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The Daily Pulse

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Wednesday, April 3, 2019 - Evening Edition

In the Spotlight

John Wallwork, FRCS, Receives the ISHLT Lifetime Achievement Award

John Wallwork, professor, surgeon, mentor – and so much more – received the Lifetime Achievement Award from ISHLT today for his stellar contributions to the field and years of humble service.

Wallwork walked the crowd through a history of his career, primarily by paying

homage to the many people he worked with and learned from. After qualifying at Edinburgh University and training in cardiothoracic surgery in Scotland, the U.K. and Australia, he moved to California and trained under Norman Shunway at Stanford University. He became involved in heart and heart-lung transplants while there – and never looked back.

Among his career highlights:

- Served as chief resident during the first heart-lung transplant in the world.
- Pioneered the introduction of heart-lung transplantation in the UK
- Performed the world's first heart-lung and liver transplant with Professor Sir Roy Calne.

Professor Wallwork is credited with playing a major role in the development of the transplant program at the Royal Papworth Hospital in Cambridge. His career chronology includes:

- Serving as Director of the Transplant Service at Papworth Hospital from 1989 to 2006 and Medical Director from 1997 to 2002.
- Being awarded an honorary Chair in Cardiothoracic Surgery by the University of Cambridge in 2002.
- Becoming Director of Research and Development at Papworth Hospital in 2007 and remained in that position until his retirement in 2011.
- Being appointed Chairman of Papworth Hospital NHS Foundation Trust in 2014.

He currently serves as an Emeritus Professor of Cardiothoracic Surgery at Papworth Hospital in Cambridge.

With humor and grace, he offered the audience this advice? Have the courage to fail; always encourage younger people in their career; know when it's time to leave the stage.

Today's Highlights

When Short-Term Becomes Long-Term: Transition from Temporary to Permanent Mechanical Support

Written By: Van-Khue Ton, MD, PhD

In the past decade, there has been a dramatic increase in the use of temporary circulatory support (TCS) to rescue patients with cardiogenic shock (CS). In the following presentations, we learn about TCS use in the global IMACS registry, TCS-associated complications, as well as patients' outcomes once transitioned off of VA-ECMO to durable VAD.

Short and Long-Term Adverse Events in Patients on Temporary Circulatory Support before LVAD: An IMACS Registry Analysis

Van-Khue Ton, MD, PhD

Adult patients enrolled in IMACS who have received CF-VAD in uni- or biventricular configuration were included (n=13,511). Patients with INTERMACS profiles 1-3 at the time of durable VAD insertion were stratified into "non-TCS" vs. "TCS" groups, based on their need for pre-op TCS. TCS patients were more likely to be younger, have ischemic cardiomyopathy, and present with lower INTERMACS Profiles. Early adverse events were defined as those occurring < 3 months post VAD, and late events occurred beyond three months. Compared to non-TCS patients, those requiring pre-op TCS had more major bleeding, GI bleeding, hemorrhagic and ischemic strokes. Early device-related infection and late adverse event rates were low and similar between the 2 groups.

TCS subtypes were classified as VA-ECMO, IABP, or other TCS (including but not limited to Impella, TandemHeart and Centrimag). Within 3 months post-op, ECMO and IABP patients had the highest rates of major bleeding and strokes. IABP patients had the highest rate of GI bleeding, while other-TCS patients had the highest rate of device-related infection. Late adverse event rates were low and similar across all groups. Short and long-term survival of TCS patients was inferior to non-TCS patients (3-month survival: TCS 86 percent, non-TCS 91 percent, two-year survival: TCS 66 percent, non-TCS 73 percent, $p<0.0001$).

In summary, adverse event profiles are heterogenous across TCS types. We were unable to explain the differences in complication rates due to lack of data granularity. Pre-op TCS requirement appears to confer worse survival in patients undergoing durable VAD implant.

Find the abstract **here**.

Longitudinal Impact of Temporary Mechanical Circulatory Support on Durable Left Ventricular Assist Device Outcomes: An IMACS Registry Analysis
Jaime Hernandez-Montfort, MD

Patient selection and baseline characteristics are similar to the previous study. Survival data for IMACS patients requiring preop TCS are presented in depth here. INTERMACS Profile 1 patients shared similar survival whether or not they needed pre-op TCS (1-year survival 70-75%). However, within the TCS subgroups of patients with Profile 1, ECMO conferred the worst survival (1-year survival: ECMO 66%, IABP and other-TCS 73 percent, non-TCS 74 percent, $p<0.0001$). For all patients with Profiles 1-3, survival was again the lowest in ECMO group (1-year survival: ECMO 66 percent, IABP and other-TCS 78 percent, non-TCS 82%, $p<0.0001$). ECMO patients also had the longest ICU stay, most deranged laboratory values, most concurrent surgeries at time of VAD implant, and shortest duration of VAD support. We proposed that ECMO patients should be classified as "INTERMACS Profile 0" to denote their dismal prognosis.

Find the abstract **here**.

Transition from Short-Term to Durable Mechanical Circulatory Support Systems. Outcome and Patient Selection. On Behalf of ECMO-VAD Study Group
Diyar Saeed, MD, PhD

Large databases such as the IMACS registry provide general trends in TCS use, including ECMO, and data on survival and adverse events. However, large databases lack granularity and may suffer from inconsistent data reporting. The investigators at several European and US centers formed the ECMO-VAD Study Group to capture patients' outcomes on ECMO. A total of 531 patients were analyzed on the day of durable VAD implant, 87 percent of whom received peripheral ECMO cannulation. This

was a sick population, with 33% receiving CPR prior to ECMO and 32 percent on dialysis. Post VAD insertion, 40% of patients required RVAD, and 1-year survival was 50 percent. Multivariate predictors of survival post VAD implant were age, BMI > 30, bilirubin, WBC, lactate and MELD score. More research is needed to shed light on other factors that may impact survival such as VAD insertion strategy (sternotomy vs. lateral thoracotomy), off-pump surgery, duration of ECMO support, and methods of weaning.

Find the abstract **here**.

Clinical Designations (BTT/DT/BTC) for Mechanical Cardiac Support Should be Abandoned

Written by Yas Moayedi, MD

Clinical Outcomes by Intended Goal of Therapy in the MOMENTUM3 Clinical Trial: Analysis of the Full Cohort
Daniel Goldstein, MD

The MOMENTUM3 study is the cumulation of collaborative work that started a decade ago to develop a safe and effective mechanical cardiac device for patients with end-stage heart failure. One of the key questions in this endeavor is whether it was clinically necessary to distinguish among destination therapy (DT), Bridge to Transplant (BTT) and Bridge to Decision/Candidacy (BTD/BTC) designations. These clinical classifications have been debated in the literature as patients' comorbidities and preferences fluctuate resulting in a "meaningless" labeling.

Study Purpose: The primary purpose of the study was to conduct a pre-specified analysis of primary and secondary outcomes and adverse events in patients stratified by pre-implant strategy of BTT/BTC vs. DT. The secondary outcome was to determine the rates of transplantation vs. continuing mechanical support among these designations at 2 years.

Findings:

- Among patients included in the MOMENTUM3 trial 23% were BTT, 15% BTC and 61% DT.
- The DT population was significantly older (63 vs 56 years), more likely to have ischemic cardiomyopathy (47% vs 40%), prior CABG surgery (27% vs. 12%) and a history of atrial fibrillation (47% vs 40%).
- The absolute effect of HM3 in DT and BTT was similar in primary endpoint as defined by survival free of disabling stroke or reoperation to replace ore remove malfunctioning device and at 2 years (73.2% vs. 76.8%)
- In patients with a BTT designation, 43% of 'transplantable' patients remain supported by a HM3 after 2 years which would be similar to a 'DT' designation. Among DT patients (ie. transplant ineligible patients) 12% underwent transplantation. Similar trends were seen among HM2 patients.
- Comparable trends in hemocompatibility-related adverse events were observed among BTT/BTC and DT patients, with no significant differences with regards to stroke (ischemic, hemorrhagic or debilitating), bleeding (significant bleeding or gastrointestinal bleeding) or pump thrombosis.
- Type of device (HM3 vs HM2), Kidney function and race were better predictors of primary endpoint outcomes at 2 years than BTT/BTC vs. DT designation.
- The net clinical benefit for BTT/DTC and DT for HM3 devices are also comparable

Pre-implant strategy designations are dynamic and unpredictable. The primary endpoints and principal hemocompatibilty adverse events were similar among BTC/BTT or DT labels. This data supports abandoning the current use of pre-implant strategy and to focus on providing the patient a device which will improve survival and quality of life.

Click here to read the full abstract for this presentation.

Thoracic Registry Report Focuses on Size-Matching Using Predicted Heart Mass and Updates on European Data Regulations

Thoracic Registry Report
Josef Stehlik, MD, MPH

The 36th Annual Transplant Registry Report focuses on predicted heart mass rather than weight and height. Thoracic transplantation volumes have remained steady with over 5500 heart and 4500 lung transplantations performed worldwide in 2017 with improving graft survival.

- General Data Protection Registry (GDPR) is a new regulation for data sharing in the European Union. Prior to May 2018 each of the 28 EU now a more unified GDPR regulation. However, due to various interpretation of the regulation, ISHLT data acquisition in Europe is temporarily on hold.
- Lung Transplantation: One-year conditional median survival in adults remains 8.9 years. Pediatric one-year conditional survival is 9.4 years showing a progressive improvement. In multivariable analysis, absolute height difference was most significantly associated with 1-year mortality.
- Adult Heart Transplantation: One-year conditional median survival remains is 14.8 years. Fifty percent of patients are supported by bridge to transplantation (BTT) mechanical cardiac support (MCS). ECMO use pre-transplantation is associated with the highest mortality and we have yet to see how the new UNOS allocation system affects ECMO utilization.
- Predicted Heart Mass (pHM) is a new variable added to the analysis based on 2 recent reports (Reed RM JACC HF 2014, Kransdorf EP JHLT 2019) showing a better association with survival compared to height or weight differences.
- Pediatric Heart Transplantation recipients have the longest survival with a 1-year conditional survival will reach 30 years in the youngest cohort (recipient age of < 1year). Mechanical cardiac support in pediatrics with dilated cardiomyopathy appears to be similar to adults with 50% supported as BTT.

So Wrong It's Right: The Right Ventricle and MCS

Written By: Van-Khue Ton, MD, PhD

No longer a "forgotten ventricle," the RV now plays a central role in patients' prognosis following LVAD implantation. In the following presentations, we learn about longitudinal assessment of RV function and a novel treatment for RV failure in LVAD patients.

Serial Assessment of Pulmonary Artery Pulsatility Index Provides Incremental Risk Assessment for Early Right Ventricular Failure after Left Ventricular Assist Device Implantation

Matthew Gonzalez, MD

Early RV failure is difficult to predict, and it is one of the leading causes of poor prognosis. Current risk scores use "static" parameters obtained from TTE and clinical scenarios, and therefore might not be sufficient to accurately predict RV failure. Pulmonary artery pulsatility index (PAPi) is an emerging parameter that may allow "dynamic" assessment of RV reserve. In this study, 394 patients were retrospectively surveyed for clinical, hemodynamic and echocardiographic parameters prior to LVAD implant. Post-op RV failure rate was 20 percent. Preoperatively, 75-89 percent of patients were on inotropes and 26 percent of patients had INTERMACS Profile 1. Serial hemodynamics obtained during an inpatient stay or outpatient measurements were used. PAPi added incremental predictive power to usual clinical predictive models, with "best PAPi" having the best AUC. More research is needed to validate this novel parameter in predicting post-op RV failure.

Find the abstract **here**.

Early and Late Right Heart Failure Following LVAD Implantation: Epidemiology, Natural History and Outcomes. An Analysis of the STS INTERMACS Database

Chris Kapelios, MD

At total of 5537 adults CF-LVAD enrolled in STS database between 2014 and 2016 were included in this analysis. RV failure was monitored at 1, 3, 6 and 12 months following durable LVAD insertion. In this cohort, 14 percent of patients had INTERMACS Profile 1. The prevalence of RV failure was 24 percent at one month post-

op, but decreased and stayed steady at 10% through three years. Incident (new) RV failure cases were approximately 5 percent between three months and one year post-op. Notably, if patients developed RV failure at six months post-op, 25 percent still had persistent RV failure at one year, while RV failure that developed early (within one month) post-op did not seem to persist long-term. Survival of patients with RV failure was inferior to those without RV failure. For those alive at six months post LVAD, survival of patients with persistent and de novo RV failure was significantly worse than survival of patients with resolved RV failure.

Find the abstract **here**.

Oral Milrinone for the Treatment of Right Ventricular Failure in LVAD Patients
Nir Uriel, MD

The treatments of refractory RV failure include heart transplantation (which may not be available to all), medications (diuretics, inotropes, pulmonary vasodilators), LVAD speed optimization, or RVAD. Quality of life and prognosis for patients on IV inotropes or RVAD remain marginal at best. In the 80's, oral milrinone provided symptomatic relief for patients with end-stage heart failure, but the drug faded into obscurity as clinical trials showed increased mortality. Oral milrinone, in its extended-released formulation known as CRD-102, received renewed interest today as it was shown in a pilot trial to be safe and tolerable for 5 patients suffering from refractory RV failure post LVAD implant. With a half-life of seven to eight hours, CRD-102, given over two weeks, proved to be promising in improving cardiac output and patients' sense of well-being. CRD-102, if shown to be effective in a larger clinical trial, would serve as first ever, easy-to-administered therapy for a population of patients with many adverse events, poor survival and few options. We anxiously await more research aimed at bringing "sexy back" to oral milrinone in LVAD patients in the near future.

Find the abstract **here**.

Pediatric Donor Utilization, MCS, Readmissions and More

Written By: Roy Lee, PharmD

Two Freaky Reasons Pediatric Anticoagulation Management Could Get You
Christina VanderPluym, MD

Let's be honest. We all hate anticoagulation and managing anticoagulation. It's a fickle beast. It's a fickle mistress and probably doubly so in the pediatric world.

There are two reasons pediatric ventricular assist device (VAD) therapy could get you: It's associated with high rates of stroke and bleeding. There are multiple factors that can impact these adverse events, including patient factors, device factors, and management factors.

Today, C. VanderPluym, MD, Boston Children's Hospital, targeted anticoagulation management as a quality improvement initiative through the ever-expanding ACTION network that might offer help to us all. Their goal was to report the baseline anticoagulation data obtained from ACTION. As one might expect, they found that anticoagulation practices for pediatric VADs varied quite a bit across centers. However, the two most commonly used anticoagulants were unfractionated heparin (UFH) and bivalirudin.

While most patients reached anticoagulation target goal within the first day of therapy, there were outliers. And of those using UFH, less than or equal to 50 percent of patients were within target range during therapy. This is an abysmal statistic. In contrast, roughly 73 percent of patients were within target range using bivalirudin! While more needs to be done, could bivalirudin become standard of therapy? Stay tuned to ISHLT 2020!

Find the abstract **here**.

Is Omega-3 the Alpha and Omega of Gastrointestinal Bleeding in LVADs?

Written By: Roy Lee, PharmD

Omega-3 Suppresses Gastrointestinal Bleeding by Reducing Angiopoietin-2 Expression in LVAD Patients
Teruhiko Imamura, MD, PhD

Gastrointestinal bleeding (GIB) in LVAD patients. We all hate it. We hate it because there's no definitive treatment. At the moment, our options include endoscopy, blood products, proton pump inhibitors, or other intensive therapies. Another option includes stopping anticoagulation and antiplatelet therapy, which is a prospect that many of us are loathe to do due to the increased risk of thromboembolic events. However, T. Imamura et al. may offer an alternative approach that may bring us renewed hope and it involves the use of a simple, everyday ingredient…omega-3 fatty acids.

Specifically, his group looked at the use of Lovaza® (which is a FDA regulated product unlike many over-the-counter omega-3 products) at a dose of 4 grams per day. At this dose, they found a lower risk of GIB in LVADs. By what mechanism could omega-3 be exerting its effects? The answer seemed to lie with angiopoietin-2, a biomarker involved in abnormal angiogenesis. When they examined 18 angiogenesis biomarkers, only angiopoietin-2 levels were significantly lower. Could it really be that simple? Can omega-3 be our savior? To further help elucidate the answer to this question, his group has embarked on a journey to conduct a prospective, randomized controlled trial. Hopefully, they'll have results to present at next year's ISHLT meeting!

Find the abstract **here**.

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to-MAY-to, to-MAH-to. Is There a Difference Between Bortezomib and Carfilzomib Desensitization in Heart Transplant Candidates?

Written By: Roy Lee, PharmD

Comparative Efficacy of Bortezomib and Carfilzomib Desensitization Protocols in Highly Sensitized Cardiac Transplant Candidates
Minoosh Sobhanian, PharmD

Antibodies! We all hate these pesky little critters. Specifically, we hate donor specific antibodies (DSAs). If it weren't for them, we could much more easily transplant all our heart transplant candidates with little fear of retribution. Sadly, this is not the case. Many of our candidates have increased rates of sensitization due to factors such as LVADs, pregnancy, and blood transfusions that can negatively impact their probability of finding a suitable donor and, subsequently, their rates of rejection and survival post-

transplant.

And, as with life, how to rid ourselves of these antibodies is, to say the least, complicated. Although we have several options to deploy in our armamentarium to attempt to desensitize our patients, one of which is to use proteasome inhibitors (PIs), how to exactly use them is still up for debate and none have proven to be our golden ticket.

Currently, there are two PIs available on the market: bortezomib and carfilzomib. The biggest difference between the two agents is that one is a reversible PI (bortezomib) and the other is irreversible (carfilzomib). However, no one has every demonstrated that one is superior over the other. Is one better at reducing anti-HLA antibodies? To that end, M. Sobhanian et al. set out to see if they could shed some light on this matter. If I was a betting man, I would wager that carfilzomib would have been superior. However, in their retrospective study, they found that a bortezomib-based desensitization protocol was associated with a greater percent reduction of anti-HLA antibodies compared to a carfilzomib-based protocol. Additionally, a larger reduction was seen with class I antibodies versus class II antibodies. Does this result in any meaningful difference in terms of clinical outcomes? Unfortunately, a larger, prospective randomized study will need to conducted to confirm these results. Is there anybody out there who is willing to take up the challenge?

Find the abstract **here**.

Reducing Total Ischemic Time: An OCS Trial to Improve the Utilization of Marginal Hearts

Written By: Yasbanoo Moayedi, MD

Successful Utilization of Extended Criteria Donor (ECD) Hearts for Transplantation - Results of the OCS™ Heart EXPAND Trial to Evaluate the Effectiveness and Safety of the OCS Heart System to Preserve and Assess ECD Hearts for Transplantation
Jacob Schroder, MD

Two thirds of donor hearts are discarded in the United States. Therefore, strategies to improve donor utilization are critical to meet the donor heart shortage. The Organ Care

System (OCS) is a portable device that can provide warm organ perfusion. The OCS expand trial is a single-arm prospective multisite trial that allowed the evaluation of donor hearts meeting extended criteria. The aim of this trial was to improve current donor heart utilization. Declined OCS hearts were based on biomarkers hemodynamic parameters or the surgeon's ultimate decision.

- Extended donor criteria included a total expected ischemic time equal or greater than 4 hours, or an ischemic time of greater than 2 hours plus one of the following criteria: left ventricular hypertrophy, ejection fraction 40-50%, downtime equal or greater than 20 minutes or age greater than 55 years.
- 33% had multiple inclusion criteria.
- Ninety-three donor hearts meeting expanded criteria were eligible. Among these donors, there was a utilization rate of 81% (75/93).
- Mean ischemic time 102 mins and out of body time of 380 minutes
- The incidence of severe primary graft dysfunction was 10.7% which is significantly lower than the national reported rates of non-OCS perfused marginal donors.
- Short term outcomes were within national trends with a 30-day and 6-month survival of 94.7% and 88%, respectively.

The OCS device provides a safe and effective means of assessing marginal donors. The transplantation of these extended organs which would have otherwise been discarded shows promise in improving donor utilization. The lower rate of primary graft dysfunction in this study is likely associated with the reduced total ischemic time which is a well-established risk factor.

Find the abstract **here**.

#ISHLT2019 Announcements

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Remember to follow us on Twitter **@ISHLT** and use **#ISHLT2019**. Feel free to post pics, follow your peers and spread the word about the amazing research being presented.

On the Horizon

IEC Regional Meeting

Be sure to attend the **Latin American Regional Meeting** from 7:15 – 8:15 PM on Thursday, April 4 in Oceana 3-5, held in conjunction with ISHLT's International Engagement Committee. All are welcome!

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.