Operating in the Dark
When Is Surgery Necessary for Left Ventricular Assist Device Hemolysis?

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The benefits of left ventricular assist device (LVAD) therapy in advanced heart failure are clear—device implantation can prolong patient survival, enhance functionality, and improve quality of life. Since US Food and Drug Administration approval of the first continuous-flow LVAD in 2008, utilization has grown rapidly, and now, >2500 devices are placed annually. Given the current epidemic of heart failure, this volume may only be scratching the surface. Current estimates suggest that there are upwards of 250,000 to 300,000 potential LVAD candidates in the United States alone. Despite technological and design advances, broader application of LVAD therapy remains limited in part by its relatively high rate of adverse events (AEs). Six-month freedom from rehospitalization is only 40%, whereas 70% of patients will experience an AE within the first year of support.

In this issue of Circulation: Heart Failure, Levin et al retrospectively described hemolitic events of HeartMate II (St. Jude Medical, Pleasanton, CA) patients at 2 large academic medical centers. Specifically, they compared outcomes for patients with hemolysis managed with surgical versus medical therapy, to determine the most effective strategy. Their findings were humbling. One-year freedom from stroke or death was 87.5% and 49.5% in the surgical and medical cohorts, respectively. Resolution of primary hemolysis without stroke, death, or recurrent hemolysis was only 44% in patients treated with medical therapy, compared to 63% in patients treated operatively. Even more sobering is the realization that the surgical cohort first failed medical therapy, and thus, the true treatment response to medical therapy alone was a paltry 29%. In summary, the principal finding was that for patients meeting the author’s definition of hemolysis, a surgical strategy (after failed medical intervention) resulted in less death or stroke than a medical strategy alone, as well as greater resolution of hemolysis.

Hemolysis, a harbinger of LVAD thrombosis, remains one of the most common and feared complications of LVAD therapy, occurring in as many as 33% of patients in the first year after device implantation. In a multicenter analysis of hemolytic events from the Interagency Registry for Mechanically Assisted Circulatory Support, hemolysis was associated with an increased risk of thrombotic device malfunction, device exchange, and death. Management guidelines for hemolysis have been poorly vetted, and hence, recommendations are based largely on expert opinion. Nonetheless, several observational reports have recently demonstrated that medical therapy is associated with substantial treatment failure, and intensification of antithrombotic therapies may be associated with a high risk of complications, including intracranial hemorrhage.

From a medical perspective, heparin was the primary antithrombotic therapy utilized at these 2 centers to treat hemolysis and, similar to other reports, was largely ineffective. What is less clear is whether or not alternative antithrombotic regimens may have resulted in greater success. Data from other recent reports would suggest that the answer to this question would likely be no. When used to treat LVAD hemolysis, platelet glycoprotein IIb/IIIa inhibitors have been associated with high rates of bleeding and limited therapeutic efficacy. Additionally, although a small case series did describe a potentially favorable clinical response to the direct thrombin inhibitor, Bivalirudin, half of the patients ultimately had recurrent hemolysis after transitioning to oral Coumadin.

Early experiences with device exchange, on the other hand, were associated with high perioperative morbidity and mortality. Additionally, exchange of continuous-flow LVADs after prolonged hemolysis resulted in high rates of death. More recent reports, however, have revealed favorable outcomes after continuous-flow LVAD exchange and have reported 30-day mortality rates as low as 6.5%. In the initial report by Starling et al, highlighting changes in temporal trends of LVAD thrombosis, mortality among patients treated medically was 48.2%, whereas those treated with urgent transplantation or device exchange had survival similar to patients without thrombosis. Furthermore, evolving surgical techniques, including a nonsternotomy approach to exchange, may be associated with decreased morbidity and mortality.

The study by Levin et al begins to address the large gap that still exists in our understanding of optimal hemolysis management. Although the risks associated with hemolytic events have been described previously, this analysis provides insight into outcomes associated with specific treatment strategies. Similar to the approach taken in the current report, LVAD exchange has been historically reserved for patients with refractory hemolysis or those with overt device malfunction and hemodynamic compromise. Although operative
intervention has anecdotally become more commonplace, it has been hard to make a compelling case in favor of a potentially high-risk surgical strategy without comparative data, and clinicians have likely been reticent to pursue operative intervention without more rigorous guidance. The findings from this study vastly improve our understanding of the relative risks and benefits associated with device exchange versus watchful waiting. These data should assuage some of the fears that exist regarding earlier invasive management, even among patients who seemingly responded favorably to initial antithrombotic therapy. What remains unclear—and not addressed in this study—is the role of surgical intervention for less severe hemolysis.

It is also evident that a “one-size fits all” strategy cannot be assumed for all hemolytic events. For instance, the pathophysiology of LVAD thrombosis is likely distinct for the HeartMate II and HVAD (HeartWare, Framingham, MA) devices. Although hemolysis has been described with the HVAD device, the preponderance of data comes from the HeartMate II population. Response to medical therapy is low with both devices, although it is unclear if they might respond differently to specific interventions. The onset of hemolysis with the HeartMate II is typically subacute over weeks, and the source of thrombus is commonly associated with pannus formation at the inflow or outflow bearings. In contrast, HVAD hemolytic events are typically more acute in presentation, and abnormalities in pump parameters are often present at the time of diagnosis because of laminar fibrin formation on the impeller itself. Long-term outcomes after hemolysis episodes in HVAD recipients also remain poorly characterized, and it is unknown whether the findings associated with watchful waiting in this article can be extrapolated to the HVAD population. Device-specific algorithms for monitoring, prevention, and long-term management are likely required.

It is troubling to note and important to emphasize that device exchange does not always equate to long-term cure, as >1 out of every 4 surgically treated patients had a future hemolytic event. Recurrent hemolysis is distressing to patients, caregivers, and providers alike. Factors triggering recurrent hemolysis remain unknown. Mechanical causes related to surgical technique have been reported. The authors did not think that recurrence was related to residual thrombus in the outflow graft or inflow cannula because hemolysis cleared in all patients and screening for additional thrombus was meticulously performed. They conclude that the risk of recurrence was more likely attributable to patient-level factors. It cannot be excluded, however, that mal-positioning of the inflow cannula or outflow graft, which often was unaddressed at the time of operative exchange, predisposed to delayed recurrence. Although a nonsternotomy approach has been associated with favorable outcomes among patients undergoing exchange, it is not clear whether this approach favorably impacts recurrence risk. A recent study from Columbia University did describe similar recurrence risk with either a sternotomy or subcostal exchange. These unanswered questions further underscore the need for prospective evaluation in larger LVAD populations.

The nuances of the LVAD patient also affirm the need for individualized decision making, particularly as it relates to device strategy. Surgical exchange likely increases the risk of allo-sensitization, and its impact on transplant-related outcomes has been incompletely explored. The median time to hemolysis recurrence in a series of medically managed patients was 50 days; therefore, if a short wait time to transplant is anticipated, an attempt to bridge patients to urgent transplantation may be a rational approach. For those unlikely to be transplanted soon, however, a lower threshold for exchange would seem pragmatic. In point of fact, a higher proportion of bridge-to-transplant patients in the current study were managed medically (59%) compared with surgically (41%).

Despite the merits of this study, it is important to remember that these findings are observational. With that come inherent limitations, including the inability to assign causality. The data were pooled from 2 large academic medical centers, and institutional variations in rates of thrombosis have already been described. These are likely, at least in part, because of differences in surgical technique, medical management strategies, and the rigor by which patients are routinely monitored. The authors do not provide details regarding center-specific outcomes as related to management strategies, and therefore, a center-specific effect cannot be excluded. It is difficult to differentiate the risk of hemolysis associated with device-, patient-, or center-level factors. It is also not possible to adjust for factors that influenced the decision to operate, and it is clear that patients who were managed surgically were inherently different than those treated medically. These differences may account partially for the subsequent risk of stroke or death. Finally, it remains unclear whether an interaction could exist among patient, device type, and the individual risk of thrombosis: could individual A have a higher risk of hemolysis with device B, while individual B has a higher risk with device A? As a result, among patients with recurrent hemolytic events, whether exchange to an alternative device is safe or if it reduces the risk of subsequent events has not been answered.

The Interagency Registry for Mechanically Assisted Circulatory Support registry has been pivotal in describing the evolving risk of LVAD thrombosis over time. What Interagency Registry for Mechanically Assisted Circulatory Support lacks, however, is the granularity of data that would facilitate comparative effectiveness studies of hemolysis management strategies. The article by Levin et al highlights the need for collaborative data collection and prospective research to define best practices for the management of LVAD-related AEs. No randomized investigations to date have examined the benefits of specific interventions targeting a reduction of AEs in LVAD patients. The HeartMate 3 (Thoratec, Pleasanton, CA) is a new centrifugal continuous-flow LVAD with large gaps between the pump housing and perimeter of the rotor, as well as a biocompatible surface designed to minimize shear stress and blood trauma. Results of 50 patients who underwent implantation as part of the Conformite’ Européene Mark clinical trial remarkably had no episodes of hemolysis, pump thrombosis, or the need for exchange at 6 months. The larger US pivotal trial (Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3” [MOMENTUM 3]) is ongoing (ClinicalTrials.gov Identifier: NCT02224755). Although the device industry focuses on
technological advancements, further effort by clinical investigators should be placed on evaluating novel management strategies to mitigate the risk of AEs. The medical complexity and small sample size make conducting clinical trials in this population challenging, but our patients are depending on us to better define best practice. Results are forthcoming from the recently completed, industry-sponsored, multicenter Prevention of Heartmate II Pump Thrombosis (PREVENT) observational study investigating the risk of early HeartMate II thrombosis in 300 patients receiving standardized surgical and medical care (ClinicalTrials.gov Identifier: NCT02158403). Whether strategies targeting antplatelet therapy or novel anticoagulants could minimize the risk of bleeding and thrombotic events also remains largely unexplored. The failure of Dabigatran to prevent thrombosis in patients with mechanical valves, as well as concerns regarding the reversibility of novel anticoagulants, have limited their current investigation as viable antithrombotic agents in LVAD patients. However, the recent US Food and Drug Administration approval of new reversal agents may provide greater opportunity to study these alternative therapies.

Each patient presenting with hemolysis requires individualized decision making in the context of their history, implant strategy, and personal goals and values. The study by Levin et al is an important first step in establishing a more pragmatic algorithm for hemolysis management. The data support the evolving dogma that LVAD thrombosis is a surgical condition with perhaps a limited role for medical therapy in patients who are not surgical candidates, those who refuse repeat surgical intervention, or those in whom urgent transplantation is feasible. It is necessary to inform patients and caregivers regarding the high risk of recurrence, although stroke-free survival rates after LVAD exchange seem promising when performed at experienced centers. Reduction in LVAD-related AEs will permit expansion of this life-saving and restorative technology to a broader and potentially less sick population. So that we are no longer operating in the dark, and novel methods to improve granular data collection, enhance collaboration, and facilitate comparative effectiveness research are critical.

Disclosures

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