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The Daily Pulse

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In the Spotlight

Hepatitis C+ Cardiac Donors: Do They Get an A+?

Written By: Van-Khue Ton, MD, PhD

HCV-positive cardiac donation has been traditionally avoided due to recipient's increased mortality and coronary allograft vasculopathy (CAV). HCV viral load is detected via nucleic acid amplification test (NAT). Since 2015, direct acting antiviral drugs (DAA), curative of HCV infection, have heralded a new era in organ donation from HCV+ donors. In this symposium, we learn about the increased trend in HCV+ organ utilization, decreased wait time, and favorable short-term outcomes.

Early Utilization Trends and Outcomes of Hepatitis C Donor Hearts in the Era of Nucleic Acid Amplification Testing (NAT) and Direct Acting Antivirals (DAAs)
Shivank Madan, MD

The UNOS database was queried, and 7708 patients transplanted between 2015-2018 with HCV viremic (NAT+), HCV non-viremic (NAT-, Ab+) and non-HCV hearts were included. There has been a steady increase in the use of HCV+ donors across the US, though heterogeneity exists among different regions, with some using a lot, and some using very few of HCV+ hearts. Compared to recipients of non-HCV hearts, HCV+ recipients tended to be female with blood type O, and they were less likely to be on inotropes. Propensity matching analyses were performed between NAT+ vs. non-HCV patients, as well as NAT-/Ab+ and non-HCV patients, showing that survival and rates of primary graft dysfunction were comparable between the groups.

Use of Donor HCV NAT Positive Hearts: Expanding the Donor Pool?
Eugene DePasquale, MD

Moving on to NAT+ donors only, the UNOS database was queried for all adult recipients between 2010 and 2018. Those with multiorgan transplant and retransplant were excluded. There were only 88 patients who received NAT+ hearts (1.1 percent) vs. 8168 with NAT- hearts. Baseline characteristics between the two groups were generally similar except that NAT+ recipients were less likely to be on inotropes. Ischemic time appeared longer in the NAT+ group, perhaps due to younger donor's age and longer travel time. Notably, 1-year survival was similar between NAT+ and NAT- recipients. More data are needed for long-term outcomes including CAV development.

Clinical Experience with Heart Transplantation from Hepatitis C Positive Donors
Alex Reyentovich, MD

Death due to drug overdose has skyrocketed due to the opioid epidemic, and with that, the rise of HCV+ donors. New York University, with its nascent heart transplant program, elected to consent all transplant-eligible adult patients to receiving HCV+ organs (both NAT-/Ab+ and NAT+). Patients were excluded if they had active HIV or HBV infection, and donors were excluded if they had failed HCV treatment in the past, or had active HIV or HBV infection. A total of 40 patients underwent HCV+ transplant from 1/2018 to 2/2019, of whom 90 percent were listed as status 1A, and 40% had LVAD. Mean time on the wait list decreased drastically to 69 days for recipients of HCV+ donors (vs. 186 days for non-HCV donors). HCV treatment was started as outpatient, and viremia clearance was achieved within five days to four weeks. There was one death (unrelated to HCV+ organ). However, there appeared to be a slight increase in grade 2R AMR in the NAT+ group, though p value was not significant. This

study stimulated many questions regarding the timing of HCV treatment initiation to decrease viremic time and perhaps minimize long-term complications such as CAV.

Successful Transplantation of 74 Hepatitis C-Exposed Donor Hearts in the Era of Direct-Acting Antiviral Therapies
Kelly Schlendorf, MD

This study is the largest single-center experience to date of HCV+ transplantation. A total of 74 patients received HCV+ hearts between 9/2016 and 3/2019. Of these, 6 were multiorgan recipients, eight were retransplanted, two had been treated for HCV in the past, and 40 percent had LVAD (1 with TAH). Of the 63 patients with NAT+ hearts, 60 became viremic, and 41 had completed HCV treatment to date, with 100 percent viral clearance and sustained virologic response at 12 weeks after treatment cessation. Notably, median time on wait list was a mere four days! One-year survival was 83% for recipients of HCV+ organs vs. 90% for those with non-HCV organs ($p>0.05$). HCV treatment was started at a median of 55 days post-op. There was no signal for increased graft dysfunction, rejection, stroke, or liver failure. However, two patients developed necrotizing pancreatitis during the viremic phase which resolved with DAA initiation, raising the possibility of extra-hepatic manifestation of viremia. The investigators had no problem obtaining DAA for patients.

In conclusion, evidence supporting transplantation from HCV+ donors is mounting. Short-term outcomes (survival, rejection, HCV-related complications) are quite favorable and deserve an A. In order to achieve an A+, we still need more data on long-term outcomes, as well as the optimal initiation time and duration of HCV treatment.

Find all the abstracts **here.**

Today's Highlights

Mechanical Lung Support for Isolated Organs and Patients

Written By: Nirmal S Sharma, MD

A Clinical Trial Evaluating the Effects of Ultra-violet C Treatment During Ex Vivo Lung Perfusion as a Method of Inactivating Hepatitis C Infection in Donor Lungs

Marcelo Cypel, MD

Is Ultra-violet C (UV-C) treatment the next paradigm shift in Hep C positive lung donor organ management? Researchers from Toronto have reported that UV-C treatment during ex-vivo lung perfusion (EVLP) lowers Hep C virus infectivity of transplanted Nat positive donor lungs.

The study team enrolled 22 subjects in the trial with equal number in both the UV-C and control non-UV C EVLP hepatitis C positive donor lungs. The team followed blood HCV virus levels for up to 6 months post-transplant. In the event of a positive HCV load, treatment was initiated with Epclusa for 12 weeks. Baseline HCV loads pre-transplant were similar between both the groups.

Outcomes of UV-C treated Hep C Nat positive donor lungs

The study results suggest that post-operative outcomes including ICU LOS, need for post-operative mechano-circulatory support and 90-day mortality are similar between the UV-C and control groups. Post-operative Hep C infection was noted in 100% of the non UV-C control group and 82% of UV-C treatment groups. However, the median Hep C viral load was significantly lower in UV-C group at day 7.

Conclusion

The study demonstrates safety and feasibility of UV-C delivery in Hep C positive donor lungs. UV-C treatment did not eradicate hep C from donor lungs but reduced the viral load post-transplant. The researcher team concluded that UV-C treatment for Hep C positive donor lungs may serve as an adjuvant and significantly reduce the treatment duration of established anti-viral therapies. The therapy seems promising but long-term effects of these therapies including recurrence of Hep C still need to be studied.

Find the abstract **here.**

Total cf-DNA Ready for Primetime?

Written By: Yasbanoo Moayedi, MD

Increase in Total Cell-Free DNA Correlates with Death in Adult and Pediatric Heart Transplant Recipients: DNA Based Transplant Rejection Tests (DRTR) A Prospective Blinded Multicenter NIH/NHLBI Funded Clinical Study

Shriprasad Desphande, MD

Non-invasive methods that reliably predict clinical events following heart transplantation are needed to improve short and long term outcomes. Total cell-free DNA (TcfDNA) has been found to be at elevated levels in sepsis, oncology and maternal/fetal medicine. This biomarker may identify increased risk in several clinical scenarios including death, rejection, cardiac allograft vasculopathy (CAV) and infection.

The DNA based Transplant Rejection Tests (DRTR) multicenter blinded prospective clinical trial enrolled 241 heart transplant (146 pediatric, 95 adults) patients. Samples were collected at routine catheterization visits, admission, events. Samples were analyzed by TAI diagnostics to quantify TcfDNA.

Findings:

- 197 patients included in the analysis with a total 21 deaths
- Pediatrics AUC 0.903 for a cut off of 77.2
- Adults AUC 0.865 cut off of 64.6
- Hazard Ratio stratified for TcfDNA cutoff is shown below in Table 1
- Unlike donor fraction DNA, total cf-dna did not predict coronary allograft vasculopathy or rejection
- TcfDNA but not donor fraction was associated with infection

Table 1

Total cell free DNA	> 50 ng/ml	>25 ng/ml	>10 ng/ml
HR	12.1	5.4	7.6
95% CI	4.6-31.3	2.3-12.9	2.6-22.7
NPV	92%	93%	97%

Total cfDNA is associated with death in both adult and pediatric patientsThere may be a temporal relationship with higher levels of cfDNA 30 days prior to death. The mechanism has yet to be elucidated. Criticisms of this study were the lack of serial monitoring leading to clinical events and the need for more granularity with regards to cause of death. Before cfDNA is brought to clinical practice there needs to be further validation and development of surveillance algorithms.

Find the abstract **here.**

Overcoming the Hurdle: Chronic Lung Allograft Dysfunction

Written By: Nirmal S Sharma, MD

Prognostic Significance of Mesenchymal Cell Colony Forming Units in Bronchoalveolar Lavage Fluid for Restrictive Chronic Lung Allograft Dysfunction
Michael Combs, MD

Biomarker for CLAD onset? A higher bronchoalveolar lavage (BAL) mesenchymal stem cell (MSC) colony forming units (CFU) is associated with restrictive chronic lung allograft dysfunction. Presentation by Combs and Colleagues from Michigan reported that BAL MSCs are increased at the onset of chronic lung allograft dysfunction (CLAD)

MSC differences in CLAD and Non-CLAD
Mean MSC CFU was significantly increased at CLAD onset versus CLAD free subjects (4.54(10.5) per $2*10^6$BAL cells vs 10.99(20.6) per $2*10^6$BAL cells, P=0.007). Among the CLAD subjects, restrictive allograft syndrome (RAS) had significantly higher mean MSC CFU compared to the BOS and indeterminate (neither RAS or BOS) groups (16.5 (22.5) per $2*10^6$BAL cellsvs 5.9 (17.9) per $2*10^6$BAL cells vs 15.5 (22.2) per $2*10^6$BAL cells, P=0.02).

Higher MSC CFU counts are associated with worse survival
The study suggests that a higher MSC CFU count (>10 per $2*10^6$BAL cells) predicts with worse survival in CLAD subjects (p=0.01). Multivariate analysis revealed that an elevated MSC CFU count (>10) increased risk of death, hazard ratio of 2.77 (1.07-7.17), P=0.03.

Bottom line
MSC CFU count may be a potential biomarker to identify onset of CLAD and help better understand the pathogenesis of CLAD.

Find the abstract **here.**

Using Machine Learning to Tailor Precision Led Medicine: Use of Gene Expression Profiling in Heart Transplantation

Written By: Yasbanoo Moayedi, MD

Distinct Patterns of Gene Expression Profile Identified Longitudinally and within AlloMap Score Ranges are Associated with Clinical Outcomes

Jon Kobashigawa, MD

Gene expression profiling (GEP) include 11 genes associated with rejection predicated on the CARGO study. The GEP score ranges from 0-40 and is used for non-invasively monitoring for acute cellular rejection in low risk individuals. The Outcomes AlloMap Registry (OAR) is an ongoing multisite US prospective registry that includes over 1,900 adult heart transplant recipients.

The aims of this study were to: 1) Identify patterns of GEP within the GEP score, and; 2) Investigate the association of individual genes with clinical outcomes.

To identify patterns of individual GEP patterns, archetypal (unsupervised) analysis was used.

Findings:

- 1977 patients were followed for a mean follow up of 1.5 years (IQR 0.8-2.1)
- Eight archetypes were developed using seven metagenes
- There was a total of 38 deaths and 22 ACR, 139 CAV ABMR 67 events
- The metagene of MARCH8/WDR40A was associated with death HR 0.61 [0.46-0.81] p<0.001, both MARCH8 and WDR40A have unclear roles but may be involved as regulatory type immune genes.
- IL1R2/FLT3/ITGAM is associated with OR 1.36 [1.011.87] p=0.05 for CAV

Important points:

Kobashigawa et al. identified metagenes that are associated with increased risk of events from the OAR registry. Given the low risk of these patients, few events occurred with fewer than 2 percent deaths over a mean follow up of 1.5 years. Despite the low risk, individual components of the gene expression profile may provide personalized led heart transplantation monitoring. A 'one-size fits all' is no longer acceptable in this

patient population. Further validating work specifically in the racial differences in this cohort is required to bring this type of monitoring to clinical practice.

Find the abstract **here.**

Directly to Apixaban in Patients with VADs?

Written By: Yasbanoo Moayedi, MD

Apixaban in HVAD Pateints Non-Compliant to Standard Vitamin-K-Antagonism
Sebastian Schulte-Eistrup, MD, PhD

Schulte-Eistrup et al. presented a provocative study on the use of apixaban in patients with HVAD. In light of the variable time in therapeutic range (TTR) of vitamin-K-antagonists, prevention of complications related to thrombosis can be challenging. Recent data has shown increased thromboembolic events with dabigatran in patients with VAD. The purpose of this study was to assess the safety and effectiveness of apixaban in patients non-compliant with VKA anticoagulation.

Findings:

- 22 HVAD patients were included
- All patients were started on apixaban 5 mg twice daily in combination with either aspirin or clopidogrel
- Mean time on the device was 408 +/- 296 days (45-1554)
- There were 2 cases of intracranial hemorrhage
- There was no evidence of ischemic stroke or pump thrombosis
- Plasma LDH remained in near physiologic range for all patients

Important points:
This small single center study shows that apixaban may be tolerated and associated with fewer pump thrombosis and ischemic stroke in patients supported by an HVAD. The dose of apixaban may need to be decreased in patients who have poor kidney function along with low body weight and older age. While previous studies have shown that dabigatran may be associated with increased complications, this study warrants further investigation.

Find the abstract **here.**

Clot pre-LVAD Leads to Increased Stroke in Death

Written By: Yasbanoo Moayedi, MD

Presence of Left Atrial or Ventricular Thrombosis at the Time of CF-LVAD Implantation is Associated with Increased Post-operative Risk of Stroke or Death
Justin Fried, MD

Continuous flow LVADs offer a clear survival benefit over optimal medical therapy and first generation LVADs. Adverse events have limited the benefit of this technology. The highest risk of stroke is in the early perioperative period. Intracardiac thrombus formation (in left atrium and left ventricle) is a relatively common occurrence in patients with end stage heart failure. The aim of this study was to assess the impact of preoperative intracardiac thrombus on post-surgical outcomes.

Findings:

- Retrospective cohort study from 2009-2018 in patients supported by a HeartMate two ventricular device
- Primary outcome was survival free from stroke at 6 months
- A total of 372 patients were included of whom 26 had intracardiac thrombus prior to LVAD implantation
- Columbia institutional practice was to perform of thrombectomy at the time of device implantation, however it was not routine practice to perform left atrial closure
- six of 26 patients had a stroke post LVAD within 6 months
- 58.8 percent survival free-stroke compared to 82.7 percent in those with and without intracardiac thrombus respectively at 6 months
- Only independent predictor of stroke or death was intracardiac thrombus with an OR 3.1 (1.3-7.1, p=0.01) in the multivariable analysis

Important points:
Patients with intracardiac thrombus have a higher risk of perioperative stroke and

death despite thrombectomy after LVAD implantation. Postulated reasons for this association include increased hypercoagulability (though the risk was early and not continuous), inadequate thrombectomy or the process of thrombectomy predisposes more nidus of thrombus. Formal protocols for anticoagulation, left atrial ligation and the role of thrombectomy are needed to address intracardiac thrombus prior to LVAD implantation.

Find the abstract **here.**

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mTOR Inhibitors and Statins: Is There Anything New?

Written By: Roy Lee, PharmD

Late-Breaking Clinical Trial: 10-Year Follow-Up of the Everolimus Versus Azathioprine Multi-National Study
Jon Kobashigawa, MD

Effect of Donor Simvastatin Treatment on Gene Expression Profiels in Human Cardiac Allografts during Ischemia-Reperfusion Injury
Rainer Krebs, MSc, PhD

Higher Intensity Statin Therapy Reduces Clinical Endpoints after Heart Transplantation Independent of Lipid Levels
Jessica Golbus, MD

Many in the heart transplant community wonder how much more they can prolong a patient's life and how to prevent or attenuate the progression of cardiac allograft vasculopathy (CAV). A couple of drug options that are commonly used include the deployment of mTOR inhibitors (e.g. everolimus) and statins.

Today, Dr. Kobashigawa presented results from a study that was 10 years in the making. This study was a 10 year follow-up of a randomized, double-blind prospective trial that compared everolimus (EVR) to azathioprine (AZA) in de novo heart transplant recipients. In the original study, there were significantly fewer patients on everolimus who reached the six-month composite endpoint of death, graft loss or re-transplantation, loss to follow-up, biopsy-proven acute rejection, or rejection with hemodynamic compromise. Furthermore, a decrease in CAV development as assessed

by IVUS (intravascular ultrasound) was seen at 12 months in favor of the EVR arm. Unfortunately, in this 10-year follow-up study, there were no significant differences between early EVR versus AZA treated patients for 10 year survival, freedom from LV dysfunction, freedom from NF-MACE (non-fatal major adverse cardiac events), and freedom from cardiac composite endpoints. Additionally, a change in first-year IVUS parameters [including a change in MIT (mean intimal thickness) of >0.5 mm] did not predict 10 year survival, angiographic CAV, or NF-MACE.

So what do these results mean?

Even though short-term results looked very promising 10 years ago, should we now give up on EVR? In short, the answer is no! Drilling down into the details, there was a possible trend to beneficial significance in early EVR initiation arm to prevent CAV at 10 years versus AZA. CAV, itself, is a big cause of morbidity. Additionally, there was a very significant amount of patients who eventually discontinued EVR due to issues such as intolerance that would have skewed this analysis. Thus, all is not lost for this beloved drug and more research needs to be conducted.

While everolimus and sirolimus are commonly used agents to help prevent or attenuate the progression of CAV, statins are also widely used early after heart transplantation as they have been shown to have beneficial effects. It is unknown, however, whether they act through their lipid lowering effects or through other mechanisms. Additionally, it is not completely clear whether or not high intensity statin therapy is better than low intensity statin therapy. To that end, J. Golbus today presented data that showed that moderate to high intensity statin therapy was associated with decreased risk for rejection, CAV, and cardiovascular events compared to low intensity statin therapy. This benefit appears to have been independent of its lipid lowering effects. Unfortunately, this was a retrospective study and a prospective study would ideally be conducted for clarification. If true, however, move over pravastatin! Everyone should be switched to more potent statins such as atorvastatin or rosuvastatin.

Finally, R. Krebs et al. previously showed in a randomized clinical trial that simvastatin treatment of brain-dead donors conditioned the heart to withstand ischemia-reperfusion injury. Today, he presented data from a study that analyzed myocardial gene expression profiles in allografts after donor simvastatin treatment. His team was able to detect differentially expressed genes in over 100 genes in those treated with simvastatin. However, how this newfound knowledge of differential gene expression

can be utilized to the benefit of the patient will have to wait and further studies will need to be conducted.

While nothing presented today in these three sessions will probably change clinical practice too much for now, who knows what the future will hold for these pillars of heart transplant therapy as more data comes forth.

Find all the abstracts **here.**

#ISHLT2019 Announcements

Follow Us, Already!

If you haven't followed us on Twitter yet, what are you waiting for? Be part of the very active conversation online. **@ISHLT** and be sure to use **#ISHLT2019**.

Today's Press Releases

- **Researchers call for national guidelines on marijuana use and heart transplant eligibility**
- **New system to preserve donor hearts could expand donor pool by using organs outside of standard scope**
- **Hearts from Hepatitis C patients are safe to transplant, research shows**
- **HeartMate 3 heart pump reduces burden of bleeding and stroke rates, eliminates pump thrombosis**

On the Horizon

Must-See Plenary Session

Be sure to attend the Plenary Session tomorrow morning from 8 to 10 AM in Grand Caribbean 1-7 for a riveting lineup of speakers and presentations.

- Transplant from Every Angle. Susan Hou MD will talk about her experience being a living donor, an organ recipient and a transplant surgeon.
- Astronaut Col. Mike Mullane will inspire us on working with a team under stressful situations, drawing on his experience flying through space and in Vietnam.

If you can't make it, you can live stream it too! Just register **here**.

Asia Pacific Group to Meet

ISHLT's International Engagement Committee is hosting its second regional meeting tomorrow, Friday, from 7:15 to 8:15 PM in Oceana 3-5. All are welcome so swing by and meet some of your peers.

Have You Visited with Our Exhibitors Yet?

If not, get on over there and see what they've got in store. The Hall closes at 4:30 PM Friday so be sure to visit before they close.

Live Stream the Plenary Session

Be sure to tell your friends who can't be here to **live stream the Friday Plenary Session** so they can hear some incredible keynote speakers, including Astronaut Mike Mullane. Also on the agenda: Susan Hou, MD, who will talk about being an organ recipient, a living donor and a transplant surgeon. Register **here** to livestream or send them to **www.ishlt.org** and they'll find a link there.