THE INTERNATIONAL SOCIETY FOR HEART & LUNG TRANSPLANTATION
ISHLT2019
Orlando, Florida USA

The Daily Pulse

39th Annual Meeting and Scientific Sessions APRIL 3–6, 2019

CONGRATULATIONS TO THE 2019 O.H. FRAZIER AWARD RECIPIENT

Dr. med. Jasmine Hanke
Hanover Medical School

Friday, April 5, 2019

In the Spotlight

'Genius is Overrated' and Other Life Lessons from an American Hero

Astronaut Col. Mike Mullane entertained the crowd at today's Plenary Session with inspiring stories from his career as a U.S. Astronaut and Vietnam War veteran, sharing his most important life lesson: Tenacity matters.

Mullane walked the crowd through his incredible career, which started with an obsession with rockets at the age of 12, just as Sputnik was dominating the news. From homemade rockets in the New Mexico desert – where he learned about true risk mitigation

– to vowing at the age of 14 that he would be an astronaut, Mullane was laser-focused on his goal.

In fact, he credits his success to focus – and not to superior schoolwork or a connected upbringing.

“Genius is overrated,” he said. “Tenacity matters so much more.”

Mullane recounted the many times he needed a tenacious attitude to get ahead, from lackluster SAT scores, which prevented him from getting into the Air Force Academy, to weathering his father’s polio diagnosis.

“You don’t have to be extraordinary to achieve extraordinary results,” he said. “Just do your best.”

Mullane graduated from **West Point** in 1967. He completed 134 combat missions as an RF-4C weapon system operator while stationed in **Vietnam**. He then served a four-year tour of duty in England.

In 1976, he completed the USAF Flight Test Engineer Course at **Edwards Air Force Base**, **California**, where he was assigned as a flight test weapon system operator .

Mullane’s boyhood dream finally came true in August, 1979, when he became an official NASA astronaut. He flew on three **Space Shuttle** missions from 1984 to 1990.

Mullane is the author of four books:

- ***Riding Rockets: The Outrageous Tales of a Space Shuttle Astronaut***
- *Red Sky: A Novel of Love, Space, & War*
- *Do Your Ears Pop in Space and 500 Other Surprising Questions about Space*
- *Liftoff!: An Astronaut's Dream*

Today's Highlights

Is the Future Now with Alternatives to Cardiac Transplantation?

Written By: Roy Lee, PharmD

Copy and Paste vs. Renovate: Cardiac 3D Printing and Its Future Direction
Doris Taylor, PhD, FAHA, FACC

'When Pigs Fly': Where Are We Now with Xenotransplantation
Richard Pierson, MD

Cardiac transplantation has a come a long way since the first human transplant several decades ago. However, one of the major limitations to transplantation is the availability of donor organs. In the United States alone, hundreds of thousands of Americans die each year from heart disease. There are thousands of patients on the waiting list daily. Unfortunately, there are always too few donors to meet this demand. As such, new strategies are being pursued to meet this demand. Three such strategies include 3D printing, xenotransplantation, and stem cell transplantation. However, are we anywhere close to being able to use these technologies? As exciting and sexy as these technologies are, today's symposium on this question appears to leave you with one simple answer: No. There are still many hurdles to overcome before even the first alternative human cardiac transplant is attempted.

To illustrate why, let's look at 3D printing that Doris Taylor, MD talked about. The take home message here is that the infrastructure is nonexistent. Each heart requires billions of cells and existing technologies do not allow for such printing. We also seem to be able to create only two to three layers of cells. Building organs even for research is expensive and hugely time-intensive. And the tools and assays needed for clinical use do not exist. However, like a turtle, progress is slowing being made. Companies and labs such as ETH Zurich, BioLife4D, and WFIRM are pushing forward. Not too long ago, ETH Zurich 3D-printed a "soft" silicone heart that beat almost like a human heart (although it lasted only for about 3,000 beats). BioLife4D demonstrated bioprinting of a patch of vascularized and conducting cardiac tissue. And WFIRM 3D printed a function and contractile "cardiac tissue" using rate heart cells.

Another illustration in xenotransplantation illustrates the challenges that are present. One challenge with xenotransplantation is coagulation dysregulation once

human blood starts coursing through. But as Richard Pierson, MD pointed out, advancements in the ability to perform genetic modification has allowed certain animal models to live greater than 180 days!

So while the future is not now with alternatives to traditional human cardiac transplantation, the future is slowly creeping in on us and many are tenaciously working on alternative transplantation technologies. It'll be an exciting journey!

Find both the abstracts **here.**

Leukotriene B4 as a Mediator of CAV and Potentially Treatable with Bestatin

Written By: Yasbanoo Moayedi, MD

Leukotriene B4 Contributes to Development of Cardiac Allograft Vasculopathy
Kiran Khush, MD, MAS

Cardiac Allograft Vasculopathy (CAV) remains the Achilles heel of long-term outcomes after heart transplantation. It is often diagnosed at a late stage at which time progression is inevitable. While the pathogenesis is not completely elucidated, histologic evidence is suggestive of a macrophage response an important part of the immune pathway. Previous literature in pulmonary arterial hypertension (PAH) has shown that macrophage-derived leukotriene B4 (LTB4) induces proliferation of the pulmonary artery smooth muscle. The authors hypothesized that LTB4 may also play an important role in the development of CAV.

Findings:

- In patients following heart transplantation, CAV positive coronary arteries have increased levels of CD68 (macrophage marker) and 5-LO (an LTB4 producing enzyme) compared to CAV negative on autopsy specimen
- Levels of LTB4 are also significantly higher in 14 patients CAV+ matched with 14 CAV - controls

- In rat models, aortic transplants in Fischer to Lewis aortic transplants compared with syngenic transplants showed increased CD68 and 5-LO markers on cross sections.
- Rats treated with bestatin showed significantly reduced neo-intimal hyperplasia and LTB4 levels.
- Bestatin was well-tolerated in rats with physiologic levels of liver enzymes and kidney function but had an increased triglyceride level compared to case controls.

Important points:
Leukotriene B4 may be an important biomarker for the early detection of cardiac allograft vasculopathy in heart transplant patients. Bestatin therapy (an LTB4 inhibitor) prevented the progression of CAV. Further tests to assess the effect of Bestatin in heart transplant patients are warranted.

Find the abstract **here.**

DCD Lung Transplantation: A Promising Future

Written By: Nirmal S Sharma, MD

5-Year Results from the ISHLT DCD Lung Transplant Registry Confirm Excellent Recipient Survival from Donation after Circulatory Death Donors
Dirk Van Raemdonck, MD, PhD

Is Donor after Cardiac Death (DCD) lungs the answer to the ever-growing shortage of donor lungs? Researchers looking at the ISHLT thoracic transplant registry data for lung transplant reported that long term survival of DCD lungs were comparable to Donor after Brain Death (DBD) lungs.

Utilization and long-term survival in DCD lungs recipients
Five-year survival data of lung transplant after both DCD and DBD were evaluated from 23 DCD centers around the world. Of the 11,516-lung transplant from 2003 to 2017, 1090 (9.5 percent) were from DCD donors. Recipient hospital stay was noted to be significantly higher in the DCD group post transplantation. Five-year survival rates were similar (63 percent vs 61%, p=NS) among the DCD and DBD groups. Adjusting for

confounders, only general recipient/donor factors including recipient and donor ages, transplantation type (single vs double) and pre-transplant diagnosis impacted survival and not DBD or DCD status.

Conclusion

The ISHLT DCD registry data suggests that long term outcomes are similar among recipients receiving either DCD or DBD lung transplantation. However, short term outcome data including PGD rates, acute rejections, impact of longer length of stay or hospital readmissions must be investigated further. The utilization of DCD lungs especially in the United States remains very low. This current data provides further support for the feasibility of DCD donors utilization in lung transplantation. It remains to be seen if DCD utilization and increase in donor organ pool will ultimately impact the waitlist mortality for lung transplantation.

Find the abstract **here.**

Gene Expression Profile Score to Predict CAV Needs Further Studies

Written By: Yasbanoo Moayedi, MD

Are Gene Expression Profile Scores Associated with New Onset CAV
Anuradha Lala, MD

Gene Expression Profile as defined by the AlloMap (CareDx, Brisbane) is a score that ranges from 0-40 as a surrogate for acute cellular rejection. The Outcomes AlloMap Registry (OAR) is an ongoing multisite prospective registry including 35 sites in the United States enrolling highly-selected, low- risk patients. Detection of early cardiac allograft vasculopathy (CAV) may improve long term outcomes.

Findings:

- Retrospective study including 629 patients included
- Only the first angiogram was used in the analysis to classify patients as CAV- (ISHLT grade 0-1) and CAV+ (ISHLT grade 2-3)
- There was a small but significant difference in GEP score between those who had CAV+ vs. CAV-

Important points:
The association between GEP score and CAV could eventually be translated into a screening strategy for CAV, however this will need further studies including longer term follow. It remains uncertain whether the association between GEP score and CAV is independent of other known risk factors for CAV.

Find the abstract **here.**

Chasing the Golden Snitch: Optimizing Outcomes of MCS Infections

Written By: Van-Khue Ton, MD, PhD

Infections plaguing patients with LVAD have been linked to decreased survival and increased morbidity. Treating VAD-related infections can be challenging and the best prevention and treatment strategies remain elusive (like the golden snitch in a heated Quidditch match!). In this session we learn about the possible use of medical-grade honey in drive line dressing kits, the impact of delayed sternal closure on infections, and the mechanisms of …

A Comprehensive* In Vitro *Evaluation of Medihoney as an Anti-Biofilm Agent in Preventing Ventricular Assist Device Driveline Infections
Anton Peleg, PhD MBBS

Medihoney, or "medical-grade" honey, has natural antimicrobial properties. *In vitro* studies have demonstrated medihoney's properties against planktonic cultures, biofilms and drug-resistant pathogens. The antimicrobial mechanism is unclear, as medihoney is comprised of not only the active ingredient methylglyoxal (MGO), but also many bee peptides. Medihoney has an acidic pH and high osmotic pressure which might be toxic to bacteria and fungi. Medihoney has been routinely used at 3 Australian centers for drive line dressing. In an *in vitro*model that mimics exit wound conditions, medihoney demonstrated good activity against the growth of *S. aureus*and *S. epidermidis*(low MIC of 10-20%). However, medihoney could not completely eradicate biofilms by Staphylococcus, Pseudomonas or Candida. Medihoney had some activity against early bacterial adhesion. At this point it is unclear whether medihoney is the "golden snitch" for infection treatment in VAD patients.

Primary versus Delayed Sternal Closure in Left Ventricular Assist Device Implantation Patients: Impact on Infection
Mehmet Akay, MD

A total of 294 consecutive patients implanted with CF-LVAD at a single center between 2012 and 2018 were analyzed for infection rates between delayed sternal closure (DSC) vs. primary sternal closure (PSC) technique. There were 107 patients who had DSC, and 181 had PSC. DSC was performed mainly due to coagulopathy. Compared to the PSC group, the DSC group was sicker with lower platelet counts and more deranged laboratory values. Regardless, they had similar rates of sternal infection, pump pocket infection, and slightly lower rate of drive line infection than the PSC group. The author noted that antimicrobial prophylaxis did not differ between the 2 groups, and included vancomycin, a cephalosporin and an antifungal agent for 48 hours post-op.

A Study of Infected Drivelines from Ventricular Assist Device Patients: The Presence of Microbial Biofilms and Micro-Gaps in the Driveline Tunnel
Anton Peleg, PhD MBBS

This presentation gives us an up close and personal look at biofilm formation along LVAD driveline. Drivelines explanted at time of heart transplant from infected and uninfected patients were examined for biofilm characteristics. Infected patients spent more time on VAD support (307 vs. 204 days), and the median time to infection onset was 192 days. There was high concordance between swab culture at exit site and that of the explanted drive line (velour & tissue). Electron microscopic images revealed micro-gaps in the velour that might have promoted biofilm migration. Bacteria (*S. aureus*) were seen forming microcolonies deep inside the velour, and appeared resistant to antimicrobial agents. One may speculate that data from this study could help modify future designs of the velour to be more resistant to bacterial adhesion. We eagerly await more data from the authors on the roles of microbiomes on LVAD components and in patients' gut in relation to VAD-specific infection.

Find all the abstracts **here.**

The Heart Transplant Community is in Need of a Better Tool to Predict Primary Graft Dysfunction

Written By: Yasbanoo Moayedi, MD

Development and Validation of a Risk Model and Primary Graft Failure after Heart Transplantation and Comparison to the RADIAL Risk Score
Alexander Bernhardt, MD

Primary Graft Dysfunction (PGD) hinders short-term outcomes as the leading cause of early death after heart transplantation. Current tools to predict PGD include the RADIAL score (RAP > 10 mmHg, Age recipient> 60 yrs, DM, inotrope dependence, Age donor > 30, Ischemic time > 240 min). The authors of this study developed a new risk score and compared to the existing RADIAL score.

Methods:

- ISHLT Registry data 57,188 transplant patients were screened and included 23,000 patients from January 2005-Jun 2017
- Multiorgan or retransplantation were excluded
- Comparisons were made to a modified radial score (RAP was not included)
- LASSO algorithm for variable selection; excluded variables that had more 30% missing data
- 27 variables were derived; AUC 67%; in the test dataset 0.72; while RADIAL score AUC57%

Important points:
The 'modified' RADIAL score underperforms compared the new 27 variable-derived score. The score does not however distinguish the severity or whether it affected the RV/LV or BIV dysfunction. This study underscores the limited validity of the RADIAL score in the contemporary era with increasing use of mechanical cardiac support.

Find all the abstracts **here.**

DCD Lung Transplantation

Written By: Nirmal S Sharma, MD

Center Variability in Organ Offer Acceptance and Waitlist Mortality in Lung Transplantation

Ashley Choi, BA

Variable donor organ acceptance practices are linked to lung transplant waitlist mortality. Duke researchers reported that every 10 percent increase in adjusted center organ acceptance rate results in 36 percent reduction in waitlist mortality.

The study was a review of UNOS database of organ offers to lung transplantation centers in the US. Out of the 15,847 organ offers between 2007 to 2017, only 29.9 percent donor organs were accepted for the first-ranked patients. Interestingly, a wide variability (9% to 67%) was noted in lung donor organ acceptance rates across various transplant centers. Lower acceptance rate resulted in a higher waitlist mortality. Centers that had an acceptance rate of >40 percent of their first ranked offers had a higher one-year post transplant survival compared to centers with first ranked organ acceptance rate of <25 percent (88.7 percent vs 82.7 percent, P=0.003).

Conclusion

The study excluded data from smaller volume centers for their analysis and it will be important to know how inclusion of all center data impacts the study results. Nevertheless, this study highlights a potentially important factor for increased waitlist mortality. It is important that the lung transplant community works towards standardized practices for both donor organ management and acceptance criteria to minimize this gross variability seen across centers.

Find the abstract **here.**

Diagnostics and Immunosuppression in Lung Transplantation

Written By: Nirmal S Sharma, MD

Ten-Year-Experience with Alemtuzumab as Induction Therapy: A Single-Center Analysis of More Than 500 Patients reduction of CNI doses led to low incidence of kidney insufficiency

and long freedom rates from severe CLAD
Alberto Bennazo, MD

Is Alemtuzumab the wonder drug that will reduce chronic lung transplant rejection (CLAD) and transform long term survival in lung transplantation. Researchers from Vienna have reported in their retrospective study that alemtuzumab induction reduces long term CLAD rates and renal dysfunction.

Effect of Alemtuzumab induction on long term outcomes
The study was a retrospective analysis of a single center data from 2007-2017 in the use of alemtuzumab induction. The group utilized a specific maintenance immunosuppression regimen consisting of only a CNI and steroid in the first-year post transplant followed by use of Mycophenolic acid, CNI and steroids from the second year onwards. Incidence of acute cellular rejection was less than 3% in the first-year post transplantation. Infection rate within the first year was 68% in their cohort with only 22 percent needing hospitalization for treatment. Incidence of CNI related renal dysfunction was 18 percent with only 3 patients needing renal replacement therapy. Freedom from CLAD and survival at 5 years were 72 percent and 74 percent respectively.

Conclusion
The researchers report a very remarkable CLAD free survival rate in their cohort. Given that the data is retrospective and from a single center, it needs further validation in a prospective multicenter study. Nevertheless, these results will usher further research to better understand if an alternative immunosuppression regimen with alemtuzumab induction may help improve outcomes.

Find the abstract **here.**

To Divorce or Not to Divorce CMV Prophylaxis?

Written By: Roy Lee, PharmD

Quantiferon-CMV Guided Virostatic Prophylaxis after Heart Transplantation
Gregor Poglajen, MD, PhD

Cytomegalovirus (CMV) remains a significant cause of morbidity and mortality in the heart transplant community. Nearly all transplant centers practice some form of prophylaxis (whether universal or preemptive), though duration of prophylaxis can vary. Valganciclovir remains the most commonly used agent for prophylaxis. However, prolonged use is not without its side effects and leukopenia is one of the biggest issues regarding valganciclovir use. Practicing a personalized approach to CMV prophylaxis remains a relatively unexplored area, but if possible, it could greatly decrease the risk CMV infection and disease while, at the same time, significantly decrease the risk of side effects from drug use.

One possible technology that may help us personalize CMV prophylaxis is the use of Quantiferon-CMV for CMV-specific immune monitoring. This test looks for the secretion of interferon-gamma (IFN-g) by stimulated CD8+ T-cells in whole blood in response to exposure of CMV peptides. A robust IFN-gresponse is indicative of immunity to CMV and, thus, presumably a decreased risk of developing CMV disease. Thus, if a clinician is wondering whether or not he or she can stop CMV prophylaxis or should extend prophylaxis therapy, the Quantiferon-CMV test can potentially help guide the decision making process.

Today, G. Poglajen et al. presented results of a retrospective study that showed that a Quantiferon-CMV guided approach to CMV prophylaxis rather than standard-of-care 100 days valganciclovir prophylaxis approach was significantly superior. In the Quantiferon-CMV guided approach, fewer percentage of patients were observed who developed late CMV reactivation versus the standard-of-care approach (7 percent versus 26 percent, respectively). Thus, using this novel approach may offer superior efficacy without increasing the risk of valganciclovir related adverse events. A more robust prospective study would be ideal, but we may now have a new technology that will allow us to determine whether or not to cut our losses and divorce valganciclovir from the patient for the betterment of their health.

Find both the abstracts **here.**

#ISHLT2019 Announcements

We Want Your Opinions! Be Sure to Take the Survey

Help us make next year's event as strong as possible by giving us feedback. Take the survey. You'll find it in the app under Attendee Information or **click here** to take it online.

Thanks in advance from the ISHLT Staff!

Today's Press Releases

- **Special Ops approach to transplants boosts patient outcomes, lowers cost**
- **New approach to assessing rejection in heart transplant patients far more effective**

On the Horizon

And the Winner Is…Find out at Tomorrow's Awards Ceremony in Pacifica 6

Our final Plenary Session is tomorrow morning from 8 to 10 AM in Pacifica 6 – a new location – and it's a must-see event. On the agenda:

- Awards Presentation! Who won what? Come find out.
- What's Hot. What's New. Basic Science Overview.
- The President's Debate: Is it time to abandon retransplantation?