Invited Review

What Did We Learn about VADs in 2016?

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Introduction

The field of mechanical circulatory support is evolving rapidly and new data are published at a rate that can be overwhelming. The last two years, we published reviews entitled “What Did We Learn about VADs in 2014?”(1) and “What Did We Learn about VADs in 2015?”(2). Both papers were well received – the full texts were downloaded 570 and 440 times, respectively, by readers around the globe. Encouraged by this, we wrote the present review, where, like before, we summarized some of the publications from 2016 that we think are particularly important. There may be slight overlap with the end of 2015, because some papers are being published online first.

Readers who wish to supplement this review or to argue with the author’s statements or article selection are encouraged to do so 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/

Finally, many sources were so recently published, electronically ahead of print, that full bibliography is not available yet. In the References, we put doi for each source without volume/issue/pages.
HeartMate III

As last year, the greatest focus of interest for the mechanical circulatory support (MCS) community was Heartmate III (HMIII) (St. Jude Medical, Pleasanton, California) which already received the Conformité Européene (CE) Mark approval in Europe for advanced heart failure patients (HF), both as bridge to transplantation and as destination therapy. For the benefit of the readers, we will reiterate the key features of the device (3):

- Intrapericardial position
- Fully magnetically levitated rotor
- Rotor speed range of 3,000 to 9,000 revolutions per minute (rpms)
- Maximum flow rate of 10 L/min
- No friction, heat generation, wear and tear
- Wide gaps for the blood flow (blood flow paths) through the device (10-20 times wider than in currently used pumps)
- Pump speed change 30 times per minute to create pulsatility
- External portion of the driveline can be changed without pump exchange
- Texturing of the internal surface with titanium microspheres

These features are designed to achieve following effects:

- Minimization of blood stasis
- Minimization of shear stress to blood
- Development of a pseudo-intima on the inside of the pump to prevent pump thrombosis
- Maximizing of the aortic valve opening

This pump has some distinct features on echo (Figure 1) (4):

- Reverberation artifacts during color flow Doppler examination (Figure 2)
- Device-induced pulsatility of blood flows (Figure 3).
Figure 1. Transesophageal echo: inflow cannula. From Magunia et al.(4), with permission.

Figure 2. Transesophageal echo: the turbulent pattern is due to a reverberation artifact and occurs when inflow and rotor are directly opposite of the ultrasound beam source. From Magunia et al.(4), with permission.
Figure 3. Transesophageal echo: pulsatility of blood flow. The pulsed wave Doppler shows the heart’s cycle and pump-augmented baseline inflow into the device. Within 15 ms, pump speeds are decreased by 2,000 rpm from baseline, then increased by 4,000 rpm before being adjusted back to previously programmed values. From Magunia et al. (4), with permission.

From hemodynamic standpoint, this pump performs well. A ramp test with simultaneous hemodynamic and echocardiographic recordings in 16 patients with HMIII measured the changes with the speed ranging 4,600 rpms to 6,200 rpms. Remarkably, a majority of patients (10 of 16, 62.5%) had normal parameters of left ventricular (LV) (pulmonary capillary wedge pressure) and right ventricular (RV) function (central venous pressure) already at the mean original speed of 5,306 +/- 148 rpms. With gradual speed increase, per each step of 100 rpms, cardiac output increased by 0.08 +/- 0.08 L/min (total change 1.25 +/- 1.20 L/min) and pulmonary capillary wedge pressure decreased by 0.48 +/- 0.27 mm Hg (total change -6.13 +/- 3.72 mm Hg). There were no significant changes in central venous pressure or systolic blood pressure. LV end-diastolic dimension decreased at a rate of -0.15 +/- 0.09 cm per 100 rpms. The speed was adjusted based on test results to achieve a central venous and wedge pressure as close to normal as possible, which was feasible in 13 (81.3%) patients. The remaining 3 patients were optimized medically (5).
Last year (2015), a single-arm, prospective, multicenter study, designed to evaluate the performance and safety of the HMIII, enrolled 50 patients. The primary endpoint was 6-month survival compared with the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) data. The 6 month survival was 92%, with 88% of patients continuing on support and 4% transplanted, which exceeded the 88% goal. Major adverse events included re-operation for bleeding (14%), driveline infection (10%), gastrointestinal bleeding (8%), and debilitating stroke (8%). There were no pump exchanges, pump malfunctions, pump thrombosis, or hemolysis events. Overall stroke rate was 12% which was higher than expected (6).

In 2016, the first results from the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3), a nonblinded randomized trial that comparing HMIII and HMII, were published. The primary end point was a composite of survival free of disabling stroke or pump replacement at 6 months.

Patients were randomly assigned to HMII or HMIII irrespective of treatment strategy (bridge to transplant or destination therapy). The survival without stroke or pump replacement was better in HMIII (86.2%) than in HMII recipients (76.8%), with P<0.001 for noninferiority and P=0.04 for superiority. There were no significant differences between the groups in the rates of death or disabling stroke. Reoperation for pump malfunction was less frequent in HMIII than in HMII recipients. Remarkably, there were no cases of pump thrombosis in the HMIII arm, whereas 10.1% of HMII patients had this complication. There was no difference in bleeding. Overall, HMIII was associated with better outcomes at 6 months, mostly due to fewer reoperations for pump malfunction (7).

Outcomes

Because all potential candidates for VAD are in New York Heart Association (NYHA) III/IV class, there is a need to risk stratify patients in the advanced HF cohort. Traditionally, an assessment of patients’ acuity is done and recorded as INTERMACS profile. Several years ago Cowger et al.(8) introduced a HMII risk score (HMRS), calculated as

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\text{HMRS} = (0.0274 \times \text{[age in years]}) - (0.723 \times \text{[albumin g/dl]}) + (0.74 \times \text{[creatinine mg/dl]}) + (1.136 \times \text{[INR]}) + (0.807 \times \text{[center LVAD volume <15*]}) - \text{(Enter value of 1 if total center LVAD volume is <15 and 0 if ≥15)}.
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The risk, predicted by the score, is categorized into low (<1.58), mid (1.58 to 2.48), and high (>2.48), providing a good discrimination in terms of outcomes: a ninety-day mortality in these 3 groups was 4%, 16%, and 29%, respectively (p < 0.001)(8).

This year, two different groups of investigators applied this score to the INTERMACS data and arrived to different conclusions.
Kangar et al. found the score to be a weak tool for prognostication. At 90-days, 18% patients with high HMRS died, compared to 13% with medium risk and 7% low risk patients. The 90-day and 1-year mortality prediction had an area under curve at only 61% and 59%, respectively, making the score a poor discriminator of the mortality risk (9).

In another study, the score was not simply applied to the INTERMACS data, but its ability to predict outcomes was compared with INTERMACS profiles. Patients in the highest and lowest HMRS group had a 90-day mortality of 12.9% and 4.6 %, respectively. However, the score provided better discrimination in terms of mortality prediction than INTERMACS profiles. Moreover, after stratifying patients within each INTERMACS profile by HMRS class, authors found that INTERMACS profile 1 patients with a low-HMRS had a 90-day mortality similar to INTERMACS profile 3 with a high HMRS. In other words, HMRS identified patients from lower (poorer) INTERMACS profile with more favorable prognosis than in patients with higher INTERMACS profile. Applied to patients with INTERMACS profile 1 and 2, typically seen as unfavorable candidates for VAD implant, the score can identify patients who should be offered the treatment because their risk in reality is not that high. The score performed equally well in HMII and Heartware (10).

The outcomes of patients supported with Heartware devices for longer than 2 years were reported based on the data from the Registry to Evaluate the HeartWare Left Ventricular Assist System (ReVOLVE), which is an investigator-initiated multicenter, prospective, single-arm database established to collect post-Conformite Europeenne Mark clinical information on HeartWare. Overall survival through 5 years was 59% (11).

Speaking about quality of life as a valid outcome, several authors suggested integrating sexual function in the quality of life evaluation tools for patients with LVADs (12)

**Recovery**

A large review article in two parts on ventricular recovery on VAD by Dandel and Hetzer (13,14) was published in the very end of 2015 and was not included in the last year summary. The authors underscore the higher recovery rates in postcardiotomy syndrome and acute myocarditis, lower in nonischemic cardiomyopathy, and rare in ischemic cases. Overall, the recovery due to LV unloading occurs in less than 10% of patients. They also discuss in detail the whole process of evaluation for recovery and weaning off LVAD.

Last year, the query of the United Network for Organ Sharing (UNOS) registry found that LVAD explant due to recovery was done in 5% of patients, mostly young and non-ischemic. In the first year, one third of these patients either died or had heart transplant, therefore bringing the rate of true recovery down to slightly over 3% (15).
This year, analysis of the INTERMACS revealed similar low recovery rates: 0.9% at 1-year, 1.9% at 2-year, and 3.1% at 3-year follow-up. Independent predictors of device explantation for recovery were age <50 years (odds ratio [OR] 2.5), nonischemic etiology (OR 5.4), time since initial diagnosis <2 years (OR 3.4), suboptimal HF therapy before implant (OR 2.2), LV end-diastolic diameter <6.5 cm (OR 1.7), pulmonary systolic artery pressure <50 mm Hg (OR 2.0), blood urea nitrogen <30 mg/dL (OR 3.3), and axial-flow device (OR 7.6). Patients with myocarditis (7.7%), postpartum cardiomyopathy (4.4%), and adriamycin-induced cardiomyopathy (4.1%) had highest rates of device explantation for recovery. Use of neurohormonal blockers on LVAD support was significantly higher in patients who were explanted for recovery (16).

Partial recovery, i.e. LV improvement not reaching normal parameters, is far more common. In patients supported with LVAD for at least 6 months, 5% of subjects with ischemic cardiomyopathy and 21% of subjects with nonischemic cardiomyopathy achieved left ventricular ejection fraction ≥40% (p = 0.034). The degree of improvement by echocardiographic criteria was similar in recovered hearts regardless of the etiology (17).

No difference was found in LV ejection fraction or volumes between axial flow and centrifugal flow LVADs. LV ejection fraction increased significantly from a mean of 18% pre-VAD to 28% and 26% post-LVAD, respectively (18). By other data, conversely, axial design provided a greater reduction of right atrial pressure, pulmonary capillary wedge pressure, mean pulmonary artery pressure, and left ventricular internal diameter during diastole, as well as greater improvement in cardiac output (19).

In the process opposite to recovery, lack of LV function due to complete surgical closure of the aortic valve may result in cardiac atrophy. One study noted that after 4 years on LVAD support, a heart weight only 280 g in a 220 pound man (20).

**Candidate selection**

**Elderly**

There is currently no established age limit for LVAD implant. When Mechanical Circulatory Support Research Network was queried, patients ≥70 years of age constituted only 14% of LVAD implants. Their rates of device thrombosis and stroke were similar to younger patients, but older patients had more gastrointestinal (GI) bleeds. Their unadjusted survival at 1 year was 75% compared with 84% in younger patients, and at 2 years it was 65% versus 73% (P =0.18). The only predictor of mortality was creatinine (HR 2.1, 95% CI 1.2-3.4; P = .007). Creatinine >/=1.4 mg/dL was associated with a 1-year survival of 65%, compared with 84% when the creatinine was <1.4 mg/dL (P = .009). If renal function was normal, survival was similar to younger patients (21).
Small Body Size

Outcomes in patients with body surface area < 1.5 m² (mostly women) with HMII were analyzed in the INTERMACS and found to be similar to the overall LVAD population (22,23).

Adult Congenital Disease

In 2016, the American Heart Association published a scientific statement on transplantation and mechanical circulatory support in congenital heart disease. The document approaches MCS in congenital cardiac cases quite cautiously, saying that despite an overall growth in VADs, the volume of implants for congenital heart disease has not grown. Complexity of anatomy and physiology, together with multiple prior surgeries and interventions, creates many challenges, especially because in most cases the ultimate goal is cardiac transplant. Moreover, authors state that MCS is associated with significant morbidity and uncertain long-term outcomes in adult patients with congenital heart disease. Most currently available information is coming from case reports and small series. There is a need for a multi-institutional MCS single-ventricle registry in order to better define selection criteria for MCS (24).

Meanwhile, case reports and small series keep being published. In a series of 5 patients with a failing single-ventricle circulation (hypoplastic left heart syndrome, pulmonic atresia with intact ventricular septum, tricuspid atresia, double-outlet right ventricle with unbalanced atroventricular canal, and situs inversus with pulmonary atresia and left atroventricular valve atresia, four of them with Fontan and one with bidirectional Glenn), MCS helped to bridge three of them to heart transplantation (25). Another Fontan patient with acute ventricular failure was sequentially bridged to transplant with temporary and then durable support devices (26). A detailed discussion of the approach to decision, candidate selection, and surgical technique of MCS in Fontan patients is given by Woods et al. (27).

In another case, MSC was used to successfully bridge an adult with congenitally corrected transposition of the great arteries and situs inversus (28).

Management of patients on LVAD support

There is a growing realization that LVAD usually provides incomplete compensation of HF, and therefore hemodynamic monitoring and medical management may be of value.

Specifically, left atrial pressure monitoring with a wireless microelectromechanical system pressure sensor (Titan, ISS Inc., Ypsilanti, MI, USA), placed during LVAD implantation in 4 patients, demonstrated good correlation between sensor pressure and pump speed, LV and left atrial size and pulmonary capillary wedge pressure, respectively ($r= 0.92$-$0.99$, $p < 0.05$) (29).
Remote hemodynamic with Cardiomems (St. Jude Medical, Inc., St. Paul, MN) was also tested in VADs with promising results (30,31).

Because of incomplete hemodynamic compensation with LVAD, use of HF medications after LVAD can be of value. In the INTERMACS, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) were used in 38%, beta blockers in 55%, mineralocorticoid receptor antagonists in 40%, and loop diuretics in 87% of patients before implant. By 3 months after implant, the rates were 50% for ACE inhibitors or ARBs, 68% for beta-blockers, 33% for mineralocorticoid receptor antagonists and 68% for loop diuretics (32).

Importance of medical management of HF even on LVAD support was proven by Grupper et al. In a retrospective review they found that a statistically significant improvement in NYHA class, six minute walk distance, ejection fraction, decrease in LV end-diastolic diameter index and LV mass index, and a sustained reduction in N-terminal pro B-type natriuretic peptide occurred to a greater extent in those who were treated with ACE inhibitors and beta blockers after LVAD than in patients who did not receive these therapies. Also, a combined end point of cardiovascular death or HF hospitalization at 6 months was significantly reduced in patients receiving medical management (p = 0.013) associated primarily with a 12.1% absolute reduction in HF-related hospitalizations (33).

It appears that pacing can have consequences in LVAD patients as well. In a patient with Heartware and intermittent RV pacing, episodes of pacing were associated with hemodynamic compromise including a decrease in the systemic blood pressure, pulse pressure, pulsatility index, and estimated flow, recorded by the VAD control module, and an increase in the central venous pressure and severity of tricuspid regurgitation. All the changes reversed with intrinsic rhythm and conduction (34).

**Obesity**

Some patients with end stage cardiomyopathy and obesity receive LVAD as a bridge to transplant, but then are unable to lose weight, and never become transplant candidates. Several cases of bariatric surgery were reported last year, and there was another one in 2016 – a patient underwent laparoscopic sleeve gastrectomy, achieved significant weight loss, and cardiac transplantation was performed (35).

**Arrhythmias**

Interesting data were obtained on interrogation of ICDs of LVAD patients. Ventricular arrhythmia was occurring more often after the implantation, including treated-zone ventricular arrhythmias (p < 0.01), monitored-zone arrhythmias (p < 0.01), antitachycardia pacing-terminated episodes (p < 0.01), and shocks (p = 0.01), although administered shocks later decreased (p < 0.01). Presence of a preimplant ventricular arrhythmia was associated with postoperative episodes (OR 4.31; CI 1.5-12.3, p < 0.01). ICD shocks either before or after implant were not associated with survival (36).
Same phenomenon was described by Yap et al., but their follow-up was longer. Overall, 30% of patients experienced ventricular arrhythmia on VADs. The burden of ventricular arrhythmia followed a U-shaped curve, with the highest incidence in the first postoperative month, a nadir at 15 to 18 months, and a rise after that time. Pre-LVAD ventricular arrhythmia was the only independent predictor of post-VAD arrhythmia. Post-LVAD arrhythmia was not associated with increased mortality (37).

Similar proportion (28%) of the VAD patients experienced ventricular arrhythmia in another study (70% of them had ventricular tachycardia and 30% had ventricular fibrillation), with history of ventricular arrhythmia or atrial fibrillation before VAD being the most powerful predictors of ventricular arrhythmia post-VAD. However, unlike in the last paper, ventricular arrhythmia after LVAD was associated with a significantly higher risk of all-cause mortality (HR 7.28; 95% CI 3.50-15.15; P < .001) (38).

Not surprisingly, discussions about role of implantable cardioverter-defibrillators (ICDs) in VAD patients continued in 2016. A meta-analysis of three observational studies (39-41) with a total of 292 patients (69.5% with ICD versus 30.5% without ICD) found no survival benefit in patients with ICD (42). It would be difficult to expect a different result since none of the three studies included in the analysis showed such benefit (MG).

Another systematic review and meta-analysis on ventricular arrhythmia in LVAD population included six observational studies with a total of 937 subjects, but because older studies were included, only 40% of them were on continuous-flow pumps. During a mean follow-up of 7 months, 16% died in the ICD group vs 32% in the no-ICD group. Presence of an ICD was associated with a 39% relative risk reduction in all-cause mortality (RR: 0.61; 95% CI: 0.46 to 0.82; p < 0.01). Unfortunately, in a subset of patients supported with continuous flow VAD, survival difference did not reach significance (43).

The search of UNOS database revealed that presence of ICDs in patients bridged to transplantation with LVADs was not associated with lower total or cardiovascular mortality on the waiting list; however, there were numerically fewer arrhythmic deaths in the ICD group (44).

Because of conflicting results and scanty data, there were calls for MADIT-VAD trial (45,46).

Anecdotally, subcutaneous ICD inappropriately shocked a patient with LVAD because R waves were diminished and superimposed by electric noise caused by the LVAD. Oversensing of electromagnetic interference led to multiple shocks. Replacing subcutaneous defibrillator with a usual transvenous system eliminated the problem. Obviously, relying on surface ECG with smaller R waves may create additional difficulties for arrhythmia-recognizing algorithm in subcutaneous ICD (47).
LVAD and kidneys

Longitudinal changes in renal function after LVAD were reported previously. Last year, we cited the paper of Brisco et al. (48) who showed that although renal function, after initial improvement, deteriorates on LVAD support, in patients with lower baseline glomerular filtration rate the function is still better than before the implant. This was confirmed in 2016 by Raichlin et al. who demonstrated that when renal function before the LVAD was stratified by glomerular filtration rate into ≤40 and >40 ml/min/1.73 m, dynamic changes after LVAD were different. In all patients, renal function initially improved and then declined. But in a year after the implant, patients with more preserved renal function at baseline returned to the pre-VAD values, while those with more severe impairment pre-VAD had better function one year after. Although patients with worse baseline impairment required hemodialysis after VAD more often, this group of patients can benefit the most from improved hemodynamics on LVAD support (49).

Hemodialysis in LVAD population remains a topic of interest. In the past, very few articles addressed the issue (50-53). There was some further progress in 2016.

Two groups of authors described normal maturation of arteriovenous fistula with subsequent uncomplicated hemodialysis in a total of four patients. Calenda et al. reported a series of 3 patients on continuous LVAD support who had dialysis via fistula which also matured normally (54,55).

Intermittent inpatient hemodialysis (170 sessions in 9 patients with HMII) was well tolerated, with only 6.5% of sessions terminated early, mainly because of hypotension. Six out of nine patients (66.7%) recovered kidney function and became dialysis independent (56).

LVAD and mitral valve

There is no consensus on surgical correction of mitral regurgitation (MR) during LVAD implantation. Sometimes, severity of MR decreases after LVAD. Tanaka et al. studied 110 patients in whom MR resolved after LVAD implantation, with surgical correction or spontaneously. Surgical correction was associated with better hemodynamics during follow-up: lower pulmonary wedge pressure (12 mm Hg vs 17 mm Hg, p = 0.015) and pulmonary vascular resistance (1.7 vs 2.0 Wood units, p = 0.047). Overall survival rate and freedom from recurrent MR were also significantly better in the surgical correction group compared with the spontaneous correction group (1-year survival, 69.6% +/- 6.4%, vs 59.4% +/- 6.9%  p = 0.030; 1-year freedom from recurrent MR, 95.0% +/- 3.5% vs 76.2% +/- 7.5%, p = 0.028. Aggressive surgical mitral valve intervention during LVAD implantation may be recommended (57).

Concurrently, a retrospective review of patients with significant (greater than mild) residual MR after LVAD implantation demonstrated a larger RV size, worse RV function, higher pulmonary arterial pressures, and shorter time to rehospitalization and death (58).
Anticoagulation in VADs

There is an ongoing discussion on whether aspirin should be a mandatory component of management of patients on LVAD support. Studied in the experiment, aspirin reduced platelet activation under low shear stress, but was minimally effective at the shear stress produced with VAD (59).

Last year, we included the results of the TRACE U.S. (STudy of Reduced Anti-Coagulation/Anti-platelet Therapy in Patients with the HeartMate II LVAS), which looked into safety of reduced anti-thrombotic therapy in HMII recipients, who had bleeding events. The enrolled 100 participants were outpatients on warfarin only (38%), aspirin only (28%), or no anti-thrombotic agent (34%). Freedom from ischemic stroke at 1 year was 93.8% ± 2.5%, and freedom from device thrombosis was 92.7% ± 2.7%. Despite reduced anticoagulation and antithrombotics, a subsequent bleeding event occurred in 52%, although there were no intracerebral bleeds. There was no comparison of strategies against each other (60).

In 2016, the results of European TRACE study were published. Unlike in the US study, majority of participants (94%) did not have prior bleeding episodes. Rather, they were managed without antithrombotic agents - on anticoagulation only, with median INR 2.3 – based on physicians’ preferences. At 2 years, freedom from bleeding, ischemic stroke, hemorrhagic stroke, and pump thrombosis was 81% +/- 6%, 96% +/- 2%, 94% +/- 3%, and 94% +/- 3%, respectively. Investigators concluded that warfarin alone without aspirin may help to reduce the incidence of major bleeding without increasing the risk of thromboembolic events, including ischemic stroke and pump thrombosis (61).

Unlike with the aspirin, nobody questions the need for anticoagulation. In view of recent rise in pump thrombosis (62), there are ongoing efforts to find the optimal protocol for anticoagulation management in LVAD patients. An important step was accomplished in 2016 with the completion and publication of the PREVENT (PREVENtion of HeartMate II Pump Thrombosis Through Clinical Management) trial. This was a prospective, multi-center, single-arm, non-randomized study of 300 patients with HMII. Investigators agreed on the best practices in terms of implant technique, anti-coagulation strategy, and pump speed management. The study looked at the ability of these practices to prevent early (<3 months) pump thrombosis.

The study investigators hypothesized that they will achieve a ≤ 4% rate of pump thrombosis at 3 months with the implementation of recommended rules. In fact, the pump thrombosis rate was 2.9% at 3 months and 4.8% at 6 months. Adherence to key recommendations included 78% to surgical recommendations, 95% to heparin bridging, and 79% to pump speeds >/=9,000 rpms. Full adherence to all three components resulted in a significantly lower risk of pump thrombosis (1.9% vs 8.9%; p < 0.01) and lower composite risk of suspected thrombosis, hemolysis, and ischemic stroke (5.7% vs 17.7%; p < 0.01) at 6 months (63). The summary of recommendations from the trial is summarized below:
Surgical recommendations

- Adequately sized pocket
- Inflow cannula parallel to the septum
- Outflow graft to the right of mid-sternum in order not to compress RV
- Pump below the diaphragm
- Fixate the pump to the diagram or chest wall

Anticoagulation/antiplatelet management

- Bridging with low molecular weight heparin within 48 hours of implant, PTT goal 40-45 sec, increase goal to 50-60 sec by 96 hours
- Start warfarin within 48 hours of implant, INR goal 2-2.5, stop heparin when achieved
- Aspirin 81-325 mg/day 2-5 days after implant if no bleeding
- INR goal stays 2-2.5 indefinitely

Pump speed>9000 rpms

Mean arterial pressure <90 mmHg

As more centers are switching from traditional monitoring of heparin concentration by PTT to antiXa factor, there are some discrepancies observed. PTT is a test that reflects an overall status of anticoagulation, while antiXa specifically measures heparin concentration. Last year Adatya et al. (64) found disturbingly high discordance in paired blood samples. The results of the two essays were considered concordant if they both indicated that anticoagulation was within therapeutic, subtherapeutic, or supratherapeutic range. The discordance was 63.8% in the bridging cohort (initial anticoagulation after the implant) and 84.2% in the pump thrombosis cohort, where therapeutic level of anticoagulation is critically important. The most common pattern of discordance was a supratherapeutic PTT value and a therapeutic anti-Xa level (49.1% for bridging vs. 75.8% for pump thrombosis; p < 0.001), likely because hemolysis per se, as well as elevated INR, which was frequent in these patients, can prolong PTT. Authors concluded that Anti-Xa assay may therefore give a more accurate guidance on heparin concentration in this population (64).

This year, it was confirmed that the type of discrepancy where PTT is prolonged and antiXA is therapeutic is very common in LVAD population and is observed in 68-84% of patients when PTT is above 100 sec or 112 sec, respectively. Rate of bleeding within 30 days was similar with antiXa vs PTT monitoring, while the rate of pump thrombosis seemed to favor PTT monitoring. At the current state of knowledge, it seems reasonable to use both tests in parallel (65,66). Specifically,
authors suggest that in an uncomplicated post-operative patient, escalating heparin when PTT is prolonged and anti-XA is therapeutic may unnecessarily increase bleeding risk. Conversely, in cases of device thrombosis, heparin titration based on both PTT and anti-Xa may provide more adequate anticoagulation and possibly improve outcomes (Ton et al).

**Noncardiac surgery**

Outcomes of noncardiac surgery in LVAD population were reported before, but the analysis of large cohort from the National Inpatient Sample Database, published in 2016, is of interest. Noncardiac surgery is common and is done in over 20% of patients on LVAD support. After surgery, these patients experienced more wound infections than all patients with VADs (9.1 vs. 4.6%, p = 0.004), greater bleeding complications (44.0 vs. 24.8%, p < 0.001) and were more likely to develop any complication (87.2 vs. 82.0%, p = 0.001). Mortality difference did not reach significance. Authors suggest that even low-risk non-cardiac surgery should be performed in VAD centers (67).

**Complications of the VADs**

**Stroke**

In a large single-center study, strokes occurred in 13.2% of patients on VADs. Treatment of ischemic stroke included intra-arterial embolectomy when appropriate; while treatment of intracerebral hemorrhage included reversal of coagulopathy. Most strokes (80%) were ischemic. Half of patients with hemorrhagic stroke and third of those with ischemic stroke died, but some survivors of ischemic event underwent successful heart transplant (68).

The anticoagulation reversal may vary in between institutions as well as individual cases. The report by Wong et al. shows that administration of 4-factor prothrombin complex concentrate may safely shorten the time to reversal and decrease the requirements in fresh frozen plasma (69).

In the series of 5 patients with LVAD, two of them therapeutic on warfarin, with acute ischemic stroke, who underwent thrombectomy with or without thrombolitics, none developed intracerebral hemorrhage as a complication. Their functional status improved (70). Being on a VAD and therapeutically anticoagulated should not be considered a contraindication to thrombectomy.

**Pump thrombosis: diagnosis**

Most of the literature on pump thrombosis was focused on the events in patients with HMII. In 2016, a detailed analysis of diagnosis and treatment of Heartware thrombosis was described by Scandroglio et al. (71).
Pump thrombosis was diagnosed by laboratory signs of hemolysis, LVAD alarms and waveforms, imaging, and acoustic analysis of the pump noise. They classified all obstructions to blood flow into 1) pre-pump, with thrombus obstructing the inflow cannula (0.037 events per patient-year); 2) intra-pump (0.1 events per patient-year); and 3) post-pump, with the thrombus in the outflow graft or stenosis of the anastomosis to the aorta (0.006 events per patient-year). While intra-pump thrombosis was accompanied by power spikes, pre-and post pump obstructions caused low flow alarms, but the onset was more abrupt in the inflow cannula obstruction (Figures 4, 5).

Pre-pump obstruction was treated by washout maneuver (success rate, 100%), thrombolysis (success rate, 56%), or pump exchange (success rate, 100%). In washout maneuver, the LVAD was turned off and then back on, in order to dislodge the clot. There were cases of peripheral embolization, but carotid arteries were protected by filters, introduced bilaterally to capture thrombus released from the pump, and to prevent stroke.

For intra-pump obstruction, thrombolysis was successful only in 33% cases, and pump exchange in 94%; most patients who died were in this group. For post-pump obstruction, two patients were successfully treated with stenting, and other two were left untreated (71).

Figure 4. Abrupt drop of flow due to obstruction of the inflow cannula (Reproduced from Scandroglio et al. (71), with permission.)
Figure 5. Gradual decrease of flow due to obstruction in the outflow graft. Reproduced from Scandroglio et al. (71), with permission.

We reported the case of complete pump thrombosis with normal LDH (72).

**Pump thrombosis: treatment**

Comparing surgical (device exchange) and conservative approaches to pump thrombosis, the superiority of surgical management was again confirmed. The 1-year freedom from stroke or death was 87.5% and 49.5% in the surgical and medical cohorts, respectively (P=0.027). Resolution of a primary hemolysis event without CVA or death occurred in 87.5% patients treated with surgical interventions and in 52.0% on medical therapy alone. A similar association between treatment and outcome was noted in the 15 recurrent hemolysis events (73).

A meta-analysis on medical management of pump thrombosis was published by Dang et al. (74).

With different medical interventions, the success rates were as follows:

- Heparin alone 23%
- Heparin +IIB/IIIA antagonists or direct thrombin inhibitor 49%
- IIB/IIIA or direct thrombin inhibitor 49%
- Thrombolytics alone or in combination with other agents 66%
The highest rate of major bleeding was observed in the combination of heparin and IIB/IIIA antagonists or direct thrombin inhibitor at 35%. This therapy also caused the maximal amount of intracerebral bleeds (18%). Death was most commonly reported after thrombolytics (20%), and the rate of intracerebral hemorrhage was 17%, but only when thrombolytics were used in combination with two or three other agents such as IIB/IIIA antagonists and direct thrombin inhibitors.

In yet another comparison of device exchange or systemic thrombolysis for pump thrombosis, patients were not randomized. If treatment was started in the first 24 hours after the diagnosis of pump thrombosis, thrombolytics were given, specifically either Tenecteplase (100 U/10 kg body weight) or Alteplase (1 mg/kg body weight) given as bolus infusions over 1 hour. Heparin was stopped for the infusion, but restarted when it was over. If there was more than 24 hours since the beginning of pump thrombosis, pump exchange was performed. A 90-day survival was 91.0% in surgical management and 89.3% in systemic thrombolysis. Thrombolytics were associated with fewer blood transfusions, shorter intensive care unit stay, However, 90-day even free survival was 89% in the device exchange group and 60.7% in the thrombolytics group (P=0.027), and 2 year event free survival was 55.2% and 18%, respectively (p = 0.006), favoring pump exchange (75).

Gastrointestinal Bleeding

Degradation of von Willebrand factor in LVAD was tested in the mock loop at speed range 8600 to 11400 rpm, with no difference found, meaning that speed reduction by itself does not result in better preservation of this factor (76).

Sheer stress, ADAMTS-13, and dysfunctional platelets with abnormal aggregation are all essential in the development of LVAD related coagulopathy (77). In patients with HMIII, the preservation of von Willebrand factor was much better than with HMII (78).

Although platelet dysfunction and acquired von Willebrand syndrome make it easier to bleed, the source of GI bleeding in LVAD is almost always arteriovenous malformations in the small bowel, and their origin is poorly understood. Patel et al. hypothesized that easily accessible nasal mucosa can be representative of GI tract. In 80 patients with VAD, they performed a bedside nasal endoscopy and looked for hypervascularity (Figure 6). This was present in 63%, 57%, and 20% of the LVAD, HF, and control groups, respectively (p = 0.018). Although the prevalence was similar, the severity of nasal hypervascularity was significantly higher in the LVAD group compared with the HF group. Hypervascularity was strongly associated with GI bleeding in the LVAD cohort: the incidence was 32% in subjects with hypervascularity compared with 0% in subjects with normal mucosa (p = 0.023) (79). Similar prevalence of arteriovenous malformations in HF and
LVAD is an interesting finding which likely means that changes related to VADs are not responsible for growth of small bowel arteriovenous malformations.

Figure 6. Arteriovenous malformation in the small gut and in nasal mucosa. Reproduced from Patel et al. (79), with permission.

Anecdotally, a patient who had multiple episodes of GIB after LVAD due to angiodysplastic lesions in the upper GI tract, managed with heparin alone, warfarin alone with subtherapeutic or therapeutic INR, topical argon plasma coagulation of the lesions, and being off aspirin, stopped bleeding only when anticoagulation was changed to apixaban 2.5 mg twice daily, and there was not a single episode in the next year (80).

In a single center retrospective study, concomitant use of antidepressants in LVAD patients, specifically selective serotonin reuptake inhibitors, was associated with higher rate of GI bleeding. Both unadjusted relative risk (2.35 with 95% CI, 1.05–5.28; p = 0.04), and odds ratio after adjusting for age, sex, and use of GI prophylactic agents (3.72 with 95% CI,1.16–11.89; p = 0.03) indicated connection between the two variables (81).

Infections in LVADs

The review on endocarditis in VAD patients was published in 2016. LVAD-associated endocarditis is defined as clinical evidence of pump and/or cannula infection along with the presence of vegetation on echocardiography or a vascular phenomenon as defined by modified Duke’s criteria. Mortality is high around 60%. The common pathogens include Staphylococcus, Pseudomonas and Streptococcus species, as well as fungi. Aggressive management of infection, with prompt device removal and prolonged antibiotic therapy targeting the specific organism, is crucial to prevent catastrophic events, and the threshold for use of antifungal agents such as fluconazole should be low (82).
Right ventricular failure

Right ventricular failure after LVAD remains a serious problem, and no single measurement or criterion can reliably predict it. A review paper on predictors of RV failure after LVAD implant was published by Neyer et al. Clinical right HF, with the need for inotropic support and occurring more than 30 days after discharge from the LVAD implant (late right heart failure) was studied by Rich et al. This complication developed in 8% of patients after a median time of 480 days on support. These patients had worse quality of life, poorer functional capacity by 6-minute walk distance, and more rehospitalizations. A higher preoperative blood urea nitrogen and increased central venous pressure-to-pulmonary capillary wedge pressure ratio were independent predictors of this condition (83).

In terms of treatment of RV failure, both planned implantation of biventricular pump (84) and use of two Heartware devices are viable options. In a series of 13 patients (10 of them INTERMACS level 1, including seven patients on extracorporeal life support or intra-aortic balloon pump), transplantation was successfully performed in 5 patients, and overall survival for the entire cohort was 54%. RVAD pump thrombosis occurred in 4 cases (85).

The need of RVAD + LVAD before transplantation is independently associated with post-transplant mortality (hazard ratio 1.22, 95% confidence interval 1.01-1.49, p = 0.04) (86).

Driveline fracture

Driveline fracture is a serious complication. To our knowledge, the largest study on driveline fracture and a procedure for full external lead replacement was published in our journal.

A total of 321 repairs were attempted in 297 patients with suspected isolated external lead damage after a median of 2 years of support. In 37 (12.5%) patients, attempts at external repair were unsuccessful due to concomitant internal lead damage. 31 patients (10.4%) had additional serious malfunctions after lead repair resulting in 17 with repeat repairs and 14 who continued on ungrounded cables, and ultimately 14 of these 31 patients required pump exchanges. 27 of the 297 patients (9.1%) with lead repairs had only minor additional problems, including cuts or abrasion in the insulation which was fixed with tape or external reinforcement. There was only one catastrophic failure during attempted lead repair requiring emergent pump exchange. Three patients died within 14 days of attempted repair related to continued percutaneous lead damage. Majority (68%) have had no recurrence of lead problems. Authors provided an algorithm for evaluating potential lead damage (87).
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