



Kim Anderson, MD, FRCPC
Advanced Heart Failure,
Mechanical Circulatory Support
and Transplantation
Toronto General Hospital
Kim.anderson@mail.utoronto.ca



Farooq Sheikh, MD, FACC
Advanced Heart Failure, Mechanical
Circulatory Support and Cardiac
Transplantation
MedStar Washington Hospital Center
Fsheikh22@gmail.com

Reviews:

The 36th ISHLT Annual Meeting/ Scientific Sessions held in Washington D.C. in April offered a deal of information and knowledge to please MCS clinicians and researchers. Along with multiple retrospective studies from registries, exciting experiences from multiple centers on new therapies and new devices were presented. Many amazing sessions with debates and discussions gave us the opportunity to rethink our own practices and exchange experiences. Tremendous speakers and funny session titles also made us laugh throughout the whole meeting. For this What's New in MCS edition, we prepared a summary of the MCS highlights from the last ISHLT meeting.

Anticoagulation... too thick or too thin?

Monitoring

- Monitoring LVAD patients for device thrombosis with early intervention when suspected has important implication; LDH 2.5 times the normal value was associated with stroke in 50% of patients at 6 months. Moreover, devices' log files hold yet unrealized potential to help us catch this life-threatening complication earlier.
- Keeping the anticoagulation on target isn't always easy but worth the work; patients who had out of therapeutic range INR during their LVAD support had worse outcomes, even if the therapeutic range was individualized per patient.
- Patients with increased warfarin sensitivity associated with genotype variants (CYP2C9 and VKORC1) had higher risk of early GI bleed but also device thrombosis on continuous flow LVAD in the retrospective study presented. The investigators' centre now adjusts the warfarin dosage according to patient's genotype. They hope that guiding the dosage could help to prevent overshoot with subsequent hold on warfarin and subtherapeutic INR especially in the early period after the LVAD implant.
- Could patient anticoagulation self-management be a solution? With feedback and supervision it seems promising with higher time spent in the therapeutic range. Correlation between laboratory and home INR monitoring (CoaguChek) is good but not perfect. Finally, experiences from different countries must be interpreted with caution as different agents with variable half-life are used.
- The best heparin monitoring depends on multiple factors having impact on the coagulation cascade. Since there is no prospective outcome data to guide us, differences exist between laboratories and hospitals, anti-FXa and aPTT correlate poorly in available literature ($r=0.2$ to 0.7) and multiple patients specific factors potentially interacting with assays need to be considered, a combination of tests may be more appropriate. Currently, aPTT seems to be the most frequently used monitoring test.
- Genetic screening for thrombophilia is currently hard to advocate with conflicting data on the advantage of tailoring therapy and the low prevalence of genetic inherited thrombophilia.

- Topkara and colleagues showed that aspirin responsiveness (as estimated by a turbidimetric based optical assay) was highly variable in LVAD recipients. This assessment of platelet function/reactivity was associated with an increased risk for mucosal bleeding (GI hemorrhage or epistaxis). Interestingly, the incidence of pump thrombosis did not differ between aspirin sensitive and aspirin-insensitive patients. A small study from the University of Utah highlighted the potential role of platelet phenotyping (platelet isolation from peripheral blood with subsequent RNA-sequencing and transcriptional analysis) to identify which LVAD recipients may be predisposed to bleeding or clotting.
- Antiplatelet monitoring is not quite yet for prime time for clinical use. Many assays exist but none stands out as being very reliable and precise, in fact some did very poorly.
- The use of prothrombin-concentrate complex (PCC) in LVAD patients undergoing cardiac transplantation does not appear to increase the risk for thromboembolic events or inhospital mortality based on a retrospective study from Montefiore Medical Center (Albert Einstein University). Blood product use and cardiopulmonary bypass time were reduced in LVAD patients who received PCC compared to those who did not.
- Aortic root thrombus (ART) formation is common in LVAD recipients according to a single center study from Columbia University. Six percent of LVAD recipients developed ART which the 74% of the patients developing ART within 30 days of LVAD implantation. ART patients had a higher risk of stroke and MI. The investigators recommend close surveillance to avoid this potentially serious complication.

New treatments for a well-known complication

- As our understanding of the bleeding events in continuous-flow supported patients evolves, our treatments are more selective. The target is now toward the angiogenicity brought up by the loss of pulsatility and destruction of high molecular weight von Willebrand factors.
- Octreotide is used by multiple centers in patients with recurrent bleedings; one group shared with us their experience. The number of bleeding events was significantly reduced as well as the number of blood product and GI procedure when comparing the patients before and after receiving octreotide treatment. The intramuscular long-acting formulation was used with an overlap of subcutaneous formulation for the first 8 weeks without any complication.
- Danazol, a synthetic steroid having inhibitory properties on angiogenesis has also been tried in LVAD patients with GI bleeding. In a retrospective analysis from the combined cohorts of two centers, a reduction in the number of hospitalisation related to GI bleeding and a reduced use of pRBC in 69% of patients were observed. Therapy was discontinued in a small number of patients because of secondary effects.
- Finally, newer agents are tested in vitro (such as the vorapaxar); we might see them appear in clinical trials in the future.

Pump Thrombosis: What's Hot with the Clot

- A number of single center studies shed important light on the characteristics, diagnosis, and treatment of LVAD pump thrombosis at this year's scientific sessions.
- A large single center retrospective study from MedStar Washington Hospital Center demonstrated that pump thrombosis remains a common complication of MCS therapy (12% of patients during the study). Surprisingly, medical therapy for pump thrombosis was successful in treating this condition in more than 50% of cases. Overall survival of patients with pump thrombosis was 83% in this study.
- New insights into the types of blood flow obstructions that can occur with the HeartWare HVAD were elegantly presented by Scandroglio and colleagues. In an analysis involving 524 LVAD patients (652 HVADs), the group showed that HVAD recipients had 3 types of thrombotic events that led to blood flow issues: pre-pump due to thrombus obstructing the inflow cannula, intra-pump, and post-pump due to clot in the outflow graft or stenosis if the anastomosis to the

aorta. On this basis of this insight, the group employed a diagnostic algorithm using different treatment strategies for each type of obstruction which yielded excellent results.

- Additional data regarding the discordance between aPTT and anti-Xa levels was presented by Columbia University. The presence of hemolysis (as evidenced by elevated LDH) did not affect this discordance.

Infectious Complications in MCS

- Infections remain a significant source of morbidity and mortality in LVAD patients despite a reduction in this adverse event as evidenced by the INTERMACS registry.
- Individual centers have trialed and tested various strategies to reduce the risk of driveline-related infections with various degrees of success (alterations in dressing type, infection surveillance, etc).
- Barbara Cagliostro from Columbia University presented compelling data regarding the usefulness of a standardized driveline-exit site (DLES) care kit (that included silver gaze dressing and an anchoring device) in reducing the risk for infection. When compared to their institution's prior DLES dressing, the implementation of the standard kit resulted in a significant reduction in the absolute risk of DLES infection (11%) and 1 year freedom from infection.
- Abstracts from the University of Maryland and Hamburg highlighted the value of PET imaging in the diagnosis of VAD-related infections.
- Washington University (Taghavi et al.) presented a large single center experience regarding surgical management of driveline infection (DLI). Over the course of 6 years, ~10% of LVAD recipients had culture positive DLI and required surgical driveline revision. 52% of these patients cleared their infection. One year survival post-VAD was 96%. No deaths were seen in the group of patients that went on to heart transplantation (29% of the cohort with median follow up of 4 years).
- The University of Michigan Cardiac Surgical Team (Abou el ela et al,) presented data regarding the utility of pump exchange to treat major driveline and pump pocket infections. Actuarial 1 year survival after device exchange was 95% with increased freedom from recurrent infection.
- The UCSF advanced heart failure (Psootka et al.) presented a fascinating single-center study that demonstrated the utility of using a thoracic driveline exit site to reduce the risk of device-related infection.

Success stories and lessons learned from LVAD programs all around the world

Volume overload is not only about fluid but also the rising number of LVAD patients and unfortunately Lasix won't help in that case

- Plan ahead: for each additional 20 LVAD in your center, you need to re-evaluate your resources. Involve people and talk to your stakeholders, track and measure what you do so you can evolve and don't hesitate to participate in trials and benchmark programs. The website myLVAD.com contains many great tools shared by other teams; worth giving a look!
- Multidisciplinary teamwork with an integrated approach is essential but challenging at times. We have lessons to learn from other domains where good decisions must be taken consistently and effectively in a complex and changing environment under high level of stress. Leadership strategy, transparency, conflict management are key.

How to provide efficient care to LVAD patients living far far away?

- Empowering the patients is key; let them teach their local physicians and community. Making it clear right from the beginning, before the implant that the patient will be the one taking care of his own LVAD. Having a companion caregiver is not even required by some center. Of course, selection and education of patients is crucial, particularly in those living in remote area.

- Take advantage of what is already available in the patient's local community, keep it simple and delegate some of the care that can be done locally with clear guidelines, such as INR follow-up.
- Pre-emptive training of communities might not be efficient and worth the time and energy. Depending on the size of the communities and number of LVAD living there, different approach and degree of LVAD training can be offered (VAD training vs. VAD awareness) and the level of competence required can also vary between centers and their role in LVAD patient care. Individualizing the discharge process is key!
- But what if serious problem happen? Some centers will transfer the patient for any inpatient admission, some only if it is a repeated admission as worse outcomes are observed with repeated admission in a remote center. Supporting the local medical team with 24h telephone availability is recommended and pre-emptive communication with emergency services is done by some centers.

Advantages to get the patients back in their own home community are numerous. It is safe and possible but would be easier with technologic improvements including wireless real-time transfer of log-file and waveform. Hopefully this message will get to the ears of the engineers designing future LVADs...

The patient's life after an LVAD

- LVAD delivers cardiac output effectively but the functional capacity and quality of life don't necessarily follow-up and are in fact quite static post-implant. The literature is variable as is the rehabilitation offered post-implantation in different regions. Overall, survival is better in patients with good functional capacity and/or quality of life but worse if both are poor. For an optimal shared decision making and managing patient's expectations, these limitations of current LVAD should be discussed preoperatively with patients. Success of rehabilitation to improve objective markers of functional capacity is a consistent finding but many centers worldwide don't have access to exercise training program for LVAD patients.
- Newer data from post-hoc secondary analysis of the ENDURANCE trial reported an improvement in quality of life measured with KCCQ questionnaire and 6-minute walk test at 2 years in patients who received a HeartWare as destination therapy. Data from Intermacs registry also showed a statistically significant improvement in quality of life of patients at 2 years post-implant compared to pre-implant, regardless of the implant strategy. However, the gains in event-free survival and quality of life at 1 and 2 years with LVAD implantation were significant only in those with a VAS score <60, in secondary analysis of the ROADMAP trial. Generic and disease specific measurement instrument of quality of life seem to perform similarly, however none of them are designed to capture the specific issues of LVAD population.
- Can flow help anxiety and depression? They both improved post-LVAD implant in a pilot study presented during the meeting, but some of these symptoms are closely related to heart failure improvement. Next steps are to extend these observations in patients with baseline psychiatric disorder such as depression, which were not included.
- Does improvement in quality of life of patients comes at the expense of caregiver? Maybe not as much as we used to think according to one study presented where no or very little caregiver burden difficulty at 9-12 months post-implant was observed. However, the unicentric design, absence of control group and exclusion of non-English speaking subjects warrant some caution in the interpretation of the results.
- Finally, the common conception that LVAD patients are always in hospital is now challenged. Majority of patients were admitted only once after their implant, but still 26% were admitted at least 4 times in this unicentric retrospective analysis. Most common reasons for admission were bleeding, infection and arrhythmia. Terminal readmission was low in this center, observed in

only 3% of patients but it is important to notice that they had access to hospice care for dying LVAD patients.

Between a rock and a hard place: tough decisions

Even though there is no perfect answer to these challenging cases, we still need to take the good decision when the situations presents.

- Room was quite divided when reviewing heartbreaking candidacy evaluation for heart transplantation and MCS.
- Should heart failure be treated as a titanium deficiency after 70 years old and DT LVAD be the solutions? Or allowing transplant at an older age using marginal donors, knowing that nearly half of organs are discarded and older recipients have better adherence and psychosocial adjustment to transplantation and less rejection according to recent UNOS data? Though debate, with good arguments on both sides.
- Is it now the time to implant LVAD in Intermacs 4-7? The sicker is the patient at time of implant, the worst are the outcomes. However, there is currently no proven survival benefits associated with earlier implant in patient Intermacs 4-7. With the high rate of adverse events associated with LVAD, watchful waiting of patients on optimal medical therapy is opted by some.
- Mini or maxi? Sternotomy or small thoracotomy? Some technical improvements are still required to allow minimally invasive LVAD implant works better but the team in Hannover showed us very convincing data on the advantages and feasibility of this technique. An anterolateral thoracotomy with small sternotomy approach was used in more than hundred LVAD implants with success. Ideally, this should be evaluated in a prospective randomized controlled trial not biased by implant indication or surgeon preferences, as this technique is still off-label.

Recovery

The role of inflammation and fibrosis in the recovery of patients supported by LVAD has got much attention recently. However the path to recovery is complex with multiple mechanisms involved. We certainly do not understand it all but knowledge is growing with all these efforts made by the community.

- Prediction of recovery is complex but prediction models are evaluated: an Intermacs recovery score was presented with up to 25% chance of recovery in patients with the highest score.
- Anakinra, an IL-1 receptor antagonist, was studied in a small group of LVAD patients and did not show any increased risk of infection. A sustained decline in CRP was observed. Its effects on inflammation parameters and remodelling in LVAD recipients will need to be studied in a randomized-controlled trial.

Bright shiny toys for good girls and boys: looks like we have been good this year!

- It is with great pleasure and excitement that we finally heard the results of the Jarvik2000 bridge-to-transplant trial that started in 2005. It is undoubtedly one of if not the longest FDA's trial and many improvements were added to the device since enrolment started. The cone bearing pumps seems to perform better than the earlier pin bearing version, with 91% of patients alive or transplanted at 180 days versus 63%. A total of 150 patients were included, with 128 having the pin bearing device, which makes comparison of the two devices somewhat difficult. Important differences with current LVAD trials should be noted; near 60% had a left

thoracotomy approach with majority of anastomosis in the descending aorta and the population seemed sicker at baseline than in other LVAD trials (90% of patients were on more than 1 inotrope before implant and 1/3 had an IABP).

- The HeartMate 3 experiences from many countries were discussed with encouraging results. CE Mark Trial and post-trial data show a survival of more than 90% at 6 months, with implant for destination therapy in near 1/3 to 1/2 of patients, depending on cohorts. No pump malfunction and no pump thrombosis were reported but 1 outflow graft thrombosis was seen in the context of infection. Comparison between different LVAD trials should be done with caution but safety profile of this new device appears promising. Could the artificial pulse technology of the HeartMate 3 reduce some of the bleeding complications associated with continuous flow LVAD? One group presented us their data on von Willebrand factors evaluation in patients with HeartMate 3 compared to those with HeartMate 2. The former had statistically significantly more preserved high molecular weight von Willebrand factors. We are therefore awaiting further information from the MOMENTUM trial.
- The open chest 3D voltage mapping system (EnSite Velocity) is an interesting gadget that our electrophysiologist colleagues could enjoy in our LVAD patients. This system was used to visualise the voltage and activation timing in 21 patients at time of their LVAD implant with no complications. A higher burden of scar was observed in those who later presented with ventricular arrhythmia.

Pimp my Pump: Novel MCS Design and Management

- The clinical significance of invasive hemodynamic studies in LVAD recipients was highlighted in an elegant study by Abdullah and colleagues from the INOVA Heart and Vascular Institute. The group sought to compare the unloading characteristics of the HMII and the HVAD by performing ramp studies while obtaining right heart catheterization measurements. The team was able to correlate the impact of speed changes with the HVAD device to the HMII. Interestingly, the HVAD recipients had a significant drop in pulmonary capillary wedge pressure (PCWP) with speed increases which was not seen in the HMII recipients. The study will likely serve as one of the first of a series of important insights gained by invasive hemodynamic assessments in this field.
- The HVAD waveform was shown to be a surrogate marker of cardiac index and PCWP in a seminal work by the University of Chicago Advanced Heart Failure Team lead by Nir Uriel. In this study, hemodynamic measurements were obtained via invasive ramp study and the data was compared to a mathematical analysis of the HVAD screenshot. The investigators have developed a new parameter known as the ventricular filling phase slope (VFP) that was derived from the HVAD waveform. The VFP was shown to non-invasively predict high PCWP and low cardiac index (CI).

RV failure

- Multiple attempts at developing a model predicting RV failure post continuous flow LVAD implant are made but limitations persist, perhaps mostly because good RV assessment data are simply lacking in this population.
- In a retrospective UNOS registry analysis, patients bridged-to-transplant with the Thoratec PVAD compared to total artificial heart (TAH) seemed to have similar short-term survival but less multiorgan failure and rejection. The retrospective nature of this study design raises concern of biased results and the audience was not ready to take the PVAD out of museum where it now stays. An INTERMACS registry analysis showed us that TAH is implanted in patients significantly sicker than those with continuous flow LVAD as bridge-to-transplant, with

near 40% in Intermacs 1 in the former versus 10% in the latter. Center experience seems to play a key role in survival after TAH implant: 76% at 6 months in centers with >10 TAH implanted versus 50% in those with 10 or less.

- Early results of biventricular support with durable centrifugal assist device are encouraging. Reporting of biventricular devices implant and outcomes in registries is extremely important to help the community to learn from experiences and further improve care of these very sick patients. A key message was sent: centers are strongly encouraged to report their experiences even if this procedure is still considered off-label.

Too Much of Bad Thing? Complications after Mechanical Support

- The ENDURANCE Clinical Trial Investigators (Comparison of HVAD to HMII for destination therapy) assessed temporal changes in adverse events (AEs) in this study. Their hypothesis was that HVAD patients enrolled later in the final third of the study would have fewer AEs given changes in the trial "conduct" (i.e., changes in management protocols). HVAD recipients enrolled in the final third of the study had no significant differences in AEs such as hemorrhagic stroke, right heart failure. The need for device exchange was less frequent in these HVAD patients compared to HMII patients. It is important to note that the full analysis of this clinical trial has yet to be released.
- The risk of stroke remains a substantial source of morbidity and mortality in LVAD recipients. Investigators from the University of Alabama-Birmingham (Acharya et al, abstract 3) evaluated all CF-LVAD recipients in the INTERMACS registry (n=12,375). Ten percent of these patients suffered at least 1 stroke with a median follow up of 11 months (incidence rate 0.08 strokes per patient-year). Patients who suffered a hemorrhagic stroke had a worse 30 day survival than those who experienced an ischemic event. Multivariate analysis revealed female sex and more recent year of implantation as predictors of any stroke. The investigators were also able to identify individual predictors of hemorrhagic and ischemic stroke respectively.
- Sustained ventricular arrhythmias (VA) are common in LVAD recipients. A single center retrospective study from the Netherlands (abstract 6) demonstrated that 30% of LVAD recipients experienced VA. The presence of VA did not adversely impact survival.
- Interestingly, Columbia University investigators presented a single center retrospective study that showed that patients without an active defibrillator (ICD) following LVAD implantation are not at increased risk of death when compared to those with an active ICD. It is important to note that the number of patients in this study without an ICD were only 12%.

Its Tough to Make Predictions, Especially about the Future: Outcomes and risk factors in MCS

- We were happy to see that physician gestalt is still valuable in predicting death of ambulatory patients with advanced heart failure; however the need for stage D heart failure therapy was more difficult to predict.
- The ROADMAP investigators presented the 2 year results of the pre-specified primary endpoints of the study. To review, ROADMAP was prospective, multi-center, non-randomized observational study of 200 ambulatory NYHA class IIIB/IV patients who were not dependent on inotropic therapy. Two year as treated on original therapy survival was greater for LVAD recipients (70±5%) vs. the optimal medical management (OMM) group (41±5%, P<0.001). There was no difference in survival by intention to treat analysis. LVAD adverse events declined at 2 years (when compared to the initial 12 month analysis). Measures of quality of life (QOL) were higher in LVAD recipients vs. OMM patients.

- Dr. Robert Kormos and colleagues analyzed the INTERMACS Registry in attempt to identify predictors of futility in LVAD therapy using Classification and Regression Tree (CART) analyses. The strongest discriminator of in-hospital mortality in the INTERMACS Registry was the need for RVAD therapy at the time of LVAD implantation. Additional discriminating variables included older age and the need for pre-operative dialysis.
- Morbidly obese (BMI >35) LVAD recipients do not appear to have an increased risk for death after heart transplantation based on a single center analysis from the Virginia Commonwealth University. In their single center study, morbidly obese LVAD recipients had an increased risk for bleeding requiring reoperation and driveline infection, however, heart transplant survival did not differ between patients with a BMI >35 (n=36) and BMI <35 (n=121). The follow up time was 2.3±1.6 years after cardiac transplantation. Interestingly, a separate large study utilizing the UNOS database from the Cleveland Clinic showed that obese LVAD patients (BMI >30) did not experience worse wait-list survival.
- Red cell distribution width added slightly to the predictive power of the HeartMate II risk score in the unicentric retrospective analysis presented.
- Obesity in heart transplant candidates supported by LVAD is not a small problem; in UNOS registry only 15.5% of them were able to decrease their BMI while on support. Even though there was no significant difference in the rate of delisting or death while on support, they had a longer median waiting time, more graft dysfunction post-transplant and a trend toward increased risk of infection and thromboembolism while on LVAD support.
- Patients bridged to transplantation with HeartWare HVAD and HeartMate II had similar rates of complications post-transplantation and survival in analysis up to 2012.
- Ischemic heart failure aetiology was associated with an increased risk of neurologic events after LVAD implant but not on other outcomes after accounting for confounders.

Pediatric Mechanical Circulatory Support

- Preliminary data regarding HeartWare HVAD use in pediatric patients around the world was presented. Data was obtained via survey. The mean age of recipients was 12.2±3.9 years. A total of 99 implants were analyzed in this study. The median duration of LVAD support was 80 days. Forty-seven percent of patients were discharged. The need for temporary RVAD support and pump exchange were factors shown to increase the risk for death on the device. At 12 month follow up, 46% of patients had been transplanted or weaned from therapy. Forty-four percent remained on HVAD support and 10% had died.
- PediMACS is a NIH-funded national VAD registry that contains clinical data on MCS patients implanted before age 19. Data regarding utilization and outcome of children undergoing temporary VAD therapy was presented. The majority of recipients had an underlying cardiomyopathy (59%). Congenital heart disease patients represented 37% of the recipients. The majority of patients had an INTERMACS profile 1 status at the time of implantation. Most recipients received a LVAD as the MCS therapy (76%). The majority of pediatric temporary MCS recipients (75%) had a favorable outcome which was defined as bridge to recovery or transplantation or alive on device or transition to durable device. Unsurprisingly bleeding was the most common adverse event seen in this cohort.
- The PediMACS registry also served as the data resource for an analysis of infectious complications in pediatric durable MCS recipients. Infectious complications occurred in 18% of recipients. The data consisted of 222 durable VAD implants in 200 patients (91 patients had a pulsatile device, 109 patients had a continuous flow device). The median follow up was 2.3 pt-months and the mean age of the recipient was 10±6.5 yrs.