Invited Review

What Did We Learn about VADs in 2017?

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Introduction

The field of mechanical circulatory support is evolving rapidly and new data are published at a rate which can be overwhelming. For the last three years, we published annual reviews of the current literature entitled "What Did We Learn about VADs?" in the past year (1-3). All three papers were well received as the full texts were downloaded 704, 676 and 413 times, respectively, by the readers around the globe. Continuing the tradition, we have written the present review and as with all previous reviews, we summarized some publications from 2017 that we think are of particular importance and interest. There may be some slight overlap with the end of 2016 due to some papers having been published online first.

For the first time this year we added a section on extracorporeal membrane oxygenation (ECMO), primarily addressing new developments in the veno-arterial (VA) ECMO. We plan to make it a regular feature of these reviews.

Readers who wish to supplement this review or to argue with the author's statements or article selection are encouraged to do so by sending letters to the editor or posting on our Facebook page at https://www.facebook.com/TheVADJournal. Comments are welcome via the link "Readers comments" on our homepage http://uknowledge.uky.edu/vad/.

HeartMate 3

In August 2017, HeartMate 3 (HM3) (Abbott, Abbott Park, IL) was approved by Food and Drug Administration (FDA) as a bridge to transplantation. As we are awaiting further results from the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate3 MOMENTUM 3), a randomized trial comparing HM3 and HM2 (Abbott, Abbott Park, IL), new information about this pump has been accumulating.

The outcomes continue to be encouraging. In a single-center study, survival on HM3 was 88.9% at 30 days and 85.2% at 6 months. During this time no strokes were observed (4). Per previous reports, six month survival was 92%, with a 12% stroke rate (5). In the MOMENTUM 3 survival without stroke or pump replacement was 86.2%. Remarkably, no pump thrombosis or pump exchanges occurred in any study (6) .

One-year outcomes have already been reported from the European HM3 study and are consistent with 18% mortality, 18% strokes, and 2% outflow graft thrombosis. There were no cases of pump thrombosis or pump malfunction (7) .

The 2% outflow graft thrombosis represents a single patient and was a true thrombosis with embolization to the brain. This is worth explaining because there was also a report of HM3 outflow graft stenosis by extraluminal thrombotic masses accumulating between the bend relief and the outflow graft, which was diagnosed by direct inspection during subsequent heart transplantation (8). Also, late post-pump stenosis due to twisted outflow graft was reported (9). Finally, there was a report of HM3 thrombosis triggered by a shock from an automatic implantable cardioverter defibrillator, triggering the release of a left ventricular (LV) thrombus which was sucked in the left ventricular assist device (LVAD) inflow cannula (10).

There is already an experience of exchanging older pumps, both HM2 and HeartWare, to HM3 (11).

Hemocompatibility of HM3 was systematically studied in the MOMENTUM 3 trial, where the freedom of the combination of nonsurgical bleeding, thromboembolic events, pump thrombosis, or neurological events was 69% of the HM3 group and 55% of the HM2 group (hazard ratio (HR) 0.62; confidence intervals (CI) 0.42-0.91; *P*=0.012). Specifically, patients on HM3 had less pump thrombosis and nondisabling strokes (12).

HeartWare

In October 2017 HeartWare (Medtronic, Minneapolis, MN) was approved by FDA for destination therapy. This happened after the publication of the prospective, randomized, controlled, un-blinded, multicenter clinical trial to Evaluate the HeartWare Ventricular Assist System for Destination Therapy of Advanced Heart Failure (ENDURANCE) comparing safety and effectiveness of the HeartWare pump with HM2.

The Kaplan–Meier estimates of survival free from disabling stroke or need for device replacement at 2 years, which was the study primary end point, were 55.0% for HeartWare and 57.4% for HM2 (not significant) and met the criteria for non-inferiority. The Kaplan–Meier rate of overall survival at 2 years was 60.2% in the HeartWare group and 67.6% in the HM2 group (P = 0.17). The rates of major bleeding, cardiac arrhythmias, renal dysfunction, and infections, including percutaneous drive-line infections were similar on both devices; however, there were more strokes on HeartWare than on HeartMate II (29.7% vs. 12.1%, P<0.001). On the other hand, more patients in the HM2 group than in the Heartware group had device malfunction or required pump replacement (16.2% vs. 8.8%). Quality of life and functional capacity improved to a similar degree in the two groups (13).

A post hoc analysis of HeartWare recipients revealed that mean arterial blood pressure measurements of ≤90 mm Hg were associated with a lower frequency of strokes, particularly hemorrhagic strokes.

Fortunately, the rate of adverse events on HeartWare decrease with time. The analysis of the HeartWare Ventricular Assist Device for the Treatment of Advanced Heart Failure (ADVANCE) Bridge to Transplant trial and continued access protocol found that there were significantly fewer total adverse events after first 30 days post implantation with the lowest rates after six months. For instance, rates of hemorrhagic strokes decreased from 0.23 events per patient-year in the first 30 days to 0.08 after 30 days and up to 6 months, 0.09 between 6 months and one year, and 0.06 after the first year. Additionally, the corresponding decrease in ischemic strokes was 0.36 to 0.05 after 30 days and remained unchanged thereafter (14).

 An excellent analysis of HeartWare waveforms was published by Rich and Burkoff.(15) They presented changes in the morphology of waveforms in multiple clinical scenarios including blood pressure changes (a low flow, high-pulsatility waveform in hypertension versus high-flow, low-pulsatility waveform in relative hypotension due to excessive vasodilatation), arrhythmia, abrupt or gradual pump thrombosis, suction events, etc.

Importantly, it appears that HeartWare waveforms can be used for noninvasive assessment of hemodynamics. As described by Grinstein et al.(16), the slope of the ventricular filling phase on the HeartWare waveform correlates

with pulmonary capillary wedge pressure (PCWP). Specifically, the slope was significantly steeper in patients with the wedge pressure ≥ 18 mm Hg than in patients with PCWP < 18 mm, and the slope threshold of 5.8 L/min/s predicted a wedge pressure ≥ 18 mm Hg with a sensitivity of 87% and specificity of 95% (area under curve 0.95).

Outcomes

According to the 8th annual INTERMACS report, overall survival while on LVAD support continues to remain 81% at one year and 70% at 2 years. There is an increasing proportion of implantations in lower risk profile 3, stable inotrope-dependent patients, which currently account for 38% of new implants. Analysis of causes of death on LVAD support showed that in the first 6 months after surgery patients die from multisystem organ failure, right ventricular (RV) failure, and strokes (ischemic or hemorrhagic). After the first half a year stroke dominates as the major cause of death. The biggest contributor to early mortality is the need for right ventricular assist device at the original operation, with a hazard ratio of 3.76. Patients who undergo surgery while being in cardiogenic shock have a two-fold or greater propensity for severe RV failure comparing to more stable patients. On total artificial heart support, one year survival remains less than 60% (17).

When the INTERMACS data were stratified by center volume the worst survival was observed at very low volume centers, performing ≤10 implants a year, and the best at medium volume with 30 to 50 LVAD implantations per year (18).

There was also a report of a single-center study with the data on 5-year survival of patients on HM2, which was 54% (19).

Interesting analysis of adverse events on two different VADs, HM2 and HeartWare, summarized the experience of several institutions and included hundreds of patients. Overall mortality was similar (7.3% and 7.5%), as were the rates of gastrointestinal (GI) bleeding (P =0.63), any infection (P =0.32), driveline infection (P = 0.10), and pump thrombus (P =0.64). At the same time, HeartWare was associated with higher risk of stroke (HR: 1.8, [1.25, 2.5], P = 0.003). Because of a major manufacturing change in the sintering of the HeartWare in August 2011, authors analyzed cumulative incidence of stroke for patients who were implanted with the HeartWare before and after this change, which was 36% and 28%, respectively, the difference not being significant (20).

Recovery

In terms of myocardial recovery on LVAD support, there was more skepticism than optimism in 2017. Farris et al. (21) studied the samples of cardiac muscle before and after several months of support on LVAD and found no difference in capillary density, cardiac fibrosis, or macrophage density. On the other hand, there was a very significant, almost 17-fold, decrease in fibroblast-specific collagen expression. This shows that despite the normal appearance of the ventricle,

achieved with mechanical unloading, there is persistent abnormal gene expression. Reversal of the geometric alternations by mechanical unloading does not equate to reversal of the cellular and transcriptional machinery to normal, as stated in the editorial suggesting that recovery may be an illusion (22). The same editorial introduces the term "heart failure remission" rather than recovery.

Candidate selection

The ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management) was a prospective, multicenter observational study of 200 patients (97 LVAD, 103 medical management) who had at least one hospitalization for heart failure (HF) in the last year and walked less than 300 m on 6-min walk, i.e. were functionally limited but not inotrope-dependent. They can be managed by either medical therapy or LVAD based on subjective factors. Although patients who opted for LVAD were sicker at baseline, the primary endpoint, survival with improvement in 6 minute walk distance by more than 75 m at 12 months, was achieved by 39% patients on LVADs versus 21% on medical management (OR 2.4, p = 0.012). Survival per se was also greater for LVAD versus medical management (80 ± 4% vs. 63 ± 5%; p = 0.022). Even despite more hospitalizations on LVADs, mostly for GI bleedings, quality of life improved greater than in the medical arm (23). In 2017, two-year outcomes of the ROADMAP were published (24). They were very consistent with the one-year outcomes of 30% patients on LVAD versus 12% on medical management survived with improved functional status (odds ratio: 3.2 [95% CI: 1.3 to 7.7]; p = 0.012). Survival as treated on original therapy at 2 years was greater 70 ± 5% for LVAD versus 41 ± 5% for medical management, p < 0.001. In the medical arm, 22% received delayed LVADs. Also, LVAD-related complications declined after one year on support (24).

Shah et al.(25) stratified the ROADMAP population by INTERMACS profile and demonstrated that patients who benefited from LVADs, in terms of both survival and functional status, had profile 4 ("resting symptoms on oral therapy"), while in profiles 5,6I, and 7 ("exertion intolerant/exertion limited/tolerates minimal exertion") medical management may be sufficient.

Basically, this study means that many INTERMACS class 4 patients, or the first class of patients who are not inotrope dependent, can benefit from LVAD support.

Frailty

Frailty before destination LVAD implantation is associated with increased risk of death (26), however in 50% to 90% of patients, frailty at least partially reverses in six months on LVAD support (27, 28). Caution is needed before denying LVAD implant due to frailty.

Pulmonary function

Most centers do routine pulmonary function testing prior to decision on LVAD candidacy. However, no established parameters exist in order to accept or not to

accept the patients for LVAD based on the results. When patients were stratified in five groups by forced expiratory volume in one second and diffusing capacity for carbon monoxide, ranging from <40% predicted to normal, there was no association with survival and no difference in mortality at 1 and 3 years between the groups. Only diffusing capacity of the lungs for carbon monoxide was associated with increased intensive care unit length of stay in the group analysis (P =0.001). Ventilator times, postoperative pneumonia, reintubation, and tracheostomy rates were similar across the groups. These findings suggest that abnormal pulmonary function tests alone should not exclude patients from consideration of mechanical circulatory support (29).

Adult Congenital Disease

Adult patients with congenital heart disease are rarely supported with long-term VADs. In the INTERMACS, 128 such patients were identified. Comparing with propensity-matched cohort, they have longer hospital stay, higher mortality, especially in the first 5 months after implantation, and lower probability of receiving a transplant (p = 0.003). Risk factors for early mortality were biventricular support with two VADs or total artificial heart device implant and age > 50 years old (30).

Survey of LVAD programs

Many programs implanting LVADs, struggle with the same questions and there is no literature to guide decision-making. A break-through paper by Kilic et al. (31) was published in our journal. It appeared, for example, that current practices in candidate selection with regards to substance abuse stand as the following: require abstinence from marijuana, but not tobacco 11%, require abstinence from tobacco, but not marijuana 2%, require abstinence from both 42%, do not require abstinence from either 38%, and have a don't ask/don't tell policy 6%.

Management of patients on LVAD support

Hemodynamic optimization

In the past issues of this annual review, we extensively covered the topic of incomplete hemodynamic compensation and residual LV failure after LVAD implantation. In 2017, new evidence was presented showing that right heart catheterization three months after the LVAD implantation was abnormal, with decreased cardiac index or elevated pulmonary capillary wedge pressure or both in almost 30% of the patients. With ramp test, normalization of hemodynamics was achieved in 68% patients with initially abnormal hemodynamics. This resulted not only in better hemodynamic parameters but in increase in 6 minute walk distance (32).

The same concept, some degree of HF on LVAD, is indirectly proven by high prevalence and doses of loop diuretic use after LVAD implantation. Almost all patients, 95%, require loop diuretics before the LVAD. Although this proportion

decreases after the implant and remains below this level for two years of follow-up, more than half of patients were on loop diuretics even 2 years after LVAD implantation (33).

There is a growing interest to remote invasive hemodynamic monitoring with Cardiomems (Abbott, Abbott Park, IL) in LVAD population. Our experience has been published in the Journal before (34, 35). In 2017, data were published on 27 patients from the CHAMPION (CardioMEMS Heart sensor Allows for Monitoirng of Pressures to Improve Outcomes in NYHA Class III heart failure patients) trial, who required LVAD while the study was in progress. There was a trend toward a shorter length of time to LVAD implantation in the treatment group where hemodynamic information was available to physicians than in the control arm where medical management was guided by clinical information only. After LVAD implantation, decline in pulmonary artery pressure was also greater in patients with Cardiomems (36).

Cardiomems may also be helpful in management of patients with total artificial heart (37, 38).

Mechanical device failure

As patients live longer with LVAD, mechanical device failure or hardware issues such as driveline fracture or damage, or problems with inflow and outflow graft, electrical power, drive unit, or motor become more common, and sometimes fatal. In a single center, such failure occurred in 13% of patients on HM2 at a median time of about three years after implantation, increasing from 0% in the first year to 36% in the third. Longer time on pump predisposed to hardware failure. Driveline fracture was by far the commonest problem (89%) (39).

Other series report much lower incidence of driveline fracture at 3.2%. Although some cases of driveline fracture required device exchange, the majority of cases (88%) were fixed with driveline repair which was durable with no related fatalities (40). We reported the University of Kentucky experience with almost 12% of patients having driveline complications, mostly with external fractures or injuries, and with high mortality rate (41).

In the most detailed report, including both HM2 and HeartWare LVADs, types of device malfunction included controller failure (30%), battery failure (19%), driveline failure (14%), or pump failure (13%) and were more common in HM2 (3.73 per 1000 patient-days versus 3.06 per 1000 patient-days for the Heartware, P<0.01). Patients with HVAD were 90% free of a pump-specific malfunction at 3 years compared with 56% for the HM2 (log-rank *P*<0.003). Only 74% of the patients with HM2 were free of pump thrombosis at 3 years compared with 90% of the patients with HVAD. Freedom from failure of the integrated driveline was 79% at 3 years for the HM2 but 100% for the HVAD (log-rank *P*<0.02) (42).

Obesity

Laparoscopic sleeve gastrectomy was reported again last year as an option for patients who want to have cardiac transplantation after LVAD implant (43), adding to already existing literature (44). After driveline mapping by ultrasound or fluoroscopy, bariatric surgery was successfully performed in three patients. All achieved sufficient weight loss to be listed and two were transplanted.

CPR in VAD

Cardiac arrest in a patient with LVAD is one of the most challenging situations in management of this population. In 2017, the most comprehensive document covering this topic, a scientific statement from the American Heart Association, was published (45). This and other algorithms are discussed in detail in the current volume of the Journal (46).

Arrhythmias

It is well known that ventricular arrhythmias are much better tolerated on LVAD support, sometimes to the degree that ventricular fibrillation is discovered incidentally, in alert patients with normal end organ function and mild symptoms (47). The role of implantable cardioverters-defibrillators (ICDs) remains controversial.

The INTERMACS analysis performed with propensity matching in order to generate similar cohorts, one with ICD and another without, included over 2000 patients per arm. The presence of an ICD was associated with an increased mortality risk (HR 1.20; 95% CI 1.04 to 1.39; $p = 0.013$) and an increased risk of unexpected death on device support (HR: 1.33; 95% CI: 1.03 to 1.71; $p = 0.03$). Patients with an ICD were more likely to undergo transplantation (HR: 1.16; 95% CI: 0.99 to 1.35; $p = 0.06$) and less likely to have LVAD explant for recovery (HR: 0.53, 95% CI: 0.29 to 0.98; $p = 0.04$). They also had higher hospitalization rates (48).

Although propensity matching is not perfect and there may be still baseline differences, this is the largest dataset currently available and, clearly, ICDs were not associated with any benefit.

Electrical storm in patients not on hemodynamic support is a very difficult to manage and frequently fatal condition. Typically, the combination of antiarrhythmic drugs and ECMO for hemodynamic stability is used with or without ablation attempts. The usual argument against LVAD is that LVAD does nothing for ventricular tachycardia/fibrillation. One case report, published in 2017, showed that mechanical unloading of LV, in this case by Impella, can terminate ventricular tachycardia (49).

Under other circumstances, LVAD may directly cause refractory ventricular arrhythmia by tissue damage and inflammation at the inflow cannula site, which can be treated by ablation (50).

Atrial arrhythmias in LVAD population are prevalent and occur in about half of patients. Interestingly, patients with paroxysmal atrial fibrillation before the implantation have less episodes on LVAD support, presumably due to improvement in geometry and shrinking in size of the left atrium (51).

Atrial fibrillation may contribute to morbidity and mortality on LVAD or be a marker of more severe disease. In a single center study, two year survival was 65.4% in the sinus rhythm group and 51.3% in the atrial fibrillation group, HR 1.48, 95% CI: 1.02-2.15; p = 0.038). Also, patients in atrial fibrillation more commonly had RV failure, but there was no difference in bleeding and thromboembolic events (52).

LVAD and Valves

Mitral valve

Almost all LVAD candidates have some degree of mitral regurgitation (MR). LVAD unloads the LV irrespective of preoperative MR severity and results in partial resolution of mitral insufficiency. Less than 10% of patients who had at least moderate to severe MR before the implantation still have that degree of regurgitation after 6 months on LVAD (53).
At the same time, patients with significant residual MR have larger RV size, worse RV function, higher post-implantation pulmonary artery pressures, and shorter time to re-hospitalization and death (54).

There is still no consensus on surgical correction of MR during LVAD implantation. In the past years we cited studies revealing detrimental effects of residual, more than mild MR(55), and advocating aggressive correction of MR (56). In 2017, the INTERMACS analysis showed that two-year survival was 76% for concomitant mitral valve repair, 57% for valve replacement, and 71% for no mitral valve intervention (non-significant), but there were fewer readmissions in patient with concomitant surgical procedures on the valve (57). Also, in the experience of Columbia University, mitral valve repair effectively prevented RV failure and hospital readmissions after surgery (0.03 vs 0.15 readmissions per patient-year for repaired and non-repaired MV; P =0.011)(58). No difference in terms of survival or admissions was found in a single center (Barcelona, Spain) study with a trend to better outcomes in those whose valve was repaired (59) .

Aortic valve

Aortic regurgitation is very prevalent (may exceed 40%) in patients on LVAD support and contributes to higher baseline central venous pressure, PCWP, and lower pulmonary artery pulsatility index. While increase in LVAD speed improves hemodynamics, it also deteriorates aortic regurgitation. The question of aortic valve repair during the LVAD implant is being debated (60).

As many as 12.6% of LVAD recipients were found to have baseline pre-LVAD mild aortic insufficiency. If the valve was repaired during LVAD implantation, freedom from moderate or severe aortic regurgitation was $81.8 \pm 9.7\%$, versus $45.0 \pm 21.1\%$ ($P = 0.031$) in patients who did not undergo the repair. The likelihood of aortic regurgitation progression was particularly common in patients with larger aortic roots (61).

Anticoagulation in VADs

While the need to maintain therapeutic anticoagulation on LVAD is accepted as standard of care, the rigor of standards for daily use is still debated. The question of bridging patients with subtherapeutic international normalization ratio (INR) using other anticoagulants is currently unresolved. In retrospective analysis from University of Chicago, bridging with enoxaparin resulted in a fourfold increase in major bleeding episodes during the bridged period (2.02 vs. 0.45 events per year in non-bridged patients; $p = 0.03$). There was also a trend towards higher rate of thromboembolism in bridged patients (0.20 vs. 0.11 events per year; $p = 0.08$). Average INR at the time of initiation of enoxaparin was 1.46 (62).

The discussion on whether aspirin should be a mandatory component of management of patients on LVAD support continues. Our prior reviews included results of both European (63) and American (64) STudy of Reduced Anti-Coagulation/Anti-platelEt Therapy in Patients with the HeartMate II LVAS (TRACE), but no prior study directly compared the incidence of bleeding and thrombotic events between antithrombotic regimens with and without aspirin. A single-center, retrospective analysis of patients with HM2 receiving warfarin and aspirin 81 mg/day versus warfarin alone, showed no significant difference in bleeding (34% versus 43%, respectively, $p = 0.48$) or thrombotic events (9 versus 11%, respectively, $p = 1.00$) (65). It might be safe to manage patients on warfarin alone.

Given the amount of time we all spend on daily adjustment of warfarin dose, it is very tempting to anticoagulate patients on LVADs support with direct thrombin inhibitors. The first attempt was made and failed. Thirty patients on HeartWare with stable renal function were randomized to receive either phenprocoumon (vitamin K antagonist) or dabigatran 110 or 75 mg twice a day in addition to aspirin. The trial was stopped after only 16 patients because thromboembolic events occurred in 50% on dabigatran (four out of eight patients) and only in one patient (13%) on phenprocoumon (66).

Heparin Induced Thrombocytopenia

The group from Columbia University described their protocol for LVAD implantation in patients with heparin induced thrombocytopenia, which they used successfully in 6 patients, four of which had confirmed heparin induced thrombocytopenia. They give abciximab, 0.25 mg/kg loading dose, followed by continuous infusion of 0.125 mcg/ kg/min throughout cardiopulmonary bypass.

With abciximab infusion established, and before cardiopulmonary bypass, they start full-dose heparin to maintain an activated clotting time of ≥ 400 s. At the end of cardiopulmonary bypass, they reverse heparin with protamine, and stop abciximab 15 minutes after heparin reversal. They follow with transfusion of 18-24 units of platelets, and start argatroban with transition to warfarin when drainage from mediastinal tube became serosanguineous (67).

Noncardiac surgery

The question about management of LVAD patients, primarily in terms of anticoagulation, around planned interventions or surgeries is poorly investigated. In a retrospective large single center series from Duke, 32 patients with average preoperative INR 1.76 ± 0.47 underwent extractions and minor oral surgeries. In about 40% of anticoagulated patients warfarin was held while in the rest it was not; there was no difference in drop of hemoglobin post procedure, and only one patient required transfusion. Bridging with heparin was done in four patients (68). From this experience, dental procedures are safe and may not require interruption in anticoagulation.

LVAD and sex, driving, etc…

Decrease in quality of sexual activities was noted in over 50% of patients with LVADs, likely contributing to high rate of depression (69).

Successful pregnancy and delivery via cesarean section was also reported, suggesting that LVAD can adequately support increased hemodynamic needs during pregnancy (70).

Driving habits of LVAD recipients were also reported and it appeared that majority (70%) of patients return to driving after LVAD (71).

Complications of the VADs

Orthostatic hypotension

A newly recognized complication of chronic LVAD support was described by investigators from Duke who reported a series of three patients with orthostatic hypotension due to acquired autonomous dysfunction, confirmed by tilt table test. Upright position decreases preload, resulting in a reduction in chamber size in the setting of continuous unloading. Midodrine, fludrocortisone, compression stockings, and diuretic restriction may alleviate the symptoms (72).

Pump thrombosis

Further contributions were made in 2017 to understanding of the genesis of pump thrombosis. Bartoli et al. (73) reported that although lactate dehydrogenase (LDH) remains elevated on LVAD support, plasma free hemoglobin decreases after initial post-implant peak.

In patients who developed pump thrombosis, both LDH and plasma free hemoglobin remained elevated, unlike in patients without thrombosis before (p < 0.001) and after 3 months (p < 0.05) of support. In the in vitro study, free hemoglobin inhibited ADAMTS-13 activity during shear stress and therefore protected von Willebrand factor from degradation. The authors concluded that higher degree of hemolysis may create a prothrombotic state which can increase the risk of pump thrombosis (73).

Last year, we included the results of the PREVENT (PREVENtion of HeartMate II Pump Thrombosis Through Clinical Management) trial in our annual review. This was a prospective, multi-center, single-arm, non-randomized study of 300 patients with HM2. Investigators agreed on the best practices in terms of implant technique, anti-coagulation strategy, and pump speed management. In 2017, the substudy of 268 patients included in this trial, who had two or more LDH measurements at ≥30 days post-implant, was published. Out of these patients, 14% had elevated LDH, defined as ≥2.5× upper limit of normal for two consecutive measurements. Stroke-free survival at 6 months was lower in patients with elevated than with normal LDH (83 ± 6% vs 93 ± 2%, p = 0.035). Elevated LDH resolved without intervention in 19% of patients, with intensified medical therapy in 43% and required surgical intervention for suspected pump thrombosis in 38%. For patients receiving only medical therapy, including one or more of the following: intravenous heparin, low-molecular-weight heparin, intravenous direct thrombin inhibitor, and/or new anti-platelet therapy, survival was excellent at 94 ± 6% at 6 months post-treatment, with pump thrombosis in only one patient. The authors conclude that early medical intervention for elevated LDH is justified (74).

Gastrointestinal Bleeding

An ongoing frustration with management of GI bleedings on LVAD results in continuous search of new diagnostic and treatment options. It was discovered that LVAD causes a distinct form of intestinal angiodysplasia. Patients on LVAD not only have higher intestinal vascularity, but they also have abnormal vascular architecture in the submucosa of the jejunum (75).

Deregulation of an angiogenic factor, angiopoietin-2, may be responsible for increased angiogenesis. Serum levels and endothelial expression of this factor were higher in LVAD patients than in patients with heart failure but without LVADs or with heart transplantation (P=0.001 and P<0.001, respectively). Moreover, LVAD patients had an elevated thrombin activation, and thrombin is known to induce angiopoietin-2 secretion.

LVAD patients with higher angiopoietin-2 levels bled more, which led the authors to conclusion that this factor may contribute to development of arteriovenous malformations (76).

Angiotensin II is another factor involved in angiogenesis through the vascular endothelial growth factor and angiopoietin-2 pathways. It appeared that angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapy

is associated with a lower rate of GI bleeding, including arteriovenous malformation-associated bleeding. A retrospective review from John Hopkins hospital showed that 48% of LVAD patients not receiving either group of drugs had GI bleeding, comparing with 24% of those receiving angiotensin-converting enzyme ininhibitors or angiotensin receptor blockers. The odds ratio of all GI bleeding for patients on the therapy was 0.29, 95% CI 0.12-0.72, and for arteriovenous malformation associated bleeding it was 0.23, CI 0.07-0.71) (77).

In terms of diagnostics it appears that capsule endoscopy, traditionally utilized by most centers when upper and lower endoscopy fails to reveal the source of bleeding, is not helpful. At Stanford University, capsule endoscopy did not make difference in use of double-balloon or push enteroscopy, use of thalidomide or octreotide, 30-day outcomes, or time to re-bleeding (78). In the experience of University of Louisville, capsule endoscopy provided diagnostic yield of 4% (79). On the other hand, deep single balloon enteroscopy, reaching distal jejunum, as reported from Emory, produced a diagnostic yield of 78% with no complications (80).

In 2017, a multicenter, retrospective analysis evaluated LVAD patients who were discharged after GI bleeding and received secondary prophylaxis with octreotide. Only 24% experienced a recurrent GI bleed, comparing with 43% of historic cohort not receiving the drug; *P*=0.04 (81).

In the past, we cited recommended doses of experimental treatments for GI bleeds in LVADs: Danazol (200 mg orally twice a day) (82); octreotide (100 mcg subcutaneously twice a day in the hospital and then 20 mg depot intramuscularly monthly) (83). Other authors report 50 mcg subcutaneously twice a day (84). Thalidamide was given at 50mg orally twice a day with potential increase to maximum daily dose of 200 mg, and decrease to 50 mg every other day if toxicity develops, monitor blood count while up-titrating and try decreasing the dose when therapeutic effect achieved (85).

This year a series of patients were treated with thalidomide 50 mg a day, which led to termination of GI bleeding in all 11 patients, but two of them developed pump thrombosis. (86)

Another novel treatment, suggested last year, was inhaled desmopressin acetate 150 mcg, one nasal inhalation three days per week, in a patient with recurrent GI bleed who failed octreotide. Desmopressin is a synthetic analogue of vasopressin and is FDA approved for control of bleeding in patients with either hemophilia A or mild-to-moderate von Willebrand disease. This drug is administered as spray in one nostril 3 days a week, and has a time-to-maximal concentration of approximately 45 minutes, and a half-life of approximately 3.5 hours. This dose has been proven to increase levels of von Willebrand factor to 150-250% of normal shortly after administration. Potential significant adverse effects include hyponatremia (due to its anti-diuretic effect), hypertension and acute thrombosis (87).

Right ventricular failure

In the INTERMACS database, 38 patients had two centrifugal pumps implanted for biventricular support. RVAD was implanted in the RV in 59%, in the right atrium in 41%, and the site was not specified in 13%. Survival was below the outcomes usually reported for LV support only: 68% at 6 months and 62% at 12 months, and the complication rate was high with infection in 50%, bleeding in 44%, respiratory failure in 31.6%, malfunction in 26.3%, and neurologic dysfunction in 26.3% of patients (88). Nevertheless, considering dismal prognosis in RV failure, this still appears to be a viable option.

Various pumps

Several interesting new pumps were introduced or further developed in 2017.

The NuPulseCV (NuPulseCV, Inc., Raleigh, NC). The intravascular ventricular assist system (iVAS) is a minimally invasive, ambulatory counterpulsation system delivered via the subclavian artery and powered by a portable driver. It has a 50-cc pump, similar to an intra-aortic balloon, placed in the descending aorta (Figure 1).
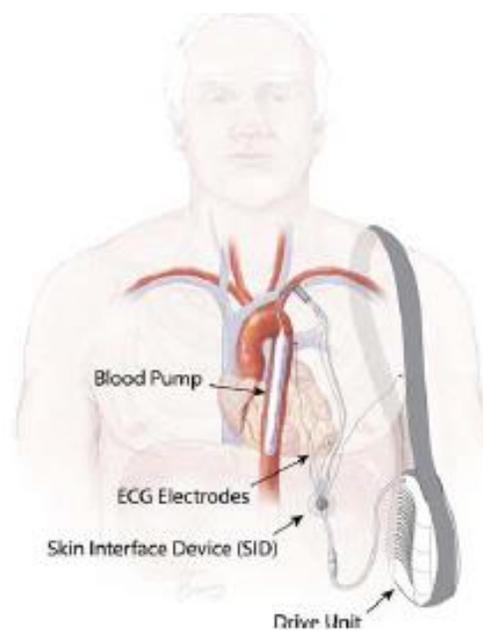

Figure 1

Figure 1, The intravascular ventricular assist system counterpulsation system. Reproduced from Jeevanandam et al (89), with permission

The skin interface device is an electro- mechanical and pneumatic conduit with a chimney that allows for shuttling of air between the pump and external driver and

communication of the captured ECG signals. An external and wearable drive unit provides compressed air to inflate and deflate the pump .Similar to an intra-aortic balloon pump, this device can be operated in 1:1, 1:2 and 1:3 modes, and the amount of augmentation is adjustable. The support can be interrupted for short periods of time and patients can ambulate while the pump is working.

This pump was tested in a prospective, non-randomized single arm feasibility trial in patients listed for cardiac transplantation. The primary end-point was survival to transplant or stroke-free survival at 30 days which was achieved in all implanted patients. One patient required escalation of mechanical support and there was one case of pericarditis and two cases of neuropathy after the pump implantation (89).

aVAD (ReliantHeart Inc, Houston, TX), approved in Europe, is a compact, axial flow LVAD which has speeds ranging between 6,000 and 12,000 rpm, and the flow up to 7 L/min. The features ofnthe device include
  1) real flow measurement with ultrasonic flow probe positioned around the outflow graft
  2) remote device monitoring
  3) a miniaturized pump housing. It is positioned within the LV through the apex with a 90-degree outflow elbow positioned just outside the heart but within the pericardial space (Figure 2).
  4) adjustment of pump depth within the ventricle, which allows adjustment of pump depth to accommodate different ventricular cavity sizes and avoid suction events.

This device was implanted to a 61-year-old woman with severe HF. Following uneventful surgery, the patient recovered and was successfully discharged from the hospital (90).
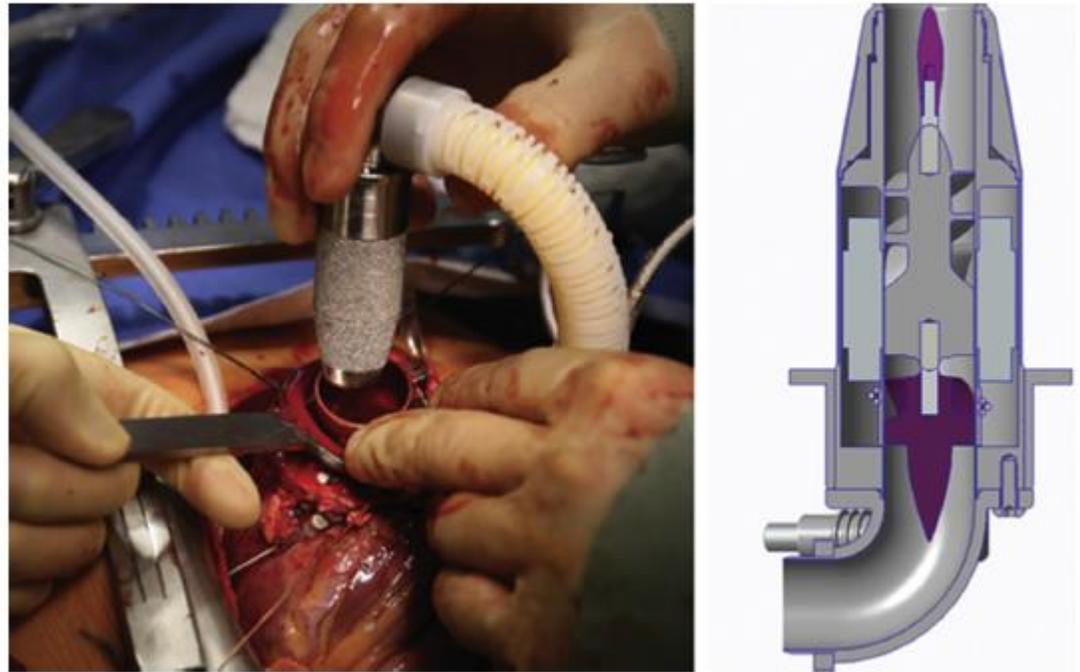
Figure 2. aVAD (ReliantHeart Inc, Houston, TX). Reproduced from Schmitto et al.(90), with permission

What is new in VA ECMO World?

This year, we are introducing a new section and hope to make it a regular part of this review series. We will summarize what was published in 2017 on veno-arterial ECMO, which is not a LVAD, but certainly part of mechanical circulatory support.

Cardiogenic shock and acute decompensated HF

Interestingly, in a large series including 132 patients isolated LV failure was a risk factor for mortality, while patients with RV failure or biventricular failure had better prognosis (91). This differs from our results, where we found no difference in mortality between RV and LV failure (92). In our experience, patients supported with VA ECMO due to pulmonary embolism and HF had better survival to hospital discharge (83.3% and 54.2%, with p = 0.003 and p = 0.011, respectively) then patients with postcardiotomy syndrome (7.7%).

In some cases, ECMO in cardiogenic shock becomes a bridge to LVAD. Patients with INTERMACS profile 1, who had an LVAD, were analyzed based on being or not being on the ECMO support before the LVAD. The ECMO bridge group was generally sicker, with lower hemoglobin and prealbumin, requiring more transfusions and vasopressors, but had better hemodynamics than patients without ECMO as a bridge, with lower central venous pressure, PCWP, and mean pulmonary arterial pressure. Survival at 30 days postoperative and at 1 year (77%

vs. 88%; p = 0.6) was similar. ECMO, therefore, is a viable option to bridge very unstable patients to LVAD (93).

Left ventricular decompression

It is known that VA ECMO in patients with failing LV can frequently cause LV distention and pulmonary edema. A 30-day survival on ECMO with LV decompression is better than without LV venting (55% vs. 25%, p=0.034) (94). Some new options for LV decompression on VA ECMO were suggested in 2017. The most interesting one uses central biventricular cannulation with LV approached via left mini-thoracotomy, with off-pump transapical placement of ProtekDuo cannula, with the inflow port located in the LV and the outflow port and cannula tips situated 2–3 cm above the aortic valve. The pump was TandemHeart, and the oxygenator was included. For RV support, inferior vena cava- superior vena cava venous cannula was inserted via the femoral vein and connected to the inflow of transapical cathteter. Later, the venous catheter was stitched to internal jugular vein and the patient was able to walk. In essence, it was placement of the central ECMO with LV decompression, allowing patient's mobility (95).

A large review on LV unloading was published by Meani et al.(96). They divide all methods into

1) surgical techniques
- Implant of a LV venting catheter (cannula through the right superior pulmonary vein either in the left atrium or LV and connected with a Y-connector to the venous line of the circuit
2) minimally invasive surgical techniques
- Cannula implanted in the LV and then tunneled through a subxiphoidal incision to the extracorporeal side
- Cannula inserted into LV apex via left anterolateral thoracotomy
- Transdiaphragmatic approach is used
3) Percutaneous options
- Pulmonary artery drainage with a venous cannula placed into the main pulmonary artery, connected to the venous limb
- Trans-aortic catheter venting with pigtail inserted directly across the aortic valve from femoral artery, connected to the venous limb
- Pediatric cannula placed into the LV through the aortic valve and connected to the femoral arterial line
- Blade or balloon septostomy
- Transseptal left atrial drain connected to the venous limb

Indirect venting includes increasing forward flow with intra-aortic balloon pump, TandemHeart, or Impella (96).

Electrical storm

Another indication for VA ECMO is incessant ventricular tachycardia (VT) or electrical storm. Patients may need ECMO to provide hemodynamic stability,

although it does not help ventricular arrhythmia per se. Besides, ventricular stunning due to multiple shocks by defibrillator may temporarily compromise LV to the degree of circulatory shock.

ECMO provides an opportunity to perform VT ablation or to suppress VT/ventricular fibrillation by antiarrhythmics. A series of 21 patients in electrical storm on ECMO support was reported by Enriquez et al. (97). Mortality was high with 16 patients (66%) being dead in a median of 10 days, but the remaining survived arrhythmia free.

Cardiopulmonary resuscitation

A systematic review and meta-analysis of ECMO in out-of-hospital cardiac arrest, summarizing 15 studies with a total of 841 patients, reported following predictors of survival: initial shockable cardiac rhythm, shorter low-flow duration, higher arterial pH, and lower serum lactate (98).

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