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NONPHARMACOLOGIC THERAPY: SURGERY, VENTRICULAR ASSIST DEVICES, BIVENTRICULAR PACING, AND EXERCISE (A HASAN, SECTION EDITOR)

Right Ventricular Strain to Assess Early Right Heart Failure in the Left Ventricular Assist Device Candidate

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Abstract

Purpose of Review Right heart failure (RHF) following left ventricular assist device implantation (LVAD) remains the primary cause of postoperative mortality and morbidity, and prediction of RHF is the main interest of the transplantation community. In this review, we outline the role and impact of right ventricular strain in the evaluation of the right ventricle function before LVAD implantation.

Recent Findings Accumulating data suggest that measurement of right ventricular longitudinal strain (RVLS) has a critical role in predicting RHF preoperatively and may improve morbidity and mortality following LVAD implantation. However, the significant intraobserver, interobserver variability, the lack of multicenter, prospective studies, and the need for a learning curve remain the most critical limitations in the clinical practice at present.

Summary This review highlighted the importance of right ventricular strain in the diagnosis of RHF preoperatively and revealed that RVLS might have a crucial clinical measurement for the selection and management of LVAD patients in the future with the more extensive multicenter studies.

Keywords Left ventricular assist device · Right ventricular failure · Right ventricular longitudinal strain · Speckle tracking echocardiography · Strain

Abbreviations

CI	Cardiac index
CMR	Cardiac magnetic resonance
Cr	Creatinine
CVP	Central venous pressure
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction
FAC	Fractional area change
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IVC	Inferior vena cava
LVAD	Left ventricular assist device
SvO_2	Mixed venous oxygen saturation
RHC	Right heart catheterization
RHF	Right heart failure
RV	Right ventricle
RVFWLS	Right ventricular free wall longitudinal strain
RVGWLS	Right ventricular global wall longitudinal strain
RVLS	Right ventricular longitudinal strain
RVSWI	Right ventricle stroke work index
STE	Speckle-tracking strain echocardiography
TAPSE	Tricuspid annulus peak systolic excursion
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography

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Introduction

Improvements in mechanical circulatory support have increased the survival and quality of life among patients with advanced heart failure. Continuous-flow left ventricular assist device (LVAD) implantation has recently gained extensive application from using as a bridge-to-transplantation or bridge to candidacy to using as the destination therapy [1]. However, despite the last technological applications and evolving surgical experience, the incidence of right heart failure (RHF) is ranging from 9.4 to 44% after LVAD therapy, and approximately 6 to 10% of patients require right ventricular assist device support. Post-LVAD RHF remains a significant reason for morbidity and mortality and associated with more than 20% reduction in perioperative survival [2–10]. After reducing the load of the left ventricle with LVAD, increased right ventricular (RV) preload, decreased RV contractility, loss of septal contribution to RV function resulting mechanical desynchrony, and perioperative transfusions of blood products all contribute RHF after LVAD implantation.

Currently, RVF risk assessment strategies are under intense investigation. Even though the introduction of new parameters has been identified to improve our ability to predict RHF before LVAD therapy so far, the prediction power of the systems is still low [6, 7, 9, 11•]. Several studies have been reported using right ventricular longitudinal strain (RVLS) as a tool for assessing RV function in patients with different cardiac diseases; however, the clinical relevance and the prediction power of RVLS in patients with heart failure and undergoing LVAD are still unknown. This review aims to identify the role of preoperative RV strain in the evaluation of postoperative RHF. We will also review the recent studies about the role of RV strain in different scenarios and highlight recent developments.

Table 1 Definition and severity scale for RHF by the INTERMACS

Diagnostic criteria for RHF (in the absence of cardiac tamponade)
• The mean arterial pressure < 55 mmHg
• Central venous pressure or right atrial pressure > 18 mmHg
• Cardiac index < 2 l/min/m^2
• Requirement of prolonged postimplant inotropes (inotropic score > 20 units)
• Inhaled nitric oxide or intravenous vasodilators continued beyond postoperative day 14 following LVAD implant or requiring RVAD or ECMO support
Severity scale of RHF
• Mild (meeting at least two of the four following criteria below)
CVP or mean RAP > 18 mmHg
CI < 2.3 l/min/m^2 (using a pulmonary artery catheter)
Presence of ascites or moderate to high peripheral edema
Evidence of elevated CVP by transthoracic echocardiography (dilated inferior vena cava without collapse or IVC diameter < 21 mm with less than 50% collapsibility)
• Moderate
Requiring inotrope infusion or usage of IV or inhaled pulmonary vasodilator (iNO or prostaglandin E)
• Severe
Requiring of RVAD implantation

CI, cardiac index; *CVP*, central venous pressure; *ECMO*, extracorporeal membrane oxygenator; *IV*, intravenous; *IVC*, inferior vena cava; *LVAD*, left ventricular assist device; *RHF*, right heart failure; *RVAD*, right ventricular assist device

Definition and Classification of Right Heart Failure

The definition of postoperative RHF after LVAD implantation has been inconsistent in several clinical studies [5, 12–15]. To standardize the universal definition, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has created a definition of RHF following LVAD implantation as summarized in Table 1 [16, 17]. INTERMACS has also revealed a severity scale of RHF ranging from severe, moderate, to mild depending on the treatment status.

Diagnostic Tools for the Assessment of RV function

Predicting the vulnerability of the RV after LVAD implantation has been challenging and is still the central issue of heart failure teams. There are many scoring models and new parameters identified to increase the prediction power. However, most of them were organized in a single-center retrospective fashion and within a limited patient population.

There are several clinical diagnostic tools to evaluate RV function preoperatively. Echocardiography is a well-validated, noninvasive tool for evaluating the contractility and loading status of RV and the severity of tricuspid regurgitation. Routine assessment of RV includes RV end-diastolic diameter, end-systolic and end-diastolic RV areas, isolated right ventricular ejection fraction (EF), right atrium area, right ventricle myocardial performance index, fractional area change (FAC), tricuspid annulus peak systolic excursion (TAPSE), pulsed Doppler tricuspid E wave, tricuspid annular motion, right-to-left ventricular diameter ratios, systolic pulmonary arterial pressure, and mean diameter of the IVC. Cardiac magnetic resonance (CMR) imaging could be utilized as a reference diagnostic technique for the quantitation of RV volumes and systolic function with better endocardial border delimitation. Furthermore, tissue characterization is also possible. Preoperative right heart catheterization (RHC) is an invasive but critical tool for assessing hemodynamics and correctly diagnosing pulmonary hypertension. Comprehensive hemodynamic assessment is performed comprising the direct measurement of CVP, pulmonary capillary wedge pressure, right ventricular pressure, mixed venous oxygen saturation (SvO_2), and systolic and diastolic pulmonary artery pressures. Calculations from these data include cardiac output, cardiac index, pulmonary and systemic vascular resistance, transpulmonary pressure gradient, right ventricle stroke work index (RVSWI = [mean pulmonary artery pressure − mean

CVP] × stroke volume/body surface area). Pulmonary vasoreactivity testing may be critical and useful in advanced cases.

Assessment of the right heart function in candidates undergoing LVAD therapy and choose the best candidate for the surgery are the main anchors of the success of this treatment. For this purpose, many predictive risk scoring systems were identified in patients receiving LVAD only with the help of these tools. Matthews et al. [6] designed a scoring model in a population of 197 patients, identified the following parameters; the use of vasopressor, creatinine (Cr) ≥ 2.3 mg/dL, bilirubin ≥ 2 mg/dL, and aspartate transaminase ≥ 80 IU/L as the independent risk factors for RVF. Fitzpatrick et al. [9] designed a scoring model in a population of 266 patients receiving different types of LVAD, identified the following parameters: CI ≤ 2.2 L/min/m2, RVSWI ≤ 0.25 mmHg mL/m^2, severe RV dysfunction, Cr ≥ 1.9 mg/dL, previous cardiac surgery, and systolic blood pressure ≤ 96 mmHg as the independent risk factors for RHF. Drakos et al. [7] studied a population of 175 patients retrospectively receiving either pulsatile or continuous flow LVADs, identified the following parameters: the use of intra-aortic balloon pump, pulmonary vascular resistance value, inotropic dependency, obesity, angiotensin-converting enzyme inhibitor, and beta-blocker use and destination therapy as independent risk factors for RHF. Aissaoui et al. [18] studied a population of 42 patients undergoing LVAD and established a scoring model with independent predictors of RHF by rounding the exponentiated regression model coefficients to the nearest 0.5. An ARVADE score was calculated as the sum of points attributed according to the values of three variables: 3.0 points for Em/S_{LAT} (Em: pulsed Doppler trans-mitral E wave, S_{LAT}: tissue Doppler lateral systolic velocity) ≥ 18.5, 2.0 points for basal RV end-diastolic diameter ≥ 50 mm, and 1.5 points for INTERMACS level 1. An ARVADE score > 3.0 was predictive of post-implantation RHF, with a sensitivity of 89% and a specificity of 74%. Wang et al. [19, 20] also created a model by using a decision tree classifier, but it was also limited to a single center and continuous-flow LVADs even though it provided promising results in the related population. Although the scores developed for RHF prediction (Matthew's, Drakos', Fitzpatrick's, ARVEDE) seemed to be accurate in their limited populations, they are not applicable for all populations in high accuracy due to deriving from the limited population in retrospective manner and lack of emerging new promising parameters such as RV strain into the models. In a recent study performed in our center, we revealed that currently available prediction risk scores mentioned above had the modest power of accuracy in the low INTERMACS profile Turkish population and believed that new scoring models developed with multicenter, prospective studies with the addition of new promising hemodynamic and echocardiographic measurements (such as right ventricular free wall longitudinal strain (RVFWLS) and RVSWI) may facilitate a clinical decision, while screening candidates for RHF before LVAD implantation in the future [21•]. So far, traditional echocardiographic measurements and hemodynamic evaluation of the right heart missed critical regional variations in contractility and had low prediction power [22, 23]. To deal with these problems, Loghmanpour et al. designed a Bayesian analysis that showed great promise as a reliable and accurate risk stratification tool for clinical decision making to predict the risk of RHF in a large, multicenter LVAD cohort by using INTERMACS registry [11•]. They also evaluated the accuracy of existing scores (Matthew's, Drakos' scores) which were used for predicting RHF and found that accuracy of them was virtually equivalent to the flip of a coin. Thus, this is an undeniable truth that the transplantation community should be open-minded to new scoring models with new promising parameters.

Speckle-tracking Strain Echocardiography and Right Ventricle

Speckle-tracking strain echocardiography (STE) is a recently improved and used ultrasound imaging technique for the assessment of myocardial deformation [24]. One of the most important goals of STE is to evaluate the ventricular systolic function properly and overcome the many limitations of ejection fraction. The type of measurements is performed in three steps, as summarized in Fig. 1. Although STE is mainly utilized for assessing left ventricular function at the beginning with high reproducibility, minimal intraobserver and interobserver variability, independent of angle of incidence, and from cardiac translational movements [25–27], it also allows for rapid and correct evaluation of lateral wall motion of ventricles nowadays and might help the prediction of RV function more accurately preoperatively even in the patients undergoing LVAD implantation [27–31].

In this manner, in a recent study, it has been shown that STE analysis of RV function complying well with other parameters regarding the evaluation of RV including RVSWI, and also they showed that RV strain provided the best estimation of RV systolic function preoperatively compared to other traditional parameters [32, 33]. In contrast to the traditional parameters identified for evaluation of RV such as TAPSE, RV FAC, the main advantage of the STE allows a global evaluation of a sophisticated RV chamber following the myocardial damage of each RV segment during the entire cardiac cycle [22]. As all we know, ejection fraction is the most frequently used parameter to describe the systolic cardiac functions of the right and left ventricles. However, it usually might be affected by poor imaging windows, the requirement of tracing endocardial borders and loading status. A more accurate evaluation of myocardial contraction can be performed by measuring myocardial strain. Moreover, one other superiority

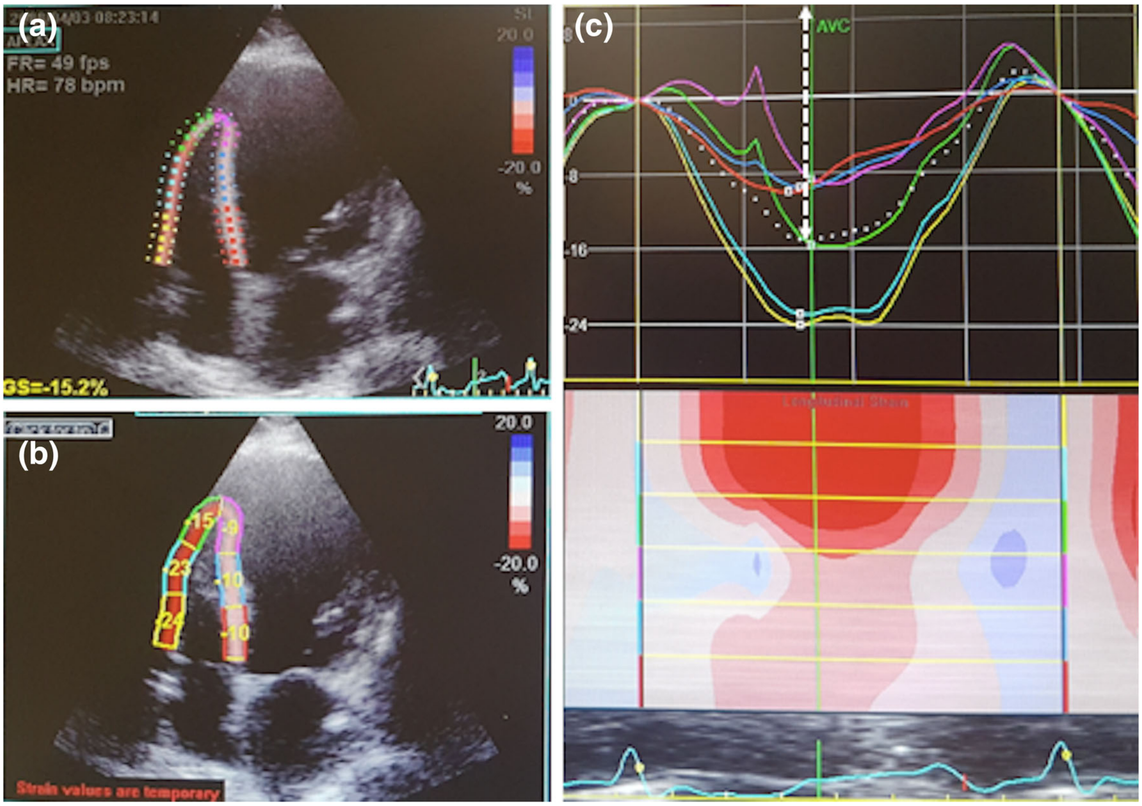

Fig. 1 Performing the speckle-tracking echocardiography for the right ventricle. **a** The septal and free wall of the myocardial border is manually marked in the end-systolic frame **b** The software is used to measure the strain for each wall. **c** The strain curves. The dashed curve demonstrates the average right ventricular longitudinal strain of the global wall

of the strain against EF is that subendocardial fibers create the longitudinal strain, so it gets progressively impaired in the early phase of any cardiac disease extending to only subendocardial region, unlike ejection fraction which is progressively impaired very lately because the transmural wall dysfunction is required [24, 34, 35].

Literature Review of Right Ventricular Strain

A relatively new approach, STE, which has the advantage of differentiating active motion from passive motion, uses the strain imaging to assess the ventricular function [36–38]. Fukuda et al. [39] presented that RVFWLS significantly complies with pulmonary arterial pressure and pulmonary vascular resistance in patients with pulmonary hypertension. Cameli et al. [33] designed a study including 47 patients awaiting cardiac transplantation and performed echocardiographic examination. They revealed that RVFWLS had the sufficient power to predict reduced RVSWI with a cut-off value of < 11.8%, also found that right ventricular global wall longitudinal strain (RVGWLS) had highest predictive value among other echocardiographic parameters. Following year, in a study by the same physicians including 98 patients with advanced heart failure and on the list of cardiac transplantation, RVFWLS also was found to be the most significant power in predicting of cardiovascular events (cardiovascular death, rehospitalization due to acute heart failure, heart transplantation, intra-aortic balloon pump implantation, and ventricular assist device implantation) [40].

Similarly, a study by Vizzardi et al. [41] found that RVGWLS was the only parameter significantly associated with adverse cardiac events. Moreover, Garcia et al. [42] reported that RVGWLS had the most potent discriminatory power compared to other parameters for heart failure development. A study published recently also confirmed that RVGWLS was a good predictor of low functional capacity (peak oxygen consumption < 20 ml/kg/min) [43]. Seo et al. [44•] from the Republic of Korea enrolled 143 dilated cardiomyopathy patients with sinus rhythm in the study and followed up the patients for 4 years. They demonstrated that RVFWLS was associated with a significant prognostic impact using a cut-off value higher than − 16.5%.

One of the most extensive studies including 332 patients with reduced ejection fraction heart failure revealed that RVGWLS and RVFWLS were significantly associated with adverse events and mortality with the cut-off values of − 14.0% and − 20.6%, respectively [45]. In a recent study performed by Lisi et al. [46] also demonstrated another feature of RV strain, which RVFWLS was the primary determinant of myocardial fibrosis in patients with heart failure.

Table 2 Summary of clinical studies using right ventricular strain in the LVAD patients

Author, date, journal and country Study type (level of evidence)	Patient group	Key results	Comments
Cameli et al. (2013) J Heart Lung Transplant (Italy) Case series (Level IV)	Study population: 10 patients Procedure: Jarvic 2000 LVAD implantation. RHF definition: the need for placement of an RV assist device, or the use of inotropic agents for > 14 days. Aim: Observing RV function by STE in patients with advanced heart failure before and after LVAD implantation.	The prediction performance of RHF with RVLS was satisfactory (AUC 0.93)	Not including newest generation devices. Single center Limited number of patients No data for comparison
Grant et al. (2012) JACC (USA) Retrospective cohort (Level III)	Study population: $n = 117$ Procedure: CF LVAD implantation RHF definition: the need for placement of an RV assist device, or the use of inotropic agents for > 14 days.	RV failure occurred in 47 of 117 patients (40%) The 1-year mortality rates were 9 of 47 (19%) and 13 of 70 (19%) in the groups with and without RV failure, respectively ($p = 0.94$). RVGWS > − 9.6% predicting RHF with 68% sensitivity and 76% specificity.	Not including pulsatile devices Single center Retrospective origin Excluding the measurement of septal wall strain due to the software issue
Kato et al. (2013) JACC (USA) Prospective observational study (Level III)	Study population: $n = 68$ Procedure: CF LVAD implantation RHF definition: the need for placement of an RV assist device, or the use of inotropic agents for > 14 days; or inhaled or oral pulmonary vasodilators (iloprost, inhaled nitric oxide, or sildenafil) at 14 days after surgery. Monitoring right heart via TTE within 72 h before and after surgery	RV failure occurred in 24 of 68 patients (35.3%) RVLS significantly lower in the group of RHF ($p < 0.001$) Preoperative S' < 4.4 cm/s, RV-E/E' > 10 and RV-strain < – 14% discriminated patients who developed RHF at day 14 with a predictive accuracy of 76.5%.	Single center Limited number of patients The value of RV strain can be different depending on different software
Gumus et al. (2018) ICVTS (Turkey) Retrospectively cohort study (Level III)	Study population: $n = 57$ Procedure: CF LVAD implantation RHF definition: In the absence of cardiac tamponade within the first 48 h after surgery: • The mean arterial pressure < 55 mmHg • Central venous pressure or right atrial pressure > 16 mmHg • Cardiac index < 2 $l/min/m^2$ • Requirement of prolonged postimplant inotropes (inotropic score > 20 units) •Inhaled nitric oxide or intravenous vasodilators continued beyond postoperative day 14 following LVAD implant or requiring right ventricular assist device or extracorporeal membrane oxygenation support.	RHF occurred in 20 of 57 patients (35.1%) Right ventricular free wall longitudinal strain > − 15.5% was an independent predictor of RHF following LVAD implantation with a resulting area under the curve value of 0.94 (95% CI 0.55–0.89, $p = 0.03$)	Single center Limited number of patients High number of the patients with INTERMACS I or II profiles

Importance of Right Ventricular Strain in Patients Undergoing LVAD Implantation

Despite the technological advances for the detailed evaluation of the right ventricle, especially with echocardiographic parameters, designing methods, and creating new measurements to assess reliably for RHF had been difficult. Depending on the different types of definitions of RHF in the series, the incidence of RHF is still high, with high perioperative mortality and morbidity [7, 8, 12, 47]. Many risk factors have been identified so far and incorporated into the scoring models; however, as we mentioned before, they all had low predictive power. A recent study by Loghmanpour et al. [11•] also confirmed with a Bayesian analysis that many different independent risk factors were affecting the various stages of RHF with different power.

Regarding the right ventricular strain in the LVAD patients (Table 2), a study by Cameli et al. [22] presented the changes of RV longitudinal strain values before and after LVAD implantation in 10 patients and revealed that those patients who presented a depressed longitudinal strain of RV at the preoperative echocardiographic assessment demonstrated a worse prognosis due to having higher probability of RHF postoperatively. Grant et al. [48] also designed a study including 117 patients undergoing continuous-flow LVAD implantation with a 40% incidence of postoperative RHF. They used the 2-dimensional STE and reported that reduced RVFWLS represents a new parameter to predict RHF with good sensitivity and specificity of 68% and 76%, respectively, using a cut-off value of higher than − 9.6%. Moreover, they emphasized that RV strain may assist in the decision-making process and may augment the accuracy of Michigan score. Similarly, we also designed a retrospective observational cohort study in 2018 including 57 patients and confirmed that RVFWLS was an independent predictor of RHF in the patients undergoing continuous LVAD implantation and demonstrated the highest diagnostic accuracy with good sensitivity and specificity of 86% and 84%, respectively, using a cut-off value of higher than − 15.5% [21•]. A study by Kato et al. demonstrated that RV strain could be the right candidate for predicting RHF preoperatively [49]. Finally, a large metanalysis including 4428 patients and undertaking a systematic review and meta-analysis of observational studies of risk factors associated with RHF after LVAD implant showed that RVFWLS had the largest sufficient size in predicting RHF preoperatively with the value of 0.73 standard mean difference [50].

Despite the high mortality due to the RHF after LVAD implant, the noninvasive and invasive assessment of the right ventricle and predicting RHF is exceptionally challenging. As all we know, TTE and TEE are the most commonly utilized imaging modalities for evaluating right heart functions; the anatomical characterization of the right heart decreases the ability to assess the right ventricle accurately. Even though there are only a few studies focusing on the impact of strain on the right ventricle function in the patients undergoing LVAD implant as also mentioned above in advance, it might clearly be defined that RV longitudinal strain is an excellent alternative to the invasive methods in assessing perioperative right heart function even after LVAD implantation [50].

Conclusion

Postoperative RHF is a critical prognostic factor in patients undergoing LVAD implantation. Several diagnostic tools are available, including echocardiography, right heart catheter, and CMR imaging. Currently, available risk models incorporated patients' clinical condition and biochemical markers but require proper external validation. RV strain measurements have rapidly emerged as a popular and promising technique for the assessment of right heart function. We believe that after the evolution and standardization, RV strain measurements would have the potential to be a standard diagnostic tool in the decision-making process of LVAD therapy. However, the significant intraobserver and interobserver variability remain the most critical limitation in clinical practice at present. Incorporating the strain measurements into the magnetic resonance imaging and three-dimensional echocardiographic evaluation routinely, and standardization of the image processing might minimize this variability in the future. Moreover, it might be one of the influential predicting risk factors for the scoring models.

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Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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