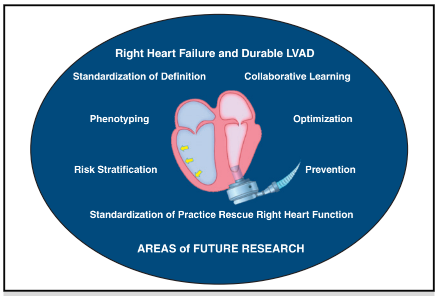
Rescuing the right ventricle: A conceptual framework to target new interventions for patients receiving a durable left ventricular assist device

Michael J. Pienta, MD, MS,[a] Pierre-Emmanuel Noly, MD, PhD,[a] Allison M. Janda, MD,[b] Paul C. Tang, MD, PhD,[a] Abbas Bitar, MD,[c] Michael R. Mathis, MD,[b] Keith D. Aaronson, MD, MS,[c] Francis D. Pagani, MD, PhD,[a] and Donald S. Likosky, PhD,[a] on behalf of the Michigan Congestive Heart Failure Investigators*

Right heart failure (RHF) is a frequent comorbid condition in patients being evaluated for durable, left ventricular assist device (LVAD) therapy. RHF is defined by the incapacity of the right ventricle (RV) to provide adequate cardiac output to the LV and LVAD device and is associated with poor systemic perfusion resulting in renal and hepatic failure, venous and hepatic congestion causing bleeding requiring transfusion, and increased risk of mortality.[1] RHF occurs when the RV function is no longer adapted to the loading conditions because of intrinsic RV dysfunction; elevated pulmonary vascular resistance; or more commonly, a combination of both. Depending on the definition, RHF is observed in 4% to 40% of patients undergoing durable LVAD implant, independent of the type of continuous flow device.[2-4] Patients requiring concomitant RV assist device (RVAD) support at the time of LVAD implant have increased mortality, with a 1-year survival of only 56% compared with 82% for patients requiring an LVAD implant alone.[1]

The RV's complex anatomy and load-dependent physiology contribute to the difficulty of predicting, preventing, and managing post-LVAD implantation RHF. Despite significant advances in device technology and knowledge, failure to rescue the RV following durable LVAD implantation remains an important issue requiring further critical and strategic investigation. Previous literature has mainly focused on the mechanisms and the predisposing patient characteristics associated with RHF, although this multifaceted disease remains insufficiently explored.

A conceptual model that integrates RHF determinants is proposed. Further, this conceptual model details a broad approach to RHF that may assist researchers with identifying and directing future areas of inquiry and clinicians with providing new approaches for improving patient outcomes.



Axes for future research in right heart failure after LVAD implantation.

CENTRAL MESSAGE

Despite significant advances in durable LVAD technology, right heart failure remains a morbid and fatal condition that is difficult to predict, prevent, and successfully treat.

See Commentary on page 2132.

THE COMPLEX PUZZLE OF RHF FOLLOWING DURABLE LVAD IMPLANTATION: WHAT WE KNOW

Preoperative Risk Prediction of RHF Following LVAD Implantation

RHF following LVAD implantation is the culmination of an interplay of intrinsic RV dysfunction due to the underlying cardiomyopathy, patient comorbidities, pressure and/

From the [a]Section of Health Services Research and Quality, Department of Cardiac Surgery, [b]Department of Anesthesiology, and [c]Division of Cardiovascular Medicine, Department of Internal Medicine, Michigan Medicine, Ann Arbor, Mich.

Funded by the Michigan Society of Cardiovascular Surgery Quality Collaborative (MSTCVS-QC), which is supported by Blue Cross and Blue Shield of Michigan (BCBSM) and Blue Care Network as part of the BCBSM Value Partnerships program. Although BCBSM and MSTCVS-QC work collaboratively, the opinions, beliefs, and viewpoints expressed by the author do not necessarily reflect the opinions, beliefs, and viewpoints of BCBSM or any of its employees.

Drs Pienta and Noly contributed equally to this article.

* A full list of the Michigan Congestive Heart Failure Investigators is provided in the Acknowledgments.

Received for publication Jan 24, 2022; revisions received March 14, 2022; accepted for publication March 22, 2022; available ahead of print April 7, 2022.

Address for reprints: Donald S. Likosky, PhD, Section of Health Services Research and Quality, Department of Cardiac Surgery, University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109 (E-mail: likosky@med.umich.edu).

J Thorac Cardiovasc Surg 2023;165:2126-31
0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2022.03.025

or volume overload, dynamic ventricular interactions and pathophysiological changes after pump insertion, intraoperative insults, and perioperative patient and LVAD management[5,6] (Figure 1). Among hundreds of parameters studied, no single parameter has accurately characterized the risk of RHF in the perioperative setting.[2] Many preoperative prediction models have been developed for postimplant RHF, but their utility has been limited due to poor discrimination outside the derivation cohorts and limited and variable RHF definitions.

Prior research has evaluated the role of both hemodynamic and echocardiographic assessments for RHF prediction. Although lacking rigorous sensitivity and specificity, a number of hemodynamic assessments have been evaluated, including central venous pressure, pulmonary artery pulsatility index, right atrial pressure to pulmonary capillary wedge pressure ratio, RV power output, and RV strokework index.[1,7] Regarding echocardiographic parameters, investigators have evaluated measures reflecting the longitudinal shortening of the RV (eg, RV free-wall longitudinal strain or tricuspid annular plane excursion).[8-10] Further external validation of these parameters is necessary.

RV Pathophysiology in the Setting of LVAD Implant

RV function is determined by its preload, afterload, interventricular interactions via the interventricular septum and the pericardium, rhythm integrity, and myocardial contractility.[11] Durable LVAD implantation acutely influences each of the determinants of RV function, either in deleterious or beneficial ways.[12] The increase in systemic perfusion and the reduction in LV end-diastolic pressure may improve coronary perfusion and myocardial contractility (eg, RV contraction assessed by end-systolic elastance). Conversely, acute unloading of the LV as a consequence of the LVAD, may lead to acute right to left interventricular septal shift, decreasing RV contractility and rendering it more sensitive to RV afterload changes.[13] The loss of pericardial constraint resulting from surgical pericardiotomy combined with the increase of venous blood return can lead to RV volume overload and dilation, especially in a previously maladapted RV. Although increases in pump speed and LV unloading can reduce RV afterload (ie, pulmonary arterial pressure, elastance, and resistance), conductance catheter studies have demonstrated that RV-PA coupling is minimally influenced by acute modulations in pump speed.[14] Thus, the benefit of RV unloading in the acute setting may be limited.

THE MISSING PIECES: KNOWLEDGE GAPS

Understanding the Mechanisms Leading to RHF

A better understanding of the pathophysiological mechanisms leading to RHF in patients with an LVAD is a prerequisite for the development of new biomarkers and targeted

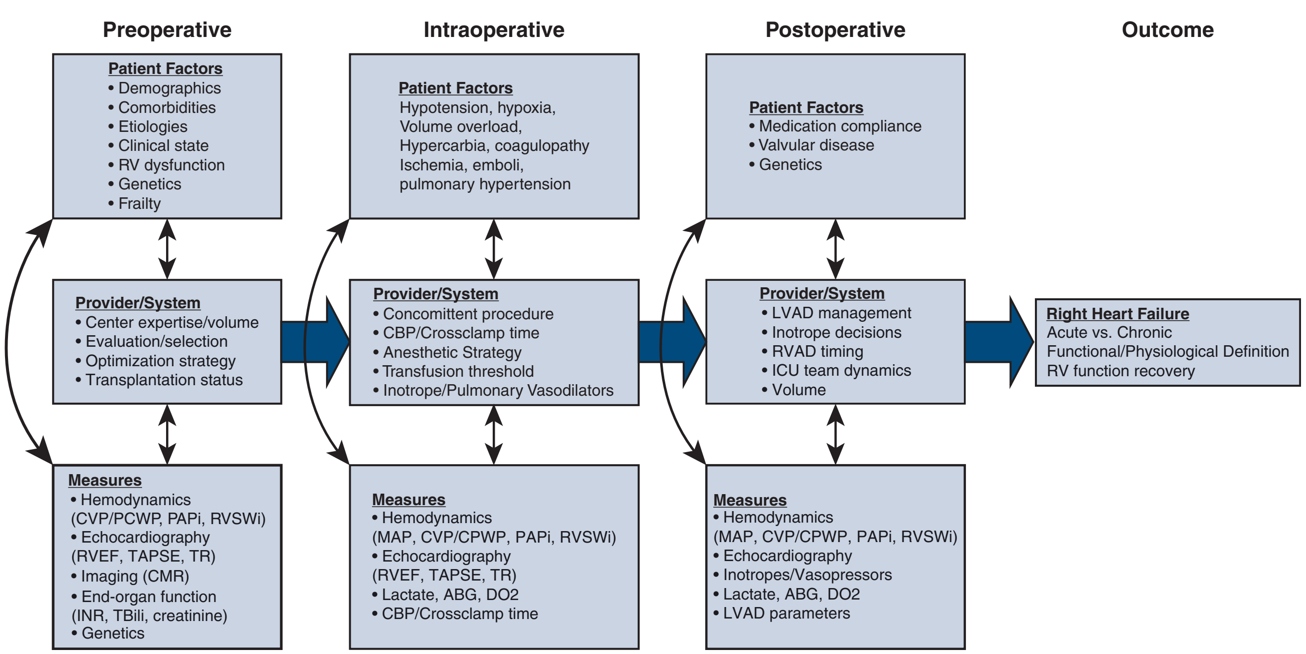


FIGURE 1. Conceptual framework summarizing the interactions between patient factors, provider, system factors, and measures involved in the understanding of right heart failure in patients receiving a durable left ventricular assist device (*LVAD*). *CBP*, Cardiopulmonary bypass; *RVAD*, RV assist device; *ICU*, intensive care unit; *RV*, right ventricular; *CVP*, central venous pressure; *PCWP*, pulmonary capillary wedge pressure; *PAPi*, pulmonary artery pulsatility index; *RVSWi*, right ventricular stroke work index; *RVEF*, right ventricular ejection fraction; *TAPSE*, tricuspid annular plane systolic excursion; *TR*, tricuspid regurgitation; *CMR*, cardiac magnetic resonance; *INR*, International Normalized Ratio; *TBili*, total bilirubin; *MAP*, mean arterial pressure; *ABG*, arterial blood gas; *DO2*, oxygen delivery.

therapies. The development and the use of biobanks may assist in identifying specific features of the genetic, molecular, and cellular patterns of RHF in the setting of advanced HF and LVAD therapy.

A Need for a More Physiology-Guided Definition of RHF After LVAD Implant

Weaknesses in the rigor of the prior literature (eg, lack of standardization of RHF definitions) contribute to the inability to derive accurate estimations of the incidence of RHF. The recently described Mechanical Circulatory Support—Academic Research Consortium definition relies on inotropic duration, inhaled pulmonary vasodilators, and RVAD implantation as measures of RV function severity.[15] Rather than leveraging physiological parameters, these criteria reflect clinical decisions that may vary by surgeon and center and cause significant variability in actual risk factors. Further, each of the multiple phenotypes of post-LVAD implantation RHF (ranging from severe acute RHF requiring intraoperative RVAD implantation at the time of LVAD implantation, to prolonged perioperative inotrope requirements, to late RV failure requiring rehospitalization) may require objective and individualized evaluation and treatment. Establishing a definition of RHF based on nontherapeutic measurable indices (eg, imaging, biomarkers, and hemodynamic parameters) is an important area of future investigation.

Intraoperative Assessment and Management of the RV

During LVAD implantation, the RV is subject to the detrimental influence of general anesthesia, the loss of pericardial interaction, inflammation, ischemia-reperfusion injuries secondary to cardiopulmonary bypass, fluid overload, and increase in pulmonary vascular resistances (eg, increased afterload).[16] Intraoperative management consists of limiting cardiopulmonary bypass duration, maintaining adequate perfusion pressure, minimizing transfusion, providing hemodynamic-guided fluid repletion, and instituting pulmonary vasodilator therapy and inotropic support. Although those principles are generally well established, there remains significant variation in intraoperative management across centers and teams.[17] Preservation of the pericardial-RV interaction using less-invasive approaches for LVAD implantation has been believed to reduce the incidence of RHF. However, a recent Society of Thoracic Surgeons-Intermacs analysis did not support this hypothesis and further research into the effects of alternative surgical implant techniques is necessary.[18]

Although associations between intraoperative hemodynamic (eg, central venous pressure and pulmonary artery pulsatility index) and echocardiographic (eg, right atrial and ventricular diameters and tricuspid annular plane excursion) parameters with severe RHF following LVAD implantation[19] have been reported, further studies focusing on hemodynamic variations during surgery and their association with RHF are needed.

IMPLICATIONS OF THIS CONCEPTUAL MODEL: FUTURE DIRECTIONS

The total interaction of patient comorbidities, genetics and cellular biology, preoperative risk factors, intraoperative insults, provider decision making, and hospital-level system factors in relation to the incidence and management of postoperative RHF has not been thoroughly evaluated. This framework identifies new areas for research and opportunities to influence outcomes in patients with RHF following LVAD implantation (Figure 2).

Phenotyping the RV Before LVAD Implantation

We postulate that there are unexplored patient, provider, and system factors that may influence the incidence and severity of RHF. These factors could include patient genetics, evaluation and selection practices, optimization strategies, as well as hospital characteristics (eg, patient to nurse ratios, transplant center status, and number of beds).[20] Further evaluations of interhospital variation in RHF incidence using standardized definitions would permit granular comparison of preoperative management strategies and patient characteristics that may contribute to an improved understanding of the varying phenotypes comprising RHF. Novel assessments of RV function with pressure-volume loops generated from conductance catheters have recently been performed in the setting of LVAD implantation and represent a gold standard methodology to assess myocardial contractility, RV-PA coupling, and provide information to differentiate adaptive and maladaptive phenotypes.[21] Cardiac magnetic resonance (CMR) is now the gold standard to assess RV morphology and function.[22,23] As the number of CMR-compatible pacemakers or internal defibrillators increases, the place of CMR for RV assessment before LVAD implant may be more feasible. Less-constrained methods to measure RV-PA coupling using the ratio of RV free wall longitudinal strain derived from speckle-tracking echocardiography and noninvasively calculated RV systolic pressure are promising.[24] Multimodal monitoring that integrates continuous RV and PA pressure, 3-dimensional volumetric and strain assessments, and assessment of congestive end-organ consequences will help delineate diastolic and systolic RV function.

Focus on the Intraoperative Period

Preoperative risk models, which lack dynamic intraoperative factors associated with LVAD implantation, have focused on the decision to implant an LVAD and assessing the need for RVAD support.[1] Recently, the focus has shifted to evaluating intraoperative predictors of severe postoperative RHF and identifying modifiable targets/practices. The

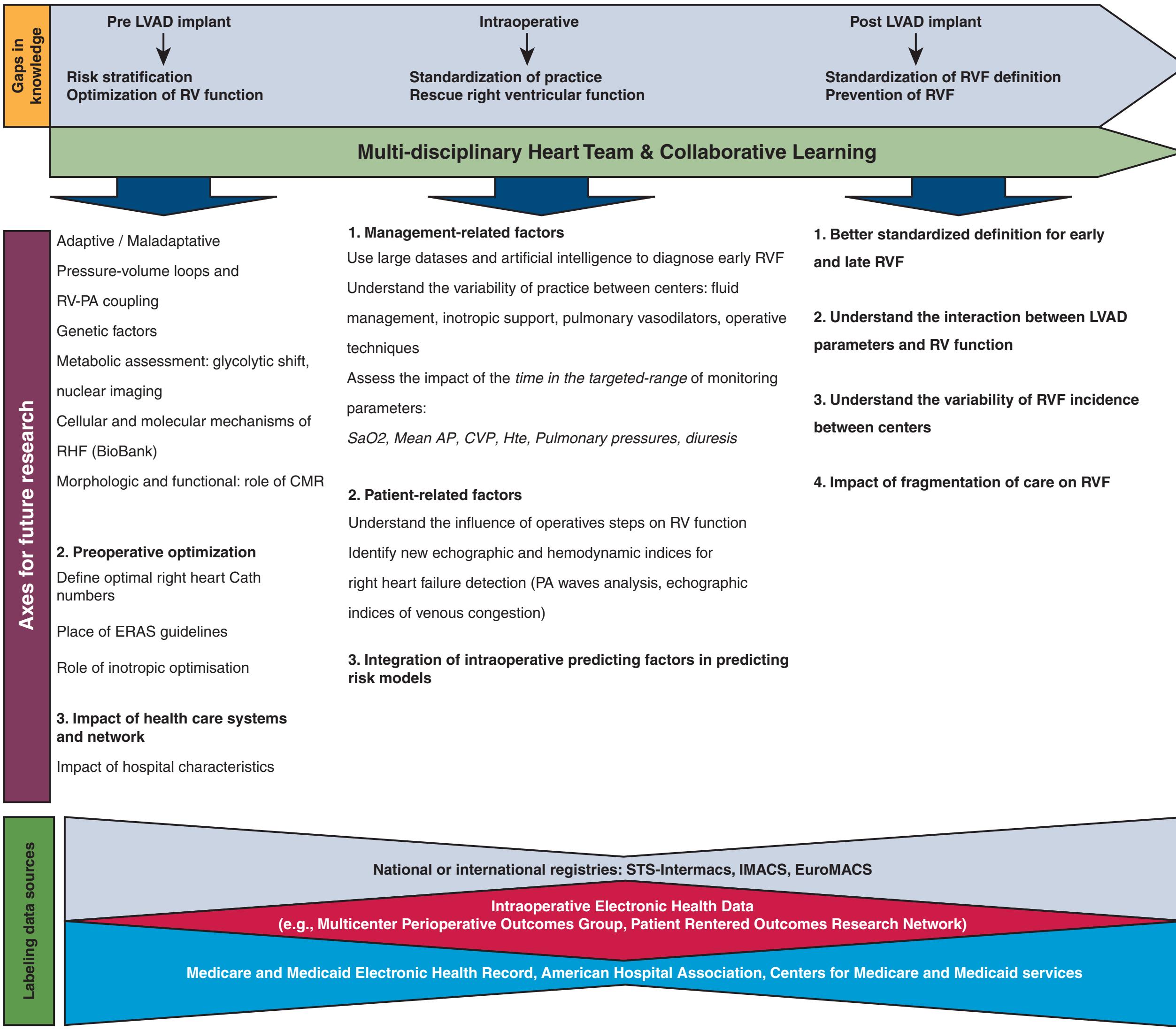


FIGURE 2. Axes for future research in right heart failure after left ventricular assist device (*LVAD*) implantation. The approach to improved understanding of right heart failure (*RHF*) in the setting of durable LVAD implantation will require a multidisciplinary heart team approach. Expertise in areas of cardiovascular genetics and biology, imaging, critical care, analyses of large datasets, and surgical care will be required to explore important issues. *RV*, Right ventricle; *RVF*, right ventricular failure; *RV-PA*, right-ventricular-pulmonary arterial; *CMR*, cardiac magnetic resonance; *ERAS*, enhanced recovery after surgery; *SaO2*, oxygen saturation; *AP*, arterial pressure; *CVP*, central venous pressure; *Hte*, hematocrit; *PA*, pulmonary artery; *STS-Intermacs*, The Society for Thoracic Surgeons-Interagency Registry for Mechanically Assisted Circulatory Support; *IMACS*, International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support; *EuroMACS*, European Registry for Patients with Mechanical Circulatory Support.

influence of intraoperative practice patterns on RV function, and hemodynamic responses to surgical and anesthetic interventions (eg, induction of anesthesia, sternotomy, and initiation/cessation of cardiopulmonary bypass) used as a means to characterize RHF phenotypes, have not been previously well described. Furthermore, the ability of such practice patterns to predict and potentially modify the risk of RHF has not been thoroughly assessed. Cross-institutional collaborative research groups like the Multicenter Perioperative Outcomes Group,[25] which collects granular intraoperative electronic health record data and early postoperative outcomes from more than 50 hospitals, including more than 20 LVAD centers, could provide critical insights into determinants of intraoperative RV function and variation in intraoperative management practices across institutions. Furthermore, these data could be linked to The Society of Thoracic Surgeons Intermacs database and administrative datasets such as Medicare, to allow for detailed analyses of the effects of intraoperative management on postoperative outcomes.

Postoperative

Postoperative structural and system factors may contribute to observed interhospital variation in RHF incidence. However, factors contributing to these differences have not been fully captured and evaluated. Similar to the intraoperative environment, there has been little investigation into postoperative factors related to RHF and threshold for RVAD support initiation. However, multiple factors may alter risk, including perioperative inotrope management, pulmonary vasodilator use, blood transfusion practices, ventilator management, LVAD speed titration, staffing models, and care team dynamics (eg, teamwork and communication).

CONCLUSIONS

This conceptual framework summarizes the knowledge gaps in the understanding of RHF in the setting of LVAD implantation, including the need for widespread adoption of standardized definitions, consideration of the influence of intraoperative management, and new strategies to manage RHF and to prevent significant morbidity or mortality. Further research is necessary to characterize genetic underpinnings, biomarkers, practice pattern variation in preoperative optimization and intraoperative management, and optimal practices to reduce morbidity and mortality associated with RHF. Multicenter collaborative studies will be necessary to elucidate optimal strategies.

Conflict of Interest Statement

Dr Likosky receives research funding from the Agency for Healthcare Research and Quality (No. R01HS026003), and the National Institutes of Health (No. R01HL146619) and serves as a consultant for the American Society of Extracorporeal Technology. Dr Likosky receives partial salary support from Blue Cross Blue Shield of Michigan to advance quality in Michigan in conjunction with the Michigan Society of Thoracic and Cardiovascular Surgeons and Michigan Society of Cardiovascular Surgery Quality Collaborative. Dr Pagani is an uncompensated scientific advisor for FineHeart and CH Biomedical. He is also a member of the Data Safety Monitoring Board for Carmat and National Heart, Lung, and Blood Institute, PumpKIN Study. Dr Aaronson has received an honorarium for participation in the Medtronic Independent Physician Quality Panel, and from Abbott. Dr Mathis receives research funding from the US National Institutes of Health National Heart, Lung, and Blood Institute (No. K01HL141701). All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

The Michigan Congestive Heart Failure Investigators include Donald S. Likosky, PhD; Francis D. Pagani, MD, PhD; Ashraf Shaaban Abdel Aziz Abou El Ela, MB, BCH; Paul C. Tang, MD, PhD; Michael P. Thompson, PhD; Robert B Hawkins, MD, MSc; Peter Sassalos, MD, MSc; Pierre-Emmanuel Noly, MD, PhD; Keith Aaronson, MD, MS; Supriya Shore, MBBS; Thomas Cascino, MD, MSc; Min Zhang, PhD; Jeffrey S. McCullough, PhD; Grace Chung, BA, MPH; Michelle Hou, MS; Allison M. Janda, MD; Michael R. Mathis, MD; Tessa M. F. Watt, MD, MSc; Michael J. Pienta, MD, MS; Alexander Brescia, MD, MSc; Gardner L. Yost, MD, MS; James William Stewart II, MD; Austin Airhart; Daniel Liesman; and Khalil Nassar.

References

1. Kiernan MS, Grandin EW, Brinkley M Jr, Kapur NK, Pham DT, Ruthazer R, et al. Early right ventricular assist device use in patients undergoing continuous-flow left ventricular assist device implantation: incidence and risk factors from the Interagency Registry for Mechanically Assisted Circulatory Support. *Circ Heart Fail*. 2017;10:e003863.
2. Frankfurter C, Molinero M, Vishram-Nielsen JKK, Foroutan F, Mak S, Rao V, et al. Predicting the risk of right ventricular failure in patients undergoing left ventricular assist device implantation: a systematic review. *Circ Heart Fail*. 2020;13:e006994.
3. Bellavia D, Iacovoni A, Scardulla C, Moja L, Pilato M, Kushwaha SS, et al. Prediction of right ventricular failure after ventricular assist device implant: systematic review and meta-analysis of observational studies. *Eur J Heart Fail*. 2017;19:926-46.
4. Shah P, Yuzefpolskaya M, Hickey GW, Breathett K, Wever-Pinzon O, Khue-Ton V, et al. Twelfth Interagency Registry for Mechanically Assisted Circulatory Support report: readmissions after LVAD. *Ann Thorac Surg*. 2022;113:722-37.
5. Ali HR, Kiernan MS, Choudhary G, Levine DJ, Sodha NR, Ehsan A, et al. Right ventricular failure post-implantation of left ventricular assist device: prevalence, pathophysiology, and predictors. *ASAIO J*. 2020;66:610-9.
6. Sanz J, Sanchez-Quintana D, Bossone E, Bogaard HJ, Naeije R. Anatomy, function, and dysfunction of the right ventricle: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;73:1463-82.
7. Morine KJ, Kiernan MS, Pham DT, Paruchuri V, Denofrio D, Kapur NK. Pulmonary artery pulsatility index is associated with right ventricular failure after left ventricular assist device surgery. *J Card Fail*. 2016;22:110-6.
8. Aymami M, Amsallem M, Adams J, Sallam K, Moneghetti K, Wheeler M, et al. The incremental value of right ventricular size and strain in the risk assessment of right heart failure postleft ventricular assist device implantation. *J Card Fail*. 2018;24:823-32.
9. Grant AD, Smedira NG, Starling RC, Marwick TH. Independent and incremental role of quantitative right ventricular evaluation for the prediction of right ventricular failure after left ventricular assist device implantation. *J Am Coll Cardiol*. 2012;60:521-8.
10. Liang LW, Jamil A, Mazurek JA, Ugo KA, Wald J, Birati EY, et al. Right ventricular global longitudinal strain as a predictor of acute and early right heart failure post left ventricular assist device implantation. *ASAIO J*. 2022;68:333-9.
11. Sanz J, Garcia-Alvarez A, Fernandez-Friera L, Nair A, Mirelis JG, Sawit ST, et al. Right ventriculo-arterial coupling in pulmonary hypertension: a magnetic resonance study. *Heart*. 2012;98:238-43.
12. Lampert BC, Teuteberg JJ. Right ventricular failure after left ventricular assist devices. *J Heart Lung Transplant*. 2015;34:1123-30.
13. Kanwar M, McDonnell BJ, Rosenblum H, Cockcroft JR, Stöhr EJ, Cornwell WK III. Bionic women and men–part 3: right ventricular dysfunction in patients implanted with left ventricular assist devices. *Exp Physiol*. 2020;105:759-62.
14. Tran T, Muralidhar A, Hunter K, Buchanan C, Coe G, Hieda M, et al. Right ventricular function and cardiopulmonary performance among patients with heart failure supported by durable mechanical circulatory support devices. *J Heart Lung Transplant*. 2021;40:128-37.
15. Kormos RL, Antonides CFJ, Goldstein DJ, Cowger JA, Starling RC, Kirklin JK, et al. Updated definitions of adverse events for trials and registries of mechanical circulatory support: a consensus statement of the mechanical circulatory support academic research consortium. *J Heart Lung Transplant*. 2020;39:735-50.

16. Haddad F, Couture P, Tousignant C, Denault AY. The right ventricle in cardiac surgery, a perioperative perspective: II. Pathophysiology, clinical importance, and management. *Anesth Analg*. 2009;108:422-33.
17. Cowger JA, Stulak JM, Shah P, Dardas TF, Pagani FD, Dunlay SM, et al. Impact of center left ventricular assist device volume on outcomes after implantation: an INTERMACS analysis. *JACC Heart Fail*. 2017;5:691-9.
18. Lampert BC, Teuteberg JJ, Cowger J, Mokadam NA, Cantor RS, Benza RL, et al. Impact of thoracotomy approach on right ventricular failure and length of stay in left ventricular assist device implants: an intermacs registry analysis. *J Heart Lung Transplant*. 2021;40:981-9.
19. Gudejko MD, Gebhardt BR, Zahedi F, Jain A, Breeze JL, Lawrence MR, et al. Intraoperative hemodynamic and echocardiographic measurements associated with severe right ventricular failure after left ventricular assist device implantation. *Anesth Analg*. 2019;128:25-32.
20. Walmsley J, van Everdingen W, Cramer MJ, Prinzen FW, Delhaas T, Lumens J. Combining computer modelling and cardiac imaging to understand right ventricular pump function. *Cardiovasc Res*. 2017;113:1486-98.
21. Simon MA. Assessment and treatment of right ventricular failure. *Nat Rev Cardiol*. 2013;10:204-18.
22. Galea N, Carbone I, Cannata D, Cannavale G, Conti B, Galea R, et al. Right ventricular cardiovascular magnetic resonance imaging: normal anatomy and spectrum of pathological findings. *Insights Imaging*. 2013;4:213-23.
23. Hundley WG, Bluemke DA, Finn JP, Flamm SD, Fogel MS, Friedrich MG, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the American College of Cardiology Foundation task force on expert consensus documents. *J Am Coll Cardiol*. 2010;55:2614-62.
24. Fortuni F, Butcher SC, Dietz MF, van der Bijl P, Prihadi EA, De Ferrari GM, et al. Right ventricular-pulmonary arterial coupling in secondary tricuspid regurgitation. *Am J Cardiol*. 2021;148:138-45.
25. Colquhoun DA, Shanks AM, Kapeles SR, Shah N, Saager L, Vaughn MT, et al. Considerations for integration of perioperative electronic health records across institutions for research and quality improvement: the approach taken by the Multicenter Perioperative Outcomes Group. *Anesth Analg*. 2020;130:1133-46.

Key Words: right heart failure, left ventricular assist device, hemodynamics, conceptual framework

ADULT