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Increase in Frequency of Terminally Differentiated and Exhausted CD8+ T Cells Is Associated with Worse Clinical Outcomes after Mechanical Circulatory Support Device Implantation

J.M. Schaenman,[1] Y. Korin,[2] T. Sidwell,[2] E. Chang,[3] M. Bakir,[3] N. Wisniewski,[4] G. Bondar,[3] M. Cadeiras,[3] M. Kwon,[5] E. Reed,[2] M. Deng.[3] [1]Medicine/Infectious Diseases, UCLA School of Medicine, Los Angeles, CA; [2]Pathology, UCLA School of Medicine, Los Angeles, CA; [3]Medicine/Cardiology, UCLA School of Medicine, Los Angeles, CA; [4]Department of Integrative Biology and Physiology, UCLA School of Medicine, Los Angeles, CA; [5]Cardiovascular Surgery, UCLA School of Medicine, Los Angeles, CA.

Purpose: To determine whether analysis of the immune phenotype of T cells found in peripheral blood is a feasible method for patient assessment before MCSD implantation and whether it can provide a mechanistic explanation for the development of multiorgan system dysfunction post operatively.
Methods: Peripheral blood mononuclear cells were isolated from 28 patients ages 25-81 at days 0, 1, 3, 5, 8, and 10 after MCSD placement. Immune phenotyping was performed by multichannel flow cytometry. Statistical analysis was performed using JMP Pro 11. Impact on frequency of cell type was evaluated by linear regression for numeric and Kruskal-Wallis test for categorical variables. Model of End-Stage Liver Disease (MELD) and Sequential Organ Failure Assessment (SOFA) score was assessed at each time point and used as a marker of clinical status.
Results: A decreased frequency of naïve (CCR7+/CD45RA+) CD8+ T cells was associated with increased MELD ($p<0.001$) and SOFA ($p<0.001$) scores, and an increased frequency of terminally differentiated (TEMRA, CCR7-/CD45RA+) CD8+ T cells was associated with increased MELD ($p=0.03$) and SOFA scores ($p=0.001$), increased patient age ($p<0.001$) and death by 3 months, at all time points. Increased frequency of the marker of exhaustion KLRG-1 was associated with increased MELD score ($p=0.003$). Increased frequency of KLRG-1+/PD-1+ T cells was associated with INTERMACs score ($P=0.04$), MELD score ($p=0.001$), and death at three months ($p=0.01$).
Conclusion: CD8+ T cell maturation phenotype correlates with MELD and SOFA scores, patient age, and death. Increased markers of exhaustion are correlated with INTERMACS score, increased MELD, and death after MCSD implantation. This suggests that immune dysfunction may be part of the underlying mechanism leading to multiorgan dysfunction despite restoration of cardiac output, suggesting that noninvasive monitoring of markers of immune phenotype could be used to improve candidate selection and post-implant surveillance. Regression analysis via lasso method can be used to determine which variables are most predictive of clinical outcomes.

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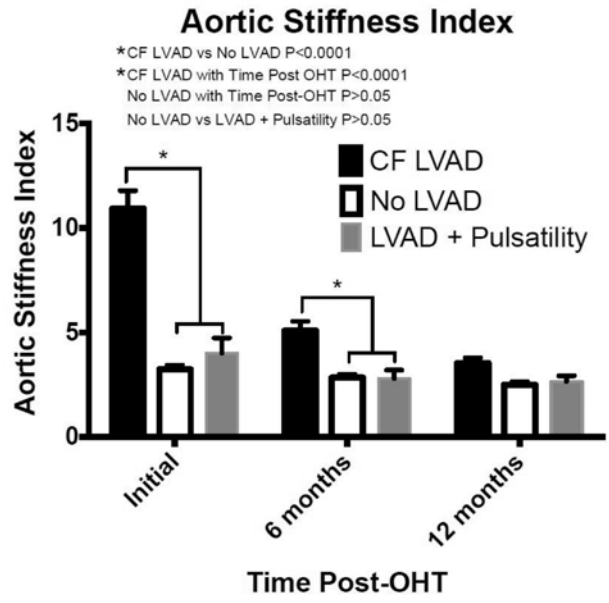
Increased Aortic Stiffness Index Among Patients Bridged to Transplant with Non-Pulsatile Left Ventricular Assist Devices

A.C. Patel,[1] R.B. Dodson,[1] K.S. Hunter,[1] A. Brieke,[1] J. Lindenfeld,[2] A.V. Ambardekar.[1] [1]University of Colorado, Aurora, CO; [2]Vanderbilt Heart and Vascular Institute, Nashville, TN.

Purpose: The effects of continuous-flow left ventricular assist devices (CF-LVAD) on vascular stiffness are unknown. Our aim was to measure aortic stiffness over time from a cohort of orthotopic heart transplant (OHT) patients exposed to varying types of flow as a result of the presence or absence of LVAD support pre-OHT.
Methods: Blood pressures and echocardiograms were retrospectively analyzed from 82 consecutive OHT patients between 01/2008-12/2013 at three time points: initial, 6, and 12 months post-OHT. For each study, blinded measurements of aortic end-systolic and diastolic dimensions from parasternal long-axis M-Mode images of the aorta were used to calculate aortic stiffness index. Patients were categorized into three groups: No LVAD (N=45), CF-LVAD (N=30), and pulsatile forms of LVAD (LVAD+Pulsatility, N=7).
Results: Mean age and duration of LVAD were similar among the groups: 51±11 yrs (No LVAD), 47±13 yrs, 194±183 days (CF-LVAD), and 42±14 yrs, 110±55 days (LVAD+Pulsatility). The aortic stiffness index among No LVAD and LVAD+Pulsatility patients was similar to age-referenced controls and did not vary over time post-OHT (Figure). By contrast, the aortic stiffness index was significantly higher among CF-LVAD compared to No LVAD and LVAD+Pulsatility immediately post-OHT, with partial attenuation of this difference by 6 months, and normalization by 12 months post-OHT.
Conclusion: Aortic stiffness is markedly increased immediately post-OHT among patients bridged with CF-LVADs, with attenuation of this increased stiffness over the first year after transplant. These results suggests that aortic vascular properties are dynamic and may be influenced as a result of alterations in the pulsatility of flow. As a greater number of patients are supported with CF-LVADs and as newer pump-technology attempts to modulate pulsatility, further research examining the role of alterations in flow patterns on vascular function and the potential resultant systemic sequela are needed.



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Changes in Metabolic Substrate Utilization and Pyruvate Mitochondrial Oxidation Mismatch during Mechanical Unloading of the Failing Human Heart: Implications for Cardiac Reloading and Conditioning

N. Diakos,[1] S. Navankasattusas,[1] S.H. McKellar,[1] A.G. Kfoury,[1] P. Ferrin,[1] L. McCreath,[1] D. Miller,[1] S. Wright,[1] K. Skedros,[1] M. Al-Sari,[1] A. Ragnhildstveit,[1] O. Wever-Pinzon,[1] G. Russel,[2] A. Koliopoulou,[1] B. Reid,[1] J. Stehlik,[1] C.H. Selzman,[1] S.G. Drakos.[1] [1]UTAH Cardiac Transplant Program, Salt Lake City, UT; [2]Intermountain Donor Services, Salt Lake City, UT.

Purpose: Mechanical unloading induced by left ventricular assist devices (LVAD) reverses several but not all aspects of myocardial remodeling and usually leads to incomplete cardiac recovery in a subset of advanced heart failure (HF) patients. We sought to investigate the effects of mechanical unloading on myocardial energetics and the metabolic perturbation of HF in an effort to identify new therapeutic targets that could enhance the unloading- induced cardiac recovery.
Methods: We prospectively examined paired myocardial tissue procured from 31 advanced HF patients (HF history duration 5.2±0.6 yrs; age 48±2 yrs) at LVAD implant and at heart transplant plus tissue from 11 normal donors.
Results: We identified a post LVAD upregulation of the glycolytic metabolites, such as pyruvate (fold change 1.9, $p<0.0001$), however there was no corresponding increase in the Krebs cycle first intermediates such as citrate (p=ns). We found 2.3 fold increase in lactate after LVAD unloading ($p<0.0001$) suggesting that the increased pyruvate from the upregulated glycolysis was not directed towards the mitochondria and the Krebs cycle for complete oxidation but instead was mainly converted to lactate in the cytoplasm. In agreement with these findings our evaluation of the mitochondrial function and structure revealed lack of post LVAD improvement in i) the oxidative functional capacity and ii) the volume density and DNA content. Finally, amino acid levels post LVAD unloading were found to be significantly increased (fold increase 1.4-2.5) acting as a compensatory

mechanism and an alternative energy source through the Krebs cycle anaplerosis entry points.
Conclusion: We report evidence that LVAD unloading induces glycolysis upregulation and subsequent pyruvate mitochondrial oxidation mismatch likely due to persistently impaired mitochondrial density and function. These findings suggest that interventions known to improve mitochondrial biogenesis, structure and function such as controlled cardiac reloading and conditioning warrant further investigation to enhance the unloading- induced cardiac recovery.

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A Gene Expression Biomarker Panel for Predicting Mechanical Circulatory Support Outcomes

N. Wisniewski,[1] G. Bondar,[1] C. Rau,[2] J. Chittoor,[1] E. Chang,[1] A. Esmaeili,[1] M. Deng.[1] [1]Department of Medicine (Cardiology), University of California, Los Angeles, Los Angeles, CA; [2]Department of Anesthesiology, University of California, Los Angeles, Los Angeles, CA.

Purpose: To identify a biomarker panel predictive of survival in mechanical circulatory support (MCS) device implantation. Furthermore, the model should apply at all timepoints surrounding the surgery, both preoperative and postoperative.
Methods: To avoid selection bias, we measured whole-genome mRNA expression (~40k transcripts). We sampled peripheral blood mononuclear cells from 22 consecutive heart failure patients undergoing MCS surgery, at 5 timepoints: day -1 preoperative, and days 1, 3, 5, and 8 postoperative.
We developed a statistical model using Cox regression on survival outcomes in two steps. We first selected top genes by univariate statistical significance across all timepoints. We then trained a multivariate model with an elastic-net penalty. The elastic-net addresses both colinearity and overfitting, finding an optimal model in terms of both the number of biomarkers and the residual error, using randomized cross-validation.
Results: The optimal biomarker panel consisted of 10 genes: IL2RA, HSPA7, AFAP1, SYNJ2, LOC653406, GAPDHP35, MGC12916, ZRSR2, and two currently unidentified genes, warranting further investigation. This panel, when trained on only preoperative data, was able to predict survival across all postoperative data with no misclassifications, demonstrating applicability at all timepoints.
The identified biomarkers are involved in a variety of processes relevant to multiple organ dysfunction syndrome. AFAP1 and SYNJ2 are known mediators of cell division, while ZRSR2 plays a critical role in the development of blood cells from the bone marrow, indicating replenishment of blood cells is important to survival outcomes. Immune regulation is also important to survival: IL2RA is a regulator of regulatory T-cell function, and HSPA7 helps mediate cellular apoptosis under stress conditions. The remaining genes have little annotation available, and their role remains unknown.
Conclusion: A small biomarker panel is able to predict outcomes at any timepoint within our cohort, suggesting potential applicability to clinical assessment of MCS after validation on an independent cohort. Furthermore, the biomarkers are biologically relevant, and consistent with hypotheses involving coagulopathy resulting from a systemic inflammatory response.

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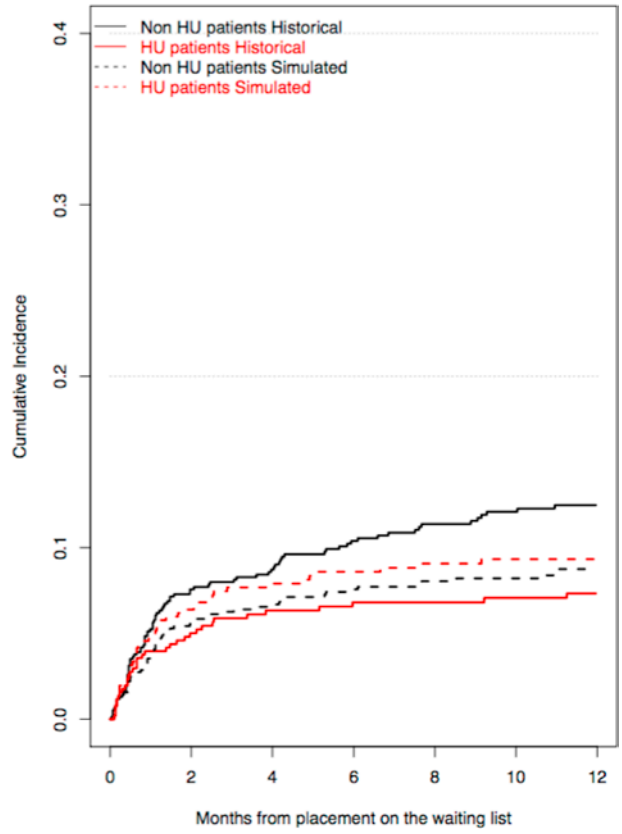
Impact of a New Urgency-Based Cardiac Allocation System on Candidate Outcomes: Results from a Simulated Allocation Study

C. Jacquelinet, B. Audry, C. Jasseron, C. Canterelle, C. Legeai, O. Bastien, R. Dorent. Direction Médicale et Scientifique, Agence de la Biomedecine, Saint Denis la Plaine, France.

Purpose: Cardiac allocation is primary based on urgency and geography, mixing patient and center-based allocation approaches. Behind differences in priorities, urgency is usually defined according to therapies rather than objective patient criteria. Recently we developed from a national cohort, a cardiac risk score (CRS) including 4 patient variables (need for mechanical circulatory support, NT-proBNP, bilirubin level and glomerular filtration rate) and predicting waitlist (WL) mortality. This simulation study aimed to evaluate the effectiveness and equity of a new national cardiac allocation system (nCAS) using CRS as urgency measure.
Methods: The study included 1286 patients aged 16 years or over, registered on the WL and 788 patients transplanted, between January 2013 and December 2014. Endpoints were incidence of transplantation, waitlist dropout for death or medical worsening, and post-transplant death. Grafts were allocated by simulation to patients according to blood type, morphological and age matching and CRS value, with national sharing. Simulated and historical cumulative incidences of events were compared using a competing risk model for WL events and a Cox model for post transplant death.
Results: nCAS significantly decreases the overall mortality from the placement on the waiting list and improves both pre and post transplant patient outcomes. In reducing the transplant access rates gap between High Urgency (HU) and non HU patients, it also provides more equitable dropout risks.
Conclusion: A patient-based allocation system including a CRS with objective criteria would correct the excess of positive discrimination for HU patients, providing more equitable results and a very promising alternative to our current CAS. Its combination to a national sharing of all organs would also decrease both WL and post transplant mortality, providing a « just in time » heart allocation for all candidates, improving both efficacy and efficiency.



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Prolonged Cardiac Allograft Donor Distance Does Not Impact Long-Term Survival

A.C. Gaffey,[1] C.W. Chen,[1] J.J. Chung,[1] J. Wald,[2] M.A. Acker,[1] P. Atluri.[1] [1]Department of Surgery, University of Pennsylvania, Philadelphia, PA; [2]Department of Cardiology, University of Pennsylvania, Philadelphia, PA.

Purpose: Long-distance procurement of cardiac allograft, outside of traditional organ procurement organization (OPO) boundaries, may be used to increase the supply of donors. However, given concerns of allograft function, ischemic time is limited to four hours or less, thereby abandoning far distance donors. With improvements in allograft perfusion and surgical technique, both distance and ischemic time may be pushed to greater boundaries. We hypothesized that recipients of allografts from greater distance should have excellent long term survival.
Methods: We retrospectively analyzed UNOS adult heart transplant data from June 2004 to December 2013. Recipients were stratified by donor distance. Demographic and outcomes data was analyzed, with a primary end point of survival.