	Implantation	30 days Post-Implantation	60 days Post-Implantation	90 days Post-Implantation	Explantation
Echocardiographic Analysis:					
LVEF (%)	19.3±6.62	43.5±8.51***	40.7±10.9***	36.0±12.7***	-
LVEDD (mmHg)	6.94±1.40	3.31±0.97***	4.42±1.00***	4.90±1.40**	-
LV mass (gm)	-	193±102	192±90.1	220±90.1	-
Tissue Analysis:					
Myocyte Area (μm^2)	562±122	-	-	-	290±63.3***
Myocyte Diameter (μm)	16.9±2.49	-	-	-	13.0±1.87***
% Collagen Deposition	35.7±7.14	-	-	-	27.1±4.27***
Serological Analysis:					
BNP levels (pg/mL)	225±148	63.8±42.7*	-	-	16.3±7.71**
Electrophysiologic Analysis:					
QTc (msec)	472±56.0	448±48.1	434±34.5*	-	461±70.0
QRS (msec)	121±30.4	104±20.3**	104±17.4**	-	114±45.4
Notes: Values are the means ± SD of the listed parameters.	All p-values are for t-tests vs values at implantation.	* p-value < 0.05.	**p-value < 0.01.	***p-value < 0.001.	

1050-122 Outcomes With Patients of Variable Body Surface Area and Long-Term Use of the DeBakey Ventricular Assist Device®

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Background: Ventricular assist devices (VADs) are now accepted treatment for end-stage heart failure as bridge-to-transplant.Based on the REMATCH trial, the HeartMate® device has been approved by the FDA for destination therapy. New generation devices offer the hope for smaller, more reliable support as we move to new indications such as destination therapy. The miniaturized, continuous flow DeBakey VAD® has been the most widely used new generation VAD, with over 200 implants worldwide.
Methods: The clinical report forms for completed patients and notes from weekly patient monitoring conferences for ongoing patients were examined on 157 patients at 6 sites in Europe.
Results: At pump speeds ranging from 8-11,500rpm (mean 9600 rpm) regardless of BSA, pump output (mean 4.5 l/min) increased with increasing BSA (slope 1.77)($p < 0.001$). Mean arterial pressures and end organ function, as indicated by BUN, creatinine, and total bilirubin remained in the normal range regardless of BSA. Twenty-five patients were supported > 6 months and 6 patients were supported > 1 year. Of the 25 who were supported > 6 months, 16 (64%) went on to transplant, 2 (8%) are still on support, and 7 (28%) died. Five of the patients on support over a year were transplanted and one died. Forty-three were discharged for a total of 3821 discharge days, or 10.46 patient-years. (2-342 days). (Some patients were not eligible for discharge because of institutional or regulatory constraints.) Twenty-five patients had 50 hospital readmissions. These readmitted patients spent 2974 days out of the hospital (8.15 patient-years). 70% of those discharged, were either transplanted or remain well on long-term support at home.
Conclusion: The DeBakey VAD adequately supports patients from 1.2-2.3 m^2 BSA. DeBakey VAD patients on long-term support can be successfully managed at home with excellent outcomes.

1050-123 Neurological Events With a Totally Implantable Left Ventricular Assist System: The European LionHeart Clinical Utility Baseline Study (CUBS)

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We recorded neurological events in patients with end-stage heart failure not eligible for transplant undergoing left ventricular assist device (LVAD) placement with the totally implantable pulsatile LionHeart LVAS as alterntive to medical therapy (AMT).
Twenty-three patients underwent implantation of the LVAS in a non-randomized, observational study. Neurologic events were pre-specified as a class of adverse events, reported by sites, and adjudicated independently. The events were further sub-classified as stroke (CVA), transient ischemic attack (TIA), intracranial bleed (ICB), or other (e.g., brain abscess), and whether they were either permanent/disabling or transient/reversible.
there were 24 neurologic events in 13 patients (56.5%). Nine patients experienced either ICB or CVA, five of which also had a TIA. There were a total of 12 TIAs occuring in eight patients, five of who also had either an ICB or CVA. Three patients were reported to have an "other" neurologic event. A total of 11 patients had either a CVA or a TIA as a primary event, producing an event rate of 0.69 events per pateint-year of follow-up. Placed in terms of functional outcomes, 8 of the LVAD patients had a permanent/disabling neurological injury and 7 had a transient/reversible episode. Importantly, at least 1/3 of events (8/24) occuring in four patients were preventable with improved patient selection and management.
Neurologic events constitute a significant portion of adverse outcomes in this population of AMT following LVAD placement. TIA is the most common neurologic event, with 12 events occuring in eight patients. The incidence is similar to that of the REMATCH LVAD group where 52.9% of patients had neurological dysfunction and 21% were reported to have experienced either an ICB or at least one TIA. Improvements in device design and patient selection as well as management will be needed to reduce the risk of neurologic events in patients supported with LVADs as AMT.

1050-124 Left Ventricular Ejecting Force of the Intra-Aortic Balloon Pump Assisted and Nonassisted Beats

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Background: The benefits of the Intra Aortic Balloon Pump (IABP) have been widely demonstrated, but the underlying mechanisms of these benefits are not fully described. The left ventricle (LV) ejects the stroke volume with a force that is equal to blood mass multiplied by its acceleration.
Methods: Aortic root, LV early diastolic filling (E-wave) and left anterior descending coronary (LAD) flow velocities were recorded in 20 patients requiring IABP in the intensive care unit using transesophageal Doppler echocardiography. Recordings were made at pumping rates 1:2 and 1:3, leaving a minimum of 15 minutes between recordings to allow for the return to control state. Flow acceleration at the aortic root was calculated as the slope of the early part of the velocity curve and velocity time integral (VTI) was calculated to indicate stroke volume. Diastolic VTI of LAD and LV E-wave velocity curves were also calculated to indicate LAD and LV filling flow.
Results: LAD peak diastolic flow velocity and its VTI increased significantly at IABP 1:2 by (22±2%), (79±15%), and 1:3 by (17±2%), (67±10%) respectively, compared to non assisted beats. LV E-wave peak velocity and its VTI increased significantly at IABP 1:2 by (20±5%), (75±6%), and 1:3 by (11±4%), (60±4%) respectively, compared to non assisted beats. Although a change in flow acceleration at the aortic root was not observed between the assisted and non assisted beats, peak velocity and VTI increased significantly at IABP 1:2 by (25±4%), (35±5%) and 1:3 by (20±3%), (25±4%) respectively, compared to non assisted beats. The increase in LAD diastolic VTI correlated with the increase in diastolic E-wave VTI (r = 0.82), which correlated with the increase in aortic root systolic VTI (r=0.87).
Conclusion: The increase in LAD diastolic flow due to balloon inflation results in an increase in LV filling flow. The increase in LV filling augments the stroke volume ejected into the aorta, which is in agreement with Starling law. The increase in the stroke volume despite the unchanged aortic flow acceleration suggests an increase in the LV ejecting force of the assisted beats, elucidating one of the benefit of IABP.

1050-125 Clinical Application of a Wear-Resistant Axial Flow Pump With an Intelligent Control Algorithm as a Left Ventricular Cardiac Assist Device

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Background: Since the early application of assist devices it has been a goal to have a totally wear-resistant system. INCOR, an axial flow pump for left heart support, has a virtually unlimited life due to magnetic suspension of the rotating impeller. Patients with axial flow pumps show a reduced pulsatility of the blood flow. In order to avoid significant arrhythmia due to sucking in of myocardial tissue INCOR is implemented with an anti-suction control algorithm.
Methods: Out of 72 patients supported with the device since June 2002, 31 (1f, 30m; mean age 53, range 36–65 years) with end-stage heart failure received the system in this institute. Anticoagulation consisted of heparin postoperatively and of Aspirin, clopidogrel, and Warfarin later on. For dosage adjustment, INR, thrombelastography and platelet aggregometry were performed. Furthermore, anti-heart-failure medication was administered.
Results: Mean follow-up is 127 (range, 12-454) days; 19 patients are still being supported. Two patients could be weaned because of cardiac improvement after 178 and 206 days. Two were transplanted and eight died due to multi-organ failure after a mean of 49 (range 22 – 126) days. Three patients showed signs of a transitory ischemic attack and two had cerebral bleeding. Due to the implemented anti-suction algorithm suction did not occur in any patient. After 2 months, blood chemistry showed normal values for all organ functions, in particular no hemolysis (LDH, LDH1 normal) and no deviation of any blood cell count. None of the patients showed signs of infection (CRP normal). Auto-antibodies against cardiac structures like the beta-1-adrenoceptor disappeared within six weeks after the implantation.
Conclusions: Application of up-to-date technology in the design of axial flow pumps significantly improves the clinical outcome. Especially the problems resulting from chronic systemic infection and elevated inflammatory status, known as a major problem of cardiac assist device therapy, seem to be solved. The disappearance of the antibodies after only six weeks is a sign of a fast immunological recovery. No side effects due to reduced pulsatility of the blood could be observed.

1050-126 Left Ventricular Assist Device Implantation in Patients With Viral Myocarditis-Induced Heart Failure

Nicholas C. Dang, Ranjit John, Jeffrey A. Morgan, Brian J. Lee, Mehmet C. Oz, Yoshifumi Naka, Columbia-Presbyterian Medical Center, New York, NY

Background: Viral myocarditis (VM) is a disease entity that exhibits a broad range of clinical pathways to the onset of cardiac symptoms, but the progression to severe congestive heart failure, both chronic and acute, carries significant morbidity and mortality. Left ventricular assist device (LVAD) implantation has gained acceptance as a modality

for providing mechanical support to the failing heart in these settings.
Methods: We retrospectively reviewed all patients who received a Thoratec Single-Lead-Vented-Electric LVAD at our institution between August 1990 and February 2003. Twenty-five patients with viral myocarditis were identified. Twenty-five patients whose primary indication for LVAD was coronary artery disease (CAD) were randomly selected from the same database to serve as a control group. Variables analyzed included patient demographics, duration of LVAD support, preoperative white blood cell (WBC) count and erythrocyte sedimentation rate (ESR) values, percent explanted, success rate of bridge to transplantation, and post-transplant survival rates.
Results: The VM group was younger than (35.88+/-16.43 years vs. 58.88+/-4.30 years) ($p<0.01$) and consisted of a greater proportion of female patients than (36% vs. 8%) ($p=0.02$) the CAD group. Duration of LVAD support, preoperative WBC and ESR values, and percent explanted were similar between the two groups. Bridge success rates and post-transplant survival rates were also comparable (64% transplanted in VM, 60% transplanted in CAD ($p=0.86$); 1- and 5-year post-transplant survival rates of 86.67% and 72.80% in VM, 71.43% and 62.50% in CAD, respectively ($p=0.34$)).
Conclusions: These findings suggest that despite the variable clinical course of VM and the potential to rapidly progress to end-stage heart failure, LVAD implantation in these patients yields outcomes similar to those receiving LVADs for CAD. Device support permits decompression of the dilated ventricle, facilitating myocardial recovery and the likelihood of bridging successfully to transplant or explant.

POSTER SESSION

1051 Cardiac Transplantation: Cellular Mechanisms and Rejection

Sunday, March 07, 2004, 3:00 p.m.-5:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 4:00 p.m.-5:00 p.m.

1051-127 Molecular Pathways of Cardiac Allograft Dysfunction Independent of Acute Cellular Rejection

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Background: The biology of allograft dysfunction independent of cellular rejection remains poorly understood. B-type natriuretic peptide (BNP) can serve as a sensitive marker of graft dysfunction despite normal systolic function. This investigation was designed to evaluate gene expression (GE) patterns associated with graft dysfunction and to identify underlying molecular pathways independent of cellular rejection.
Methods: Cardiac allograft recipients were prospectively enrolled as part of The Cardiac Allograft Rejection Gene Expression Observational (CARGO) multi-center study. Subjects were followed at each post-transplant visit with biopsy (read by 3 pathologists blinded to clinical data), whole blood BNP, echocardiography and hemodynamics. GE profiles of circulating cells were evaluated using leukocyte microarrays with > 8,000 genes and validated with real-time PCR (RT-PCR).
Results: 42 subjects were followed for two years. For 342 encounters the median BNP level was 190 pg/ml. Levels differed significantly as a function of gender and ethnicity (higher in women and black Americans, $p < 0.05$). BNP levels were elevated in those with Grade 3A rejection (n=9) compared to Grade 0 (n=35, $p < 0.003$) but lacked specificity for acute rejection. GE profiles of patients with elevated BNP levels ($\geq$295 pg/ml) compared to those with lower levels ($\leq$182 pg/ml, n=27) identified 25 genes correlated to BNP ($p=0.035$). The genes were associated with granulocyte and monocyte lineages and included elastases, adherence receptors, metalloproteinases and cytokine receptors. They were distinct from genes correlated to acute cellular rejection using microarrays and RT-PCR in the multi-center study. For 35 patients, BNP levels were compared to quantitative results of a clinically validated 14 gene RT-PCR test for acute cellular rejection. No correlation was found.
Conclusions: Peripheral immune cell molecular pathways indicative of allograft dysfunction are associated with elements of innate immunity distinct from cellular immunity pathways. GE assays for acute rejection and assessment of graft function by BNP may be complementary for detection of the quiescent state in cardiac allograft recipients.

1051-128 Infant Norwood Patients Become Sensitized to Donor HLA Antigens but Not Tolerized to Incompatible Donor ABO Antigens Following Homograft Implantation

Natalia E. Lobach, Lisa Hornberger, Jeffrey F. Smallhorn, Anne I. Dipchand, Neal denHollander, Glen VanArsdell, Stacey M. Pollock-BarZiv, Lori J. West, Hospital for Sick Children, Toronto, ON, Canada, University of Toronto, Toronto, ON, Canada

Background: In heart transplantation, pre-transplant anti-HLA antibody (sensitization) increases risk of antibody-mediated rejection and other post-transplant problems. Tissue allografts (homografts) used for aortic arch reconstruction and blood products used in the Norwood procedure may cause HLA sensitization in infants, some of whom may need subsequent heart transplantation. This study aimed to determine the incidence of HLA sensitization after homograft implantation in infants.
Methods: In this cross-sectional analysis, patients who underwent the Norwood procedure in infancy were tested (n=11) post-surgery and compared with control patients who received blood products during infant cardiac surgery without allograft placement (n=4). HLA sensitization was detected using Panel Reactive Antibody screening tests (PRA) and ELISA assays to detect antibody to HLA Class I & II antigens. Development of anti-blood group antibodies (isoagglutinins) was also investigated in study patients by reverse blood typing.
Results: Median age at surgery was 6 days (0-62 d) in allograft recipients, and 9 days (0-41 d) in controls. Median age at testing was 10 months (4mo-4yrs) in allograft recipients and 4 years (2-6yrs) in controls. 91% of allograft recipients were sensitized (PRA$\geq$10%), with 82% highly sensitized (PRA$\geq$4/12); 0% of controls were sensitized. 91% of allograft recipients showed positive ELISA to HLA Class I & II antigens. Two allograft recipients have undergone transplantation. Their HLA antibodies were shown in antibody-specificity assays to be directed against the HLA type of their homograft donors. Anti-blood group antibodies developed normally, even in patients whose allografts were from ABO-incompatible donors.
Conclusions: HLA sensitization develops in infants following tissue allograft placement, but not after exposure to blood products. ABO incompatible allografts did not affect normal development of isoagglutinins. These results show divergent effects on the infant immune system by exposure to T-dependent vs. T-independent antigens, and have important implications for infants eventually needing heart transplantation after Norwood palliative surgery.

1051-129 Use of Quantitative Reverse Transcriptase-Polymerase Chain Reaction for Validation of Macrophage Inflammatory Protein-1β and Vascular Endothelium-Cadherin as Important Markers of Acute Rejection After Heart Transplantation

Ana L. Roussoulieres, Olivier Raisky, Lara Chalabreysse, George Dureau, Catherine Cerutti, Pascale Boissonnat, Laurent Sebbag, Jean-Paul Gare, Jean-François Obadia, Jean Ninet, Olivier Bastien, Françoise Thivolet-Bejui, John L. McGregor, Hôpital Cardiologique Louis Pradel, Lyon, France, Inserm U331, Lyon, France

Background: Some molecules are involved in acute rejection following heart transplantation (HT). We have identified by macroarrays and immunohistochemistry (IHC), in a murine model of heterotopic HT, a number of genes implicated in acute allograft rejection. In this study, the expression of two of these genes, MIP-1β and VE-Cadherin, was investigated by quantitative real time polymerase chain reaction (RT-PCR).
Methods: We have previously studied the expression profile of genes involved in acute rejection after heterotopic HT in a murine model. Hearts from Balb/c mice were transplanted heterotopically in the abdomen of Balb/c (isografts) and C57BL/6 mice (allografts). Total RNA was extracted from mice hearts that were not transplanted (NT), from isografts and allografts. Using the technique of macroarrays and IHC, we have shown that MIP-1β was over expressed and that VE-Cadherin was under expressed in the acute rejection group (allografts). To validate the macroarrays and immunohistochemical results, the mRNA copy numbers for MIP-1β and VE-Cadherin were determined in the 3 groups using quantitative RT-PCR and TaqMan technology. Levels of the gene transcripts between the 3 groups were compared using the Kruskal-Wallis test. Mann-Whitney U test was used when comparing between 2 groups. P values $\leq$0.05 were considered to indicate significant statistical differences.
Results: The results showed that MIP-1β and VE-Cadherin were differentially expressed between the 3 groups ($p=0,01$ and $p=0,009$ respectively) as observed in the macroarray data and IHC staining. The relative amount of MIP-1β was significantly increased in allografts compared to isografts and NT ($p=0,01$ and $p=0,02$ respectively). The relative amount of VE-Cadherin was significantly decreased in allografts compared to isografts and NT hearts ($p=0,05$ and $p=0,02$ respectively).
Conclusions: We have identified 2 genes (MIP-1β and VE-Cadherin) as markers of acute rejection after HT in a murine model. Several lines of evidence, obtained by macroarrays and validated by IHC and quantitative RT-PCR confirmed the above statement. Validated genes can be used as potential targets in acute rejection after HT.

1051-130 Inhibition of p38 Mitogen Activated Protein Kinase Mediates Endothelial Cell Survival During Cardiac Transplantation

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Background: The hypothermic ischemic preservation required for cardiac transplantation exposes the donor heart to myocardial ischemia/reperfusion (I/R) injury upon implantation. p38 mitogen-activated protein kinase (MAPK) has been directly linked to increased apoptosis in models of myocardial I/R injury and its inhibition has significantly improved post-ischemic myocardial function in *in vivo* models. However, the intracellular signaling pathways responsible for these changes are not well determined. Additionally, the incorporation of p38 MAPK inhibitors into myocardial preservation solutions has yet to be examined. Here we hypothesize that the incorporation of the p38 MAPK inhibitor, SB239063, into University of Wisconsin (UW) preservation solution results in effective inhibition of TNF-α-induced p38 MAPK activation. The inhibition of p38 MAPK may play a key role in mediating endothelial cell survival through the activation of the pro-survival signals, AKT and ERK1/2.
Methods: Confluent cultured human umbilical vein endothelial cells (HUVEC) at 37°C are pre-incubated in cold (4°C) UW solution at 4°C with or without SB239063 (50μM, 4°C, 12hr). Cells are rewarmed and activated with TNF-α. Lysates are analyzed for p38, AKT, and ERK1/2 activities by Western blotting.
Results: 1) UW solution with SB239063 successfully inhibited TNF-α-induced p38 MAPK activation (n=3). 2) Inhibition of p38 MAPK produced an average upregulation of AKT activity of 42% and an average upregulation of ERK1/2 activity of 148% (n=3).
Conclusion: The p38 inhibitor, SB239063, has been effectively incorporated into UW solution to inhibit TNF-α-induced p38 MAPK activation in HUVEC. Inhibition of p38 MAPK upregulates the activities of the anti-apoptotic signals AKT and ERK1/2. These data suggest that p38 MAPK is a pro-apoptotic signal whose inhibition may represent a novel method to mitigate apoptosis and improve myocardial performance following cardiac transplantation.