scar size and better functional recovery as compared to controls. He is now optimizing the process parameters.

J. Barasch of Columbia University described his work on identifying the specific growth factors involved in the development of the kidneys. He described a series of cell culture

experiments in which he identified the individual roles of FGF-2, LIF, Ngal and iron in the development of the kidneys. The idea of iron (I assume oas Fe^{2+}) is news to me.

B. Ratner from the University of Washington (and editor of the biomaterials book we use) described the large research initiative he is leading. The goal of this initiative, Bioengineered Allogeneic/Autologous Tissue or BEAT, is to develop an engineered tissue for the repair of damaged hearts. He started his talk by stressing the unique nature of heart tissue (mechanical strong, electrically conductive and highly vascular). He went on to describe a systems engineering approach to addressing these issues raise by what I would call a traditional tissue engineering approach to repairing damaged hearts. He described possible functional tissue patches for damaged hearts or the creation of a muscle driven VAD (what he called a third ventricle). He went on to briefly describe the work of the 10 groups that make up the BEAT project. He mentioned that they are searching to alternatives to PLA/PGA as bioresorbable materials. He called PLA/PGA degradation products "harsh." He described efforts to produce tissue scaffolds with very uniform micro-porosity. He described efforts to develop a HEMA material with biodegradable cross-links. He described what he called non-covalent polymers consisting of amino acids and PVA. These materials form biocompatible gels of various consistencies. He describe alginate aphrons foams and a ppNIPAM material that goes from hydrophilic at 37°C to hydrophobic at 23°C (which appears related to the material described by H. Naito) and can be used to produce sheets of cells. He described efforts to produce very fine (< 5 μm) fibers that are not recognized as foreign by the body. He agreed with previous speakers that cell sources are a major problem. He noted that embryonic myocytes seem to come in multiple phenotypes (one or more of which may be endothelial in nature). He identified vascularization as another major area of concern and suggested that growth factor approaches may be too slow. He stated that BEAT is working on bioresorbable artificial vascular networks to address this problem.
B. Dekel of Safra Children's Hospital in Israel described his work in growing kidneys in living host organisms. His current host organisms are what he called "humanized mice." These are mice that have been irradiated to destroy their immune system and then have been given human bone marrow. This results in mice with human immune systems. He then implants fetal renal tissue into these mice. There is a "window of opportunity" in gestational age during which the implanted tissue grows into kidney like structures and actually produces urine like fluid. He used gene chips to study gene expression in his tissues. He noted that the CD40 and B7-1 markers are deficient in the cells produce the best results (largest growth of renal like tissues).

My Comments

During the discussion after this session, it was noted that moving immature cells from one tissue to another often results in the cells developing into the tissue they are moved into rather than that of their origin.

It appears that amazing progress is being made towards the application of tissue engineering techniques. However, none of these techniques will be easy to apply. The *in vivo* regeneration approaches may be somewhat easier than *in vitro* repair (growing

chunks of tissue for implantation) or *in vivo* replacement (growing complete organs in living hosts) methods.

Cardiopulmonary Lung and ECMO (Slide Session)

K. Cook now at the University of Michigan (formerly at Northwestern University) described the latest iteration of the thoracic artificial lung (TAL). This version has a more compliant housing to overcome the excessive impendence of previous versions. Previous versions were design to have an appropriate resistance to steady flow, but resulted in excessive after load on the right ventricle due to their low compliance. The version described in this presentation has a segmented polyurethane (BioSpan®) outer cover. The device was tested in pigs and found to fully support their oxygen and carbon dioxide transfer requirements without overt damage to the heart.

D. Wang from the University of Texas Medical Branch described animal testing results for an ambulatory artiovenous (AV) CO_2 removal ($AAVCO_2R$) device. The hollow fiber device contains OxyPlus PMP 90/200 (Membrana GmbH) with an outer skin to reduce plasma leakage. It was shown to be capable of meeting the metabolic CO_2 elimination needs when subject to 10 to 15% of the total cardiac output. Use of the device required heparin anticoagulation to maintain ACT's at about 200 seconds.

H. Sato from the Okayama University Medical School in Japan described results of *in vitro* and *in vivo* studies of a prototype implantable artificial lung. The device described was the result of a redesign intended to reduce its impendence. The *in vitro* study used fresh bovine blood. The *in vivo* study involved a 6 hour experiment on a single goat. In the *in vivo* experiment the device was placed in parallel with the natural long and subject to 15 to 65% of the cardiac output.

L. Mockros from Northwestern University presented the results of an animal study on the hemodynamic effects of the thoracic artificial lung (TAL) as described in K. Cook's earlier presentation. C. Perlman was originally scheduled to present the results. The study involved 6 six health pigs subject to a sequence of TAL connection configuration (series, hybrid and parallel). The series arrange provided full exposure of the cardiac output to the metabolic processes of the natural lung at the expense of increased impedance. The parallel arrangement provided the lost blood flow impendence but the least contact between the blood and the natural lung. The hybrid configurations were compromises between the series and parallel arrange with some of the blood passing through both the TAL and the natural lung. While the results were generally promising (adequate gas exchange without excessive after load on the right ventricles, the researchers were concerned by an unexplained gradual increase in left arterial pressure during every experiment.

E. Tatsumi from the National Cardiovascular Center Research Institute in Japan brought the house down with his report on a study in which a goat was maintained on ECOM for over 5 months without heparin. All but one of the 16 animals (41 to 65 kg) used in the study survived to scheduled termination. In all cases the catheters and oxygenator fibers

were essentially free of thrombi at the completion of the experiments. The circuit used was coated with heparin (T-NCVC®) using a novel ionic technique. The oxygenator used was referred to as the α-Cube (or Platinum Cube) and is a descendent of the Menox and Menox-α oxygenators. This oxygenator contains fibers specially designed to resist plasma leakage. According to Tatsumi, the oxygenator is approved for use in Japan but not Europe or the U.S. and is produced by Edwards. A Rotaflow centrifugical pump was used in the experimental circuit. He reported that the system has now been use on two humans with both surviving. During the study, bypass flow rates ranged from 1.6 to 3.0 l/min and O_2 and CO_2 transfer rates ranged from 70 to150 ml/min and 50 to 110 ml/min , respectively.

A. Undar described the outcomes of patients requiring extracorporeal life support (ELS) at Texas Children's Hospital between 1995 and 2002. He summarized 17 cases (8 Biomedicus LVAD's, 4 Thoratec LVAD's and 5 ECMO) in which 12 patients survived. Although he acknowledged that the need for ELS is small (0.2% of the cases at Texas Children's), he stressed the need for FDA approved devices for neonatal and pediatric use. He attributes much of the success of their cardiac surgery program to teamwork and specific perfusion techniques. These techniques include the use of relatively high flow rates, and fresh whole blood prime for patients massing less that 8 kg. During the question and answer period, one of the moderators recalled the value of the use of fresh whole blood and indicated that it is generally no longer available from blood banks.

My Comments

Considering that my Master's research involved extracorporeal CO_2 removal ($ECCO_2R$), it was great to hear presentations on ECMO and $ECCO_2R$. It seems that technology is finally catching up with the concepts we invested 17 years ago at Ohio State.

Breaking News (Symposium)

S. Timmis from William Beaumont Hospital in Michigan describe a case in with he infused autologous stem cells harvested from peripheral blood into the coronaries of a young patient who had suffered an MI after a penetrating heart injury. He started his talk with a review of the literature on which he based his procedure. His treatment protocol involved implanting a stent immediately following the discovery of the MI. When the patient exhibited what appeared to be serious and irreversible myocardial damage, the decision was made to try stem cell therapy. This therapy involved giving G-CSF for 4 days prior to harvesting cells. Stem cells were then harvested from the circulation using leukophaeresis. The resulting concentrate contained about 2 to 3% cells expressing CD34 or AC133. These are the cells suspected to be endothelial and cardiomyocyte progenitor cells. The concentration stem cells were infused into the coronary arteries such that they entered the damaged area and the immediate vicinity. Three month follow-up shows improved cardiac function. During the question and answer period Timmis stated that he got local IRB approval for his procedures, but not FDA approval (he and his institution felt that it involved no more than off label use of a drug and a "blood" transfusion). The

point was made from the audience that the inequality between experimental cellular and "mechanical" treatments needs to be addressed by the FDA.

A. Friedman from the Yale New Haven Organ Transplant Center spoke about safeguards in organ transplant procedures. She began her presentation by while her talk was clearly motivated by the recent heart transplant ABO mismatch error, she had no specific knowledge of the incident. She stated that her intent was to examine the overall organ distribution process in terms of fairness, patients dieing before getting organs, organ function after transplantation and transmission of disease (both infectious and neoplastic) by organ transplantation. She noted that data for all recipients and donors are entered into a single UNOS computer where matches are made using a point system. Organs are then offered to transplant teams on a priority basis. Transplant teams have just one hour to decide to accept or reject and offered organ. Rejected organs are then offered t the next patient on the list. The donor's center's transplant coordinator typically has to make about 50 phone calls to distribute the organs from a patient. While every precaution is taken to prevent mistakes, time constraints and complex risk-benefit situations result in mistakes (or at least bad decisions) sometimes occurring. She ended her talk by stating that organs for transplant do not come with guarantees, but that the current system is a good one.

W. Warren from Sciperio Inc. next talked about *in-situ* formation of 3-D tissue structures. His company does research into what are essentially 3-D printing techniques. They envision endoscopic devices that could "landscape" tissue and then apply scaffolding, growth factors and/or cells to the area organized in 2 or 3 dimensions. He used the term "conformal printing" to describing printing onto non-planar surfaces. He noted that his companies technology could print onto non-planar and even moving surfaces (using closed loop feedback control). Their devices are designed to handle fluids with viscosities from 1 to 10^6 cp. There devices are capable of producing complex 3-D structures small enough to be injected. Examples he showed included a 3-D outer ear scaffold and print the U.S. air force emblem on the wing of a fly (for possible use in delivery of biowarfare agents?) and the production of artificial alveoli.

R. Crane from the Armed Forces Research Lab at Wright-Patterson Air Force Base then gave a very engaging presentation described his work on adapting military near infrared (NIR) imaging technology to the location of veins. His approach is to use low intensity near infrared light (the same intensity as emitted by a typical remote control) and night vision equipment to image veins through the skin. He should impressive videos of the technique. They showed that bone, fat and skin are relatively transparent in the wavelengths he is using. He cited the need for better battlefield triage and statistics from the Agency for Health Care Research and Quality (AHRQ) to support his claim that there is a need for his technique.

My Comments

Crane's technique appears to be quite promising and might be relatively easy to reproduce for teaching proposes.

ASAIO Hastings Lectures on Advances in Mechanical Circulatory Support

A. Klaus from the Biofluidmechanics Laboratory at Humbolt University in Berlin gave an entertaining talk on his prospective on cardiovascular applications of fluid mechanics. He started by showing Newton's law for fluids (the one defining viscosity). He pointed out that while blood is non-Newton at low shear rates (due to cell stacking and network formation) that it is Newtonian at the shear rates found everywhere in the body except small portions of the great veins. He showed images of flow separation at low angle expansions but noted that in pulsatile flow, momentary flow reversals often periodically turn expansions into contraction and wash away any recirculation blood. He presented a Computational Fluid Dynamics (CFD) model of flow through leaflet and ball and cage valves and claimed the ball and cage valve is hydrodynamically superior. He noted that thrombi tend to form in areas of both unusually high and low shear. He showed some experimental and model results for platelets in plasma illustrating this point. He ended his presentation by talking about the similarity between the hydrodynamics of blood and sand. He noted that both can behave as shear thinning fluids. He is currently developing a technique for raising the level of Venice by pumping sand under the city.

Bioengineering/Tissue (Slide Session)

Y. Grad of MindGuard Ltd. described his company device to protect the brain by diverting emboli from the internal to the external carotid arteries. The device consists of a fine mesh (with 500 μm openings) of standard stent material (stainless steel?). He showed *in vitro* and *in vivo* flow steadies demonstrating the effectiveness of the device. In use, only aspirin anticoagulation is expected to be requirement.

K. Dumont from Ghent University in Belgium discussed his computational fluid dynamics (CFD) model of pulsatile flow through a bioprosthetic type artificial heart valve. The specific model he presented assumed rigid leaflets, but he stated his plans include a more realistic model involving flexible leaflets represented as series of rigid segments connected with springs and dashpots. He used Fluent to solve his equations. He plans to compare his 2-D model 3-D experimental data from an experimental bioreactor. The bioreactor is intended for production of tissue engineered heart valves.

Exhibitor Information

Two battery vendors had booths confirming my contention that battery technology plays a critical role in modern biomedical engineering.

There were so many competing VAD companies with booths that I found myself thinking, "yea, just another VAD." This was quite a change from a few years ago when TAH's and VAD's were cutting edge.

I talked to a vendor for a dialyzer company (Fresenius Medical Care). He indicated that to consolidation of service providers and buyers is having an impact on the medical device market with physicians having less influence on the selection of devices. He also

indicated that a number of dialysis clinics in the U.S. are still reusing membranes (but always with the same patient). He indicated that his company is trying to get them to switch to single use devices.

A new museum, the International Center for Medical Technologies (ICMT), had a booth at the show. They are located in Houston and display a collection of artifacts documenting the history and development of medical devices. They have published a series of books documenting the history of the artificial kidney, lung and heart. I will request that the MSOE library get copies of these books.

Suzanne Parisian, who spoke a one of the Great Lakes Biomedical Conferences, had an ad for her new book “The FDA Inside and Out” in the conference program. The book addresses IRB, IDE and PMA issues along with a number of other topics (24 chapters). I will request the MSOE library get a copy.