When VAD Things Happen to Good People

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Running Title: Right Heart Failure Following LVAD

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In his book, *When Bad Things Happen to Good People*, Harold Kushner explores explanations for human pain and suffering (1). He notes that while many of the afflictions of the human condition are beyond our understanding, none of us are exempt from the common experience. Despite the original publication of this thesis more than 35 years ago, Kushner’s musings draw parallels to the patient experience with mechanically assisted circulation. The underlying mechanism and management of several morbid and mortal left ventricular assist device (LVAD) complications are beyond contemporary understanding but are sufficiently frequent to be considered common. The paper by Soliman in this issue of *Circulation* adds clarity to the question about why VAD things happen to good people by defining pre-operative risk factors that predispose patients to the development of right heart failure following implantation of a left-sided mechanical blood pump (2).

Over the past decade, mechanically assisted circulation has been validated as an important addition in the treatment of advanced heart failure. Left ventricular assist device therapy has consistently been shown to reduce mortality, improve submaximal exercise performance, and enhance quality of life in patients suffering from advanced heart failure failing guideline directed medical and electrical therapies. However, these improvements are not without potential and real risk. The INTERMACS registry has demonstrated that 70% of patients treated with an LVAD experience a serious adverse event in the first year of support including hemorrhage, stroke, infection, device malfunction, or death (3). As a result, physician-scientists, engineers, and patients have banded together to generate hypotheses and knowledge designed to mitigate adverse events associated with therapy. Perhaps the most important challenge is hemocompatibility - the complex interplay between underlying disease,
pharmacotherapy, the clotting system, and the blood-contacting surface of the LVAD. It is reasonable to assume that development of novel materials lining the blood-contacting surfaces of the device coupled with new anticoagulation and antiplatelet agents will reduce the bleeding and clotting complications. Development of LVAD components that obviate the requirement for a percutaneous driveline should decrease the frequency of infectious complications.

While pump design changes and novel drugs may favorably impact hemocompatibility and infectious complications, the pathway to reducing the incidence of right heart failure using left-sided circulatory support systems is less clear. The most commonly described form of right heart failure occurs early after LVAD implantation and is variably attributed to intrinsic right ventricular (RV) dysfunction, pre-implant severity of illness, end-organ dysfunction, pulmonary hypertension, intraoperative transfusion, tricuspid insufficiency, and VAD management strategies. INTERMACS has developed a meaningful framework to diagnose RV dysfunction and stratify its severity (Figure; 4). Patients with clinical evidence of RV failure requiring prolonged inotropic support, inhaled pulmonary vasodilators, or a right ventricular assist device have statistically worse survival outcomes.

An ounce of prevention is worth a pound of cure. The challenge of post-LVAD RV failure has been the development of robust predictive models to guide patient and physician decision-making. Retrospective analyses of clinical trial databases and single center experiences have been used to develop multivariable models. While the ability of these models to predict RV failure is superior to individual risk factors, their accuracy when tested in new patient cohorts has been modest (5).
In the current issue of *Circulation*, Soliman and colleagues use patient-level data from the EUROMACS registry linked to common definitions of adverse events and outcomes to derive and test a new clinical model for the preoperative prediction of right heart failure after continuous flow LVAD placement. The investigators retrospectively analyzed 2988 patients treated with a primary LVAD and randomly stratified them into derivation (n=2000) and validation (n=988) cohorts. Preoperative predictors (n=82) including demographics, clinical variables, comorbidities, medications, echocardiographic factors, hemodynamic parameters and laboratory values as well as cardiopulmonary bypass time were entered into a univariate logistic regression model and retained for inclusion in a multivariable model if marginally significant. The final model was constructed from variables with standard statistical significance. Using INTERMACS definitions, the overall incidence of right heart failure in this cohort was 22% based primarily on the need for prolonged postoperative inotropic support. Smaller numbers of patients required a mechanical right ventricular support device or prolonged administration of nitric oxide inhalation therapy. Five variables were associated with early postoperative RV failure including INTERMACS class, use of multiple intravenous inotropic agents, qualitative determination of severe right ventricular dysfunction on echocardiography, a right atrial:pulmonary capillary wedge pressure that exceeded 0.54, and hemoglobin. These variables were used to create a numerical score to predict right heart failure (range 0-9.5). When the EUROMACS right heart failure scoring system was applied to both the derivation and validation cohorts, the model stratified risk better than previously published models. Inclusion of cardiopulmonary bypass time more than 100 minutes did not improve the predictive accuracy of the model.
While EUROMACS right heart failure score appears to be an important addition in the toolbox of LVAD clinicians, thoughtful application is necessary. For example, the relatively young patient age of this cohort and the small number of patients with high EUROMACS right heart failure risk scores raise the possibility that predictive accuracy may vary when applied to other patient cohorts. The EUROMACS investigators have recently published that women in this registry have nearly a four-fold higher risk of right heart failure following VAD implantation (6) yet the cohort upon which this right heart failure score is derived is comprised of only 18% women. The accuracy of this right heart failure score and its importance for women requires further testing. Finally, as this study only evaluated peri-operative RV failure, its applicability in the diagnosis of late right heart failure should not be assumed.

One of the challenges in the use of risk scores is clinical utility. In the end, the clinician is left using imperfect tools to counsel patients and families about the risks and benefits of high-risk interventions. While we know that while right ventricular failure following LVAD implantation is associated with increased morbidity and mortality, the vast majority of patients ultimately have good outcomes and a superior survival to that expected with advanced heart failure. The savvy clinician will continue to view risk modeling in the context of other data inputs, patient preference and tolerance for adversity, and clinical experience to guide patients along this journey.

Disclosures: Neither Dr. Samsky nor Dr. Rogers have disclosures related to this manuscript.


**Figure Legend. INTERMACS Definition of Right Heart Failure**

Definition and severity of early (<30 days) right heart failure following LVAD implantation.

LVAD: left ventricular assist device; CVP: central venous pressure; RAP: right atrial pressure; IVC: inferior vena cava; JVD: jugular venous distention; RHF: right heart failure; IV: intravenous; iNO: inhaled nitric oxide; MCS: mechanical circulatory support

**Right heart failure following LVAD implantation: must have documented evidence of elevated CVP plus manifestations of volume overload.**

**Documented elevated central venous pressure via:**
1. Direct measurement of CVP or RAP > 16 mmHg via Swan-Ganz catheter or right heart catheterization
2. Dilated IVC without inspiratory collapse by ultrasound
3. Elevated JVD at least half way up neck while sitting upright

**Manifestations of elevated central venous pressure:**
1. Peripheral edema
2. Presence of ascites or palpable hepatomegaly
3. Laboratory evidence of worsening congestion via elevated total bilirubin or serum creatinine

**Once the diagnosis of post-operative right heart failure is made, severity can be characterized via the following criteria:**

- **Mild**
  - RHF requiring IV inotropes or vasodilators and/or iNO used for ≤ 7 days post-implantation

- **Moderate**
  - Persistent RHF requiring IV inotropes or vasodilators and/or iNO used for > 7 days post-implantation but ≤ 14 days post-implantation

- **Severe**
  - Persistent RHF requiring IV inotropes or vasodilators and/or iNO used for > 14 days post-implantation or implantation of MCS device for RV support at any time
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Circulation. published online August 27, 2017;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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http://circ.ahajournals.org/content/early/2017/08/25/CIRCULATIONAHA.117.031081

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