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Editorial Review

What Did We Learn about VADs in 2021?

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Abstract

This is our 8th annual literature review on mechanical circulatory support (MCS) devices.

Our previous reports were well received by the readers. The full text of the reviews for 2014, 2015, 2016, 2017, 2018, 2019, and 2020[1-7] were downloaded 821, 861, 701, 869, 951, 272, and 365 times, respectively.

In this review, we summarized the most interesting and important, from our standpoint, publications from 2021. There may be some slight overlap with the end of 2020 because some papers were published online first, and the year of the publication changed when they became available in print.

For the fifth time, we added a section on extracorporeal membrane oxygenation (ECMO), which primarily addresses new developments in veno-arterial ECMO.

Readers who wish to supplement this review, argue with the author's statements, or express their opinions are encouraged to do so by sending letters to the editor at mguglin@iu.edu or posting on our Facebook page at https://www.facebook.com/TheVADJournal.

Outcomes

The Society of Thoracic Surgery and the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) 2020 Annual Report reviewed outcomes in 25,551 patients undergoing primary continuous flow left ventricular assist device (LVAD) implantation between 2010 and 2019. In 2019, a total of 3,198 primary LVADs were implanted, which is the highest annual volume in the registry history. The HeartMate 3 (HM3) device (Abbott Laboratories, Abbott Park, IL) became the dominant choice and accounted for 77% of LVAD implants in 2019.[8] There was no difference in 2-year survival (72% versus 74%) between those who received LVADs from 2014-2016 and those implanted during 2017-2018, respectively.[9] However, this recent analysis also showed that both 1- and 2-year survival improved when outcomes from 2015-2019 were compared to 2010-2014 (82.3% and 73.1% versus 80.5% and 69.1%, respectively; P < .0001),[8] which indicates overall progress and signals that, as a whole, the field is moving in the right direction.

There were interesting developments in the outcomes of patients with two centrifugal devices implanted in the right and left sides (biventricular support). A systematic literature review of biventricular support was completed by Farag et al.[10] Studies that analyzed cases with right atrium (45%) and right ventricle (RV) cannulation (55%) were included in the review. Thirty-day survival had a median of 90% (interquartile range [IQR] 82–97.8%), and 12-month survival had a median of 58.5% (IQR 47.5–62%). These results are consistent with prior reports.[11] According to data from several centers, when biventricular support used the Heartware ventricular assist device (HVAD, Medtronic, Minneapolis, MN), survival for 1- and 2-years was 56% and 47%, respectively, and there was no difference in survival when comparing the right atrial and RV implantation techniques of the right-sided device.[11] However, per the systematic literature review, a Kaplan-Meier analysis showed a higher 1-year survival with implantation in the right atrial versus the RV (91.7% versus 66.2%, P = .036). Pump thrombosis occurred at a similar rate of 30%.[12]

For the first time, the outcomes of biventricular support with two HM3 pumps were published in 2021. Previously, a case report referred to this configuration as a "HeartMate6."[13] In a single-center study from Australia, McGiffin et al. described their experience with biventricular support (using the HM3 with left ventricle [LV] and right atrium implantation) in 12 patients.[14] The outcomes were dramatically different from all previous reports. At 18 months after the procedure, 42% (5/12) of cases received a heart transplant, another 42% (5/12) were alive on biventricular support, 1 (8.3%) patient died, and 1 (8.3%) patient underwent VAD explantation for myocardial recovery. Actual survival at 18 months was 91.7%.[14]

In 2021, the HVAD was taken off the market; however, 4,000 patients remain supported with this device worldwide. In cases of device failure, the only option for patients who are not transplant candidates is an exchange to the HM3. The outcomes of such exchanges were collected from the INTERMACS registry. Although feasible, such exchanges were associated with significantly reduced survival compared with survival while remaining on HVAD support. At 6 months after exchange, survival was 73.8% (70% confidence interval [CI], 68.6-77.8%) for an HVAD to HM3 exchange as compared to 79.0% (70% CI, 78.3-79) for continued HVAD support. Furthermore, at one year, HVAD to HVAD exchanges had a survival

of 85.9% (70% CI, 79.5-90.5%) as compared to the 66.6% (70% CI, 63.0-70.0%) (P = .009) documented after HVAD to HM3 exchanges.[15]

HeartWare: The End of the Chapter

In the world of mechanical circulatory support (MCS), 2021 will always be remembered as the year when the HVAD was pulled from the market. The HVAD is a remarkable device, with an elegantly designed, durable pump. It was the first intrapericardial LVAD, and it saved or prolonged the lives of thousands of people. The size and design of this pump allowed for biventricular support. For the first time, two LVADs could be implanted in the LV and either in the RV or right atrium. Thus, it is worth reviewing the history of the HVAD and giving credit to notable studies that advanced the field and taught us many lessons.

- A clinical trial demonstrated the noninferiority of Heartware to HMII in terms of survival on the originally implanted device, transplantation, or explantation for ventricular recovery at 180 days as well as improvement in functional capacity and quality of life.[16]
- The FDA approved the device in 2012.
- Heartware became the first continuous flow pump used for biventricular support.[17]
- The Evaluate the HeartWare Ventricular Assist System for Destination Therapy of Advanced Heart Failure (ENDURANCE) proved a non-inferiority of HeartWare to HMII in safety and effectiveness. Briefly, survival free from disabling stroke or need for device replacement at 2 years was 55.0% for HeartWare and 57.4% for HMII (not significant). The rates of complications were similar except for stroke which was more prevalent in HeartWare (29.7% vs. 12.1%, P < .001).[18]
- A post hoc analysis of HeartWare recipients revealed that mean arterial blood pressure measurements of ≤90 mmHg were associated with a lower frequency of strokes, particularly hemorrhagic strokes. The ENDURANCE Supplemental Trial tested the enhanced blood pressure protocol and showed that it significantly reduced both blood pressure and the incidence of ischemic stroke.[19]
- The LATERAL trial established that Heartware can be implanted through a less-invasive approach using a thoracotomy. Over a 6-month follow-up period, 88% of patients were alive on the original device and free from a disabling stroke, proving that this approach was a safe and effective alternative to median sternotomy.[20]
- More than 19,000 devices were implanted over the lifecycle of Heartware.[21]
- The FDA terminated the use of the Heartware device in 2021.

Why did the company and the FDA decide to pull it off the market? Having no access to inside information, what we can conclude comes from published sources. There were multiple reasons for the termination of the device's production.

- **Cerebrovascular accidents.** The higher rate of cerebrovascular accidents (CVAs) in patients supported with Heartware as compared to those supported with HeartMateII (HMII) (Abbott Laboratories, Abbott Park, IL) or HM3 haunted the device for years after the publication of the ENDURANCE

study.[18] Although there was never a randomized controlled trial, when testing Heartware against other devices, all comparisons favored other pumps. The most recent INTERMACS analysis, using propensity score matching, showed that freedom from stroke of any kind was 82% in Heartware versus 92% in HM3 (P < .001). This difference was bigger in the chronic phase than in early post-implant.[22]

- **Pump thrombosis.** The rate of pump thrombosis was reported at 8.1% for Heartware[23] and 1.5% for HM3.[24]
- **Recalls.** Heartware was the subject of 35 FDA recalls, which was 7-fold that of HeartMate II. The reasons for recalls included electric discharges leading to pump failure, malfunctions of the pump controller, and numerous issues relating to adapter cables and batteries.[21,25]

It certainly looks like the fully magnetically levitated technology used in the HM3 is delivering overall better clinical outcomes than hybrid levitation used in the HVAD. As new data were published, the ability to compete against the HM3 was getting progressively more difficult. Today, HM3 data has demonstrated superiority in terms of survival, pump thrombosis, CVA, and gastrointestinal (GI) bleeding. The HM3 pump can support patients with decreased doses of antithrombotics and anticoagulants, which further diminishes the risk of bleeding complications. All of the data supports the resulting increasing share of HM3 in new LVAD implants. Yet, the HVAD remains more suitable for smaller patients, which is a meaningful clinical advantage. Unfortunately, the number of patients with small torsos is not large enough to offset all other disadvantages. Kirklin and Stehlik stated, “Medtronic would have to determine whether improvements to identified shortcomings of the HVAD would improve clinical outcomes to approximate the results seen with HM3.”[26] Thus, the Medtronic decision to discontinue the pump altogether, except for ongoing support of already implanted devices, may appear reasonable and responsible from a business perspective, although it took many physicians by surprise. It is important to note that prominent figures in the field disagree with the decision. According to O. Frazier, the decision to abandon HVAD was a “premature and unjustified choice.”[21]

Candidate Selection

Adult Congenital

Worldwide experience with the use of durable VADs in adult congenital heart disease is limited, especially when dealing with decompensated systemic RV or a single ventricle. Several recent publications prompted us to look into this topic. Although we focus on the adult patients in the present review, some sources referenced in this section have mixed or even predominantly pediatric cohorts.

As patients with congenital heart disease enter adulthood, their care is often switched to adult cardiologists; however, the majority of these physicians are not trained to deal with complex issues such as systemic RV or Fontan circulation. While adult congenital heart disease specialists take care of such patients, there are overlapping areas where cardiologists, who were trained in traditional, adult-oriented programs, have to make decisions on adult congenital patients. Such areas include cardiac transplantation and MCS. The experience of durable LVADs (whether used for RV or LV support) in adult congenital heart disease is limited.

Because a number of papers on the topic were published in 2021, including a thorough review by Villa et al.,[27] we are briefly reviewing them here.

Single Ventricle (Fontan)

Complications of Fontan circulation include:

- Protein losing enteropathy
- Renal insufficiency
- Sarcopenia
- Plastic bronchitis
- Liver insufficiency
- Hepatocellular carcinoma

Like in traditional cardiomyopathy, the pump is beneficial in VAD patients with dilated and failing systemic ventricles. In a patient with Fontan circulation, the VAD is going to be of most benefit when there is systolic dysfunction of a systemic ventricle with increased end diastolic pressure.

Surgical planning for the VAD implantation in a patient with Fontan circulation is more complex when compared to adult patients with common ischemic or nonischemic cardiomyopathy. The VAD implantation in this patient population commonly results in:

- A decrease in Fontan pressure
- An increase in pulmonary blood flow
- An increase in cardiac output
- Improved oxygen saturation

Given the frequency and severity of liver disease in patients with Fontan circulation, some advocate for a low threshold for liver biopsy if the noninvasive imaging provides any concerning results.[27] Some centers employ 3-D modeling and virtual implantations before actual surgery.[27] Despite a potential risk of thromboembolism, placement of fenestrations is also recommended for improved blood oxygenation.[27]

Existing veno-venous (V-V) collaterals may result in postoperative cyanosis. If the patient is an adult and has had a Norwood, the ascending aorta is usually quite large (59 cm), short, and thinned out; therefore, axillary, femoral, or innominate cannulation should be entertained so placement of a side-biting clamp is possible.[27] Other technical challenges to LVAD implantation in patients with Fontan circulation include:

- Multiple prior sternotomies (can be as many as seven)
- Arterio-venous and V-V collaterals along with liver dysfunction increase the risk of bleeding
- Arterio-venous collateral flow may require upsizing of bypass cannulas
- If there are concerns about placing the outflow graft on the ascending aorta (i.e., calcified homograft patch), an outflow graft may be sewn to the innominate artery
- In RV systemic ventricle, extensive trabeculation excision is required[27]

Patients with Fontan circulation have one of the highest mortality rates (up to 33%) on the waiting list for cardiac transplantation.[28,29] LVADs are one of very few means to support them. Last year, the largest study of this patient population (n = 55)

receiving LVAD support was published on data from INTERMACS and PediMACS. Only 12 (22%) patients were older than 18 years of age (median age at implantation was 10.2 years [IQR, 6.4-16.9 years]).[30] While 89% of devices were implanted as systemic VADs (systemic LV support in 66% and systemic RV support in 24% of patients), the remaining patients received biventricular support or a total artificial heart. At 6 months, the mortality rate was 76% with 58% of the deaths occurring during the first month of device support. The median length of support was 3.8 months (IQR, 0.6-6.9 months). Five patients were supported for over one year with no added mortality; the longest support time was 4 years and 7 months. Adverse events included pump thrombosis (4%), stroke (5.5%), GI bleeding (7%), and other bleeding (9%).[30] The authors did not provide an analysis of the outcomes based on the type of support or age of the patients.

Another analysis of patients with Fontan circulation was published from the Advanced Cardiac Therapies Improving Outcomes Network.[31] A total of 45 adult patients were included in this analysis, and the most commonly employed device was the HeartWare (56%). A total of 28.9% of patients were discharged on device support, and 67% of patients experienced adverse events, the most common of which were neurologic (25%). At 1 year after device implantation, the rate of transplantation was 69.5%, while 9.2% of patients continued to be VAD-supported, and 21.3% of patients died. Hemodynamically, VADs were effective in decreasing both Fontan and ventricular end-diastolic pressures in some individuals. Importantly, it is unclear how many of these patients overlap with the above-mentioned study that used the INTERMACS and PediMACS registries.[30]

Three adult patients (aged 22, 32, and 47 years) received HM3 for systemic ventricular support at Cincinnati Children's Hospital. Two patients had Fontan circulation, and one had transposition of the great arteries, status post Mustard operation. All three patients survived with a satisfactory quality of life. After the procedure, both patients with Fontan circulation had a decrease in Fontan and pulmonary capillary wedge pressure. All three patients experienced an increase in arterial and mixed venous oxygen saturation. One patient ultimately underwent heart transplantation 1,104 days after VAD implantation, and the other two patients remained on HM3 support for 952 and 407 days.[32]

Another case report described a 22-year-old man with a history of double outlet RV and mitral atresia. He underwent a Norwood procedure, followed by a bidirectional Glenn, tricuspid valve annuloplasty, and fenestrated lateral tunnel Fontan with repeat tricuspid valve annuloplasty by the age of 4. He had mild-to-moderate systolic dysfunction and tricuspid regurgitation through his teenage years with minimal functional limitations. He decompensated and required inotropic support with associated acute kidney and liver injury and new onset atrial tachycardia. He also later developed aortic insufficiency. He received an HM3 and was successfully bridged to heart/liver transplantation.[33]

Systemic RV

Patients with systemic RV typically develop heart failure (HF) in adulthood. Tadokora et al.[34] reported the outcomes of LVAD implantation in four patients. Two patients underwent congenitally corrected transposition of great arteries and received EVAHEART (Sun Medical, Nagano, Japan) and HM3 devices. The other

two patients underwent a Mustard procedure (atrial switch) for transposition of great arteries and received HMII and HM3 devices. The age of the patients ranged from 34 to 56 years. The median intensive care unit (ICU) stay was 5 days (range 4–17 days), and all patients were discharged from the hospital. One patient was transplanted four years later, and the others remained on support at the time of publication. All patients showed increased cardiac output and a substantial reduction in pulmonary capillary wedge pressure, pulmonary arterial pressure, and pulmonary vascular resistance. In addition, the severity of tricuspid regurgitation markedly decreased.

Elderly Patients

In yet another INTERMACS analysis, mortality in patients aged <65 years, 65-75 years, and >75 years was 34%, 54%, and 66%, respectively, with a median follow-up of 15 months.[35] In the most recent years, mortality has decreased with newer-generation devices. When stratified by era, 3-year survival on support significantly improved in patients >75 years of age. From 2010-2012, survival was 43% for elderly patients receiving durable LVADs as compared with 46.3% from 2013-2016 and 55.7% from 2017-2020. Interestingly, and paradoxically, complications such as stroke, device malfunction or thrombosis, and rehospitalizations decreased with increasing age (all $P < .01$). Functional status, assessed by a 6-minute walk distance, and quality of life improved in all age groups.[35] Therefore, age over 75 cannot be considered a solo contraindication to LVAD implantation.

Non-inotrope Dependent Patients

Out of the seven profiles of the INTERMACS classification, profiles IV to VII include patients who do not require inotropic support. The decision to initiate LVAD support in this group of patients is the most difficult. They are at a relatively low risk of surgical and early postoperative death; thus, they need to attain a major improvement in functional status to justify the risk of complications and lifestyle modifications that come with LVAD implantation. In the past, the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) study addressed this group of patients. The ROADMAP was a prospective, multicenter, observational study. The primary composite endpoint was survival on original therapy with improvement in 6-minute walk distance. After a two-year follow-up, survival with improved functional status was better with the HMII LVAD as compared with medical management alone.[36] In 2021, the data from a large French registry studied mortality in non-inotrope dependent patients receiving an LVAD (303 patients). The overall likelihood of being alive while on LVAD support or having a transplant at 1, 2, 3, and 5 years was 66%, 61.7%, 58.7%, and 55.1%, respectively. Based on their analysis, the authors cautioned that such patients might not be the candidates to benefit most from LVAD implantation.[37]

Left Ventricular Size

Two studies, published in 2021, addressed the issue of LV size and outcomes after LVAD implantation. In the first one, the analysis of the INTERMACS database (centrifugal devices only) showed that increased LV end-diastolic dimension was associated with lower mortality (hazard ratio [HR], 0.91; 95% CI 0.84–0.98; P = .01), stroke (HR, 0.85; 95% CI 0.77–0.93; P < .001), and GI bleeding (HR, 0.88; 95% CI 0.80–0.97; P = .01). Although, there were more arrhythmias in this group (HR, 1.14; 95% CI 1.05–1.24; P = .003). The patients in the lowest quartile with an LV size <6.1 cm had the worst survival rate.[38]

In another cohort of 313 patients with a centrifugal-flow LVAD from the Medstar Washington Hospital Center, a cut-off point of 59 mm for LV end-diastolic diameter predicted worse survival. In patients with smaller ventricles, survival was lower than in larger LV end-diastolic diameter patients (71% versus 85% at 1 year; 58% versus 80% at 2 years, P = .003). The incidence of late RV failure (23% versus 12%, P = .02) and need for temporary RV mechanical support was significantly higher in the smaller LV cohort (11.5% versus 1.9%, P = .002). Pump flows at the time of discharge were lower in the smaller LV group (3.8 versus 4.2 L/min, P = .005). The smaller LV group also had a higher rate of GI bleeding (0.416 versus 0.256 events per patient-year, P = .025), and higher readmissions secondary to low flow alarms (0.429 versus 0.240 events per patient-year, P = .007).[39]

Management of Patients on LVAD Support

Aortic Changes

Chronic LVAD support changes cardiovascular physiology and results in structural changes. Investigators reported a significant increase in the thickness of the collagen-rich adventitial layer in the aorta, and the amount of fibrosis correlates with the duration of LVAD support.[40] The aortic wall becomes stiffer on LVAD support, especially if the device is run at a high speed. Patients with increased aortic stiffness have a higher rate of a composite outcome of GI bleeding, stroke, and pump thrombosis.[41]

Pregnancy on LVAD

A review included all publications on LVAD-supported pregnancies and described 6 women from 19 to 36 years of age. All cases suffered from nonischemic cardiomyopathy and conceived while on LVAD support. One pregnancy ended with fetal demise, but the other five women delivered, mainly via cesarean section.[42] Another case report, not included in the above review, described a successful pregnancy of a 23-year-old woman on LVAD support who delivered a healthy baby via cesarean section. Of note, the LVAD speed was increased in the last trimester.[43]

Medical Management

In our prior annual reviews, we summarized papers reporting beneficial effects of the continuation of guideline-directed medical therapy. Last year, another study highlighted the difference between angiotensin-converting enzyme inhibitors

(ACEI/ARB) and mineralocorticoid receptor antagonists.[44] Per the analysis of the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support (ISHLT IMACS), the Kaplan-Meier survival was significantly better for patients receiving ACEI/ARB (P < .001) but not aldosterone antagonists. A Cox proportional hazard analysis was adjusted for known predictors of mortality following LVAD implantation, and ACEI/ARB (HR 0.81 [95% CI 0.71-0.93], P < .0001) but not aldosterone antagonists (HR 1.03 [95% CI 0.88-1.21], P = .69) were independently associated with lower mortality. Among patients treated with ACEI/ARB, there was a significantly lower unadjusted risk of cardiovascular death (P < .001), GI bleeding (P = .01), and a lower creatinine level (P < .001). Aldosterone antagonist therapy was associated with a lower risk of GI bleeding (P = .01), but a higher risk of hemolysis (P < .01).[44]

With the ongoing enthusiasm for sacubitril/valsartan in the HF community, the experience of using this drug in the LVAD population is also growing. After the first series of 5 patients was published in 2020,[45] more reports were published in 2021. The use of angiotensin receptor-neprilysin inhibitors (ARNIs) was reported in a 10-patient cohort from the Cleveland Clinic,[46] and another report included 22 patients from several European countries.[47]

One study analyzed 21 patients on stable LVAD support who were initiated on sacubitril/valsartan. While 5 patients could not tolerate the drug, 16 (76%) successfully initiated sacubitril/valsartan therapy and were assessed at baseline and 3 months. Sacubitril-valsartan was kept at 24/26 mg (twice a day) in 37% of patients, uptitrated to 49/51 mg (twice a day) in 44% of patients, and reached 97/103 mg (twice a day) in 19% of patients. The mean arterial pressure trended lower at 3 months (89 ± 8 to 83 ± 10 mmHg, P = .09). Daily loop diuretic requirements also decreased significantly as furosemide equivalents fell from 143 ± 145 to 79 ± 94 mg/day (P = .007), and functional capacity improved.[48]

In a study out of Columbia, 30 patients tolerated ARNi for at least 3 months. The NT-proBNP levels significantly decreased from a median of 1265 pg/mL at initiation to 750 pg/mL at 3 months and 764 pg/mL at 6 months (P = .01). There was a trend toward a decrease in blood pressure, with a median mean arterial pressure of 91.5 mmHg at initiation, 88.5 mmHg at 3 months, and 83.0 mmHg at 6 months (P = .14).[49]

Kidneys

The renal function typically improves after LVAD implantation; improvement is very steep in the first month and then incurs a subsequent and gradual decline.[50] Patients with severely compromised function before the LVAD implantation experience a greater improvement. By the end of the first six months of support, the estimated glomerular filtration rate is usually greater than before the surgery.[50] Last year, a detailed study on renal function post-LVAD implantation described changes over 8 years of support.[51] Although a gradual decline in function continues, at the end of the study, the glomerular filtration rate was still very good (50 to 60 mL/min/1.73m^2). Patients with a preoperative estimated glomerular filtration rate less than 50 mL/min/1.73m^2 benefited the most. The post-LVAD implantation survival did not differ between patients with pre-LVAD glomerular filtration rates above and below 60 mL/min/1.73 m^2.[51]

Nevertheless, individual programs often hesitate to implant an LVAD in patients with severely compromised kidney function. While end-stage renal disease requiring continuous renal replacement therapy (CRRT) is a contraindication to LVAD per ISHLT guidelines,[52] there is no guidance on potential kidney failure after the implantation. Although the transition to end-stage renal disease after LVAD implantation is infrequent, it does occur, and long-term care for dialysis-dependent patients on LVAD support is challenging. We previously reported our experience with such cases.[53] The barriers to finding a hemodialysis center for an LVAD-supported patient include:

- No detectable blood pressure in a large proportion of patients, which requires the need for Doppler to monitor blood pressure
- Chronic anticoagulation resulting in increased bleeding risk
- Increased infection risk with regular intravenous access, especially in the presence of dialysis catheters
- Significant hemodynamic shifts due to rapid removal of large amounts of fluid, triggering symptoms of dehydration and suction events
- Unfamiliarity with technology among dialysis personnel and presumption of LVAD patients as “high risk”

There are also concerns about proper maturation of an arteriovenous fistula in the setting of decreased vascular reactivity, although some studies reported normal maturation.[54] Importantly, peritoneal dialysis offers advantages and disadvantages.

Advantages:

- Lower risk of infectious complications
- Opportunity to perform dialysis at home
- Sustained daily ultrafiltration with peritoneal dialysis offers more hemodynamic stability
- Better preservation of residual renal functions
- Higher chance of renal recovery

Disadvantages:

- Danger of the driveline going through the peritoneal space
- Lack of precision/predictability on the amount of fluid removal
- Potential worsening of diabetes mellitus due to the continuous glucose absorption from glucose containing peritoneal dialysis solutions
- Nutritional risk due to peritoneal albumin losses

There are very few cases published on peritoneal dialysis in patients with LVADs. Two of them were published in 2021, but because there are so few, all will be listed in this review.

- A 63-year-old man required peritoneal dialysis before LVAD implantation. As kidney function improved, he was taken off dialysis. In the postoperative period, peritoneal dialysis was again required for 11 days, after which he suffered a stroke and was transitioned to comfort care.[55]
- A 78-year-old man had cholesterol embolic disease and started on hemodialysis while on LVAD support. Unfortunately, he could not tolerate the hemodialysis because of hypotension and suction events. The lines had to be removed due to bacteremia. Because the LVAD driveline exited in the left lower quadrant of the patient’s abdomen, the peritoneal dialysis catheter was placed in the right lower quadrant as far from the driveline as feasible.

A year later, he was comfortable on home peritoneal dialysis, with no episodes of peritonitis and no hospitalizations for HF.[56]

- A 55-year-old patient developed end-stage renal disease 6 years after receiving an HVAD; peritoneal dialysis was initiated. The LVAD flow was steady. The patient died from encephalitis 16 months later.[57]
- A woman in her 50's developed end-stage renal disease after LVAD implantation and could not tolerate outpatient hemodialysis due to hypotension. She was transitioned to peritoneal dialysis and tolerated it well for 6 weeks. Her kidney function then recovered, and she was taken off dialysis.[58]

It is noteworthy that in no instance did these patients develop complications of peritoneal dialysis, providing support that this therapy might be a valuable option to explore in patients who develop end stage renal disease after the LVAD implantation.

Pulmonary Hypertension

Pulmonary hypertension in HF is well studied. It is known that compensation of HF with normalization of filling pressure alleviates pulmonary hypertension, but rarely normalizes pulmonary arterial pressure. Reactive pulmonary hypertension is of particular clinical importance because it persists after normalization of intracardiac pressures. The INTERMACS analysis provided interesting data on the effects of LVAD on pulmonary hypertension in patients with pulmonary vascular resistance greater than 3 Wood units before LVAD implantation.[59] It appeared that in these patients, pulmonary vascular resistance decreased by 1.53 Wood units (95% CI 1.27-1.79) per month in the first 3 postoperative months and by 0.066 Wood units (95% CI 0.060-0.070) per month thereafter. Severe mitral regurgitation at any time during follow-up was associated with 1.29 Wood units (95% CI 1.05-1.52) higher pulmonary vascular resistance relative to absence of mitral regurgitation at that time. Importantly, 15%-25% of patients had persistently elevated pulmonary vascular resistance of greater than 3 Wood units at any given time within 36 months after LVAD implantation.[59]

Arrhythmia and Electrophysiology

Cardiac Resynchronization Therapy

Multiple publications have reported that cardiac resynchronization therapy (CRT) does not affect outcomes in patients with LVADs. Intuitively, because the circulation in these patients is provided by *both* the continuous flow pump and the patient's own LV, biventricular pacing should still be of some benefit. Indeed, Tomashitis et al. studied patients with LVADs who underwent right heart catheterizations that were performed at different pacemaker configurations (biventricular pacing, left ventricular pacing, RV pacing, and no pacing) in a randomly generated sequence for >3 minutes between configurations. RV contractility, as assessed by RV maximal change in pressure over time normalized to instantaneous pressure, was higher in biventricular pacing as compared with unpaced conduction (15.7 ± 7.6 versus 11.0 ± 4.0 s^{-1}, respectively; P = .003). Cardiac output was higher in biventricular pacing

when compared with unpaced conduction (4.48 ± 0.7 versus 4.38 ± 0.8 L/min, respectively; P = .05). There were no significant differences in heart rate, ventricular filling pressures, or atrioventricular valvular regurgitation across all pacing configurations.[60] The data from the multinational Trans-Atlantic Registry on VAD and Transplant also showed no differences in survival when comparing the presence or absence of CRT. Interestingly, in comparison to no device, only CRT with a defibrillator was associated with late RV failure (HR 2.85, 95% CI 1.42-5.72, P = .003). There was no difference in risk of early RV failure across the groups or risk of implantable cardioverter defibrillator (ICD) shocks between those with ICD and CRT-defibrillator.[61]

This topic received an unexpected development in the prospective randomized crossover study of Chung et al.[62] LVAD patients with prior CRT devices were alternated on RV and biventricular pacing for planned 7-14-day periods. Compared with biventricular pacing, RV-only pacing resulted in a 29% higher mean daily step count, 11% greater 6-minute walk test distance, and 7% improved quality of life score (all P < .03). LV end-diastolic volume was significantly lower with RV pacing (220 versus 250 mL; P = .03). Fewer patients had ventricular tachyarrhythmia episodes during RV pacing (P = .03). RV lead impedance was lower with RV pacing (P = .047), but no significant differences were observed in impedance across other CRT leads. This study supports turning off LV lead pacing in LVAD patients with CRT. To explain this finding, the authors hypothesized that biventricular pacing may induce contraction, which places the septum or free wall closer to the LVAD inflow cannula, increasing the risk of suction events.

Ventricular Tachycardia

Ventricular tachycardia remains a problem in patients with LVADs, and it continues to contribute to mortality rates. In the cohort from Duke University, electrical storm, defined as at least 3 sustained episodes of ventricular tachycardia over a 24-hour period without an identifiable reversible cause, was experienced by 10.7% of patients at a median time of 269 (IQR 7-766) days following surgery. Following electrical storm, 41% of patients died within 1 year.[63]

Ablation may be a very effective method to treat ventricular tachycardia in LVAD-supported patients. In patients with an HM3, ablation was mostly successful. Non-inducibility was reached in 58% of patients, although 26% required a redo ablation during the follow-up.[64]

Cardiac sympathetic denervation may be an alternative or supplemental approach to reduce ventricular tachycardia and has been shown to reduce sustained ventricular arrhythmias and ICD shocks by inhibiting sympathetic outflow to the heart. Last year, the success of this strategy was described for the first time in a patient on LVAD support.[65]

Complications of LVADs

Driveline Injury

Driveline damage is rarely discussed in the literature, but last year it received some attention. D'Antonio et al.[66] analyzed 55 cases from the published literature on driveline damage. Almost all patients (53/55) were supported by HMII devices.

Internal damage was more commonly reported than external damage (69.1% versus 30.9%, respectively, P = .01). Median time to driveline damage was 1.9 years (IQR 1.0, 2.5). Most patients (94.5%) presented with an LVAD alarm, and patients with internal driveline damage had a significantly higher rate of alarm activation as compared to those with external damage (100% versus 82.4%, respectively, P = .04). In terms of management, 14.5% of patients underwent external repair of the driveline, 5.5% were treated with rescue tape, and 5.5% were placed on an ungrounded cable indicating a short-to-shield event had occurred. A total of 49.1% of patients underwent pump exchange, 5.5% were explanted, and 5.5% underwent emergent heart transplantation. The 30-day mortality rate was 14.5%.[66]

Not included in D'Antonio's[67] analysis was our cohort of 13 patients with driveline fracture (11.8% of our total LVAD single-center population at that time). We found that the mean time from implant to fracture was 23 ± 16.5 months, and the majority (62%) of fractures were external due to trauma (i.e., cut during dressing change). Usually due to unknown causes, internal injury proximal to the cutaneous exit site occurred in 38% of patients. Only 1 (7.6%) patient survived on continued LVAD support. One individual survived and underwent LVAD explantation, 2 underwent pump exchange, and 4 others underwent heart transplantation. The remaining 5 patients expired. All patients (60%) with untreated internal fractures died.[67]

Gastrointestinal Bleeding

It is widely accepted that GI bleeding in patients supported with LVADs occurs due to angiodysplasias in the small bowel that develop at an accelerated rate due to a non-pulsatile flow and bleed easily because of acquired von Willebrand factor deficiency and chronic anticoagulation. In 2021, Patel et al.[68] published a paper that challenges this concept. The authors compared the number of angiodysplasias revealed by capsule endoscopy in patients with and without HF. The prevalence of angiodysplasias was significantly higher in the HF with reduced ejection fraction group as compared to the non-HF controls (50% versus 13%, respectively, P = .0002). This association persisted after controlling for age and comorbidities. Within the HF cohort, higher angiotensin 2, NT-proBNP, and blood urea nitrogen levels were associated with the presence of angiodysplasias. Moreover, patients with severe HF (by New York Heart Association class) was associated with more angiodysplasias. Out of a total of 25 angiodysplasias, 23 were located in the small gut.[68] If indeed congestion produces angiodysplasia, it explains why optimization of hemodynamics results in reduction of GI bleeding.[69]

Another study showed that RV enlargement and tricuspid regurgitation before LVAD implantation were predictive of GI bleeding after the implantation. Also, the rate of GI bleeding in patients with LVADs without RV failure was 14.8%. In patients with mild and moderate RV failure, the rate increased to 24.2% and 23.6%, respectively (P < .0001).[70] This association of GI bleeding with RV failure may also explain another report that endoscopic evaluations and interventions for GI bleeding in patients with LVADs do not reduce further bleeding events,[71,72] but the use of digoxin does.[73] Although, Jennings et al.[74] reviewed INTERMACS data and reported that use of ACEi/ARB, aldosterone antagonists, amiodarone, and digoxin did not appear to be associated with GI bleeding during LVAD support.

Different VADs and Devices

Intra-aortic Balloon Pumps

With the new listing rules for cardiac transplantation, the use of short-term MCS devices has increased. Almost inevitably, they keep patients bedridden, which compromises their functional status. Hence, there is a growing interest in devices that allow some mobility. Intra-aortic balloon pumps (IABPs) are the easiest to place and the most used MCS devices. Axillary placement of an IABP allows patients to walk; however, the rate of complications is quite high.

In the last year's review,[7] we cited the Houston Methodist experience of 195 axillary IABPs in which 37% of patients needed replacement due to malfunction.[75] This year, investigators from the University of Chicago reported their data on 241 patients with an IABP. The devices were inserted through a graft sutured onto the axillary artery in 142 (58.9%) patients and percutaneously in 99 (41.1%) patients. The IABP was placed from the right axillary artery in 147 (61.0%) patients and left in 94 (39.0%) patients. Ambulation was possible in 90% of patients during support with this device. In total, 5.4% of patients died, and 4.1% required escalation of mechanical support. IABP-related stroke occurred in 6 (2.5%) patients. In 27.8% of cases, the pump had to be replaced due to various complications.[76] It appears that even in the best centers, the rate of complications remains high.

In the management of cardiogenic shock, in-hospital mortality was lower with the use of the IABP than without (27% versus 43%, adjusted OR 0.53, 95% CI 0.40–0.72, P < .0001). Use of the IABP was associated with lower crude in-hospital mortality in each of the Society for Cardiovascular Angiography & Intervention's shock stages (all P < .05, except P = .08 in shock stage E).[77] Moreover, it appears that in some patients, the hemodynamic benefit of the IABP may be substantially greater than the conventional estimate of 0.5 L/min increment in cardiac output. In fact, responders to IABPs demonstrated an increase of 1.21 ± 0.87 L/min. Systemic vascular resistance >1300 dynes/sec/cm^{-5} (OR, 5.04; 95% CI, 1.86-13.6; P < .01) and moderate-severe mitral regurgitation (OR, 2.42; 95% CI, 1.25-4.66; P < .001) predicted robust hemodynamic response.[78]

What is new in the V-A ECMO World?

The utilization of V-A ECMO for the management of cardiogenic shock continues to grow. There is more evidence in favor of early initiation of ECMO in shock. In a multicenter registry, participants were classified into 3 groups according to terciles of shock-to-ECMO time (early, intermediate, HR: 0.53; 95% CI: 0.28 to 0.99). Early ECMO support was also associated with lower risk for the following:

- in-hospital mortality,
- ECMO weaning failure,
- composite of all-cause mortality and rehospitalization for HF at 1 year,
- all-cause mortality at 1 year, and
- poor neurological outcome at discharge.[79]

In terms of outcomes of cardiogenic shock by etiology, a meta-analysis of patients receiving V-A ECMO support showed a mortality of 35% (95% CI: 29−42) in post-transplant patients, 40% (95% CI: 33−46) for myocarditis, 53% (95% CI: 46−59) for

HF, 52% (95% CI: 38−66) for pulmonary embolism, 59% (95% CI: 56−63) for cardiotomy, 60% (95% CI: 57−64) for acute myocardial infarction, 64% (95% CI: 59−69) for in-hospital cardiac arrest, and 76% (95% CI: 69−82) for out-of-hospital cardiac arrest (P < .001).[80] Another study on post-cardiotomy cardiogenic shock reported a very similar mortality rate of 58.3%.[81]

In past reviews, we discussed the principles and benefits of LV unloading during V-A ECMO support. A recent study highlighted the benefits of an overall negative fluid balance in such patients.[82] If patients receiving ECMO support and CRRT can achieve a negative fluid balance, they have an improved survival rate. After 72 hours, the treatment group had a fluid balance of -3840 mL versus +425 mL in patients on ECMO but not CRRT (P ≤ .05). This lower fluid balance correlated with survival to discharge (OR 2.54, 95% CI 1.10-5.87). Improvement in the ratio of arterial oxygen content to fraction of inspired oxygen was also significantly higher in the CRRT group as compared to the renal dysfunction group (102.4 versus 0.7, respectively, P ≤ .05).[82]

Additional data were published on the combination of V-A ECMO and Impella (Abiomed, Danvers, MA) support for patients with cardiogenic shock. LV unloading was studied in a propensity matched cohort of patients from 16 institutions. LV unloading was associated with a lower 30-day mortality (HR, 0.79, 95% CI, 0.63–0.98; P = .03). Complications, not surprisingly, were seen more frequently in patients with a combination of ECMO/Impella support.[83]

In a retrospective, single-center study, patients supported by V-A ECMO alone were compared to patients supported with a combination of ECMO/IABP and ECMO/Impella. ECMO/Impella patients had a higher incidence of bleeding events compared with ECMO alone or ECMO/IABP (52.8% versus 37.1% versus 17.7%, respectively; P < .0001). Compared with ECMO alone, ECMO/IABP provided better survival at 180 days (P = .005), whereas survival in ECMO/Impella was not different from ECMO alone.[84]

As the experience with V-A ECMO is growing, it is utilized in more clinical scenarios. Thus, V-A ECMO for support of thyrotoxicosis-induced cardiomyopathy complicated by cardiogenic shock was reported by several authors.[85,86] At our institution, a patient with a LVEF of 10% due to thyrotoxicosis-related cardiomyopathy underwent an emergency thyroidectomy while on V-A ECMO support which resulted in almost immediate recovery of myocardial function.[85] Another group of authors reported a case where the ECMO circuit was used for therapeutic plasmapheresis for T4 removal, which resulted in a significant improvement in thyroid and cardiac function. In their case, a total thyroidectomy was performed two weeks later.[86]

Another interesting clinical scenario was reported in several publications last year. Although rare, cardiac tamponade may occur in about 2% of patients supported by ECMO.[87] For a number of reasons, the diagnosis can be challenging. Physical diagnosis of tamponade based on the presence of pulsus paradoxus is unfeasible in a patient supported with continuous flow V-A ECMO. Hypotension with narrow pulse pressure and neck vein distension are unreliable in this situation as well. Pericardial effusion can certainly be seen on echocardiography, but ventricular interdependence may not be present because the circulation is mostly provided by a continuous flow device. It appears that any chamber collapse may be an indication for an emergency drainage of the pericardium.[88] The diagnosis may be even more

challenging in a patient on a combination of V-A ECMO and Impella support, as both provide a continuous flow circulation. In our case, a newly discovered moderate pericardial infusion and increasing pressure requirements justified the pericardial drainage with an immediate improvement of hemodynamics.[89]

V-A ECMO is also used to support patients in electrical storm to maintain hemodynamics until they are treated for electrical instability. In a single-center study, patients supported by ECMO for this indication had a survival rate of 64.7%.[90]

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