Editorial

The Inherent Fallacy of Predicting RV Failure Following Left Ventricular Assist Device Implantation

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Across the country on day one of medical school cardiovascular pathophysiology courses, professors will pose and rhetorically answer the same question, which leads to the common refrain familiar to all cardiologists that: "the most common cause of right heart failure is. . ..left heart failure". While this precept remains as true as ever, we also expect that improvements in left ventricular (LV) function and failure will in turn translate into improvements in right ventricular (RV) function and failure. However, an exception to this rule may occur with respect to the management of LV failure with durable left ventricular assist devices (LVADs).[1] Albeit RV function often improves, or at least sufficiently stabilizes via treatment of LV failure with an LVAD, sometimes it simply does not; in fact, too commonly the RV actually worsens considerably to the point of recalcitrant shock and even death.[2] Numerous investigations designed to identify variables and risk models that can be used to predict post-LVAD RV failure have been reported.[3] Yet, the incidence of RV failure does not appear to have lessened by any considerable amount. With uncertainty surrounding this clinical scenario, many impassioned discussions continue to occur at multidisciplinary selection meetings among LVAD centers across the country.

In the present issue of the Journal, Peters et al, perhaps motivated by this state of affairs, sought to determine which variables and risk models used to predict RV failure post LVAD perform "best". They retrospectively evaluated their own center's LVAD population and identified those patients (n=16/93) who developed early RV failure (17.2%) according to a previously employed INTERMACS definition (use of inotropes for >14 days, inhaled pulmonary vasodilators for >48 hours, or unplanned need for right ventricular mechanical support post-operatively during the index hospitalization). They concluded that among risk models, the Michigan RV failure risk score was the most reliable, albeit with only modest predictive power. Adding additional individual variables (ie, pulmonary artery pulsatility index [PAPi] and preoperative RV dysfunction by echocardiography) to the Michigan model improved its discriminative ability further by a small amount. The efforts by these investigators passes the all-important "so what" test but unfortunately, it is unclear whether the present investigation will translate into meaningful change in clinical management. Below, I highlight several of the challenges that currently exist when attempting to predict risk of RV failure.

Studies designed to predict post-LVAD RV failure have been limited by heterogeneity related to 1) *when* and 2) under *what* circumstances the data are collected. Some studies have included metrics collected weeks to months prior to LVAD surgery whereas others restrict data to those collected only in the immediate perioperative time-frame.[3] Albeit intuitively the latter approach might appear most logical, perioperative data are potentially fraught with serious confounding and unanswered questions. Should hemodynamics collected while a patient is on inotropic therapy be interpreted in similar fashion to the profiles obtained in patients not requiring inotropic support? Should we assign similar weight to data obtained while the patient is in a decompensated state to those data reflective of days to weeks of "tuning" up? If the latter, should we truly be comforted that a patient who previously had an exceedingly low cardiac index and elevated right atrial pressure demonstrates improvements in these values only when subjected to support with continuous inotropes or temporary mechanical support? In fact, I would argue that modest improvements in cardiorenal and other indices of end-organ function under artificially employed treatment measures are too often likely to "falsely reassure". Albeit preferable to observing a lack of improvement, we should not be overly comforted that the patient will realize a similar clinical response to an LVAD alone when the RV-supporting inotropes are discontinued. Also, in clinical practice, we routinely collect data such as invasive hemodynamics in a single "snapshot" in time (often with the patient lying supine on a catheterization table) and extrapolate the acquired data into a firm determination of patient status and future risk.

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The present study is not absolved from challenges of data heterogeneity and interpretation among different studies with differing designs: one of the more "reliable" hemodynamic predictors of post-LVAD RV failure (RAP/PCWP ratio)[4] was in fact one that performed the worst (C-statistic = 0.52). Additionally, only 7 patients in the present study had "severe" pre-LVAD RV dysfunction by echocardiography, a variable shown to be a significant predictor of RV failure in this cohort. Had one of these patients been categorized as having anything other than severe RV dysfunction, a statistically significant difference between the 2 groups would have been absent, highlighting yet another limitation encountered with relatively small cohort sizes.

In addition, what we think to be the "immediate past" is often not so immediate. Few if any studies incorporate events that occur during the surgical LVAD implant as potential explanatory variables for post-op RV failure. Blood loss and transfusions, unexpected vasoplegia associated with cardiopulmonary bypass, varying implant techniques (ie, sternotomy vs lateral thoracotomy) including on versus off-pump surgery, surgical handling of the RV, pericardial considerations, valvular interventions, and unintended mishaps (ie, air propagating down the right coronary artery) likely all contribute equally if not more so to the potential for RV failure to occur early after an LVAD implant. Albeit intraoperative events and variables are by definition "too late" to be considered during preoperative decision-making, it should not surprise us that preoperative predictor variables do not perform nearly as well as we expect them to.

Finally, perioperative and post-operative *management* heterogeneity among centers also impacts the epidemiology of early RV failure but is inadequately considered. For instance, when a somewhat arbitrary time point of "14 days" or "need" for mechanical RV support defines and triggers the outcome of interest (ie, RV failure),[5] differences in clinical practice (eg, rapidity of inotrope wean, timing of temporary mechanical circulatory support, and selection of an upfront durable RVAD or total artificial heart strategy) undoubtedly contribute to additional epidemiologic and reporting differences. Curiously, those who survive early post-LVAD RV failure are not at increased risk of developing late RV failure, a separate yet highly relevant post-LVAD complication.[6]

One thing is nearly certain—we will likely never identify a single predictor variable that sufficiently risk stratifies. Albeit models that incorporate several important clinical metrics will prove best (ie, the Michigan model[5]), they will, even when modified, remain largely inadequate. Interestingly, despite more than a decade of studying predictors of early RV failure, it is indeed one of the oldest models (Michigan) constructed and validated using a now obsolete generation of pulsatile LVADs, that continues to perform best.

So where do we go from here? Accurate prognostication relies on the complex and dynamic interaction of numerous variables that cannot be adequately captured by traditional multivariate modeling. Perhaps the use of artificial intelligence with machine learning, or the employment of large datasets and sophisticated modeling such as that by Loghmanpour et al[7] (who utilized Bayesian network algorithms to predict post-LVAD RV failure) hold promise. Albeit the Loghmanpour[7] study findings will need to be reproduced prospectively along with the creation of a platform that readily and seamlessly interfaces with electronic medical records for clinical practicality, these approaches may bring us significantly closer to knowing the future rather than perilously trying to predict it.

References

1. Barbone A, et al. Comparison of right and left ventricular responses to left ventricular assist device support in patients with severe heart failure: a primary role of mechanical unloading underlying reverse remodeling. Circulation 2001;104:670–5.
2. Kirklin JK, et al. Eighth annual INTERMACS report: Special focus on framing the impact of adverse events. J Heart Lung Transplant 2017;36:1080–6.
3. Rich JD. Right ventricular failure in patients with left ventricular assist devices. Cardiol Clin 2012;30:291–302.
4. Kormos RL, et al. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. J Thorac Cardiovasc Surg 2010;139:1316–24.
5. Matthews JC, et al. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in left ventricular assist device candidates. J Am Coll Cardiol 2008;51:2163–72.
6. Rich JD, et al. The incidence, risk factors, and outcomes associated with late right-sided heart failure in patients supported with an axial-flow left ventricular assist device. J Heart Lung Transplant 2017;36:50–8.
7. Loghmanpour NA, et al. A Bayesian model to predict right ventricular failure following left ventricular assist device therapy. JACC Heart Fail 2016;4:711–21.