High-risk Donor Lungs Can Now Be Safely Used for Transplant Due to the Toronto XVIVO Lung Perfusion

For the first time, scientists have shown in a clinical trial that the Toronto XVIVO System can safely and effectively treat, re-assess and improve the function of high-risk donor lungs so that they can be successfully transplanted into patients. The use of this technique could significantly expand the donor organ pool and improve outcomes after transplantation.

The study, “Nornothermic Ex vivo Lung Perfusion in Clinical Lung Transplantation” is published in the April 14 edition of the New England Journal of Medicine. Drs. Keshavjee and Marcelo Cypel presented the long-term outcomes of this study during the Opening Plenary Session yesterday.

The research showed that using high-risk donor lungs, which were improved and re-tested in the XVIVO Lung Perfusion System before transplantation, led to results that were similar to those using conventional donor lungs.

“This heralds a new era in transplantation where we can predict how well the organ functions before using it, we can help the organ heal itself, and ultimately, we can use the Toronto XVIVO as a platform to engineer ‘super organs’ for transplantation,” said Dr. Keshavjee.

During the study period from September 2008 to January 2010, 136 lung transplants were performed. Twenty high-risk donor lungs with impaired function and chest x-ray abnormalities, which were treated and tested for four hours with the Toronto XVIVO were transplanted, and 116 were the controls or conventional donor lungs with acceptable functioning.

“This is the most exciting advance in lung transplantation since we first started 25 years ago,” said ISHLT President John Dark.

The major endpoint was primary graft dysfunction at 72 hours after transplant, and secondary endpoints were 30-day mortality, ICU and hospital stay and length of mechanical ventilation.

Results at 72 hours showed that 15% of the lungs treated with the Toronto XVIVO had primary graft dysfunction, in comparison to 30% in the control group. Both groups had similar results in their secondary endpoints.

“The most important finding of this study was that even donor lungs previously thought to be unusable can now be used for transplantation with excellent outcomes. This will give us more lungs with more predictable, safer outcomes after transplantation, and shorter periods of mechanical ventilation and ICU stays for patients, said Dr. Cypel.

After the development of this system in Toronto, lung transplant centers in the United Kingdom, Austria, and Spain have started to successfully use this system, demonstrating that the procedure is reproducible. Drs. Keshavjee and Cypel estimate that the Toronto XVIVO System could potentially quadruple the number of transplants a year.
Mission Impossible?

Ventricular Recovery After LVAD, Heart Failure Medication and Clenbuterol in the HARPS Trial

In yesterday’s opening plenary session, Dr. K.D. Aaronson presented the featured abstract “Combination Therapy with Pulsatile Left Ventricular Assist Device, Heart Failure Medication and Clenbuterol in Chronic Heart Failure: Results from HARPS.”

In previously published work (BIRKS, NEJM), the combination of pulsatile LVAD, heart failure medication and Clenbuterol was associated with a high rate of ventricular recovery and successful LV assist device explantation in a single-center study. Patients included in that study were diagnosed with acute and chronic nonischemic dilated cardiomyopathy (NIDCM). This encouraging result led to the Harefield Recovery Protocol Study (HARPS) trial, a multicenter study which included 17 patients with NIDCM.

The protocol involved the implantation of the HeartMate XVE assist device and included administration of a maximal tolerated heart failure medication for 4 months (Phase 1). In Phase 2, patients were additionally treated with Clenbuterol for another 6 months. LVAD explantation criteria LVIDD<60mm, LVISD<50mm and LVEF>45%, PCWP<12mmHg, CI>2.4 and Peak VO2>16ml/kg/min. Results of the presented study showed that 4 patients had to be withdrawn prior to Clenbuterol treatment. Another 4 patients withdrew in Phase 2 due to death, myalgia or LVAD related complications. Of the 9 patients that remained on the protocol, only one patient showed LV myocardial recovery and underwent successful LVAD explants despite MVO2 of <10 ml/kg/min. All other patients were successfully transplanted.

Thus in the presented multi-center study, the vast majority did not reach LVAD explantation criteria. According to Dr. Aaronson, the reason for the discrepancy between the results of both studies remains unclear but could be related to the small sample size, difference in patient age, differences in racial response to Clenbuterol and a shorter duration of LVAD support.

Despite the limited success of the reported HARPS to recover ventricular function of NIDCM patients, the goal to provide the best available and most advanced medical treatment should remain a goal in treating patients with end-stage heart failure. Even if only occasional patients reach LVAD explantation criteria— for those patients it is not a “Mission Impossible,” but a “Mission Possible.”

Is Adding Everolimus and Lowered Cyclosporine dosing a Kidney-Protective Immunosuppressive Regimen?

During the Opening Plenary Session yesterday, Dr. Fiocchi presented Everolimus-based Immunosuppression versus Conventional Treatment in Long-Term Heart Transplant Patients: Three year Results of a Prospective Randomized Trial. The study was a randomized, prospective trial with 218 patients evaluating if a 75% reduction of CyA dose with the addition of Everolimus could improve renal function outcomes compared to standard cyclosporine dosing. He reported that after 3 years, an increase in creatinine was seen with conventional CyA group, but not with the Everolimus group. Additionally, there was a trend toward less lymphoma in the Everolimus group.

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### Everolimus, continued

However patients with albuminuria at randomization exhibited worse outcomes. In the remaining side effects of Everolimus were observed. This study suggests a logical approach to decide which patients might benefit from the alternative regimen.

Another study evaluating Everolimus, was Reduction of Cardiac Allograft Vasculopathy with Everolimus over Mycophenolate Mofetil: Intravascular Ultrasound Results of a Randomized Multicenter Trial, presented by Dr. Kobashigawa. This study used intravascular ultrasound (IVUS) to show a robust benefit with Everolimus relative to Mycophenolate Mofetil (MMF) at the end of one year. This study included 189 patients: 88 patients randomized to Everolimus at low dose of 1.5 mg/day and 101 randomized to MMF. There was no significant difference between the groups with regard to baseline demographics. “The fact that data was so robust in all IVUS parameters is very significant and clinically applicable” according to Dr. Kobashigawa. The data show that a significantly smaller percentage of patients had a change in intimal thickness greater than 0.5mm during the first year after heart transplant in the Everolimus group versus the MMF group. In addition to a benefit in intimal thickness there was also a significant improvement in three dimensional intimal volume in the Everolimus group. According to Dr. Kobashigawa, this data is crucial, because previous IVUS studies have shown high morbidity and mortality rates at 5 years in those patients with an increase in intimal thickness greater than .5 mm in the first year after heart transplantation.

### Are New Markers Helping to Diagnose AMR in Heart Transplant Recipients?

“Update on Pathological Diagnosis of AMR in Heart Transplantation” was the title of yesterday’s morning session chaired by Drs. Michael C. Fishbein and Claus B. Andersen. It focused on detection and relevance of C3d, C4d and donor-specific antibodies (DSA) and evaluated the significance in AMR.

As DSA are not always detectable in the blood of patients undergoing AMR, AMR is solely defined by pathologic criteria. However, it is believed that the detection of DSA during AMR episodes might be associated with worse outcomes in these patients.

In a provocative presentation, Dr. Kittleson from the Cedars-Sinai Heart Institute reported on a study analyzing 53 heart transplanted patients with treated AMR within the first year post transplant. In this cohort, 14 patients had circulating DSA, 39 did not. Results showed that 3-year survival and freedom from chronic allograft vasculopathy (CAV) and major adverse cardiac events did not differ between both groups, defined by the presence or absence of circulating DSA. Also, no difference in hemodynamic compromising rejection could be detected.

C4d has been well described as an important marker in the diagnosis of AMR. Little information is however available on the role of C3d and the utility of C3d to be used as a marker in identifying AMR.

Dr. M. Fedrigo, University of Padua, Italy, discussed biopsies from more than 100 heart patients that had been analyzed for C4d and C3d expression. Results revealed that 60% of the C4d+ biopsies also showed positivity for C3d. Biopsies being negative for C4d were also C3d- in 85%. C3d was detected in 54% of symptomatic and 60% of asymptomatic AMR. Dr. Fedrigo concluded that C4d and C3d have the same specificity and sensitivity in detection of AMR and that combined C4d and C3d positivity on myocardial capillaries did not increase the ability to identify DSA or diagnosed AMR.

Yesterday’s session on the diagnosis of AMR offered the latest results of studies on immunologic markers and analysis methods. The number of abstracts and also the lively audience participation reflects the interest in AMR, and the need to find robust, reproducible methods to diagnose AMR at an early time point, to identify which patients might benefit from treatment, and to help determine a safe and efficient therapy for the AMR patient.
Progress in Development of MCSD for Children

An Update on NIH PumpKIN Program

Promising new devices for mechanical circulatory support of children with heart defects or heart failure, and related research, was revealed yesterday. An update from the Pumps for Kids, Infants and Neonates (PumpKIN) Program was presented by J. Timothy Baldwin, PhD, during Mid-Day Symposium 4.

“Tremendous advances have been made in assist devices for adults, but there really are no devices for infants and children. The driving force of this program is encouraging development of such devices and sharing of information among developers,” said Dr. Baldwin. Baldwin supervises the PumpKIN consortium for the NHLBI branch of the NIH.

PumpKIN is supported by the NHLBI, which awarded four contracts in January 2010 to fund preclinical testing of these pediatric devices, including both miniature VADs and integrated compact ECMO devices.

According to Dr. Baldwin, the contractors are on schedule and making good progress. He said the miniature pediatric devices are based on the latest technology for VAD and ECMO devices. The preliminary data presented suggested that these devices and technology have great promise to perform well in future pediatric patients, based on work ongoing at the PumpKIN study centers.

Currently Available Risk Assessment Tools Should Assist, But Not Rule, Treatment Decisions

The HeartMate II Risk Score: Predicting Survival in Candidates for Left Ventricular Assist Device Support

Probably every doctor, taking care of critically ill patients has a some point been asked “Doctor, how long can I live?” or “...how are my chances to survive?” Especially, patients that have time to think about their situation and that can feel the loss of strength and their own illness getting worse, will want information on their life expectancy without surgery and their survival chances with a procedure.

In the session “VADs Shift the Paradigm: From Cold and Wet to Warm and Dry” chaired by Drs. Katherine Lietz and Tobias Deuse, Dr. Jennifer Cowger presented a survival model for Heart Mate II (HMII) LVAD candidates that might be useful for risk stratification of those patients.

In an analysis of more than 1100 HMII recipients, patients were randomly divided into a derivation and validation cohort. Using multivariable predictors (preoperative clinical, laboratory, and hemodynamic predictors) were used to divide patients into low, medium and high risk group in the derivation cohort. Interestingly, as a result, the only preoperative predictors of long time survival (>90 days) were the patient’s age and the implant center experience. Nutrition albumin preop INR, and creatinine were only found to be important prognostic factors in univariate analyses.

Following the presentation, a discussion about the application of risk scores brought up the question whether a patient showing high risk and only low long time survival probability in a risk score should still receive the “expensive chance” of a LVAD. As a very important message, Dr. Cowger stated that the decision about a patient’s treatment should still be a clinical, patient-based decision by the treating doctor, and that risk scores can only be a helpful tool in the individual decision for that patient and their caregivers.

You’re Invited

The President’s Gala Reception will be held this evening from 8:00pm – 10:00pm in the Sapphire Ballroom and the lovely outdoor terrace. Don’t miss the stunning views of the San Diego Bay and sunset.

Entertainment will be provided by local band, Rockola. Put on your dancing shoes and enjoy the ambience, camaraderie and fun!

Additional tickets may be purchased for $75 at the Registration Desk.

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