April 14, 2018

DAILY Links

38th Annual Meeting & Scientific Sessions
The Acropolis, Nice, France

Andy Fisher officially passed the gavel to incoming ISHLT President Jeff Teuteberg during Friday morning's Annual Business Meeting.

Gavel:

1. Small mallet used by a presiding officer

ISHLT by the Numbers……Nice by the Sea

- ✓ ISHLT Membership climbed to 3,905 (as of 12/31/2017)
  - ✦ A 42% increase in the last 10 years
  - ✦ 105% increase since 1995
- ✓ Meeting registration is up 60% 2007-2017
- ✓ 38Th Annual Meeting (2018) has the highest number of abstract submissions
  - ✦ 115% increase in abstract submissions in the last 10 years

Review Plenary Session 2: Moving Cardio-Thoracic Transplantation Forward, New Technologies to Advance Future Transplant Patient Care.

The Sun is Finally Shining in Nice, and the Future is Looking Bright

So for those of you that were out of bed early enough this morning, you might have caught a glimpse of a few rays of sun, and certainly just like the opening lecture in this morning's plenary session, the forecast is looking bright for those of us working in transplantation.

Dr. Stefan Schneeberger gave us fascinating insight into some of the new technologies we can look forward to working within the future.

Organ transplantation has been one of the top ten medical advances, but we are facing a growing global shortage of numbers in organ donations. So how do we continue to treat our ever-increasing numbers of patients with advanced heart and lung failure?

Dr. Schneeberger reminded us of our recent advances in technologies such as organ perfusion systems, and the success we are enjoying associated with this. But is enough? Global organ sharing hospitals and schemes were mentioned, however this may present us with issues across communities due to political issues.

We continue to explore tissue engineering and are seeing advancements in cell regeneration, cellularization which may result in the ability to engineer new organs, as well as in-vivo organ generation with PSCs techniques. There have been exciting advances in new areas of transplantation with new techniques in face and hand transplantation in which tissue engineering has been used. Stem cell muscle repair may assist us in the future when focusing on heart and lung transplantation.

Let's celebrate our past achievements and look to a bright future ahead.

Review Symposium 25: Crashing and Burning: Cardiogenic Shock and Short Term MCS.

Crashing Through the Burning Fire of Cardiogenic Shock using MCS!

As we hurtle towards the end of this year's ISHLT, this symposium leads us at break-neck speed through some pressing issues and dilemmas in the use of short term MCS in the treatment of cardiogenic shock. This continues to present major challenges to clinicians and how we treat this and what device was explored.

A need for a risk classification strategy was identified by Dr. Eduardo Rame from Philadelphia, USA. He showed that a risk stratification in INTERMACS class 1 patients helps us to understand the mechanisms that impact end organ damage. He argued that guidelines would assist referring centers who don't have advanced therapies available to them.

New guidelines may also assist us in determining which type of device should be used in this group of patients. We were reintroduced to new ideas in the use of an old device concept with IABP. We then delved into alternate devices and were given some interesting survival statistics by Dr. Ivan Netuka when using a variety of devices from the Impella to the Tandem Heart, Centrimag and finally, when using as described by Chair Stephan Schueler, the bazooka approach with the use of a combination of these devices. Finally, we were given wonderful presentations in the use of ECMO and how to wean from it. Still confused about which device to use? As Dr. Netuka suggested, ultimately it remains our preference; however, the important factor is having the device ready and easy to implant.

Review Symposium 29: Joint ISHLT/ESC Symposium: Pulmonary Hypertension Due to Left Heart Disease: When RIGHT Meets LEFT

What Lies Ahead: Answers to the Future or Does the Future Lie in our Past?

Friday's Symposium on Pulmonary Hypertension due to left heart disease (PH-LHD) included tough debate between Nazzareno Galie, MD and Mardi Gomberg-Maitland, MD, MSc on the topic: PH-LHD should NOT be treated with vasodilators.

Dr. Galie was the pro side of this debate and had three main points to his argument. His first point was that there is no plausible rationale for using an approved PAH therapy for PH-LHD. Pathologically speaking, PH-LHD is different than PAH and CTEPH. Currently available therapies are only approved for PAH and CTEPH. Mechanistically, PH-LHD is the only form of PH that is caused by a backward transmission of increased pressure. While there is a pre-capillary component, we aren't sure why. Dr. Galie argues that removing the precapillary component will increase wedge pressure. Rather than trying to remove the precapillary component, we should try to normalize wedge pressure and that will ultimately improve PVR. Dr. Galie's next point was that there is no evidence of a favorable risk/benefit ratio in treated PH-LHD with vPAH therapies. Out of five studies, only one showed improvement (with sildenafil) and nine out of 12 studies showed increased mortality. Finally, Dr. Galie pointed out that PH guidelines specifically recommend against the use of PAH approved therapies in this patient population but rather optimization of treatments for the underlying condition.

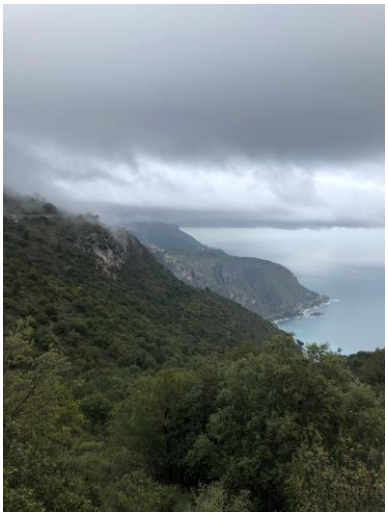
After Dr. Galie's points, Dr. Gomberg-Maitland clearly had her work cut out for her – she even admitted she had drawn the short straw to debate against the author of the guidelines! She argued that as Dr. Galie mentioned, there IS a pre-capillary component of PH-LHD and therefore there IS a rational to use vasodilators. She went through trial after trial that found some favorable outcomes and pointed out several limitations of the trials that did not find benefit. Dr. Gomberg-Maitland's main argument was that we have not studied these drugs appropriately, in the right patient, with the right dose of drug, or with an appropriately designed trial. Overall, she felt Dr. Galie had not convinced us beyond a reasonable doubt that there are NO circumstances that PAH therapies should be used for PH-LHD. Rather, we need to test these therapies in the right phenotype.

For his rebuttal, Dr. Galie pointed out that there has been no progress in this area in the past 20 years. He reminded us again of the meta-analysis that found increased mortality

in 9 out of 12 studies. He criticized that phenotyping was a "magic" word for negative RCTs. He left us with a quote by the famous philosopher George Santayana: *"Those who cannot remember the past are condemned to repeat it."*

Dr. Gomberg-Maitland's closing arguments included a survey that showed a large proportion of responding cardiologists and pulmonologists use PAH therapies in patients with RV/PH-LHD. She agreed that we should not repeat the past, but we should ensure that we have studied these therapies appropriately in this patient population. She commented on two ongoing studies that she believes will surpass the limitations of previous studies and one way or another, will be the nail in the coffin to this debate.

So, who won? The final vote was 50/50 among audience members. Will we find the answer in the future? Or will it bring us back to our past? Only time will tell…



Review Oral Session 29: Lung Donation after Circulatory Death – Current Status

Friday is DCD day! DCDs improving outcomes for lung transplant patients

The first session of the morning examined ongoing work with DCD donors from both clinical and basic science perspectives. Dirk Van Raemdonck started with an update of the ISHLT DCD registry. Results were controlled with brain dead donors matches from the contributing institutions. The results were excellent with no discernible difference in survival between DCD and DBD groups at both 1 and 5 years. Interestingly, the registry did not identify a difference in those donors with cold flush >45 minutes post treatment withdrawal compared to <45 minutes supporting the notion that time constraints imposed could be relaxed. Greg Snell further elaborated on long term results focusing on CLAD within the Melbourne cohort. In 96 patients undergoing DCD there was no difference in obstructive or restrictive CLAD over the follow-up period (up to 10 years) compared to DBD compatriots. Bronwyn Levvey described the impact DCDs have had on their program, clearly demonstrating shorter wait list time and lower mortality since their DCD programs inception.

Morvern Morrsion showed different cytokines profiles within BAL of DCD and DBD donors undergoing EVLP. DCD donors had higher IL-1A and IL-1B likely reflecting the different modes of death. She went on to speculate that further understanding will allow therapeutic intervention at the donor management / procurement stage to improve recipient outcomes. Amy Fielder presented results from the UNOS database showing recipients from DCD donors with PO2 <300 had inferior long-term survival compared to those donors with higher PF ratios. The mechanism for this was not apparent as death from respiratory failure was higher in DBD groups. Finally, Yui Watanabe from the Toronto group looked at positioning during warm ischemic time comparing supine and prone positioning in an animal DCD model. The rationale was improving atelectatic change. He went on to show a superior cytokine profiles and radiological aeration at lung bases of these donors.

Review Oral Session 39 – All is Not Lost: Improving Outcomes in Children with a Failing Heart

Can we get a Passing Grade on a Failing Heart?

What a great way to wrap up this set of pediatric Friday sessions. It started with a review of the largest prospective myocarditis registry. This showed a wealth of information including that the youngest myocarditis patients were the sickest and were the most at risk for death or need for mechanical circulatory support. The remaining abstracts were all reports from a few different registries. The first was from the pediatric cardiac critical care consortium showing that children with acute decompensated heart failure had worse outcomes but less likely to require a VAD if they had congenital heart disease. Next came the first, ground breaking analysis of the international pediatric heart failure registry. This showed most patients presenting with a diagnosis of heart failure are discharged from the hospital with medical management. We were also blessed with a myriad of research ideas for the future that could be gleaned from this registry.

The final three abstracts all used data for the PediMACs registry. The first discussed changes in the trends of mechanical circulatory support. Specifically, increased use of continuous flow devices in younger children and a decrease in the number of children transplanted after device placement. The next abstract showed that risks for poor outcomes in children on mechanical support include INTERMACS profile 1 and younger age. The final abstract concluded that children with congenital heart disease who were on mechanical support were more likely to have a paracorporeal device and had an increased risk of death compared to those without congenital heart disease.

What a great group of presenters with a wealth of important information to advance our field. A+ for all!

COMING ATTRACTIONS

New understanding and potential targets for CLAD

Kenneth Sinclair, The University of Queensland and Prince Charles Hospital, Brisbane, will receive the Early Career Scientist Award in today's plenary session. On Wednesday he professorially presented impressive research expanding our knowledge of mechanisms leading to the development of CLAD. He started by clearly demonstrating that mesenchymal stromal cells migrate from the lung interstitium to the alveolar space differentiating into fibroblasts. He

went on to prove that lysophosphatitidic acid (LPA) within CLAD BAL is responsible for this migration and driving other deleterious fibroblastic activity. Trials of LPA inhibition are underway for idiopathic pulmonary fibrosis – this research provides a much-needed therapeutic target for CLAD which can be further evaluated.

Preview Oral Session 45 – Live Long and Prosper: Long-term Outcomes after Pediatric Heart Transplant

On the Trek to Add Years of Ongoing Exploration

What a great way to start wrapping up this 2018 meeting. As many people know, outcomes for pediatric transplant have improved in each era but much of this has to do with improved care early after transplant. This session will include research evaluating these patients after transplant and how it may affect their long-term outcomes. This includes evaluating the use of intravascular ultrasound for diagnosing cardiac allograft vasculopathy, which will tie in nicely with a study on early vasculopathy and graft failure after rejection with hemodynamic compromise. There will be a review of the Loma Linda experience over the last 30 years of heart transplantation. This will be followed by an exciting study from the PHTS database looking at practice variation in the diagnosis of acute rejection. Finally, the last two presentations will look at new onset cognitive impairment after transplantation and the reality of limping into transplant. These studies will address important aspect that could affect long term outcomes of this patient population.

Preview: Oral Session 49: Rocket Fuel and Scaffolding: Alternative Bridges to Heart Transplant

The Cold Hard Truth

What do you do when a patient with end stage heart failure does not want an LVAD? Are there any other options? The presenters of this symposium will be discussing just that. Mark Belkin, MD will begin the session by discussing alarming results from a meta-analysis of over 1000 patients with advanced heart failure who underwent Mitraclip implantation. Daniel Reichart, MD will describe echocardiographic data on patients with functional mitral regurgitation who received Mitraclip. Next, Gabriella Masciocco, MD will be discussing a strategy of repeated, planned levosimendan infusions to reverse pulmonary hypertension or wean from continuous IV inotropes. Luanda Grazette, MD, MPH will then discuss and updated analysis comparing survival among patients on home milrinone versus home dobutamine as well as the impact of concomitant beta-blocks. Next, Kristjan Karason, MD, PhD will discuss a randomized controlled trial evaluating the impact of levosimendan and dobutamine on renal blood flow and glomerular filtration rate in patients with heart failure and renal impairment. Finally, Fabrizio Oliva, MD will discuss another study of repeated levosimendan that evaluated HF hospitalizations 6 months before and after the initiation of levosimendan.

So, what do you do when you're running out of options? Don't miss this session to find out the answers to end stage heart failure: the good, the bad, and the cold hard truth.

Preview Oral Session 51: I'm at risk! Outcomes and Novel Risk stratification in pulmonary hypertension

So Long, and Thanks for All the Fish

The last session of the last day is a tough gig but don't leave yet. After all you've paid money to attend! So here it is – an oral session dedicated to risk stratification in patients with pulmonary hypertension – very topical given the recommendations at the recent PH congress held close to here. Multiple facets will be explored: RV/PA coupling to predict survival, sex specific clinical risk factors, responders and non-responders to prostanoids, the role of RV evaluation under exercise stress and more… The abstracts look excellent and data will be presented that will influence your clinical practice.

Au Revoir. Adieu. Auf Wiedersehen. Arrivederci.

Links Annual Editorial Staff Dinner

Influence:

1. Capacity to compel others to action, behavior or opinion
2. Influence is an old French word with its roots in astrology: emanation from the stars that acts upon one's character and destiny.

Advance:

1. To bring or move forward; to improve
2. From the French avancier: to move forward

Intrepid (adjective)

1. Resolutely fearless, dauntless.

Sticks and stones make break our bones, but words will never hurt us? The age-old coward vs. the brave conjures up many words. The word *courage* itself is derived from the Latin root commonly spelled *cor* or *cord* meaning "**heart**." To fight with all your heart is to fight with great courage. Richard I of England was known as Richard the Lionheart or Richard Coeur de Lion, *coeur* being the French word derived from the Latin *cor*.

Give every man thy ear, but few thy voice.

- William Shakespeare

Finally, I'm tired!

As I pass on the gavel or rather the "pen" of words to the next Editor-in-Chief, David Weill, let's reflect on what has been done for the *Links*. With the realization that I shall not be writing for you again, perhaps for a very long time, the gavel raps a rite of passage with uses akin to the mallet, which can be used for pounding down by a mauler to what's in the photo, a "Put'nhead."

Few things are harder to put up with than the annoyance of a good example.

- Mark Twain, Pudd'nhead Wilson

Thanks for a great year Daily Links Team!

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