Assessment of Right Ventricular Function in Left Ventricular Assist Device Candidates

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As a result of the improved survival of patients with heart failure (HF) and the overall rise in the prevalence of HF, the number of patients in advanced (stage D) HF continues to increase, thus exceeding the limited availability of donor organs by a wide margin. Initially used primarily as a bridge to heart transplantation, mechanical circulatory support is now increasingly offered as a destination therapy to patients with advanced HF in clinical deterioration who are not candidates for transplantation. Improvement in survival to 80% at 1-year postimplantation has steadily followed the development of new technologies such as the continuous-flow pump, which now encompasses 99% of left ventricular assist devices (LVADs), and improvements in patient and device management. Far from being a panacea, mechanical circulatory support is still fraught with challenges. Among them, post-LVAD right ventricular failure (RVF) is a major cause of morbidity and mortality.

Despite (1) overall improved outcomes and lower rates of RVF with the use of the newer, continuous-flow LVADs over pulsatile-flow devices, and (2) development of clinical prediction scores to facilitate preoperative identification of patients at risk for RVF after implantation, RVF still occurs in 13% to 40% of continuous-flow device. LVAD function relies heavily on right ventricular (RV) function for adequate preload. Severe RVF cannot only lead to systemic hypoperfusion, multiorgan failure, and death but also to prolonged or recurrent hospitalization and poor quality of life even in less extreme cases. LVAD recipients who develop RVF have poor outcomes, including higher perioperative, short- and long-term mortality, and reduced survival to transplantation. RVF has also been associated with higher risk of bleeding, renal failure, and hypotension, and longer intensive care unit and hospital stays.

In the absence of durable and safe options for RV support, preoperative characterization of RV function and appropriate patient selection is of paramount importance in improving outcomes post-LVAD. In this article, we review the current evidence for preoperative assessment of RV function and RVF risk, with focus on cardiac imaging and specifically echocardiography. To put the discussion in context, we also briefly review the definitions, incidence, and pathophysiology of RVF. Finally, we discuss challenges and suggest directions for future research.

Definition and Incidence of Post-LVAD RV Failure

Although RVF is common after LVAD implantation, the precise incidence estimates vary from 9.4% to 44% depending on the definition of RVF, the characteristics of the study population, and the type of LVAD (Table 1). The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) defines RVF as (1) need of an RV assist device (RVAD), or (2) requirement of inhaled nitric oxide or inotropic therapy for >1 week any time after LVAD implantation in the presence of symptoms and signs of persistent RV dysfunction, such as central venous pressure >18 mmHg with a cardiac index <2.3 L/min per square meter in the absence of elevated left atrial or pulmonary capillary wedge pressure (>18 mmHg), cardiac tamponade, ventricular arrhythmias, or pneumonia. Most studies have used a variation of this definition combining clinical findings and hemodynamics (Table 1). Severe RVF requiring RVAD has been reported in 9.4% to 23.4% of patients, whereas definitions incorporating need for inotropes yield estimates ranging from 20.2% to 40%.

Although the need for placement of an RVAD might be viewed as an indicator of more definitive RVF, the outcomes of patients presenting with RVF, defined as the need for prolonged inotropic or other support besides RVAD, are equally unfavorable (Table 1 in the Data Supplement). Therefore, it would be important to include need for prolonged (or delayed) inotrope use when defining RVF. In this respect, following the current INTERMACS scheme for RVF severity might be reasonable. This scheme suggests that RVF be reported as (1) severe, if RVAD was implanted; (2) moderate, when inotropes or intravenous or inhaled pulmonary vasodilators were used for >1 week at any time after LVAD implantation; and (3) mild, when a combination of ≥2 symptoms and signs are present (central venous pressure >18 mmHg, cardiac index cardiac index <2.3 L/min per square meter, ascites, moderate-to-severe peripheral edema, or echocardiographic or physical examination evidence of elevated central venous pressure) but without the need for RVAD or prolonged...
### Incidence of Right Ventricular Failure After Left Ventricular Assist Device Implantation

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Single or Multicenter</th>
<th>LVAD Type</th>
<th>RVF Definition</th>
<th>RVF Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukamachi et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>N=100, BTT 97%, DT 2%, mean age 52.5, male 86%</td>
<td>Single</td>
<td>Pulsatile 100%</td>
<td>Requiring RVAD support</td>
<td>11.0</td>
</tr>
<tr>
<td>Kavarana et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>N=69, mean age 56.2, male 86%</td>
<td>Single</td>
<td>Pulsatile 100%</td>
<td>Requiring inotropic support for ≥14 d or RVAD support</td>
<td>30.4</td>
</tr>
<tr>
<td>Ochiai et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>N=245, BTT 98%, DT, mean age 64, male 85%</td>
<td>Single</td>
<td>Pulsatile 100%</td>
<td>Requiring RVAD support</td>
<td>9.4</td>
</tr>
<tr>
<td>Dang et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>N=108, BTT 100%, mean age 51, male 93%</td>
<td>Single</td>
<td>Pulsatile 100%</td>
<td>Requiring inotropic support or pulmonary vasodilators for ≥14 d or RVAD support</td>
<td>38.9</td>
</tr>
<tr>
<td>Puvanan et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>N=33, BTT 67%, DT 21%, BTR 12%, mean age 54</td>
<td>Single</td>
<td>Continuous 55%, Pulsatile 45%</td>
<td>Requiring inotropic support or pulmonary vasodilators for &gt;14 d</td>
<td>33.0</td>
</tr>
<tr>
<td>Potapov et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>N=54, mean age 52, male 91%</td>
<td>Single</td>
<td>Pulsatile 100%</td>
<td>Two of the following criteria in the first 48 h: MAP ≤55 mmHg, CVP ≥16 mmHg, MvO₂ ≤55%, CI &lt;2 L/min per square meter, inotropic support score &gt;20 U, or need for RVAD</td>
<td>16.7</td>
</tr>
<tr>
<td>Matthews et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>N=197, BTT 94%, DT 6%, mean age 50, male 79%</td>
<td>Single</td>
<td>Continuous 15%, Pulsatile 85%</td>
<td>Requiring RVAD or ECMO support, inotropic support for &gt;14 d, inhaled NO for ≥48 h, or hospital discharge with an intravenous inotrope</td>
<td>34.5</td>
</tr>
<tr>
<td>Fitzpatrick et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>N=266, mean age 52, 65% male</td>
<td>Single</td>
<td>Continuous 4%, Pulsatile 96%</td>
<td>Requiring BIVAD placement</td>
<td>37.0</td>
</tr>
<tr>
<td>Drakos et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>N=175, BTT 58%, DT 42%, mean age 57, male 83%</td>
<td>Single</td>
<td>Continuous 14%, Pulsatile 86%</td>
<td>Requiring RVAD support, inhaled nitric oxide for ≥48 h, or inotropic support for &gt;14 d</td>
<td>44.0</td>
</tr>
<tr>
<td>Kornos et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>N=484, BTT 100%, mean age 52, male 78%</td>
<td>Multicenter</td>
<td>Continuous 100%</td>
<td>Requiring inotropic support ≥14 d, starting ≥14 d postimplantation, or RVAD support</td>
<td>20.2</td>
</tr>
<tr>
<td>Hennig et al&lt;sup&gt;7&lt;/sup&gt;</td>
<td>N=40, BTT 100%, mean age 55, male 95%</td>
<td>Single</td>
<td>Continuous 77%, Pulsatile 23%</td>
<td>Two of the following criteria during the first week after surgery: MAP ≤55 mmHg, CVP ≥16 mmHg, MvO₂ ≤55%, CI &lt;2 L/min per square meter, inotropic support score &gt;20 U, or requiring RVAD support</td>
<td>35.0</td>
</tr>
<tr>
<td>Baumwol et al&lt;sup&gt;16&lt;/sup&gt;</td>
<td>N=40, BTT 83%, DT 17%, mean age 52, male 91%</td>
<td>Single</td>
<td>Continuous 100%</td>
<td>Requiring inotropic support for &gt;14 d, inhaled NO &gt;48 h or sildenafil/iloprost on cessation of inhaled NO, or right-sided mechanical support</td>
<td>32.5</td>
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<tr>
<td>Topilsky et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>N=83, BTT 33%, DT 67%, mean age 63, male 81%</td>
<td>Single</td>
<td>Continuous 100%</td>
<td>Requiring RVAD or inotropic support &gt;7 d postoperatively</td>
<td>27.7</td>
</tr>
<tr>
<td>Kukucka et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>N=115, mean age 54, male 90%</td>
<td>Single</td>
<td>Continuous 100%</td>
<td>Two of the following: MAP &lt;55 mm Hg, CVP &gt;16 mm Hg, MvO₂ &lt;55%, CI &lt;2 L/min per square meter, inotropic support score &gt;20 U, or need for an RVAD</td>
<td>13.0</td>
</tr>
<tr>
<td>Kato et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>N=111, mean age 56, male 78%</td>
<td>Single</td>
<td>Continuous 71%, Pulsatile 29%</td>
<td>Requiring inotropic support for &gt;14 d or restarting inotropes after 14 d, inhaled NO &gt;48 h, or RVAD</td>
<td>31.5</td>
</tr>
<tr>
<td>Grant et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>N=117, BTT 67%, DT 33%, mean age 58, male 79%</td>
<td>Single</td>
<td>Continuous 100%</td>
<td>Requiring inotropic support for &gt;14 d or RVAD support</td>
<td>40.0</td>
</tr>
<tr>
<td>Kukucka et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>N=122, mean age 55, male 88%</td>
<td>Single</td>
<td>Continuous 100%</td>
<td>Two of the following criteria in the absence of cardiac tamponade: &lt;48 h post-surgery: MAP &lt;55 mm Hg, CVP &gt;16 mm Hg, MvO₂ &lt;55%, CI &lt;2 L/min per m&lt;sup&gt;2&lt;/sup&gt;, or inotropic support score &gt;20 U</td>
<td>12.3</td>
</tr>
<tr>
<td>Raina et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>N=55, mean age 54, male 71%</td>
<td>Single</td>
<td>Continuous 93%, Pulsatile 7%</td>
<td>Requiring inotropic support for ≥14 d or RVAD support</td>
<td>29.0</td>
</tr>
<tr>
<td>Kato et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>N=68, mean age 63, male 90%</td>
<td>Single</td>
<td>Continuous 100%</td>
<td>Requiring inotropic support or pulmonary vasodilators at 14 d postoperatively or RVAD support</td>
<td>35.3</td>
</tr>
<tr>
<td>Vivo et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>N=109, BTT 49%, DT 49%, BTD 2%, mean age 54, male 77%</td>
<td>Single</td>
<td>Continuous 100%</td>
<td>Requiring inotropic support for ≥14 d or RVAD support</td>
<td>22.9</td>
</tr>
<tr>
<td>Atturi et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>N=218, mean age 56, male 81%</td>
<td>Single</td>
<td>Continuous 100%</td>
<td>Requiring BIVAD placement</td>
<td>23.4</td>
</tr>
</tbody>
</table>

*BIVAD indicates biventricular assist device; BTD, bridge to decision; BTT, bridge to transplantation; BTR, bridge to recovery; CI, cardiac index; CVP, central venous pressure; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; MAP, mean arterial pressure; MvO₂, mixed venous oxygen saturation; NO, nitric oxide; RVAD, right ventricular assist device; and RVF: right ventricular failure.

*Not explicitly defined; however, BTT rate was calculated with the entire cohort in the denominator. For studies without BTT vs DT information, indication was not reported in the original publication.
inotropic or vasodilator support. The latter category would not be reported in a dichotomous definition of RVF. These more granular definitions incorporate prolonged use of inotropes, which is clearly associated with adverse outcomes, and facilitate comparison between studies and reporting the effect of RVF on outcomes according to RVF severity.

Of note, no large study to date has prespecified a time frame for RVF (eg, 30 or 90 days). This would be important for consistency, which would facilitate a more valid comparison of rates and predictive modeling. In a recent large series, the time to unplanned RVAD insertion ranged from 1 to 66 days after LVAD surgery, and only 4 out of 44 patients required RVAD support later than 10 days post-LVAD. Other groups have reported similar findings. However, data on the incidence and impact of RVF after the 90-day window are limited. Finally, quantitative RV function has not been incorporated into RVF definitions to date.

Pathophysiology of Post-LVAD RV Failure
The pathophysiology of RVF post-LVAD is not well understood. Implantation of an LVAD promotes rapid and dramatic changes because cardiac output is largely restored and left ventricular (LV) filling pressures are relieved. This in turn leads to an increase in RV preload and a decrease in RV afterload. The immediate decrease in RV afterload, however, is mostly the result of reduced LV filling pressures, and the observed immediate reduction in pulmonary vascular resistance (PVR) is primarily the result of increased cardiac output. Reversal of structural changes in the pulmonary vasculature (previously considered fixed pulmonary hypertension) and further reduction in PVR may also occur but take more time to realize.

In the interim, the acute rise in venous return in conjunction with periparative transfusion and intravenous fluid administration may further strain the RV, thus increasing wall stress and exacerbating tricuspid regurgitation (TR).

Alterations in hemodynamics only partially explain changes in RV function post-LVAD. The LVs and RVs are interdependent by virtue of the interventricular septum, interlacing muscle fibers, and the pericardium. The effects of LVAD support on the septum and RV function have been controversial. In animal studies, LVAD support induces ischemia of the septum with decreased thickening and altered septal geometry. However, in other animal models, septal shift did not affect RV function.

However, it is difficult to extrapolate findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>RVF Definition and Rate</th>
<th>Multivariable Predictors</th>
<th>Echocardiographic RV Parameters Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michigan RV Failure Risk Score (2008)</td>
<td>197 LVADs, 28 continuous-flow, 94% BTT</td>
<td>Need for RVAD Need for inotropes RVF rate: 35%</td>
<td>Preoperative vasopressors (4 pts) AST ≥80 IU/L (2 pts) Bilirubin ≥2.0 mg/dL (2.5 pts) Creatinine ≥2.3 mg/dL (3 pts) Cardiac index ≥2.2 L/min per square meter RVSWI ≤0.25 mm Hg/L/m² Severe RV dysfunction Creatinine ≥1.9 mg/dL Prior cardiac surgery Systolic BP ≥96 mm Hg</td>
<td>RV systolic function (visual semiquantitative) TR (visual semiquantitative)</td>
</tr>
<tr>
<td>Penn RVAD Risk Score (2008)</td>
<td>266 LVADs, 6 continuous-flow BTT vs DT not reported</td>
<td>Need for RVAD Included ITT RVAD RVF rate: 37%</td>
<td>DT indication (3.5 pts) IABP (4 pts) PVR (1–4 pts) Inotrope dependency (2.5 pts) Obesity (2 pts) ACEI or ARB use (−2.5 points) β-blocker use (2 pts) CVP/PCWP &gt;0.63 (OR, 2.3) Need for ventilator support (OR, 5.5) BUN &gt;39 mg/dL (OR, 2.1)</td>
<td>RV systolic function (visual semiquantitative) Right atrial area</td>
</tr>
<tr>
<td>Utah RV Risk Score (2010)</td>
<td>175 LVADs, 25 continuous-flow 58% BTT, 42% DT</td>
<td>Need for RVAD Need for inotropes Need for inhaled NO RVF rate: 44%</td>
<td>DT indication (3.5 pts) IABP (4 pts) PVR (1–4 pts) Inotrope dependency (2.5 pts) Obesity (2 pts) ACEI or ARB use (−2.5 points) β-blocker use (2 pts) CVP/PCWP &gt;0.63 (OR, 2.3) Need for ventilator support (OR, 5.5) BUN &gt;39 mg/dL (OR, 2.1)</td>
<td>RV systolic function (visual semiquantitative) Right atrial area</td>
</tr>
<tr>
<td>Kormos (2010)</td>
<td>484 LVADs, All continuous-flow BTT 100%</td>
<td>Need for RVAD Need for inotropes RVF rate: 20.2%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Pittsburgh Decision Tree (2012)</td>
<td>183 LVADs, 40 continuous-flow BTT vs DT not reported</td>
<td>Need for RVAD RVF rate: 15%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CRITT (2013)</td>
<td>167 LVADs, all continuous-flow 51 BiVADs BTT vs DT not reported</td>
<td>Need for BiVAD RVF rate: 23%</td>
<td>RV systolic function (visual semiquantitative) Severe TR (visual semiquantitative)</td>
<td>RV systolic function (visual semiquantitative) Severe TR (visual semiquantitative)</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BiVAD, biventricular assist device; BP, blood pressure; BTT, bridge to transplantation; BUN, blood urea nitrogen; CRITT, central venous pressure-RV dysfunction-preoperative intubation-severe tricuspid regurgitation-tachycardia; CVP, central venous pressure; DT, destination therapy; IABP, intra-aortic balloon pump; INR, international normalized ratio; ITT, intention to treat; LVAD, left ventricular assist device; NO, nitric oxide; OR, odds ratio; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RV, right ventricle; RVAD, right ventricular assist device; RVF, right ventricular failure; RVSWI, right ventricular stroke work index; and TR, tricuspid regurgitation.
from healthy animals to humans with HF. In a study of 76 recipients with continuous-flow LVAD, persistent leftward bowing of the septum 30 days postimplantation was associated with significantly worse outcomes at 90 days.\textsuperscript{45} In an in silico cardiovascular-respiratory system model, increased LVAD pump speeds seem to reduce septal contribution to RV and LV ejection and increase RV work.\textsuperscript{46} Finally, patients with more severe RV dysfunction may be more prone to LV suction with higher LVAD pump speeds.\textsuperscript{47}

**Challenges in RVF Risk Prediction**

Although preoperative assessment of RV function with contemporary imaging has a strong potential to improve RVF risk prediction, there are 4 major challenges. First, a host of intraoperative events may impair RV function, including increased PVR secondary to suboptimal ventilation and alveolar hypoxia, hyperinflation, or atelectasis; acidosis causing ischemic injury; direct RV ischemia by injuring previous bypass grafts; and ischemia attributable to prolonged cardiopulmonary bypass, bleeding, transfusions, or shock.\textsuperscript{13,48} Second, varying practices in concomitant procedures during LVAD implantation may also alter the course of RV function. For example, there is growing evidence that concomitant tricuspid valve repair (or replacement) for severe TR results in improved RV function postimplantation.\textsuperscript{49} Third, there is wide interinstitutional variation in the use and duration of inotropes and the threshold for RVAD support after LVAD surgery. For example, extended (≥14 days) inotropic support after LVAD surgery ranged from <15%\textsuperscript{13,32} to >30%\textsuperscript{15} in recent continuous-flow LVAD series. Fourth, the population of LVAD recipients is a moving target.\textsuperscript{2} Because post-LVAD outcomes continue to improve, there is a clear trend toward more elective implantations in less sick patients over time,\textsuperscript{3} with destination therapy becoming rapidly the most frequent indication.\textsuperscript{3} Also, because LVAD technology evolves, new target populations may be identified.

Despite the aforementioned challenges and potential confounders, preoperative RV function has been identified consistently as a predictor of postimplantation RVF. Several studies have considered preoperative clinical variables and cardiac imaging (ie, echocardiography) as a means to better risk stratify recipients with LVAD for RVF. In the following section, we review the available evidence, primarily focusing on echocardiography.

**Risk Prediction Models and Risk Factors for RV Failure**

**Clinical Scores**

Current RVF prediction scores rely on HF severity, laboratory evidence of end-organ damage, right heart hemodynamics, and history of cardiac procedures as surrogates of preoperative

| Table 3. Quantitative Right-Sided Parameters Considered in Studies Evaluating Echocardiography for Prediction of Right Ventricular Failure |
|---------------------------------|--------------------------------|---------------------------------|
| Study                           | Patients                      | Echocardiographic RV Parameters Considered | Univariate Echo Predictors | Multivariate Echo Predictors |
| Potapov et al\textsuperscript{24} | N=54, mean age 52, male 91%   | RV short/long axis ratio, RV mass, RA diameter, RV EF, TR | RV short/long axis ratio, RV EF, TR | RV short/long axis ratio, TR grade III to IV |
| Puwanant et al\textsuperscript{23} | N=33, mean age 54, BTT 67%, DT 21%, BTR 12% | RV FAC, RV MPI, TAPSE, RA volume, TR, RV systolic pressure | TAPSE, RV systolic pressure | Multivariate analysis not performed |
| Kukucka et al\textsuperscript{27a} | N=115, mean age 54, male 90% | R/V EDD ratio, RV area, RV FAC RV volumes, RV EF, TAPSE | R/V EDD ratio | Multivariate analysis not performed |
| Topilsky et al\textsuperscript{26} | N=83, BTT 33%, DT 67%, mean age 63, male 81% | Qualitative RV function, TR velocity, TRDc, RV ejection time, TR vena contracta width, TAPSE, MPI | TRDc, MPI, TR-RV ejection time | LV EDD, TRDc |
| Grant et al\textsuperscript{10} | N=117, mean age 56, male 79%, BTT 67%, DT 33% | RV FAC, RV dysfunction (visual semiquantitative), TAPSE, RV ratio, TR, RV free-wall strain | RV dysfunction (visual semiquantitative), RV free-wall strain | RV free-wall strain |
| Kato et al\textsuperscript{28} | N=111, mean age 56, male 78% | RV FAC, TAPSE | LV EDD, LV ESD, LV EF, LA diameter to LV EDD (ratio) | LV EDD |
| Raina et al\textsuperscript{30} | N=55, mean age 54, male 71%, BTT 65%, DT 35% | RV dimensions and areas, R/L EDD ratio, RV FAC, TAPSE, RA pressure, RV outflow tract VTI | RV FAC, RA pressure, LA volume | None |
| Kato et al\textsuperscript{31} | N=68, mean age 63, 90% male | RV EDD, RV FAC, TAPSE, TDI S, TDI E, RV E/E, RV global strain | RV FAC, TAPSE, RV E/E, RV global strain | Multivariate analysis not performed |
| Vivo et al\textsuperscript{32} | N=109, BTT 49%, DT 49%, BTD 2%, mean age 54, male 77% | RV diameter, RV area, RV FAC, qualitative RV size and function, TAPSE, TDI S, RV CI, TR velocity and severity, RA pressure, RV/LV diameter ratio, RVSW/ | RV/LV diameter ratio, RVSW | Increased RV/LV diameter ratio |

\*Transesophageal echocardiography. For studies without BTT vs DT information, indication was not reported in the original publication.
RV dysfunction (Table 2). Importantly, these models have been derived from retrospective studies in patients with mostly pulsatile-flow LVADs and thus do not fully represent the current LVAD population. The predictors considered vary significantly across studies, as do definitions of RVF. Of note, preoperative risk factors for worse post-LVAD outcomes are also risk factors for RVF; that is, clinical HF status, high RV filling pressures, and low RV stroke work index.

The application of RVF prediction scores in clinical practice has been limited partially because of modest score performance, and only the Michigan score has seen some uptake in research and practice. Developed in 197 recipients with LVAD (94% bridge to transplantation; continuous-flow device in 28), of whom 68 (35%) recipients developed RVF, the score incorporates preoperative vasopressor requirements, liver enzyme elevations, and creatinine levels as predictors of RVF. The c statistic in the derivation cohort was 0.73. However, in a retrospective study investigating the incremental value of quantitative RV parameters, the Michigan score had only modest discrimination (c=0.66) for RVF prediction. In a small validation study in recipients with continuous-flow LVAD, no score predicted the need for RVAD. Our group has retrospectively assessed RVF scores in 69 recipients with continuous-flow LVAD and observed that, although the Michigan score offered the highest discrimination (c=0.64), all scores had modest performance and low predictive values. Of note, despite several studies investigating various echocardiographic RV function parameters, no score has incorporated quantitative RV parameters to date.

Hemodynamic Parameters

Invasive Assessment of RV Systolic Function

Although RV ejection fraction can be derived by fluoroscopy, this method is rarely used in practice. Alternatively, right-sided hemodynamics allows inference of RV function. RV stroke work index, defined as (mean pulmonary artery pressure–mean right atrial pressure)/stroke volume index, has been considered in several studies but has not been uniformly shown to predict RVF in multivariate analyses. Potential drawbacks of RV stroke work index are (1) being a derivative of multiple measures and thus more prone to error, and (2) dependence on preload. Also, the use of serial RV stroke work index for follow-up after LVAD implantation is limited.

Pulmonary Vascular Resistance and Pulmonary Artery Systolic Pressure

Although long-term unloading of the LV can lead to clinically relevant reductions of PVR and potentially restore candidacy for transplantation, elevated preoperative PVR has been identified as an independent predictor of RVF although not consistently. It is interesting that in several studies, preoperative PVR did not emerge as a predictor of RVF. This may be related to the fact that PVR is highly dependent on cardiac output and is therefore dramatically affected by LVAD-induced increases in cardiac output. Low pulmonary artery systolic pressure (PASP) has been considered a surrogate of severe RV dysfunction in advanced HF and has been associated with post-LVAD RVF in early studies. However, this is probably seen only in the extreme end of RV dysfunction.

Figure 1. Right ventricular fractional area change (RVFAC) estimation in (A) a 73-year-old male with ischemic cardiomyopathy who has become inotrope dependent in the last few months, and (B) a 43-year-old female with nonischemic cardiomyopathy awaiting heart transplantation who required an intra-aortic balloon pump for stabilization. Both patients received a Heart Mate II device 10 days later as destination therapy and bridge to transplantation, respectively. Patient A was weaned from inotropes on postoperative day 5, whereas patient B required inotropic support for 38 days. Note the heavy trabeculation and the strong echo from the defibrillator lead in B. RVAd indicates right ventricle area in diastole; and RVAs, right ventricle area in systole.
In contemporary studies, low PASP was either a weak predictor or did not confer useful predictive information. This is probably because (1) PASP is a function of both PVR and RV systolic function, and, thus, various combinations of these parameters can yield similar PASP values, blunting discrimination for RV dysfunction; and (2) LVAD support is now offered to an HF population with a smaller proportion of patients with extreme RV dysfunction from the outset, and hence the predictive ability of low PASP is less relevant.

**Echocardiography**

Accurate determination of RV function with transthoracic echocardiography has proven to be challenging, secondary to the retrosternal position of the RV and its complex geometry. The RV inflow and outflow tracts are out of plane and difficult to image simultaneously. Postimplantation changes and device-related artifacts further limit post-LVAD visualization and measurements. Despite these challenges, echocardiography is still the most available, feasible, affordable, and safe imaging modality for patients with advanced HF. However, RV contractility is often subjectively classified into normal or mildly, moderately, or severely reduced. This semiquantitative approach has poor reproducibility, accuracy, and sensitivity to detect clinically relevant changes. The American Society of Echocardiography has recently provided guidelines for objective, quantitative assessment of RV function. In Table 3, we summarize the available data on the predictive value of quantitative RV parameters in LVAD populations for RVF prediction.

**M-Mode Parameters**

Normal RV function is highly dependent on longitudinal shortening. A simple approach to study RV longitudinal function is to place an M-mode cursor on the tricuspid annulus in an apical RV view and measure longitudinal annular displacement. Tricuspid annular plane systolic excursion (TAPSE) should be ≥1.6 cm in adults. Low TAPSE has been associated with worse survival in pulmonary arterial hypertension. However, TAPSE is a regional, linear parameter for a complex structure and is dependent on loading conditions and insonation angle (Figure 1). Although TAPSE has been reported to predict RVF in a small early study, this finding has not been confirmed in subsequent LVAD cohorts.

**2-Dimensional Parameters**

RV fractional area change (RVFAC) is a feasible quantitative alternative to eyeballing RV systolic function and correlates well with cardiac MRI measurements. An RVFAC <35% is considered abnormal. A >10% reduction in RVFAC at 1 month was associated with worse quality of life and poor survival.

![Figure 2.](http://circimaging.ahajournals.org/)

**Figure 2.** Tricuspid annular systolic plane excursion (TAPSE) in the same patients as in Figure 1. A, Patient exhibits a low TAPSE (0.7 cm), indicative of severe right ventricular (RV) dysfunction despite the mildly abnormal RV fractional area change (RVFAC). B, In contrast, patient has a low-normal TAPSE (1.6 cm) despite severely depressed RVFAC. However, as evident from the elevated heart rate (105 bpm), patient B is in hemodynamic stress, which is accompanied by exaggerated translational motion of the heart, thus overestimating TAPSE. The use of color M-mode, although not necessary for TAPSE estimation, facilitates detection of directional changes in motion.
exercise capacity in patients with an LVAD. However, the reproducibility and prognostic value of RVFAC in patients with LVAD is uncertain because the available studies report suboptimal quality of assessments and fair correlation coefficients for observer variability (0.50–0.76). Heavy trabeculation and pacemaker or defibrillator lead artifacts are common challenges when evaluating RVFAC in patients with advanced HF (Figure 2). In a small retrospective study that included planned RV support in the definition of RVF, lower RVFAC predicted RVF. However, RVFAC did not predict RVF in another larger study and was only marginally or not predictive in other retrospective studies.

The size of the RV, mainly in the form of RV/LV diameter ratio, is surrogate for RV contractility and in some studies demonstrated strong association with RVF. Other studies, however, failed to confirm this finding. The main challenge with the RV/LV diameter ratio is the standardization of the acquisition plane and level (basal, mid, apical). In a study specifically assessing reproducibility of the RV/LV diameter ratio, the intra- and interobserver interclass correlation coefficients were 0.57 and 0.61, respectively.

Doppler and Tissue Doppler–Based Parameters

Although severe TR has been identified as a strong predictor of RVF in some studies, other large studies did not find such an association. Shorter TR duration, presumably a marker of early equalization of RV and atrial pressures, was associated with worse outcomes in a cohort of recipients with continuous-flow LVAD. However, TR has not been uniformly evaluated in studies investigating RVF predictors, including echocardiography-focused studies. Recently, tricuspid annular dilation assessed by transesophageal echocardiography was identified as a predictor of midterm post-LVAD survival among patients without preoperative severe TR.

Despite the strong association with RV dysfunction in the general HF population, TR may not be a suitable marker of RV function in contemporary candidates with LVAD. First, the majority of these patients have previously received an implantable defibrillator with or without cardiac resynchronization capability. Pacemaker and defibrillator lead cause or worsen TR in a considerable proportion of recipients. Although the clinical implications of lead-induced TR are still unclear and severe TR is uncommon, this effect nevertheless blunts the value of TR as an RV function surrogate. Second, a growing number of recipients with LVAD undergo simultaneous procedures for severe TR, thus confounding the use of TR as a predictor of RVF.

Tissue Doppler imaging is an attractive alternative to TAPSE because myocardial velocities are easy to obtain and reproduce. Systolic velocity of the tricuspid annulus reflects longitudinal RV function. However, velocities depend on insonation angle and loading conditions (Figure 3). Also, translational motion of the heart and tethering by adjacent diseased myocardial segments can produce velocities that are not representative of the performance of the interrogated segment. In a study of 68 recipients with LVAD, systolic tricuspid annular velocity did not predict RVF.

The myocardial performance index (MPI), defined as the ratio of isovolumic time divided by the ejection time, is considered an indicator of global RV function. An RV MPI >0.40 by pulsed-wave Doppler or >0.55 by tissue Doppler indicates RV dysfunction. Longer isovolumic phases and shorter ejection time signify worse ventricular performance as expressed by a higher MPI. Although the MPI is fairly independent of heart rate and geometry, it is highly sensitive to loading conditions and less reliable with elevated right atrial pressures. Data are largely lacking, but in a small study, the RV MPI was not a predictor of RVF postimplantation.

RV Mechanics

Strain expresses myocardial shortening or lengthening (in the longitudinal and circumferential directions) or thickening or thinning (in the radial direction), whereas strain rate is the rate of deformation over time. Strain and strain rate, collectively termed ventricular mechanics, reflect myocardial performance and provide a more direct assessment of myocardial contractility over ejection fraction or linear measurements. These
indices may be calculated from either tissue velocity measurements (tissue Doppler imaging) or tracking of unique ultrasound speckles from frame-to-frame 2-dimensional (B-mode) images. Strain and strain rate are independent of ventricular morphology and are angle independent when obtained by speckle tracking. However, strain measurements are intrinsically load dependent. The American Society of Echocardiography does not currently recommend tissue Doppler imaging–based regional RV mechanics because of high variability, lack of standardization, and paucity of normative data.53

Speckle tracking represents a promising alternative attributable to (1) automated myocardial delineation and tracking, and (2) insights into regional myocardial performance (Figure 4).53,62,63 The literature reporting on RV function using speckle tracking–based regional RV mechanics because of high variability, lack of standardization, and paucity of normative data.53

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Figure 4. Right ventricular (RV) longitudinal strain by speckle tracking in the same patients as in Figure 1. A, In patient (ischemic etiology), the interventricular septum demonstrates low peak strain (normal values: −14±4% to −22±5% from base to apex)53 suggestive of severe systolic dysfunction, whereas the RV free-wall demonstrates preserved systolic function, especially at the basal and middle segments (lower reference values: −18% to −20%).63 B, In patient (non-ischemic pathogenesis), the low peak strain values across all segments and the low global strain (−4.3%) suggest severe global RV systolic dysfunction. Note also the fragmented systolic activation in the linearized map (lower left) in B as compared with the more homogenous activation in A.

score and had incremental predictive value, increasing the C statistic from 0.66 to 0.77 (P<0.01) and improving net reclassification.10 In another study of 68 patients undergoing elective LVAD surgery, RV longitudinal strain by speckle tracking was significantly impaired preoperatively (−12.6±3.3% versus −16.2±4.3%; P<0.001) in 24 patients (35.3%) who experienced RVF by 14 days.31 Other groups have recently reported similar findings.64,65

Although the American Society of Echocardiography does not currently recommend speckle-tracking parameters as a clinical tool secondary to cross-platform standardization issues and lack of definitive data, we believe that global and free-wall longitudinal RV mechanics (strain and strain rate), preferably assessed by speckle tracking, are probably the most promising approach for RVF prediction. Strain and especially strain rate are less sensitive to loading conditions and represent systolic RV function reasonably well.66 Also, the consistency of findings on the predictive value of longitudinal RV mechanics for RVF across different research groups is promising.10,31,64,65 Of note, post-LVAD assessment of RV mechanics is feasible,31 hence facilitating tracking of RV function, and adds information incremental to that obtained from preoperative imaging.
Other Imaging

Multidetector computed tomography has been successfully used to visualize the LVAD cannulae and detect postoperative complications. In recipients with LVAD, RV ejection fraction by multidetector computed tomography was highly reproducible and correlated well with RVFAC. However, data with multidetector computed tomography in patients with LVAD are limited. Also, the need for nephrotoxic contrast precludes routine use of multidetector computed tomography in candidates with LVAD, who often have concomitant kidney disease.

Conclusions and Future Directions

RV failure remains a challenge in the era of continuous-flow LVADs. Beyond the inherent challenges in the assessment of RV function, intraoperative events, concomitant surgical procedures, and postoperative changes in pulmonary hemodynamics and device settings may confound the ability of preoperative assessment of RV function to predict RVF. Additional challenges include evolving mechanical circulatory support technology and shifts in the target population. However, the full potential of contemporary imaging, especially echocardiography, has not been fully used in the preoperative assessment of candidates with LVAD. In this direction, we believe that the following issues should be a priority.

Standardization of Echocardiographic Protocols

Preoperative RV function is still assessed subjectively in many patients. Therefore, an important first step would be the standardization of echocardiographic protocols before and after device implantation across LVAD centers. This would be greatly facilitated if the INTERMACS registry included a dedicated echocardiographic module; the currently required data are rudimentary (semiquantitative valvular regurgitation, LV ejection fraction, LV end-diastolic diameter). A common module for all centers could include quantitative data on LV and RV structure and function and a standard set of Doppler-based hemodynamics. A pilot RV mechanics module for centers able to contribute mechanics data could also be launched and expanded over time.

Refinement of RVF Definition and Serial Assessment of RV Function

Currently, the definition of RVF does not include any parameters of RV function. One way to incorporate RV systolic function parameters would be to require several echocardiographic criteria for RVF, for example, the presence of 2 out of 4 standard predefined RV dysfunction criteria (low TAPSE, low RVFAC, low tricuspid S‘, or high right ventricular index of myocardial performance, using the American Society of Echocardiography cutoffs) in addition to hemodynamic criteria. A pilot RV mechanics module for centers able to contribute mechanics data could also be launched and expanded over time.

Merging Research and Practice

The entire field is moving fast. Therefore, it is important for research and practice to converge. For example, it would be important for every center to acquire its own experience with echocardiographic parameters and communicate the results and outcomes with the LVAD team. From a practical perspective, we believe that based on the current data, it would be reasonable to cautiously re-evaluate candidacy for LVAD, and perhaps consider alternatives, for patients with an absolute value of RV free-wall or global strain of <10%, especially in conjunction with clinical surrogates of RV dysfunction.

In the same spirit, leveraging INTERMACS would be the fastest avenue forward. The derivation and validation of predictive models based on clinical and echocardiographic variables in the INTERMACS database would (1) leverage existing infrastructure, (2) ensure multicenter input and applicability of results, and (3) allow for regular updating of selection algorithms as both technology and target population evolve.

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Disclosures

None.

References


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<th>Study</th>
<th>RVF Definition</th>
<th>Outcomes</th>
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| Fukamachi et al (1999) | Requiring RVAD support                                                        | Survival to transplant: RVAD 27%, no-RVAD 83%  
Reoperation for bleeding: RVAD 64%, no-RVAD 17%                                                                                           |
| Kavarana et al (2002)  | Requiring inotropic support for ≥14 days, or RVAD support                    | Dialysis: RVF 73%, no-RVF 26%  
ICU LoS: RVF 33.6 ± 34.7 days, no-RVF 9.1 ± 6.9 days  
In-hospital mortality: RVF 42.8%, no-RVF 14.5%                                                                                       |
| Ochiai et al (2002)    | Requiring RVAD support                                                        | Reoperation for bleeding: RVAD 57%, no-RVAD 27%  
Survival to transplantation: RVAD 17%, no-RVAD 74%                                                                                      |
| Dang et al (2006)      | Requiring inotropic support or pulmonary vasodilators for ≥14 days, or RVAD support | 30-day mortality: RVF 19.0%, no-RVF 6.2%  
ICU LoS: RVF 23.8 ± 23.7 days, no-RVF 9.6 ± 7.1 days  
Re-operation for bleeding: RVF 61.0%, no-RVF 22.6%  
Renal failure: RVF 61.0%, non-RVF 22.6%  
Survival to transplant: RVF 65.0%, non-RVF 89.9%                                                                                       |
| Puwanant et al (2008)  | Requiring inotropic support or pulmonary vasodilators for >14 days           | Survival to transplant: RVF 25%, no-RVF 75%  
30-day and 180-day mortality rate: higher in RVF  
Hospital LoS: not significantly different*                                                                                                |
| Matthews et al (2008)  | Requiring RVAD or ECMO support; or inotrope support for >14 days; or inhaled NO for ≥48 h; or hospital discharge with an intravenous inotrope | Intraoperative mortality: RVF 30.8%, no-RVF 4.7%  
180-day mortality: RVF 38%, no-RVF 10%                                                                                                       |
| Drakos et al (2010)    | Requiring RVAD support, or inhaled nitric oxide for ≥48 hours, or inotropic support for > 14 days | 30-day mortality: RVF 20%, no-RVF 4%  
1-year mortality: RVF 38%, no-RVF 17%                                                                                                       |
| Kormos et al (2010)    | Requiring inotropic support ≥14 days or starting ≥14 days post-implantation; or RVAD support | 180-day mortality: RVF 29%, non-RVF 11%  
1-year mortality: RVF requiring RVAD 51%, non-RVF 21%  
LoS: RVF mean 32 days, no-RVF mean 22 days                                                                                               |
<p>| Hennig et al (2011)    | 2 of the following criteria during 1st week after surgery: MAP ≤55 mmHg, CVP ≥16 mmHg, | 30-day mortality: RVF 64%, no-RVF 19%                                                                                                       |</p>
<table>
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<th>Study</th>
<th>Criteria</th>
<th>Outcomes</th>
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| Baumwol et al (2011)          | MvO2 ≤55%, CI <2 L/min/m², inotropic support score >20 units, or requiring RVAD support | Survival to transplant: RVF 54.5%, no-RVF 90.9%  
ICU LoS: RVF mean 15.8 days, no-RVF mean 9.1 days |
| Kukucka et al (2011)          | Requiring inotropic support for >14 days, inhaled NO > 48 hours or sildenafil/iloprost on cessation of inhaled NO, or right-sided mechanical support | 30-day mortality: RVF 46.7%, no-RVF 12% |
| Grant et al (2012)            | Requiring inotropic support for >14 days, or RVAD support                 | 1-year mortality: RVF 19%, no-RVF 19% |

BiVAD: biventricular assist device; CI: cardiac index; CVP: central venous pressure; ECMO: extracorporeal membrane oxygenation; LVAD: left ventricular assist device; MAP: mean arterial pressure; MvO2: mixed venous oxygen saturation; NO: nitric oxide; RVAD: right ventricular assist device; RVF: right ventricular failure. * Actual numbers were not reported

Supplemental References


12. 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;60:521-528.