Oral presentations on Friday, January 18th
8:00 – 9:30 am

1. Matthew Hoffman – Temple University - Krüppel-like factor 5 Regulates the miR-30 Family and Promotes Cardiac Dysfunction in Ischemic Cardiomyopathy
2. Rajasekaran Namakkal-Soorappan- University of Alabama at Birmingham - Novel Redox Mechanism for Pathological Cardiac Remodeling and Diastolic Dysfunction
3. Lixue Yin, YUN. Xu- Cardiovascular Center, Sichuan Academy of Medical Science & Sichuan Provincial People’s Hospital, Cardiovascular Center, Chengdu, People's Republic of China - The systolic left ventricular energy loss in patients with hypertension assessed by ultrasonic vector flow mapping
4. Sara Kalantari, MD – University of Chicago - Reverse Remodeling Effects of Sacubitril/Valsartan: Structural, Functional and Neurohormonal Optimization in Stage C Heart Failure
5. FUSAKO SERA, MD - Osaka University Graduate School of Medicine - Clinical implication of volume loading test in patients with left ventricular assist devise support
7. Rachit Badolia- University of Utah - Mechanical Unloading-induced Reversal of Myocardial Fibrosis in Advanced Heart Failure Patients
8. Esther S. Shao M.D. Ph.D- Maine Medical Center - 3 Year Outcomes of 3 DT-LVAD patients Bridged to Recovery and Explanted
9. William K. Cornwell III, MD – University of Colorado Anschutz Medical Campus -New Insights into Right Ventricular Function Among Patients with Left Ventricular Assist Devices using High Fidelity Conductance Catheters to Generate Real Time Pressure Volume Loops
10. Michael Bonios, MD - Onassis Cardiac Surgery Center- Recovery of Right Ventricular Function with Intraaortic Balloon Pump Counterpulsation
11. Michael Yaoyao Yin MD – University of Utah - Assessment of Hemodynamic Changes during Transcatheter Aortic Valve Replacement with Real-Time Pressure-Volume Loops
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1) Krüppel-like factor 5 Regulates the miR-30 Family and Promotes Cardiac Dysfunction in Ischemic Cardiomyopathy
Hoffman, M.1,2, Lyons, W.1,2, Kyriazis, I.D.1,2, Pol, C.J.1,2, Khan, M.2,3, Selzman, C.H.4, Stellos, K5., Drakos, S6., Drosatos, K.1,2

Ischemic cardiomyopathy, resulting from coronary artery disease and myocardial infarction, is a leading cause of heart failure-associated morbidity, mortality, and healthcare expenditure. Following acute myocardial infarction, the heart undergoes adverse remodeling resulting in eccentric hypertrophy, reduced myocardial efficiency, and congestive heart failure. Therefore, understanding the molecular mechanisms underlying adverse remodeling and improving cardiac efficiency following MI will greatly benefit the management of heart failure patients. Our lab previously identified an important role for cardiomyocyte Krüppel-like factor (KLF5) in regulating cardiac PPARα and fatty acid oxidation, which constitutes approximately 70% of the heart’s ATP production. Metabolic dysfunction is well-described in heart failure and consists of reduced FAO and increased reliance on glycolysis during early stage heart failure and suppression of both glucose and FA oxidation during late stage. Because we found an important role for KLF5 in regulating cardiac metabolism, we sought to identify how KLF5 is regulated in ischemic cardiomyopathy. Gene expression analysis of myocardial samples collected from patients with ischemic cardiomyopathy (n=8) and healthy donors (n=4) showed a two-fold increase in KLF5 expression in ICM. We also found that isolated adult cardiomyocytes and heart tissue samples from mice that underwent LAD ligation had higher KLF5 mRNA and protein levels within 2 weeks (n=10) and 4 weeks (n=10) post-MI. To assess if increased KLF5 contributed to cardiac dysfunction after MI, we performed a pilot experiment to characterize the response to MI in mice with cardiomyocyte restricted KLF5 ablation. We also found that αMHC-Klf5−/− mice were protected from ischemic cardiomyopathy and had improvements in ejection fraction and wall motion of the remote myocardium within one week of MI surgery. To assess the involvement of KLF5 itself in cardiac dysfunction, we generated a novel doxycycline inducible (dox-on), cardiac specific KLF5 transgenic mouse model (αMHC-rTA-TRE-Klf5). These mice exhibited cardiac dysfunction beginning 2-weeks post KLF5 activation. We further showed that delivery of AAV9 expressing KLF5 under the cardiomyocyte-specific cTNT promoter resulted in progressive systolic dysfunction. We therefore conclude that KLF5 induces cardiac dysfunction in ischemic cardiomyopathy.

2) Novel Redox Mechanism for Pathological Cardiac Remodeling and Diastolic Dysfunction
Rajasekaran Namakkal-Soorappan

Inheritable missense mutations in small molecular weight heat-shock proteins (HSP) with chaperone-like properties promote self-oligomerization, protein aggregation, and pathogenic processes including hypertrophic cardiomyopathy in humans. We lately reported that human mutant αB-crystallin (hR120GCryAB) overexpression that caused protein aggregation cardiomyopathy (PAC) was genetically connected to impairment of the antioxidant system and reductive stress (RS) in mice. Nonetheless, the molecular mechanism that induces RS remains poorly defined. Sustained activation of nuclear erythroid-2 like factor-2 (Nrf2) causes RS, which contributes to proteotoxic cardiac disease. The objectives of this pre-clinical study were to (a) investigate whether disrupting Nrf2-antioxidant signaling prevents RS and rescues redox homeostasis in the TG hearts and (b) elucidate mechanisms
that could delay proteotoxic cardiac disease. Non-transgenic (NTG), transgenic (TG) with MPAC and TG:Nrf2-deficient (Nrf2-def) mice were used in this study. The effects of Nrf2 diminution (Nrf2+/-) on RS induced MPAC in TG mice were assessed at 6-7 and 10 months of age. The Nrf2 deficiency prevented RS and prolonged the survival of TG mice (~50 weeks) by an additional 20-25 weeks. The TG:Nrf2-def mice did not exhibit cardiac hypertrophy at even 60 weeks, while the MPAC-TG mice exhibited pathological hypertrophy and heart failure starting at 24-28 weeks of age. Preventing RS and maintaining redox homeostasis in the TG:Nrf2-def mice ameliorated PA, leading to decreased ubiquitination of proteins. Nrf2 deficiency rescues redox homeostasis, which diminishes aggregation of mutant proteins, thereby postponing the pathological cardiac remodeling caused by RS and toxic protein aggregates.

3) The systolic left ventricular energy loss in patients with hypertension assessed by ultrasonic vector flow mapping
Lixue Yin, YUN. Xu

Objective: To evaluate left intraventricular blood flow patterns and explore the clinical value of energy loss (EL) of left ventricle in patients with hypertension for precise systolic dysfunction evaluation using ultrasonic vector flow mapping, and to assess the influence of left ventricle hypertrophic remodeling in left ventricle energy loss.
Methods: Ninety-eight hypertensive patients were enrolled and divided into two groups of non left ventricular hypertrophy group (NLVH group, n=45) and of left ventricular hypertrophy group (LVH group, n=53) according to the left ventricular mass index. Another 31 healthy adult cases were employed for the control group. The 2D gray-scale echocardiographic images and standard dynamic apical 4 chambers, 3 chambers and 2 chambers Doppler flow images for 3 completed cardiac cycles were acquired for the measurement of general parameters of left ventricular structure and function. Those dynamic images were analyzed using a dedicated VFM off-line workstation. Systole of left ventricle was divided into the isovolumetric contraction, rapid ejection and slow ejection phases to derive the average energy loss (EL-T), basal energy loss (EL-B), the middle section of the energy loss (EL-M), apical energy loss (EL-A) of left ventricle.
Results: EL-T, EL-B, EL-M in isovolumic phase, EL-T, EL-B in rapid ejection phase, EL-T and EL-B in slow ejection phase of NLVH group were higher than those of the control group (P<0.05). EL-T, EL-B, EL-M and EL-A in isovolumic phase, rapid ejection phase and slow ejection phase of LVH group were higher than those of control group and NLVH group (P<0.05). There was a positive correlation between EL-T, EL-B, EL-M in isovolumic phase and LVMI (P<0.05 or P<0.01).
Conclusion: Segmental left ventricular energy loss in systole is increased in NLVH group, which suggesting that the systolic function of left ventricle in hypertensive patients even without left ventricular hypertrophy is damaged.

4) Reverse Remodeling Effects of Sacubitril/Valsartan: Structural, Functional and Neurohormonal Optimization in Stage C Heart Failure
Sara Kalantari, Kalie Kebed, Teruhiko Imamura, Diego Medvedofsky, Jonathan Grinstein, Sarah Tayazime, Sarah Weatherford, Gene H. Kim, Nitasha Sarswat, Bryan Smith, Jayant Raikelkhar, Frederico Maffessanti, David Beiser, Parker Ward, Gabriel Sayer, Roberto Lang, Nir Uriel

Background: Valsartan/sacubitril, an angiotensin receptor-neprilysin inhibitor, significantly reduced the rates of death from any cause and from cardiovascular causes as well as the rates of hospitalizations...
for worsening heart failure as compared to a target-dose enalapril-based regimen for patients with HFrEF. The pathophysiology underlying the benefit of valsartan/sacubitril and its effects on remodeling remain unknown. Here we seek to further elucidate the benefits of valsartan/sacubitril on ventricular remodeling and functional status.

Methods: In this prospective, single-arm longitudinal study, 40 patients were initiated on valsartan/sacubitril after a two week run in period of ACE or ARB alone. The primary end-point was the degree of reverse remodeling (change in LV and RV size, volume, shape, and function) as assessed by 3D-TTE with surface analysis at 1 year compared to baseline using paired t-tests. Secondary endpoints were peak VO2, 6-minute walk distance, and KCCQ scores.

Results: There was significant improvement in LVEF (31.8% vs. 44.4%, p <0.001) (Figure 1). There was significant reduction in LVEDD as well as LV and RV volumes. There was improved 6-minute walk distance (425 vs. 487 m; p < 0.001) and improved peak VO2 (18.2 vs.19.7; p < 0.001) and NYHA functional class at 1 year.

Conclusion: This is the first study to investigate the effects sacubitril/valsartan on ventricular remodeling. Results show significantly improved LV remodeling as well as functional status at 1 year.

5) Clinical implication of volume loading test in patients with left ventricular assist devise support
Fusako Sera1, Tomohito Ohtani 1, Kei Nakamoto 1, Yoshiki Sawa 2, Yasushi Sakata1

Background: Mechanical circulatory support is available as a bridge to heart transplantation (BTT) and to recovery (BTR) in advanced heart failure. Myocardial recovery that allows device removal occurs in only a small portion of patients with LVADs. During a long LVAD support, some patients develop device related complications such as infection, thromboembolism, which requires removal or exchange of the device. Although some clinical characteristics associated with cardiac recovery have been reported, the identification of candidates for device removal is still challenging. We perform LVAD off-test to assess cardiac recovery, in which LVAD speed ramp is followed by volume loading. We evaluated whether
assessment of hemodynamic response to volume loading can be useful for predicting successful device removal in patients on LVAD support.

Methods: Before volume loading, LVAD speed was decreased to the minimum setting of each device (LVAD was off, if pulsatile). Under the minimum LVAD support, saline loading (body weight×10mL in 15 minutes) was performed. Hemodynamic and echocardiographic parameters were measured before and after volume loading. LVAD off-test was completed in 12 patients on pulsatile LVAD. Among our 168 patients on continuous-flow LVAD (CF-LVAD), hemodynamic evaluation was performed in 88 (52%), and 57 (34%) completed the off-test including volume loading.

Results: Of 12 patients on pulsatile LVAD, 6 patients (group S) could be discharged from hospital within six months after removal of LVAD, whereas the other six (group F) could not due to symptomatic heart failure. Patients in group S showed a smaller increase in changes of pulmonary artery wedge pressure (ΔPAWP) (p=0.03) and ΔPAWP divided by changes of stroke volume (ΔSV) (p=0.01) between LVAD off and after volume loading, indicating better systolic and diastolic functional reserve. Of 57 patients implanted CF-LVAD for BTT indication, successful LVAD removal was performed in 9 patients, mean age 36 years, 88% males, 55% being INTERMACS profile 1. Etiology of cardiomyopathy was all non-ischemic. Median duration of LVAD support was 358 days. All but one patient had device related complications such as device infection, thromboembolism, and required removal or exchange of the device. At the minimum speed and after volume loading, PAWP was consistently lower in the patients underwent CF-LVAD removal (group R) compared to those who did not (group N). There was no significant difference in SV at the minimum speed between the groups, whereas SV became significantly higher in group R than group N after volume loading. All the patients in group R are alive and free from recurrence of heart failure for the median follow-up of 30 months, with median peak VO2 of 17ml/kg/min (range 14-23 ml/kg/min), and LVEF of 36% (26%-52%).

Conclusion: Volume loading test during LVAD support can provide additional information on systolic and diastolic reserve of native heart, which may help identify candidates for successful device removal.

Iki Adachi, MDa, Rodrigo Zea-Vera, MDa, Hari Tunuguntla, MDb, Susan W. Denfield, MDb, Barbara Elias, RNAa, Jun Teruya, MDc, Charles D. Fraser, Jr. MDa

Background Our institutional policy is to continue centrifugal-flow ventricular assist device (CF-VAD) support for ≥3 months without activation on the transplant wait-list for physical recovery and assessment of possible myocardial recovery. We evaluated our single-institutional outcomes with CF-VAD support in children.

Methods Prospectively collected outcomes data in consecutive patients ≤18 years old with CF-VAD support were reviewed.

Results There were 40 implantations in 39 patients [28 cardiomyopathy, 11 congenital heart disease (CHD) including 3 univentricular patients]. The median (range) support was 8 (1-79) months, with 13 patients (33%) supported for ≥12 months and a cumulative duration of 41 patient-years. The median age and weight at implantation were 11 (4–18) years and 35 (14–98) kg, respectively. The median body surface area was 1.1 (0.7–2.2) m2, with 16 (40%) being <1.0 m2. Thirty-four (85%) were INTERMACS 1 or 2. Children with CHD were significantly smaller (p<0.01) and had more prior cardiac interventions (p<0.01) than those with cardiomyopathy. There were two early mortalities (5%) in children with cardiomyopathy. Of the 38 successful implantation, 36 (95%) were discharged home and managed as outpatients. Overall adverse event rates were 5.1 (bleeding), 0.8 (device malfunction), 6.1 (infection), 3.9 (neurologic dysfunction), and 1.0 (renal dysfunction) [per 100 patient-month]. In the 21 patients
with cardiomyopathy supported for ≥3 months, 5 (24%) experienced normalization of left ventricular function; 4 underwent successful explantation and 1 remains on support.

Conclusions This study demonstrates favorable outcomes of CF-VAD support in children including those with CHD, with increased incidence of cardiac recovery.

7) Mechanical Unloading-induced Reversal of Myocardial Fibrosis in Advanced Heart Failure Patients
Peter C. Ferrin*2, Rachit Badolia*1, Nikolaos A. Diakos3, Dinesh Ramadurai1, Iosif Taleb6, Michael Yin6, Sutip Navanksattusas1, Thirupura S. Shankar1, Aspasia Thodou1, Timothy Parnell4, Omar Wever-Pinzon6, Craig H. Selzman1,6, Rami Alharethi5, Stavros G. Drakos1,6.

Background: Small scale studies investigating the effects of left ventricular assist device (LVAD) on myocardial fibrosis derived conflicting results. These studies took place during the pulsatile LVAD era and did not correlate their findings with the functional improvement which occurs in a subset of LVAD patients.

Methods: We prospectively evaluated total and interstitial fibrosis/collagen content using Masson’s trichome staining on epicardium-to-endocardium LV apical tissue obtained from 14 normal donors and 141 advanced cardiomypathy, chronic heart failure (HF) patients at the time of LVAD implant (i.e. Pre-LVAD) and at transplantation (i.e. Post-LVAD). “Responders” were classified by serial post-LVAD echocardiography as: relative increase in LVEF>50%, a final resulting LVEF>40% and a final LVEDD <60mm.

Results: The degree of fibrosis varied significantly in HF (pre-LVAD) with collagen content levels both within and above the range of the donor hearts (“Low Fibrosis Group”: n=53, “High Fibrosis Group”, n=89, respectively). Responders from the High Fibrosis Group had a significant reduction in total collagen content after LVAD unloading (from 31 % to 18 %, p=0.01), whereas no change of collagen content was observed in the Non-Responders. Additionally, metabolomic analysis using Gas chromatography-Mass spectrometry (GC-MS) revealed several metabolic changes such as high fatty acids and lower amino acids levels in the High Fibrosis group. Also, differential gene expression analysis between pre- and post-Responders identified genes such as, EMILIN-3 (Elastin microfibril interface-located protein -3) and DIO2 (Iodothyronine deiodinase 2), potentially implicated in the observed fibrosis reversal.

Conclusions: In this large-scale human myocardial tissue study, the failing hearts of advanced HF patients showed a broad range of the degree of fibrosis. Subsequent mechanical unloading with LVAD decreased fibrosis in the subset of responders with high fibrosis content prior to LVAD implantation. Further investigations to elucidate the mechanisms driving these differential responses are underway in our laboratory.

8) 3 Year Outcomes of 3 DT-LVAD patients Bridged to Recovery and Explanted
Esther S. Shao M.D. Ph.D, Alfred Nicolosi M.D., Samuel Coffin M.D., Christopher Link M.D., Michael Robich M.D., Douglas Sawyer M.D. Ph.D.

Background: The Maine Medical Center destination therapy ventricular assist device (DT-VAD) program began implanting in November 2014 and to date we have explanted three patients who had left ventricular recovery on Heartmate 2 (HM2) LVAD support. Their clinical course and outcomes are described in this abstract.
Methods: Patients were routinely surveyed every 3 months by echocardiogram after LVAD implantation. Heart failure (HF) goal-directed medical therapy (GDMT) was aggressively uptitrated. When ejection fractions had improved to 50-55% with LVEDD<55 mm, patients were then scheduled to undergo weaning echocardiogram, right heart catheterization, and cardiopulmonary exercise testing. The intraperitoneal HM2 LVAD pump was removed from the left subcostal space. The outflow graft was divided and oversewn. The inflow graft was divided and oversewn. As much of the drive line that could be retrieved was removed. A part of the pump sac was closed over the remaining ends of the inflow and outflow grafts to prevent fistulation within the abdomen. Patients were maintained on warfarin and aspirin for 3 months after explant followed by lifetime aspirin daily. All patients were re-initiated HF GDMT after explant and before discharge. GDMT was aggressively uptitrated as tolerated at every clinic visit. Clinic visits were scheduled monthly for the first 3 months with echocardiogram, then every 3 months with echocardiogram indefinitely. Results: The patients were all male with ages ranging 27 to 54 years old. All had a non-ischemic, dilated cardiomyopathy with LVEF<20%. Two of the 3 patients had a confirmed alcoholic cardiomyopathy. Total days of LVAD support ranged from 302 to 477 days. Test results for all 3 patients suggested high probability for successful explantation. One patient was hospitalized electively for AVNRT ablation about 6 months post-explant. None of the patients have had a heart failure exacerbation for 36 months or any other major cardiovascular adverse event. By 18 months post-explant every patient had a decline in LVEF to 35% (see Figure 1). At the time each decline was discovered on imaging, GDMT was switched to carvedilol and later Entresto. By 24 months post-explant, all patients currently have LVEF >45%. Conclusion: Optimizing HF GDMT in LVAD patients can result in myocardial recovery that is sustained after pump explant. Carvedilol and Entresto may be better agents of choice for achieving and maintaining recovery post-explant. Our limited experience supports current explant guidelines and literature.

9) New Insights into Right Ventricular Function Among Patients with Left Ventricular Assist Devices using High Fidelity Conductance Catheters to Generate Real Time Pressure Volume Loops
William K. Cornwell III, MD, William K. Cornwell III, MD, Andy Levy, MD, Tomio Tran, MD

Purpose: Determine the impact of continuous-flow (CF) left ventricular devices (LVADs) on resting and exertional right ventricular (RV) performance

Methods: Eight LVAD patients (all male, 57±8yrs) with normal resting RV function completed invasive hemodynamic assessment during submaximal (mild and moderate, defined by rate of perceived exertion score of 7-9, and 11-13, respectively), and peak exercise on an upright cycle ergometer, and up- and downward pump speed adjustments under supine resting conditions. Results were compared with 7 healthy controls (HC, five males, 37±10yrs).

Results: Compared to HC, CF-LVAD patients had a lower cardiac output (Qc), oxygen uptake (VO2), and heart rate (HR) at submaximal and peak exercise. Analysis of RV PV loops during exercise testing (Figure 1A-B, and Table 1) shows that RV contractility (Starling contractile Index and DP/DT) was greater, and RV relaxation (-DP/DT), was less than HC during all exercise stages. Among CF-LVAD patients, peak Qc was lower, and DP/DT was similar to, values observed among HC at mild exercise (ie, a similar workload). Changes in pump speed were not associated with any significant change in RV contractility, relaxation, RV end-diastolic pressure, or myocardial energetics (Figure 1C).
Conclusion: RV function among CF-LVAD patients is characterized by reduced metrics of contractility and relaxation and lower cardiac output compared to healthy individuals exercising at similar workloads. Up- and downward changes in pump speed had minimal impact on resting RV performance.

**Figure 1**

Right ventricular pressure volume loops from a healthy control (Figure 1A) and a patient with a continuous-flow left ventricular assist device (Figure 1B). Black = resting; Red = mild exercise; Blue = moderate exercise; Orange = peak exercise. Right ventricular pressure volume loops from a patient with a Heartware continuous-flow left ventricular assist device (Figure 1C). Blue = baseline speed (2580 RPM); Red = high speed (2820 RPM); Orange = low speed (2380 RPM).

**10) Recovery of Right Ventricular Function with Intraaortic Balloon Pump Counterpulsation**

Michael Bonios, Nektarios Kogerakis, Iakovos Armenis, Evaggelos Leontiadis, Aggeliki Gkouziouta, Panagiota Georgiadou, Sokratis Fragoulis, Maria Stratinaki, Stamatis Adamopoulos

Introduction: Right Ventricular (RV) Failure occurrence after LVAD implantation is a major contributor to morbidity and mortality among patients with end-stage biventricular heart failure. Patients who require biventricular support (BiVAD) consistently show worse outcome compared to LVAD recipients.

Aim: Aim of this study was to investigate the effect of Intraaortic Balloon Pump counterpulsation (IABP) on RV function in candidates for mechanical circulatory support due to end-stage biventricular heart failure.

Methods: Patients with end-stage biventricular heart failure who required IABP support due to haemodynamic compromise were studied. RV function before and after IABP placement was studied both echocardiographically (legacy methods and free wall RV strain analysis) and hemodynamically (invasive right heart catheterization).

Results: Twelve patients with end-stage heart failure aged 35±13 years were supported with IABP for 73±58 (3-180) days. Ten of the above suffered from biventricular heart failure. Three out of 10 patients presented further clinical deterioration on IABP and required ECMO/ BiVAD support, while one patient is still on IABP, without significant improvement of RV function. In the IABP recipients with biventricular heart failure, Central Venous Pressure (CVP) decreased from 17±8 to 12±9 mmHg (p=0.040), CVP/Wedge pressure decreased from 0.67±0.14 to 0.45±0.21 (p=0.022) and Pulmonary...
Artery Pulsatility index (PAPi) increased from 1.24±0.54 to 2.68±1.38 (p=0.019). RV free wall strain also improved from -12±4% to -17±3% (p=0.017). The above parameter optimization rendered 6/10 patients eligible for LVAD implantation, despite initial biventricular compromise.

Conclusion: In patients with end-stage biventricular heart failure, IABP placement might improve RV function and alter mechanical support type (LVAD instead of BiVAD).

11) Assessment of Hemodynamic Changes during Transcatheter Aortic Valve Replacement with Real-Time Pressure-Volume Loops
Michael Yaoyao Yin MD, Anwar Tandar MD, Vikas Sharma MD, Jason Glotzbach MD, Douglas Appleby MD, Saqid Gowani MD, Stavros Drakos MD, PhD, Fred Welt MD

MD, Saqid Gowani MD, Stavros Drakos MD, PhD, Fred Welt MD

Background: Improvement in ventricular function has been observed in patients undergoing Transcatheter Aortic Valve Replacement (TAVR). However, there is little data on the acute effects of ventricular unloading during TAVR. The purpose of this study was to investigate the acute hemodynamic effects of TAVR on the left ventricle (LV) using real-time pressure-volume loops.

Methods: Pressure-volume loops were recorded using high-fidelity conductance catheters immediately pre- and post-TAVR in twelve patients (8 females, age 77±7 years) with D1 (n=11) and D3 (n=1) severe aortic stenosis. Parameters of LV preload, afterload, contractility and myocardial energetics were obtained from the pressure-volume loops. Paired sample T-test was performed to compare mean values of different parameters pre- and post-TAVR.

Results: Analysis of the pressure-volume loops pre- and post-TAVR (Figure 1) showed that there is reduced LV preload (assessed by end diastolic volume) and LV afterload (assessed by end systolic pressure and systolic wall stress) and increased LV performance (assessed by end systolic volume and ejection fraction) and LV contractility (assessed by dP/dt max). In addition, there is improved LV myocardial energetics post-TAVR, illustrated by reduced external stroke work and pressure volume area (Table 1).

Conclusion: TAVR acutely improves the LV loading conditions, contractility and myocardial energetics. The magnitude of these acute hemodynamic changes may predict the eventual degree of cardiac recovery following TAVR in patients with severe aortic stenosis.

Table 1. Hemodynamic parameters pre- and post-TAVR.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-TAVR Value</th>
<th>Post-TAVR Value</th>
<th>P (Paired Sample T-Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate (BMP)</td>
<td>66.8 ± 19.4</td>
<td>67.8 ± 16.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Cardiac Output (L/min)</td>
<td>3.3 ± 1.7</td>
<td>3.1 ± 1.6</td>
<td>0.68</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>47.9 ± 13.9</td>
<td>64.3 ± 20.0</td>
<td>0.005</td>
</tr>
<tr>
<td>Stroke Volume (mL)</td>
<td>53.2 ± 31.4</td>
<td>47.6 ± 26.5</td>
<td>0.19</td>
</tr>
<tr>
<td>End Systolic Pressure (mmHg)</td>
<td>113.25 ± 19.9</td>
<td>99.7 ± 23.2</td>
<td>0.10</td>
</tr>
<tr>
<td>End Systolic Volume (mL)</td>
<td>61.1 ± 33.3</td>
<td>28.2 ± 12.9</td>
<td>0.003</td>
</tr>
<tr>
<td>End Diastolic Pressure (mmHg)</td>
<td>17.3 ± 11.3</td>
<td>19.8 ± 9.0</td>
<td>0.51</td>
</tr>
<tr>
<td>End Diastolic Volume (mL)</td>
<td>102.2 ± 44.3</td>
<td>69.6 ± 29.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Systolic Wall Stress (mmHg)</td>
<td>221.6 ± 66.0</td>
<td>144.7 ± 48.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic Wall Stress (mmHg)</td>
<td>42.1 ± 27.8</td>
<td>40.1 ± 20.1</td>
<td>0.87</td>
</tr>
<tr>
<td>dP/dt max (mmHg/second)</td>
<td>1114.3 ± 359.1</td>
<td>903.4 ± 212.4</td>
<td>0.01</td>
</tr>
<tr>
<td>dP/dt min (mmHg/second)</td>
<td>-1010.9 ± 252.17</td>
<td>-844.42 ± 280.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Starling Contractile Index (mmHg/mL*sec)</td>
<td>13.2 ± 8.4</td>
<td>15.9 ± 8.8</td>
<td>0.17</td>
</tr>
</tbody>
</table>
### Pressure-Volume Area (mmHg*mL)

<table>
<thead>
<tr>
<th></th>
<th>Pre-TAVR</th>
<th>Post-TAVR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>8606.0 ± 3682.4</td>
<td>5323.4 ± 2968.9</td>
<td>0.009</td>
</tr>
</tbody>
</table>

### External Stroke Work (mmHg*mL)

<table>
<thead>
<tr>
<th></th>
<th>Pre-TAVR</th>
<th>Post-TAVR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>5209.4 ± 2714.8</td>
<td>3872.1 ± 2475.2</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Figure 1. Pressure-volume loops in a patient pre- and post-TAVR (blue = pre-TAVR; orange = post-TAVR).

11) Reverse Remodeling Effects of Sacubitril/Valsartan: Structural, Functional and Neurohormonal Optimization in Stage C Heart Failure

Sara Kalantari, Kalie Kebed, Teruhiko Imamura, Diego Medvedofsky, Jonathan Grinstein, Sarah Tayazime, Sarah Weatherford, Gene H. Kim, Nitasha Sarswat, Bryan Smith, Jayant Raikelkhar, Frederico Maffessanti, David Beiser, Parker Ward, Gabriel Sayer, Roberto Lang, Nir Uriel

**Background:** Valsartan/sacubitril, an angiotensin receptor-neprilysin inhibitor, significantly reduced the rates of death from any cause and from cardiovascular causes as well as the rates of hospitalizations for worsening heart failure as compared to a target-dose enalapril-based regimen for patients with HFrEF. The pathophysiology underlying the benefit of valsartan/sacubitril and its effects on remodeling remain unknown. Here we seek to further elucidate the benefits of valsartan/sacubitril on ventricular remodeling and functional status.

**Methods:** In this prospective, single-arm longitudinal study, 40 patients were initiated on valsartan/sacubitril after a two week run in period of ACE or ARB alone. The primary end-point was the degree of reverse remodeling (change in LV and RV size, volume, shape, and function) as assessed by 3D-TTE with surface analysis at 1 year compared to baseline using paired t-tests. Secondary endpoints were peak VO2, 6-minute walk distance, and KCCQ scores.

**Results:** There was significant improvement in LVEF (31.8% vs. 44.4%, p < 0.001) (Figure 1). There was significant reduction in LVEDD as well as LV and RV volumes. There was improved 6-minute walk distance (425 vs. 487 m; p < 0.001) and improved peak VO2 (18.2 vs.19.7; p < 0.001) and NYHA functional class at 1 year.
Conclusion: This is the first study to investigate the effects of sacubitril/valsartan on ventricular remodeling. Results show significantly improved LV remodeling as well as functional status at 1 year.
Poster Session during lunch on Thursday & Friday, January 17-18th

Voltage Dependent Anion Channel 2 Impairs Cardiac Excitation-Contraction Coupling During Development and Leads to Cardiomyopathy Phenotypes
Thirupura S. Shankar, Sutip Navankasatusas, Dinesh K. A. Ramadurai, Aspasia Thodou, Rachit Badolia, Jing Ling, Salah Sommakia, Kenneth W. Spitzer, Stavros G. Drakos

Background: Gene expression and phosphoproteomics studies performed by our team on human myocardial tissue acquired from advanced heart failure (HF) patients undergoing cardiac mechanical support indicated a potentially important role of Voltage Dependent Anion Channel 2 (VDAC2) in myocardial recovery. VDAC2 is a porin present on the outer mitochondrial membrane (OMM) and is known to play important role in calcium handling, apoptosis, cell metabolism and steroidogenesis. Whole body (null) deletion of VDAC2 is embryonically lethal. Animal studies in mice and zebrafish investigated the role of VDAC2 in calcium homeostasis and arrhythmia but the exact mechanisms are not well understood.
Aim: We hypothesize that VDAC2 plays an important role in cardiac development by maintaining calcium homeostasis and VDAC2 deficiency might lead to cardiomyopathy and HF phenotypes by impairing EC coupling and cell contractility.
Methods: Cardiac-specific and developmentally deleted VDAC2 was generated using myh6-Cre and VDAC2 flox mice. Sixteen-week old mice were used for all experiments. Serial echocardiograms were performed from neonates up to 18 weeks post-natal to assess the progression of cardiac function.
Results: The mouse with cardiac specific deletion of VDAC2 (KO) is viable but showed bradyarrhythmia, 3rd degree AV block and left ventricular (LV) dilation. We observed significant elongation and thinning of cardiac myocytes in the KO (N=3, n=43, p<0.001). RNA sequencing data revealed altered gene expression in Ca2+ handling pathways. We also found smaller Ca2+ transients (N=3, n=42, p<0.0001), reduced rate of decline (N=3, n=42, p=0.002) and reduced rate of Ca2+ release (N=3, n=42, p<0.001). In addition, Ca2+ calibration assay showed increased diastolic Ca2+ in the KO (N=3, n=12, p=0.036) and the action potential showed an overall prolongation of action potential duration at 50% repolarization (APD50) (N=3, n=16, p=0.014). Mitochondrial Ca2+ uptake was reduced in the KO along with increased reactive oxygen species (ROS) production upon Complex I and Complex III inhibition.
Conclusion: We identified impaired EC coupling and altered calcium homeostasis after cardiac specific deletion of VDAC2. These cardiomyopathy features may predispose to severe HF when exposed to cardiovascular stress. Our ongoing studies to further understand the roles of VDAC2 and how specifically the KO mice adapted to this HF predisposition could.

FGF21 as a biomarker for heart failure
Salah Sommakia, Elizabeth Nguyen, Sandra Lee, Dinesh Ramadurai, Thirupura Shankar, Sutip Navankasattusas, Robert Campbell, Stavros Drakos, Dipayan Chaudhuri

Background: FGF21, an important metabolic regulator, has recently been suggested as a biomarker for heart failure. FGF21 is involved in the integrated mitochondrial stress response, and has been shown to be upregulated with mitochondrial DNA damage, which occurs more frequently in dilated cardiomyopathy. In this study, we investigated whether FGF21 can be used as a biomarker for heart failure with mitochondrial damage. Methods: We collected blood and cardiac tissue samples from heart failure patients who have undergone VAD transplantation. We also collected blood and tissue
from mice with heart failure due to 1) combination of transverse aortic constriction and coronary artery ligation (TAC+Lig) or 2) cardiac-specific knockout of the mitochondrial transcription factor A (Tfam). Serum FGF21 levels were measured using Enzyme-linked immunosorbent assay (ELISA). Messenger RNA was extracted from the tissue and FGF21 gene expression was measured using real-time quantitative PCR (qPCR). Immunohistochemical staining was performed on tissue sections (either paraffin embedded or frozen) to observe FGF21 levels. Results: Serum FGF21 was elevated in human heart failure patients compared to healthy controls, as well as in both mouse models of heart failure. In human patients, there was no increase in cardiac FGF21 gene expression. In the TAC+Lig mouse model we observed a 3.37-fold increase, while the Tfam knockout model which has severe mitochondrial damage exhibited a 218-fold increase in cardiac FGF21 gene expression. In all cases, there was weak correlation between serum FGF21 levels and cardiac FGF21 gene expression, suggesting an extracardiac source of serum FGF21 during heart failure. Further qPCR assays revealed changes in FGF21 gene expression in the liver and white fat, indicating metabolic stress on other organs resulting from heart failure. Conclusion: Serum FGF21 is elevated in multiple models of heart failure, but appears to have both cardiac and extra cardiac sources. Future work will investigate 1) whether there is a correlation between FGF21 levels and mitochondrial damage, and 2) the signaling pathway resulting in metabolic stress to other organs in heart failure.

**AI regurgitation worsens immediately with LVAD support: a mock loop study**

Purpose: Aortic valve (AoV) insufficiency (AI) is a serious complication in more than 20% of Left Ventricle Assist Device (LVAD) patients within 12 months of LVAD implantation. Normal AoV have developed AI following long-term LVAD support, which has been associated with a significant reduction in LVAD patient survival. During LVAD support, the AoV pressure difference is increased, which reduces systolic opening and worsens regurgitant flow through an incompetent valve. The goal of this study was to measure the effect of LVAD support on intraventricular flow during AI.

Methods: The velocity field was measured in the midplane of a dilated silicone LV model attached to a rotary LVAD (Abbott Labs, Chicago IL) in a mock circulatory loop. A Pre-LVAD without AI condition (BL) of 20% ejection fraction was established, followed by testing at three LVAD speeds (Low, Medium and High). AI was created with a small 3-D printed stent which was nonobstructive to forward flow but prevented the leaflets from fully closing. LV and aortic pressure, and LVAD and distal aortic flow, were recorded for BL and AI. Stroke volumes (SV) during diastole and systole were calculated from the integral of measured flow. An in-house MATLAB program was used to detect and characterize the size and velocity of the regurgitant jet from the measured velocity field; and the vena contracta (VC) was estimated from the RJ minimum diameter at the AoV.

Results: AI reduced cardiac output by 25% for the pre-LVAD condition, resulting in a regurgitant fraction (RF) of 33% which is considered mild-moderate AI. The regurgitant jet (RJ) reached its peak during mid-diastole, then decreased and disappeared during systole. As LVAD support increased from Low to High, total flow increased by 40-82%. AI reduced these values by approximately 28%, and increased the RF to 38-40% (moderate-severe AI). The RJ enlarged during diastole and persisted longer until mid-late systole. During High LVAD support, the RJ was present during the entire cardiac cycle. The stroke volume (SV) and velocity profiles across the AoV confirmed the decrease of net forward flow and the increase of backward flow through AoV. Overall, the RJ properties (area, VC, length, and velocity) increased as LVAD support increased, and the total SV during diastole and systole decreased when AI was present.
Conclusion: The results show that an initially mild level of AI worsens with LVAD support prior to any remodeling, simply due to the altered pressure distribution across the AoV. These findings provide a basis for estimating the RF prospectively for LVAD patients, and determine whether to repair the aortic valve prior to LVAD implantation.

**Smyd5 is a novel regulator in cardiac hypertrophy**
Ryan Bia, Mickey Miller, Caiyi C. Li, Aman Makaju, Anna Bakhtina, Li Wang, Steven Valdez, Stephen T. Smale, Sarah Franklin

Epigenetic regulation is the process of altering gene activity without changing DNA sequence including methylation, acetylation and phosphorylation of histone proteins which modify chromatin structure and allow gene expression or silencing. Heart disease, the leading cause of death in the United States, is accompanied by two hallmark features: specific alterations in gene expression and hypertrophic growth of the myocardium. However, we are only beginning to identify the proteins which regulate these changes in gene expression and contribute to heart disease. The Smyd family is a unique class of methyltransferases whose catalytic SET domain is separated by an MYND domain and consists of 5 members. This family has been shown to methylate several unique histone and non-histone proteins and has been implicated in regulating cell growth, cardiac development, sarcomere organization, and muscle differentiation. One specific family member, Smyd5 is ubiquitously expressed across various human tissues including both fetal and adult heart. However, little is known about Smyd5, which has never been studied in striated muscle. Therefore, it is completely unknown how Smyd5 regulates gene expression in the heart and how this contributes to cardiac physiology and morphology. To characterize the role of Smyd5 we generated inducible, cardiac-specific knockout mice which developed hypertrophy and fibrosis two weeks after Smyd5 knockout and ultimately heart failure at five weeks. These phenotypic changes were accompanied by a reduction in histone H4 K20 trimethylation, highlighting a mechanism by which this protein alters gene expression and cardiac physiology. In addition, proteomic analysis of cardiac tissue from Smyd5 KO mouse at various time points, and subsequent bioinformatics analysis, identified transcriptional regulation and RNA processing as the most perturbed biological processes, and identified specific proteins differentially regulated by Smyd5 in each of these pathways. Overall, these results constitute the first analysis of Smyd5 in the heart and confirm a role for this methyltransferase in regulating hypertrophic growth through methylation of histone H4 and begin to identify the downstream pathways modulated by these epigenetic changes.
Durability of Cardiac Improvement After Weaning Left Ventricular Assist Device Support in Advanced Cardiomyopathy Patients

Background: Studies have shown that a subset of end-stage heart failure (HF) patients supported with left ventricular assist devices (LVADs) can significantly improve their native heart structure and function. The long-term durability of this cardiac improvement after LVAD weaning has not been well investigated.

Methods: We included chronic end-stage non-ischemic cardiomyopathy patients (acute HF etiologies excluded) who were weaned from LVAD support based on predefined myocardial structural, functional and hemodynamic criteria. We prospectively evaluated clinical, imaging, neurohormonal and quality of life (QoL) data pre-implant, during LVAD support and post LVAD weaning. We defined “sustainable cardiac improvement” after LVAD weaning as LVEF≥ 40% and LVEDD< 57mm. Regression analysis was employed to evaluate trends.

Results: Our cohort included 6 males and 6 females, mean age 33±12. Patients achieved LVAD weaning criteria after 532 [196, 2304] days of support. LVEF improved from 18.4±5.6 % pre-implant to 46.2±10.1 % at LVAD explant (p<0.0001), LVEDD decreased from 65.0±7.0 mm to 46.0±6.0 mm (p<0.0001) and brain natriuretic peptide (BNP) decreased from 1437.8±1584.7 pg/ml to 89.6±77.2 pg/ml (p<0.02). During a median follow up post LVAD removal of 844 days, we identified a group of patients with sustainable (n=7) and a group with declining (n=5) cardiac improvement (Figure). At the most recent follow-up LVEF (52.4 vs 17.4 %; p<0.0001), LVEDD (52.0 vs 65.0 mm; p=0.003) and BNP (57.8 vs 677.4 pg/ml; p=0.04) were significantly different between the stable and declining groups, respectively. QoL assessment matched well with patients’ clinical performance (Figure). The degree of cardiac improvement (structural, functional and neurohormonal) pre-LVAD removal did not differ between the stable and declining groups and therefore was not identified as a predictor of post-weaning sustainable cardiac improvement. After LVAD weaning, 4 out of 5 patients in the declining group had chronic systemic infection, substance abuse and HF medications therapy non-adherence, which likely affected negatively the durability of cardiac improvement. One patient in the declining group passed away due to HF recurrence.

Conclusions: In this single center report the long-term durability of cardiac improvement after LVAD weaning appears to be encouraging. Larger and longer follow up clinical and translational studies are warranted to provide further clinical and mechanistic insights regarding factors associated with sustainable cardiac improvement.

Cardiac Reverse Remodeling and Recovery in Dilated Cardiomyopathy Medication-Naive Patients Requiring Durable Left Ventricular Assist Device Support

Background: Occasionally new onset cardiomyopathy patients (pts) present late and with such advanced disease stage that they cannot tolerate heart failure (HF) drug therapy. We sought to investigate the cardiac recovery (CR) potential following a combination of left ventricular assist device (LVAD) and guideline-directed HF drug therapy in this medication-naive population.

Methods: Chronic advanced HF requiring durable continuous-flow LVAD were prospectively evaluated. Patients with acute HF (myocarditis etc.) or post LVAD follow up <3 months were excluded. The “meds-
treated” group (n=203) comprised patients treated adequately with at least one neurohormonal blocking agent during their HF history (b-blocker, ACEI/ARB, Aldosterone antagonist) and “meds-naive” group (n=8) comprised patients who were never before treated adequately with any HF medication. Baseline and follow up clinical, hemodynamic, imaging and laboratory data were analyzed. LVAD patients were phenotyped as CR responders or non responders, based on published predefined criteria.

Results: Univariate analysis showed that “med-naive” patients were younger, more likely to be on intravenous vasoactive agents, temporary mechanical support and with lower INTERMACS profile before LVAD implantation. Interestingly, no differences were seen in HF symptoms duration or other comorbidities. Baseline and follow up hemodynamics were similar in both groups, besides higher right atrial pressure pre-LVAD in the “meds-naive” group (16 vs 11 mmHg; p=0.04). Baseline echocardiographic (including LV dilation) and biochemical parameters revealed no differences between the groups, besides lower LVEF and higher BNP in the “meds-naive” group (14 vs 19 %; p=0.03 and 2352 vs 1270; p=0.03, respectively). CR rates were significantly higher on “meds-naive” versus “meds-failed” group (50.0 vs 13.8 %; p=0.005). Despite higher cardiac recovery rates in the “meds-naive” group the time course and magnitude of the favorable functional and structural response was similar among the CR responders of each of the 2 groups.

Conclusion: Young patients with new onset dilated cardiomyopathy sometimes present late, with advanced disease stage, unable to tolerate HF medications and requiring durable LVAD support. This patient population appears to have a potential for CR up to 50% and this could be factored in decisions surrounding their long-term therapeutic options.

Predicting Cardiac Recovery Before Durable Left Ventricular Assist Device Implantation in Advanced Heart Failure Patients

Background: Predicting cardiac recovery (CR) in advanced heart failure (HF) patients before left ventricular assist device (LVAD) implantation remains challenging. This study sought to investigate whether CR after LVAD unloading can be predicted by cardiac functional and structural parameters together with clinical characteristics.

Methods: From 2008 to 2016, consecutive advanced chronic HF patients (N=347) supported with durable continuous-flow LVADs were prospectively evaluated. Patients with acute HF etiologies or without adequate post-LVAD follow up (<3 months) were excluded. A great variety of clinical characteristics were evaluated in the remaining 285 subjects. LVAD patients were phenotyped while on support, as CR Responders or Non Responders, based on published predefined echocardiographic criteria. Multivariable logistic regression was used to form the model and the Utah Cardiac Recovery (UCAR) score was created from the regression beta coefficients of the final model.

Results: CR occurred in 13.7% of patients. Univariate analysis showed that responders were more likely to be young, female, non-ischemic cardiomyopathy, with shorter HF symptoms duration and no prior heart surgery. They had lower blood urea nitrogen and were less likely to be on temporary mechanical support before LVAD. The multivariable UCAR model (AUC=0.755; p<0.001) predicted CR using 3 clinical parameters – Table.

Conclusion: Univariate and multivariable predictors of CR include both modifiable and non-modifiable patient characteristics that are known prior to LVAD implantation. The UCAR score can serve as a
practical tool for targeted patient selection to implement protocols that facilitate CR in the advanced HF patient subpopulation that is most likely to respond

<table>
<thead>
<tr>
<th>Table</th>
<th>Multivariable Predictors of Cardiac Recovery and Prognostic Score System</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No. of patients (N=285)</td>
</tr>
<tr>
<td>Female Gender</td>
<td>40 (14.0)</td>
</tr>
<tr>
<td>Duration of HF</td>
<td></td>
</tr>
<tr>
<td>HF duration ≤9 months</td>
<td>49 (17.2)</td>
</tr>
<tr>
<td>HF duration 10-36 months</td>
<td>57 (20.0)</td>
</tr>
<tr>
<td>No prior heart surgery</td>
<td>209 (73.3)</td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise indicated.
CI = confidence interval; CR = cardiac recovery; OR = odds ratio

UCAR score ranging 0-9, predicted recovery with: 4.6% (UCAR 0-2), 7.1% (p=0.57, OR=1.59, UCAR 3-4) and 28.6% (p<0.001, OR=8.29, UCAR 5-9)

**Effect of the p53 inhibitor-α on cardiomyocyte apoptosis induced by doxorubicin in neonatal rats**

Lixue Yin, YUN. Xu

**Background** PFT-α is a p53 specific inhibitor which is used to inhibit p53 pathway. However the effects of PFT-α on apoptosis and PUMA protein expression of cultured neonatal rat cardiomyocytes induced by doxorubicin are unclear.

**Objective** To explore the effect of the p53 inhibitor-α on apoptosis and PUMA protein expression in cultured neonatal rat cardiomyocytes induced by doxorubicin.

**Methods** Cardiomyocytes isolated from Neonatal Sprague-Dawley rats were primary cultured to establish the model of doxorubicin induced myocardial cells injury. The activity and the apoptosis rate of myocardial cells and the expression of p53 and PUMA protein in myocardial cells were measured after the treatment of doxorubicin with or without PFT - α.

**Results** (1) Cardiomyocytes was treated with different concentrations of doxorubicin during the same time, with the increasing concentration of doxorubicin, cardiomyocytes’s activity decreased gradually. The action of doxorubicin at the same concentration for different time, with the prolongation of the action time of doxorubicin, the activity of cardiomyocytes were reduced. (2) In the DOX group, the expression of p53 and PUMA protein were increased, and the apoptosis rate of cardiomyocytes was increased, while the mitochondrial membrane potential was decreased. The expression level of p53 and PUMA protein in PFT-α +DOX group were lower than that in the DOX group (P < 0.05), and the apoptosis rate of cardiomyocytes was decreased (P < 0.05). There was no significant difference in the expression of p53, PUMA protein between the control group and the PFT-α group.

**Conclusion** (1) The toxicity of doxorubicin to cardiomyocytes of the Sprague-Dawley neonatal rats is time and dose-dependent, which can cause cardiomyocytes death and apoptosis. (2) Doxorubicin treatment on SD neonatal rat cardiomyocytes resulted in the increase expression of p53, PUMA protein and the decrease of mitochondrial membrane potential. (3) PUMA was dependent on p53 pathway in the process of doxorubicin-induced cardiomyocyte apoptosis. 20μM PFT-α was suppressed the expression of PUMA protein, stable the mitochondrial membrane potential, and the injury of doxorubicin to Sprague-Dawley neonatal rat cardiomyocytes could be alleviated in some extent. It also
showed that the protective effect of PFT-α in cardiomyocytes apoptosis induced by doxorubicin in Sprague-Dawley neonatal rats.

**Global Proteomic and Transcriptomic Analyses Identify a Profile that Distinguishes Advanced Heart Failure Patients Capable of Cardiac Recovery Following LVAD-Unloading**

Sarah Franklin, Rachit Badolia, Sutip Navankasattusas, Dinesh Ramadurai, Anna Bakhtina, Aman Makaju, Christopher Tracy, Lauren McCreath, Nikolaos Diakos, Craig Selzman, Stavros Drakos

Left ventricular assist devices (LVADs) are increasingly used in everyday clinical practice as either a bridge to heart transplantation (B-T-T) for end-stage heart failure patients or as a permanent (destination) therapy. Evidence from many prospective studies indicate that a subset of patients with LVAD implants can significantly improve the structure and function of their heart and undergo LVAD explantation (i.e. “responders”) while another subset doesn’t experience such recovery, remaining B-T-T candidates (i.e. “non-responders”). This intriguing phenomenon provides great promise for heart failure patients, although the underlying mechanisms driving this recovery are largely unknown. To identify global changes in the normal and failing human heart we performed phosphopeptide profiling from cardiac tissue of 38 patients [10 donor controls, 6 recovered heart failure patients (responders), and 22 patients that did not respond to LVAD therapy (non-responders)] and RNA-Sequencing of 96 patients [9 donor controls, 26 responders and 61 non-responders]. Mass spectrometry-based analyses identified 15,816 unique phosphopeptides, and label-free quantitation further classified 288 peptides that distinguish control tissue from those in heart failure. Most intriguing however, was our analyses of heart failure patients at the time of LVAD implantation which, using a signature of 93 peptides (71 proteins), allowed complete separation of responder and non-responder samples via statistical analysis. In addition, RNA-Seq analysis identified 29 genes differentially expressed between responders and non-responders. Thus, this panel of 93 phosphopeptides and 29 transcripts enabled us to determine which patients would experience cardiac recovery following ventricular unloading, prior to LVAD implantation. Bioinformatic analyses of these proteins and transcripts, highlight key players in adherens junctions, cytoskeletal remodeling, cell cycle regulation and Jun signaling. Overall this study characterizes unique molecular changes in the normal and failing human heart and specifies those which define hearts capable of cardiac recovery, which may guide strategies to improving current heart failure therapies.

**Characterization of Smyd1 Histone Methyltransferase Enzymatic Activity**

Kathryn Davis, Li Wang, Anna Bakhtina

As the heart experiences stress, it undergoes hypertrophic growth in order to compensate for the extra work load. However, chronic hypertrophy of the heart leads to reduced ejection fraction, wall thinning, and ultimately heart failure. Prior to these morphological changes, there are a number of molecular changes within the heart including the re-express of genes normally only expressed during development, a phenomenon called the fetal gene program. For cardiomyocytes to undergo these changes in gene expression, there must be significant structural alterations of chromatin in order to activate or repress gene transcription. Recent studies of epigenetic regulation have shown in murine models that altering epigenetic mechanisms within the heart can inhibit the fetal gene program, prevent pathological growth and blunt disease development. Thus, understanding the epigenetic factors that regulate these changes in the heart under normal conditions and during disease may provide significant insights into myocyte biology and may provide the opportunity to develop unique therapies.

There are several factors involved in modifying the structure of chromatin to regulate transcription such as modification of histones. Smyd1, is a myocyte-specific histone methyltransferase which is highly expressed in both the developing and adult heart, is upregulated in human heart failure patients
and mouse models of cardiac hypertrophy and has a well-established role in cardiac development. More recently, the Franklin lab was the first to show a novel role for this protein in the adult heart by confirming its ability to regulate hypertrophic growth and cardiac metabolism. Originally, Smyd1 was thought to only activate gene expression via the methylation of a well-known gene activating mark, histone H3 on lysine 4. Yet, our recently published data (Franklin et al., 2017) has shown that while Smyd1 activates transcription of PGC-1α, it is also capable of repressing nppa gene expression. The mechanism by which Smyd1 is able to repress transcription is completely unknown. Utilizing histone methyltransferase assays, I have shown that Smyd1 can methylate histone H4 on lysine 20, which is a well-known mark of gene repression. These exciting results elucidate a novel method by which Smyd1 is able to both activate and repress transcription within the heart.

Shock Team Approach in Refractory Cardiogenic Shock: A Proof of Concept

Background: Despite efforts to improve treatment of refractory cardiogenic shock (rCS), prognosis has remained poor. Multidisciplinary “Shock Teams” have been proposed as a strategy to streamline care delivery and improve outcomes. However, the feasibility and effectiveness of this strategy has not yet been explored.

Methods: The Utah Cardiac Recovery (UCAR) “Shock Team” was established in Apr 2015 and consists of a heart failure (HF) cardiologist, an interventional cardiologist, a HF surgeon and an intensive care unit (ICU) attending. Between Apr 2015- Aug 2018, 123 consecutive patients were enrolled since program initiation (“Shock-team” cohort) and compared with the immediately preceding 126 patients (“Control” cohort). All of the patients had rCS based on predefined criteria and required mechanical circulatory support (MCS). Primary and secondary outcomes were 30-day mortality and “Shock to Support” time, respectively.

Results: The study included 249 patients, with a mean age of 58±15 years. The causes of CS were well balanced between the “Shock team” and “Control” groups. No differences were shown between the two groups in the cardiac risk factors, hemodynamic status and the echocardiographic functional parameters before the device implementation. However, more patients from the “Shock Team” cohort underwent cardiopulmonary arrest (p=0.05), were on more vasoactive medications (p=0.01) and had a trend for higher incidence of acute kidney injury (p=0.057) before MCS implantation. Despite a sicker population comprising the “Shock Team”, the primary outcome of 30-day mortality was significantly lower in a Cox regression model favoring the “Shock team” (32.5% Vs 46.0%; p=0.021) (figure) and remained significantly lower after adjusting for multiple baseline characteristics. Correspondingly, “Shock to Support” time revealed no delays in MCS utilization on “Shock Team” vs “Control” (19±5 Vs 24±8 hrs., p=0.55).

Conclusion: This prospective study demonstrates the effectiveness and feasibility of the multidisciplinary “Shock Team” in patients requiring MCS for refractory cardiogenic shock at our institution. These encouraging findings warrant validation by prospective large-scale randomized trials.
Cardiac and Systemic Inflammatory Burden Predicts Cardiac Recovery in Ventricular Assist Device Patients: A Prospective Study

Background: The identification of clinical and molecular predictors of Left Ventricular Assist Device (LVAD) induced myocardial recovery before device implantation could significantly impact the management of patients with advanced heart failure (HF). Inflammation plays a central role in the pathophysiology of HF. We sought to investigate whether cardiac or systemic inflammation could be associated with the myocardial structural and functional response after LVAD support.

Methods: We prospectively enrolled 152 patients with chronic HF supported with durable LVAD as bridge to transplant or as destination therapy (acute HF patients were excluded). Serum and cardiac tissue was collected at the time of LVAD implantation for measurement of fourteen inflammatory markers (cytokines and transcription factors). Cardiac recovery was prospectively assessed via serial turn down echocardiography studies.

Results: Thirteen percent of the study population showed significant improvement of the cardiac function (i.e. “responders”) after LVAD unloading (final LVEF>40%). At LVAD implant, serum TNFa, IL6 and IL10 was lower in responders compared to non-responders (p<0.05 for all comparisons). STAT3, a transcription factor activated by cytokines that regulates inflammatory response was less activated in the cardiac tissue of responders compared to non-responders (0.87±0.2 vs 2.4±0.7 AU, p=0.037). To further investigate the lower inflammatory burden noted in the cardiac tissue and serum of responders, we performed multivariate dichotomous regression analysis of the serum cytokines and we identified that low levels of INFg (OR 0.06, CI 0.01-0.35) and TNFa (OR 0.05, CI 0.00-0.43) were independent predictors of cardiac recovery. A multivariable model combining IFNg and TNFa was identified as a significant predictor of LVAD-induced recovery (AUC 0.93, p&lt;0.001).

Conclusions: Reduced cardiac and systemic inflammatory burden correlates with the recovery of the failing human heart after LVAD unloading. We identified a two-cytokine model with high sensitivity and specificity for pre-LVAD prediction of cardiac recovery that could serve as a decision tool in the clinical management of advanced HF patients. Further investigations to elucidate the underlying molecular mechanisms are warranted.

Evaluation of a Microscopy-Based Approach to Characterize Remodeling of Cardiac Tissues in Heart Failure Patients
Aparna C Sankarankutty (1,6), Sutip Navankasattusa (1), Iosif Taleb (2), William T. Caine (3), Rami Alharethi (4), Craig H. Selzman (5), Stavros Drakos (1,2), Frank B. Sachse (1,6)

Microscopic imaging is an essential technique to visualize the extent of remodeling associated with cardiac disease at subcellular, cellular and tissue level. Microscopic images and their analysis provide a structural foundation to explain myocardial function and dysfunction, e.g. of electrical conduction, excitation-contraction coupling, and mechanical contraction. In our prior work, we introduced an approach for three-dimensional (3D) confocal microscopy, tissue reconstruction and quantification of volume fractions of constituents of cardiac tissues.1-3 We evaluated the approach using animal models focusing on the following tissue constituents: myocytes, fibroblasts, myofibroblasts, vessels and extracellular matrix (ECM). We also introduced a metric to measure fibrosis and assessed it in an animal model of myocardial infarction. In contrast to prior metrics based exclusively on collagen labeling, the new metric accounts for further constituents of fibrosis, i.e. fibroblasts and
myofibroblasts, that are fundamental to the maintenance and remodeling of the ECM. Here, we applied and evaluated our methods to tissues from heart failure (HF) patients and donors. We investigated if the approach originally developed and evaluated in animal models can be applied to tissues from donors and HF patients.

We applied methods introduced by us previously.1, 2 In short, snap frozen human tissue samples from HF patients and donors were sectioned and formalin fixed. We fluorescently marked ECM, fibroblasts, smooth muscle cells and nuclei. We applied compression-free mounting of tissues to avoid tissue deformation. We acquired 3D image stacks with tile scanning confocal microscopy. Adjacent 3D stacks were automatically stitched together to cover a larger region of tissue without compromising spatial resolution. Subsequently, we processed the image stacks yielding 3D reconstructions of individual tissue constituents. We measured volume fractions of the tissue constituents. We also measured fibrosis defined as the excess of fibroblasts, myofibroblasts and extracellular space vs. donor heart tissue.

The approach was applied to left ventricular tissues from two HF patients undergoing LVAD implantation and two donors. We found characteristic patterns for all applied fluorescent labels. Signal intensities and signal-to-noise ratio were sufficiently large for image processing and 3D reconstruction. In HF tissue, the volume fractions of ECM, fibroblasts and myofibroblasts were 36.93%, 2.28% and 0.99% respectively. In donor tissue, the volume fractions were 19.22%, 6.47% and 1.93%, respectively. The total volume contribution of these tissue constituents was 40.19% in HF vs. 26.48% in donor. Thus, fibrosis in the HF tissues was found to be 13.71%.

Our study suggests feasibility of the previously established microscopy-based approach for quantitative characterization of tissue biopsy from HF patients. The approach yielded 3D microscopic image reconstructions that allowed us to characterize myocardial remodeling in HF. Beyond applications in HF, we suggest that our approach could be useful for assessment of tissue remodeling in other cardiac diseases, exercise and aging. A current limitation of our study is the low number of tissue samples applied for the evaluation.

Relating Microstructural Remodeling of Ventricular Tissue in Heart Failure Patients to Cardiac Recovery after Mechanical Unloading

Yankun Lyu (1), Younjee Lee (1), Sutip Navankasattusa (1), Iosif Taleb (2), William T. Caine (3), Rami Alharethi (4), Craig H. Selzman (5), Stavros Drakos (1,2), Frank B. Sachse (1,6)

A subset of end-stage heart failure (HF) patients supported with left ventricular assist devices (LVAD) can recover their cardiac function to the point that the LVAD can be removed. Patients with sustained recovery of heart function do not necessitate heart transplantation. Thus, diagnosis and facilitation of recovery promises to improve patient outcomes and attenuate shortage of heart donors. While studies have identified patients’ clinical characteristics associated with sustained recovery, insights on mechanisms and markers of recovery are still rudimentary.

In our prior work, we demonstrated a central role of the phenotype of the transverse tubular system (t-system) and its spatial relationship with ryanodine receptor (RyR) clusters in acute recovery.1 A dense and regular arrangement of the t-system and its proximity to RyR clusters is essential for efficient excitation-contraction (EC) coupling in ventricular cardiomyocytes of mammals. It is well established that the t-system undergoes remodeling in various types of heart disease and that this remodeling is associated with deficiencies of EC coupling. Studies from us and others suggested that the t-system in HF cells can recover after therapy, for instance, after cardiac resynchronization therapy.2 However, we did not find restoration of t-system in patients after LVAD implantation.3 Our
studies revealed that many HF patients exhibit a sparse and sheet-like remodeled t-system, which causes inefficient EC coupling and is incompatible with recovery. In contrast, HF patients with recovery presented a dense and regular t-system, which provides the foundation for efficient EC coupling. Here, we furthered our investigation of microstructural remodeling of left ventricular myocardium from HF patients and markers of cardiac recovery. We investigated if junctophilin (JPH), a structural protein in cardiomyocytes, and the extracellular matrix can serve as predictive markers for cardiac recovery in response to LVAD unloading. Furthermore, we explored if microstructural markers of acute recovery can serve as markers of sustained recovery.

We applied similar methods as described by us previously. We collected left ventricular tissues from donor hearts and the left ventricular apical core from LVAD patients. Tissue samples were snap frozen in OCT and cyro-sectioned. Sections were labeled for nuclei, RyR, and JPH. Also, we used wheat germ agglutinin (WGA) to label extracellular matrix as well as sarcolemma including t-system. Sections were imaged using a Leica TCS SP8 confocal microscope equipped with a 60x oil immersion lens with a numerical aperture of 1.4. Image stacks were deconvolved, processed to reduce depth-dependent attenuation and segmented. We quantified volume ratios of RyR, JPH and WGA positive regions. We assessed spatial relationships between WGA, RyRs and JPH signals. Regression analyses with linear and 2nd order polynomial models were applied to investigate relationships of microstructural features and the difference of left ventricular ejection fraction (EF) before and 6 months after LVAD implantation.

In the majority of HF patients, the t-system was sparse and irregular versus t-system from control human. Linear regression analyses supported our prior finding that close association of the t-system and RyRs is required for increased EF and acts as a marker of recovery. Polynomial regression analyses of WGA volume fraction and EF revealed that improvements are facilitated in a range of volume fractions that is characteristic for donor tissues. Regression analyses of JPH volume fractions, JPH-RyR colocalization and EF exhibited small R values. Differences between RyR-WGA relationships in tissues from sustained and non-sustained responders were not significant.

Our study indicates that integrity of tissue and cellular microstructure is a necessary precondition for cardiac recovery. We established criteria based on WGA and RyR labeling that allowed us to predict changes of ejection fraction after LVAD implantation. However, a limitation of our study is the number of patients, in particular, for assessment of sustained recovery.

The Role of Glycolysis-Dependent Pentose Phosphate Pathway and One-carbon Metabolism in Myocardial Recovery

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Background: Significant improvements in myocardial structure and function have been reported in some advanced heart failure (HF) patients (Responders-R) after chronic mechanical unloading induced by left ventricular assist devices (LVAD). Prior studies from our group have shown that the LVAD-induced mechanical unloading affects the energy balance and metabolic perturbation of chronic HF suggesting that might have the potential to reverse the deleterious metabolic adaptations of the failing heart. Specifically, our prior work demonstrated a post-LVAD mismatch: glycolysis upregulation with no subsequent increased pyruvate mitochondrial oxidation through the TCA cycle. The underlying mechanisms responsible for this mismatch are not known.
Methods: We prospectively obtained LV apical myocardial tissue obtained from normal donors and HF patients at LVAD implant (Pre-LVAD) and transplantation (Post-LVAD).

Results: Western blot analysis of the key PPP enzymes, glucose-6-phosphate dehydrogenase (G6PDH) and transketolase (TKT) indicated significant increase in Post-R compared to Post-NR. Similarly, phosphoglycerate dehydrogenase (PHGDH) and mitochondrial serine hydroxymethyl transferase (SHMT2) also showed significant increase in Post-R vs Post-NR. In agreement with the elevated enzyme levels, the metabolite levels of the enzyme products such as sedoheptulose-6-phosphate (PPP) and serine and glycine (OCM) showed a decrease in post-R as compared to post-NR. Furthermore, western blot analysis using hydroxynonenal (HNE) antibody to indirectly measure reactive oxygen species (ROS), showed significantly reduced ROS levels in R. On the contrary, NADPH level was higher while the ratio of NADP+/NADPH was lower in Post-R, further indicating increased flux of glucose into the NADPH-generating pathways of PPP and OCM.

Conclusions: The recovering human heart appears to direct the increased glycolytic metabolites into PPP and OCM, both of which play a role in cardioprotection by generating anti-oxidants and NADPH thereby reducing ROS. Further confirmation of these findings with metabolic flux studies are warranted.

Impact of Acute Antioxidant Administration on Inflammation and Vascular Function in Heart Failure with Preserved Ejection Fraction

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Background: One of the many unique features of heart failure with preserved ejection fraction (HfPvEF) is the presence of multiple comorbidities, many of which are characterized by a pro-inflammatory and pro-oxidant state which may impair vascular function. This axis of inflammation, oxidative stress, and vascular function has been well described in other patient populations, whereby increases in reactive oxygen species lead to eNOS uncoupling, reduced nitric oxide (NO) bioavailability, and ultimately, impaired endothelium-dependent vasodilation. Though there are many potential strategies for combating the damaging effects of inflammation and oxidative stress on peripheral vascular function, antioxidant (AO) administration has emerged as a simple, but effective, approach. However, no studies to date have evaluated the efficacy of AO administration to target peripheral vascular inflammation and dysfunction in patients with HfPvEF.

Purpose: The present study sought to evaluate the efficacy of an over-the-counter antioxidant (AO) cocktail (600mg alpha lipoic acid, 1,000mg vitamin C, and 600IU vitamin E) to acutely mitigate inflammation and oxidative stress, and subsequently improve vascular function, in patients with HfPvEF.

Methods: Flow mediated dilation (FMD) and reactive hyperemia (RH) were evaluated to assess conduit vessel and microvascular function, respectively, following administration of either placebo (PL) or AO in 16 HfPvEF patients (73±10yrs) using a double-blind, crossover design. Circulating biomarkers of inflammation (C-reactive protein, CRP), oxidative stress (Malondialdehyde and Protein Carbonyl), free radical concentration (EPR Spectroscopy), antioxidant capacity, and nitric oxide (NO) bioavailability (plasma nitrate, NO3- and nitrite, NO2-) were also assessed.

Results: FMD improved following AO administration (PL: 3.49 ± 0.7%, AO: 5.83 ± 1.0%), while RH responses were similar between conditions (PL: 428 ± 51ml, AO: 425 ± 51ml). AO administration decreased CRP (PL: 4429 ± 705ng/ml, AO: 3664 ± 520ng/ml) and increased NO2- (PL: 182 ± 21nM, AO: 213 ± 24nM), but did not affect other biomarkers.
Conclusions: This study has identified the efficacy of an acute, over-the-counter dose of vitamins C, E, and alpha lipoic acid to mitigate vascular inflammation and improve conduit artery endothelium-dependent vasodilation in patients with HFrEF, providing new insight into the mechanisms that govern peripheral vascular dysfunction in this patient group.

**Cardiac and Cerebrovascular Response To Exercise in the Setting of Mechanical Circulatory Support Among Individuals with Advanced Heart Failure**

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Background: Patients with heart failure with reduced ejection fraction (HFrEF) have impaired cerebral autoregulation at rest. CF-LVADs may normalize resting cardiac output, however its effects on cerebral blood flow are unknown. In addition, implantation of a CF-LVAD is associated with high rates of stroke. The primary objective of this study was to characterize the cerebrovascular response to exercise among individuals with HFrEF and those with CF-LVADs.

Methods: 9 CF-LVAD subjects, 11 patients with advanced HFrEF (all New York Heart Association III-B IV with left ventricular ejection fraction <35%), and 11 Healthy controls (HC) underwent invasive hemodynamic assessment during two submaximal levels of exercise (to simulate real-world activities of daily living) and symptom-limited cardiopulmonary exercise testing. Cardiac output (Qc) was measured by Swan-Ganz catheterization, oxygen uptake (VO2) by indirect calorimetry, mean arterial pressure (MAP) by arterial line and Middle Cerebral Artery Velocity (MCAV) by transcranial Doppler. All hemodynamic parameters were continuously recorded throughout all stages of exercise.

Results: Demographics are reported in Table 1. As demonstrated in Figure 1, workload and VO2 were similar between HFrEF and CF-LVAD groups, and significantly less than levels observed among HCs. Similarly, the increase in MAP and Qc throughout exercise was blunted among HFrEF and CF-LVAD groups in comparison to HCs. MCAV increased throughout exercise among HCs, but was relatively unchanged among HFrEF and CF-LVAD groups.

Conclusion: Despite normalization of resting Qc, CF-LVAD implantation is associated with a blunted cardiovascular and cerebrovascular response to exercise compared to HCs, with exertional hemodynamics that are similar to individuals with advanced HFrEF.

**Adiponectin Receptor Agonism Promotes Cardiac Ceramidase Activity and Ameliorates Lipotoxic Cardiomyopathy**

Ankit Sharma

During weight gain and diabetes, cardiac lipid accumulation leads to ventricle dysfunction, hypertrophy, and heart failure. Ceramide is a bioactive lipid that plays a key role in maintaining the link between obesity and tissue dysfunction, not only in heart, but across a variety of metabolically important organs. In vivo prevention of abnormal, non-adipose tissue ceramide elevation during diet-induced obesity has proven to be protective against tissue dysfunction across a variety of transgenic mouse models. In these studies, we assessed the cardio-protective potential of adiponectin overexpression in transgenic mouse models of lipid-induced heart failure, also known as lipotoxic cardiomyopathy. Secreted from adipose tissue, adiponectin has been widely shown to oppose lipotoxic conditions and promote robust ceramide reduction, amongst several other positive metabolic effects. Here we show that adiponectin overproduction in both wild-type mice and mouse models of lipid-induced heart failure potently reduces ceramide species, improves left ventricular function as
measured by fractional shortening and ejection fraction, reduces heart size, and dramatically increases lifespan – on the other hand, adiponectin ablation significantly degrades cardiac function. Overall, our results indicate that increased adiponectin receptor agonism may hold therapeutic potential in combatting lipotoxic and diabetic cardiomyopathy, particularly as research into small molecule adiponectin mimetics advances.

The Impact of Chronic Antioxidant Administration on Sympathetic Nervous System Activity and Vascular Function in Heart Failure Patients with a Reduced Ejection Fraction

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Background: Heart failure with reduced ejection fraction (HFrEF) is characterized by sympathetic nervous system (SNS) overactivation and vascular dysfunction, two important predictors of mortality and morbidity in this patient group. Importantly, oxidative stress, defined as an excess production of free radicals relative to antioxidant defenses, is prevalent in patients suffering from HFrEF. This pro-oxidant state is associated with attenuated nitric oxide bioavailability, which may contribute to increased SNS activity and vascular dysfunction. While chronic oral antioxidant (AOx) administration has been documented to mitigate oxidative stress in other populations, the efficacy of this approach to improve autonomic and vascular function in patients with HFrEF has not been evaluated. Thus, this study sought to determine the effect of chronic (30-day) over-the-counter oral AOx administration on SNS activity and vascular function in patients with HFrEF.

Methods: Five HFrEF patients (71±3 yrs; 28.5±1.5 kg/m2) were studied before and after 30 days of oral AOx administration (Vitamin C, 1000 mg; Vitamin E, 600 IU; α-lipoic acid, 600 mg; QD). Resting muscle sympathetic nerve activity (MSNA) was assessed for the determination of SNS activity, and vascular function was evaluated by brachial artery flow-mediated dilation (FMD) testing. Venous blood samples were also collected for the direct determination of plasma free radical concentration (electron paramagnetic resonance spectroscopy, EPR).

Results: Chronic antioxidant administration reduced MSNA burst frequency (pre: 44 ± 3 bursts/min; post: 38 ± 2 bursts/min, p<0.05). FMD appeared to improve following AOx administration (pre: 2.7 ± 0.7%; post: 4.0 ± 1.0%), but this change did not reach statistical significance (p=0.18). A tendency for a reduction in plasma free radical concentration following AOx administration (pre: 3.2 ± 1.6 AU; post: 0.7 ± 0.1, p=0.11) was also observed.

Conclusion: Chronic antioxidant administration significantly reduced SNS activity and tended to improve vascular function, supporting the efficacy of this simple therapeutic approach to improve autonomic and vascular function in patients with HFrEF.

A quantitative assessment of mitral valve deceleration time for the detection of LVAD pump thrombus in a mock circulatory loop

Ricardo Montes

LVAD pump thrombus (PT) is a serious complication that occurs in 8% of LVAD recipients and often requires LVAD pump exchange surgery. Early detection is key to the successful use of thrombolytic drugs, but chemical species such as LDH are insufficient to identify mild PT. Clinical studies have identified mitral valve deceleration time (MVDT) as a sensitive index for PT. Our goal in this study was to assess the MVDT in the detection of PT using an experimental model with matched flow conditions in a mock circulatory loop.
Experimental studies were performed with a silicone model of the LV with dilated cardiomyopathy (DCM; 180 ml volume, 25% ejection fraction) and the HeartMate II LVAD (St. Jude/Abbott). Neutrally buoyant fluorescent particles were added to a viscosity-matched blood analog solution. A LaVision PIV system captured a 40 Hz ensemble-averaged image sequence of the 2-D velocity field of the LV midplane for the cardiac cycle. A range of LVAD speeds were tested from 8-11krpm before (Baseline, BL) and during PT, which was simulated with a small disk centered over the rotor inflow housing that reduced the orifice area up to 76%. Localized velocity was measured for a region of interest (ROI) located in the center of the mitral valve inflow path, and MVDT calculated as the time from peak to minimum. The Pre-LVAD hemodynamics calculated a MVDT of 37.5 ms for a mean aortic pressure of 65 ± 5, and a cardiac output of 3.6 L/min. With the addition of LVAD support, these values increase as shown in the table. LVAD pump thrombus reduced the range of MAP, CO and MVDT with LVAD speed compared to the No PT condition, reflecting the increased resistance to LVAD flow. A comparison of the results to clinical data showed that the model produced MVDT values within the clinical range, but that the response of patients over the range of LVAD speed was more dramatic than the experimental model. Overall, PT increased resistance to LVAD inflow that increased with LVAD speed, reducing the force on the flow entering through the mitral valve, which was reflected in the reduced change in MVDT. These studies confirm the sensitivity of this index to PT and may aid clinicians in earlier detection of PT.

Investigating Smyd1’s role in regulating disease-induced remodeling and gene expression
Marta W. Szulik, Li Wang, Junco Warren, June Garcia-Llana, Christopher Tr

Smyd1 is a unique myocyte-specific histone methyltransferase that regulates gene expression in the cardiomyocyte. It was originally shown to play a role in cardiac development, however more recently we have determined that Smyd1 is differentially regulated in human heart failure patients and in mouse models of heart disease. Furthermore, we demonstrated that loss of Smyd1 in the adult mouse heart leads to pro-hypertrophic signaling resulting in myocyte growth, fibrosis and functional decline. Additionally, we examined two Smyd1 isoforms, Smyd1a and Smyd1b, in isolated cardiomyocytes and showed that adenoviral-mediated over-expression of Smyd1a (but not Smyd1b) can blunt phenylephrine-induced pathological remodeling. To investigate the role of Smyd1a in an animal model and its ability to inhibit hypertrophic growth we created a transgenic mice capable of inducible cardiac-specific over-expression of Smyd1a and subjected them to permanent occlusion (PO) of the LAD. As expected, three weeks after PO, wild-type animals have developed a fibrotic scar in the apical region of the heart (from cellular death) and displayed hypertrophic cell growth in the remaining live tissue which is also accompanied by a significant decline in the ejection fraction. Interestingly, however, transgenic mice, over-expressing Smyd1a, showed increased tissue survival, minimal hypertrophy and were able to maintain pump function at this same 3 week time point, suggesting that Smyd1a is capable of preserving cardiac function and inhibiting hypertrophic growth in adult mice. To delineate how Smyd1a regulates these morphological and physiological changes in the heart we have begun to identify specific genomic loci regulated by this histone methyltransferase using ChIP-Seq and RNA-seq. Originally, Smyd1 was shown to methylate only histone H3 on lysine K4, a mark of gene activation in vitro, however our targeted analyses have demonstrated that Smyd1 can both activate and repress transcription at different genomic loci including pgc1a and nppa, respectively. Together these analyses have allowed us to reveal a novel regulatory role of Smyd1 in cardiac energetics and cardiac hypertrophy.
Vascular Function in Heart Failure Patients Implanted with a Continuous-Flow Left Ventricular Assist Device: Impact of Increasing Peripheral Vascular Pulsatility

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Vascular function is thought to be attenuated in heart failure patients implanted with a continuous-flow left ventricular assist device (LVAD), likely due to a decrease peripheral vascular pulsatility, which may contribute to the observed serious cardiovascular complications. However, the impact of increasing pulsatility on vascular function in this population is unknown. Methods: Fifteen LVAD recipients and fifteen controls, matched for age and physical activity, underwent 45-minutes of unilateral arm pulsatility treatment, evoked by cuff inflation, distal to the elbow, with a two second duty cycle. Vascular function was assessed by brachial artery flow mediated dilation (FMD, Doppler ultrasound). Results: Baseline FMD, expressed as percent dilation, was not different between the LVAD recipients and controls (LVAD: 4.1±1.8; Controls: 4.1±1.5%), however, FMD/shear rate was significantly lower (LVAD: 0.10±0.04; Controls: 0.16±0.07) and time to peak dilation significantly longer in the LVAD group (LVAD: 77±21; Controls: 41±16s). The LVAD recipients exhibited a significantly attenuated pulsatility index (PI) compared to controls at baseline (LVAD: 3±2; Controls: 14±7), but experienced a similar PI during the pulsatility treatment (LVAD: 29±21; Controls: 33±15). Both % FMD (LVAD: 6.9±1.9; Controls 6.9±2.7%) and FMD/Shear rate (LVAD: 0.19±0.08; Controls 0.30±0.17) increased similarly in both groups with the pulsatility treatment, while time to peak was unaltered. Conclusions: LVAD recipients exhibit vascular dysfunction. Pulsatility treatment improved vascular function in both groups, but, most importantly, this intervention restored vascular function in the LVAD recipients to the baseline level of the controls, and may, through this improved vascular health, reduce cardiovascular complications in this population.