

Master's Thesis in Medicine N° 3482

Left needs Right – Two unequal but interdependent sides of the Heart

How can we improve Patient Selection to prevent Acute
Right Ventricular Failure after Left Ventricular Assist
Device Implantation?

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1 Abstract

Implantation of left ventricular assist devices (LVAD) is now an established treatment in patients with end-stage heart failure (HF). Despite improvements in technology and perioperative care, right ventricular failure (RVF) is still a common, poorly predictable, and often fatal complication. Planned biventricular assist device (BiVAD) therapy results in better patient outcome than delayed right ventricular assist device (RVAD) implantation in response to RVF after isolated LVAD implantation.

Therefore, the evaluation of right ventricular (RV) function prior to surgery is crucial and diverse scoring systems have been proposed. However, their sensitivity and specificity are not yet satisfactory. RV imaging is an attractive adjunct to clinical RV evaluation because it is non-invasive and may offer greater sensitivity to change than markers of pre-existing RV failure. But despite an increasing number of studies, standard echocardiographic predictors of RVF remain inconsistent.

In the normal heart, the left ventricle (LV) generates between 40 – 65% of the work of the RV through the interventricular septum and the shared myofibers. Following LVAD implantation, this ventricular contribution is diminished, while the RV output has to increase in order to provide forward flow and fill the LVAD. This might unmask a previously asymptomatic RV dysfunction.

To predict the response of the RV to the changed hemodynamic environment, we have to evaluate the functional reserve of the RV. The concept of using stress to evaluate this ventricular functional reserve is frequently applied in aortic stenosis to predict LV recovery. Dobutamine-induced changes in echocardiographic parameters such as RV longitudinal strain and systolic pulmonary artery pressure might best simulate the post-LVAD period and thereby predict how the RV will respond.

1.1 Keywords

Right Ventricular Failure; LVAD; Risk Score; Ventricular Interdependence; Speckle Tracking

Table of Contents

1	Abstract	2
1.1	Keywords	2
2	Introduction or the Rise of the LVAD	4
3	The different Origins of the Ventricles	6
4	The Ventricles are made to serve their Function	7
5	The RV and its Response to Stress	11
6	RVF post-LVAD	14
6.1	Definition of post-LVAD RVF	14
6.2	Pathophysiology or The Importance of Ventricular Interdependence	15
6.3	Post-Operative Outcome	18
6.4	Clinical Scores	18
6.5	Echocardiography	21
7	Future directions	26
8	Conclusion	29

2 Introduction or the Rise of the LVAD

Heart Failure (HF) is a global problem and contributes considerably to the overall cost of health care in developed nations(1). Population aging, in addition to improved survival in patients with HF, and successful management of acute cardiovascular disease will further increase the already high prevalence of HF(2-4). Today, HF is already the most common diagnosis in patients aged 65 years and older admitted to hospitals in high-income nations and despite some progress in treatment, the prognosis of HF is worse than that of most cancers(2).

For a long time, the only solution after exhaustion of medical and surgical techniques was heart transplantation (HTx). A shortage of available donor hearts as well as the incapability of many patients to undergo such an invasive treatment present enormous limitations to this solution, and the need to provide a better-tolerated and more available solution arose(1,5,6). Following the inception of the artificial-heart program at the National Institutes of Health (NIH) in 1964, DeBakey and Liotta reported the first successful use of a paracorporeal left ventricular assist device (LVAD) for post-cardiotomy support in 1966. The relentless drive toward miniaturized implantable support led to the placement of the first intracorporeal LVAD in 1991(7). Intensive research culminated in the Food and Drug Administration (FDA) approval of a LVAD as a bridge to transplantation (BTT) in 1994, with two more devices receiving approval in 1998(8). Successful experience with the BTT indication justified evaluation of LVADs as long-term or destination therapies (DT) for chronic HF(9). A hypothesis tested 2001 in the prospective, randomized multicenter REMATCH trail, where HeartMate XVE (Thoratec Corp.) implantation was compared to optimal medical therapy for patients not considered eligible for transplant(5). The FDA approbation of LVADs as DT followed, and since 2010, the number of DT implants has surpassed the number of BTT implants(4,7).

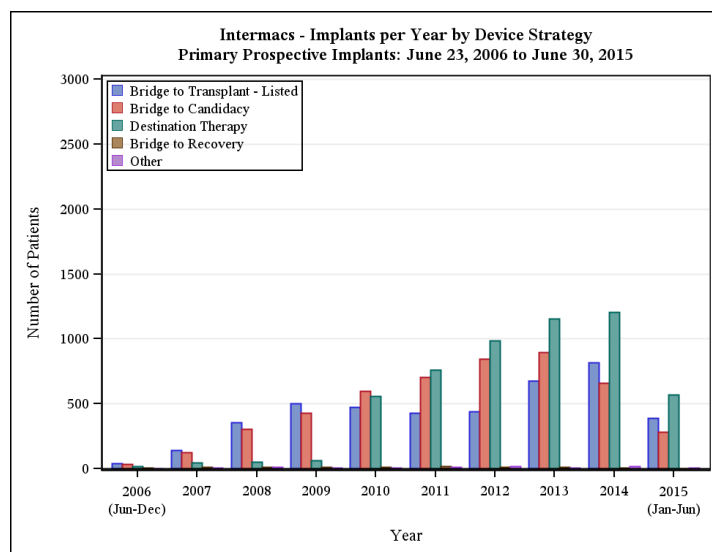


Image 1: Implants by Year by Device Strategy, per INTERMACS Quarterly Statistical Report, 2nd Quarter, 2015

The first-generation LVADs include pulsatile volume displacement pumps engineered with a pumping chamber and two unidirectional valves(10). Concerns regarding their large pump size requiring extensive surgical dissection, adverse events, and uniform failure after 18-30 months hampered their use in clinical practice(4,11). Today, they have mostly been replaced by the more recent continuous flow (CF) technology found in second- and third-generation pumps that have demonstrated their superiority in several trials, such as the HeartMate II and ADVANCE trials(12,13). Contemporary second- and third-generation LVADs are valveless pumps that utilize a permanent magnetic field designed to rapidly spin a single impeller supported by mechanical or, more recently, hemodynamic or magnetic bearings(4). These pumps offer several advantages over the previous pulsatile flow (PF) pumps. Most important, its smaller size reduces the risk of infections and permits minimally invasive implantation techniques to reduce surgical trauma. Also, there are few moving parts, absence of valves to direct blood flow, smaller blood-contacting surfaces and reduced energy requirements providing enhanced durability(1,10).

Current indications for LVAD implantation as DT include New York Heart Classification Class 4 HF patients, with optimal medical therapy for six of the past nine months, with a life expectancy greater than two years, and who are not candidates for HTx(7). LVAD implantation is contraindicated in patients with irreversible end-organ damage, especially renal, hepatic or respiratory failure, as these patients have consistently demonstrated poor clinical outcomes(8).

The 2-year survival rate in patients with advanced HF treated with LVADs is now about 75%, but LVAD remains a high-risk and high-cost option necessitating careful patient selection(2,14). A number of important complications can occur both early and late following LVAD insertion(3). Among them, post-LVAD right ventricular failure (RVF) is a major cause of morbidity and mortality with an incidence of 6-44%(15,16). Post-operative RVF has a significant effect on clinical outcomes, leading to prolonged intensive care unit (ICU) stay, increased 30-day mortality and a lower BTT rate(2). RVF also causes liver, gastrointestinal, and renal congestion, with resulting coagulopathy, altered drug metabolism, malnutrition, diuretic resistance, and poor quality of life(17). Due to the absence of durable and safe options for right ventricular (RV) support, preoperative characterization of RV function and appropriate patient selection is crucial when we want to improve LVAD outcomes(16). Many attempts have been made to predict post-LVAD RVF based on risk scores including clinical, laboratory, and hemodynamic parameters, and, most recently, also imaging techniques(18-34).

To place the evaluation of these risk scores in the right context, I will first discuss two important concepts concerning the RV. First, the RV differs from the left ventricle (LV) not only in its origin and anatomy, but also in its function and response to stress. Second, the two ventricles share

one heart, and therefore, changes in one ventricle immediately affect the other chamber through direct mechanical interactions(35). I will use the emerging picture of two different pumps within one heart that influence each other on a beat-to-beat basis to explain the pathophysiology behind RVF post-LVAD implantation and to evaluate the currently used pre-operative risk scores for RVF. Finally, I will discuss the challenges encountered and suggest future directions.

3 The different Origins of the Ventricles

For a long time, the cardiac chambers as found in the adult heart were believed to be present in the primary heart tube. In 2001, the discovery of a population of cardiac progenitor cells within the pharyngeal mesoderm, giving rise to a large part of the definitive heart, challenged this classical view and led to an explosion of work regarding the anatomical and molecular aspects of cardiac development(36–39).

The heart derives from the anterior splanchnic mesoderm emerging during gastrulation in the beginning of the 3rd week of intrauterine life(40). The precursors found within the anterior splanchnic mesoderm will give rise to all cardiovascular lineages, including myocardium, endocardium, and smooth muscle(41). The first group of cells to differentiate in response to induction signals coming from the adjacent endoderm, will form the cardiac crescent also known as the first heart field (FHF). During subsequent cephalic and lateral folding of the embryo, the cells of the cardiac crescent fuse on the midline to form a linear heart tube with an arterial outflow and a venous inflow pole(40,42,43). Most of the cardiogenic mesoderm, however, remains present as an undifferentiated subpopulation within the pharyngeal mesoderm located medially and posteriorly to the cardiac crescent and then dorsally to the primary heart tube(36,40,41). This group known as the second heart field (SHF) progressively adds to both poles of the early heart tube during cardiac looping(40,41,44). The SHF is further subdivided in two contiguous parts: The anterior heart field (AHF) and the dorsal mesocardium. Cells from the AHF give rise to the RV, the interventricular septum (IVS) and the outflow tract, while the dorsal mesocardium contributes to atrial, atrial septal and venous myocardium(40,44–53). The linear heart tube itself is thought to give rise predominantly to the LV and parts of the atria(40,41,44).

Cardiac looping, usually held to be the first visual evidence of asymmetry within the embryo, allows convergence of the inflow and outflow poles of the heart tube(54). It also positions the future cardiac chambers for proper development. A series of events leads to expansion of chamber myocardium (ballooning model of chamber formation), cardiac septation, valve formation and venous and arterial pole development(36,40,51). Finally, heart formation is completed during the 9th week of development with the connection of the coronary arteries to the aorta(40).

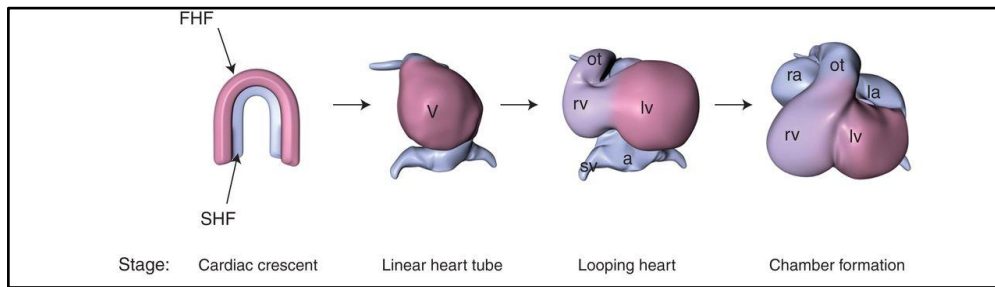


Image 2(54): FHF, first heart field; SHF, second heart field; V, primitive ventricle; ot, outflow tract; rv, right ventricle; lv, left ventricle; ra, right atria; la, left atria

Specific cellular markers and transcription factors distinguish the cells from the different heart fields. While FHF cells are marked by the T-box transcription factor *Tbx5* and the bHLH transcription factor *Hand1*, SHF cells are characterized by the presence of *Hand2*, the LIM-homeodomain transcription factor *Isl1*, and *Fgf10*. Other factors, such as homeobox gene *Nkx2-5*, are expressed in both heart fields, but depend on different regulatory elements for expression. These different cellular markers and potentially different intracellular signaling cascades may allow right and left cardiac myocytes to respond differently to stress and may explain their differences when it comes to functional recovery after noxious insult. Furthermore, the difference in cardiac progenitor cell origin may also contribute to the different morphology of the two ventricles(40,47,55).

4 The Ventricles are made to serve their Function

In the embryo and fetus, the RV is the dominant chamber accounting for about 60% of total cardiac output(56). RV and LV free-wall thickness and force development are equal as they work in parallel due to circulatory shunts. Moreover, the cardiovascular physiology during fetal period is characterized by a high-resistance pulmonary circulation and a low-resistance systemic circulation(57,58). At birth, pulmonary vascular resistance falls rapidly after expansion and oxygenation of the lungs and the closure of the circulatory shunts forces the ventricles to function in series. As a result, the LV hypertrophies as it takes over the now high-resistance systemic circulation while the RV atrophies(56,59,60).

To function in series implies that the two ventricles now eject equal quantities of blood, however, several physiological shunts bypassing the RV are also present in the adult heart. About half of the bronchial circulation empties into the pulmonary veins and is carried to the left atrium of the heart as venous admixture. Also the Thebesian veins collecting venous blood from the myocardium of the heart deliver a small amount of deoxygenated blood directly to the LV. The pleural veins present a third anatomical shunt, as deoxygenated blood from the visceral pleura is carried by the pulmonary veins to the left atrium. All together, the normal anatomic shunt consists of about 2-5% of the cardiac output of the LV(61).

In the adult heart, the primary purpose of the RV is to generate flow in order to deliver deoxygenated blood to the lungs for gas exchange. The RV serves as a reservoir for blood returning to the heart via the right atrium, thereby optimizing venous return and providing sustained low-pressure perfusion through the lungs. In contrast, the LV produces high-pressure pulsatile flow through arterial vessels with low compliance providing the entire body with oxygenated blood(55). While ventricular pressures on the right side oscillate between 25 mmHg during systole and 4 mmHg during diastole, the LV generates an oscillation between 130 and 8 mmHg(62,63).

Under normal conditions, the pulmonary vascular resistance is 1/20 of the systemic vascular resistance, and the mean pulmonary artery pressure may not be much higher than central venous pressure. Therefore, the RV can maintain a cardiac output equal to that of the LV with minimal contractile function at approximately a sixth of its energy cost(56,57,63).

The dynamics of the contracting heart are commonly analyzed in the context of pressure-volume loops representing the relation between volume and pressure during the entire cardiac cycle under different loading conditions. Height and width of these loops are determined by systolic pressure and stroke volume, respectively(40,56). For the LV, Suga et al.(64) showed that the end-systolic pressure-volume relationship (ESPVR) can be approximated by a linear relationship. The slope of this relationship is referred to as ventricular elastance (E_{es}). Because of its relative load independence, many investigators consider ventricular elastance as the most reliable index of contractility(57).

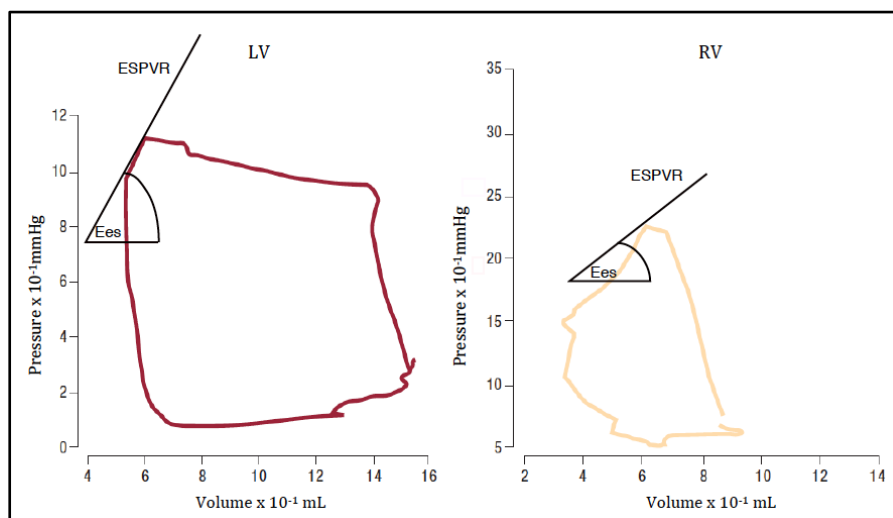


Image 3(56): Comparison of pressure-volume loops obtained by humans with micromanometer catheters and ventriculography; LV, left ventricle; RV, right ventricle; ESPVR, end-systolic pressure-volume relationship; E_{es}, ventricular elastance

The square shape of the LV pressure volume loop shows well-developed isovolumic contraction and relaxation phases, and simplifies identification of end-systole and aortic valve closure,

which occur close to the inflection point of the ejection phase(56,62). In contrast, ejection of blood through the pulmonary valve may continue even when RV pressure is falling due to momentum of the blood into the low input impedance pulmonary circuit. This late ejection, or “hangout period”(65), makes identification of “end-systole” problematic in the RV, and contributes to the more triangular shape of the RV pressure-volume loop with few if any isovolumic periods(57,59,66). However, many studies have shown that RV elastance may also be approximated by a linear relationship(66–68). RV systolic elastance is lower than that of the LV implying that the RV is far more sensitive to increases in afterload due to its limited capacity to produce elevated pressures(56,68).

The RV free wall coronary blood flow occurs continuously, whereas the LV depends on diastolic flow due to its high cavity pressure creating a higher wall stress and higher oxygen demands(62,69). In addition to the biphasic coronary flow, the RV’s more extensive collateral system within the coronary arteries and its ability to increase oxygen extraction, create a more favorable oxygen demand-supply relationship compared to the left side(58,70).

These differences in function and physiology are reflected in morphological differences between the two ventricles. In contrast to the ellipsoidal shape of the thick-walled LV, the postnatal RV becomes a thin-walled chamber appearing triangular when viewed from the side and crescent shaped when viewed in cross section(71). The shape of the RV is further influenced by the position of the IVS. Under normal conditions, the septum is concave toward the LV in both systole and diastole forcing the RV to wrap around the LV(57). The conical shape of the lumen gives the LV a smaller surface-to-volume ratio than the RV, and contributes to the ability of the LV to generate high pressures(63). The RV represents roughly one sixth of the total mass of the heart but accommodates a larger end-diastolic volume than the LV(56,57). Therefore, RV ejection fraction (RVEF) is lower than on the left side with the lower limit of normal RVEF ranging from 40-45% compared with 50-55% for LV ejection fraction(68).

Anatomic differences are also apparent in myocardial architecture. The RV wall is mainly composed of superficial and deep muscle layers. The fibers of the superficial layer are arranged more or less circumferentially in a direction that is parallel to the atrioventricular groove and continue into the superficial myofibers of the LV. The deep muscle fibers of the RV are longitudinally aligned base to apex. In contrast to the RV, the LV contains obliquely oriented myofibers superficially, longitudinally oriented myofibers in the subendocardium, and predominantly circular fibers in between(57). This arrangement leads to a distinct mechanism of ventricular contraction on either side of the heart. In the LV, development of ventricular pressure and ejection of blood is due to a concentric contraction of the LV free wall and septum, along with a twisting motion of the heart. On the other side, the RV creates through

predominantly longitudinal shortening an asynchronous peristaltic-like contraction from the inlet to the outlet (normally separated by approximately 25-50ms) and a bellows-like motion of the free wall toward the septum. Normal ejection from the RV is therefore a function of both a reduction in RV free wall surface area and a reduction in RV free wall septal distance(56,59,62,68,69,72). In addition, the contraction of the deep circular fibers of the LV forces the septum to bulge into the RV stretching its free wall over the septum and thereby contributing to blood ejection(63). Studies on electrically isolated hearts estimated that >50% of the normal RV mechanical work may be generated by LV contraction and that the LV free wall plays a central role in RV function (SeeVentricular Interdependence p.15)(62,73).

In the LV inflow (mitral valve) and outflow (aortic valve) are situated at 30° to each other and in fibrous continuity. Thus, blood enters and leaves through virtually the same orifice resulting in a bi-directional blood flow. On the right side of the heart, inflow (tricuspid valve) and outflow (pulmonary valve) are at 90° to each other and separated by the ventriculofundibular fold resulting in a linear uni-directional flow(74).

Further morphological features that best differentiate the anatomic RV from the LV are the presence of a moderator band; the presence of more than 3 papillary muscles; the trileaflet configuration of the tricuspid valve with septal papillary attachments; and the presence of coarse trabeculations, compared to the fine trabeculations displayed in a criss-cross pattern of the LV(57,71). Table 1 further highlights important differences between LV and RV.

Table 1(56,57,62): Differences between RV and LV in normal Conditions

	Right Ventricle	Left Ventricle
Pressure , average (range), mmHg		
- Atrial mean	3 (2)	7 (5)
- Ventricular systolic	25	130
- Ventricular diastolic	4 (3)	8 (4)
- Ventricular mean	15 (5)	85 (20)
Resistance , average (SD), dynes-sec-cm ⁻⁵ x m ²	123 (54)	2130 (450)
End-diastolic volume , mL/m ²	75±13 (49-101)	66±12 (44-89)
Masse , g/m ²	26±5 (17-34)	87±12 (64-109)
Thickness of ventricular wall , mm	2-5	7-11
Ejection Fraction	61±7(47-76)	67±(57-78)
Ventricular elastance (Ees), mmHg/mL	1.30±0.84	5.48±1.23
Stroke work index , g/m ² per beat	8±2 (1/6 of LV stroke work)	50±20
Origin	Second Heart Field	First Heart Field
Myocardial characteristics	Thin, heavily trabeculated walls	Thick smooth walls, fine trabeculations
Physiological pump conditions	Low-resistance, low-capacitance pump; peristaltic-like motion from inflow to outflow during ejection	High resistance, high pressure pump; dominant radial thickening and contraction during ejection
Flow characteristics	No or minimal isovolumic periods; hangout period	Well-defined isovolumic contraction and relaxation; no hangout period

5 The RV and its Response to Stress

Given the differences between the two ventricles stated so far, it should not be surprising that they respond differently to stress(75). The RV may be subject to pressure or volume overload, ischemia, intrinsic myocardial disease, or pericardial constraint(76). Although the RV is not immune to the direct effects of coronary disease with resulting global or regional ischemia, in clinical practice, RV physiology and failure are most frequently affected by increased preload or afterload(62).

RV adaptation to disease depends on many interlinked factors. Especially in the chronic setting, RV responses to an altered environment are variable and may differ regarding the type and severity of myocardial injury or stress, as well as the time of onset of the disease process (newborn, pediatric, or adult years)(76,77). Additional processes that need to be taken into account are altered gene expression, neurohormonal activation, altered mechanosensing, inflammation, and apoptosis(58,76). A detailed analyze of these factors is out of scope of my thesis and it's sufficient to say that the pathobiology of the failing RV shows similarities with that of the LV, including increased contractility, dilatation and hypertrophy, as well as a lack of adequate increase in capillary density leading to a hypoxic environment and oxidative stress, and a metabolic switch from fatty acids to glucose utilization (a more efficient carbohydrate oxidation decreasing the oxygen demand of the ventricle)(58,59). Both, LV and RV failure activates the renin-angiotensin-aldosterone system and releases endothelin and natriuretic peptides resulting in similar pathophysiologic effects and consequences(78). However, RV failure also has characteristic features and several key factors are involved in the RV but not in the LV(59,62). Furthermore, RV remodeling seems to be highly reversible when the LV is normal(78). The exact mechanisms involved remain unknown, but patients with RV failure showed significant improvement of RV function after lung transplant(58,79,80). The RV also shows a remarkable ability to regain systolic function both at rest and during exercise after acute RV myocardial infarction, and experimental animal and clinical studies(81–84) show that even after prolonged occlusion, RV performance recovers faster and more completely than the LV(75,76,85). In chronic HF, however, RV recovery takes much longer than LV recovery. This is known from the experience of LVADs and biventricular pacemakers(78).

In comparison, the RV adapts better to volume overload, while the LV better tolerates pressure overload. In atrial septal defect and tricuspid regurgitation, the RV may tolerate volume overload for a long time without a significant decrease in RV systolic function(58,76). Its thin walls account for greater compliance allowing it to accommodate a range of preloads(78). In contrast to volume-overload states, moderate to severe acquired pulmonary hypertension in the adult often leads to RV dilatation and failure(76). In animal models, acute increases in afterload

lead to profound decreases in RV stroke volume. In contrast, much larger changes in LV afterload induced only modest changes in LV stroke volume(62,86).

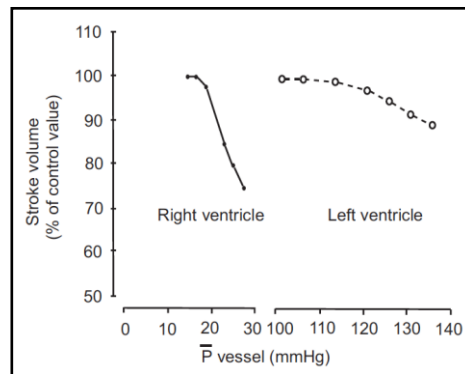


Image 4(57): Response of left and right ventricle to acutely increased afterload.

In the chronic setting, however, when changes in afterload occur progressively, the RV has time to adapt. RV hypertrophy, an adaptive response to reduce wall stress and improve contractility, allows for the generation of higher pressures to overcome the increased pulmonary afterload(59). The RV wall becomes thicker making the RV more concentric with concomitant flattening of the IVS(58). This results in increased circumferential contraction relative to decreased longitudinal shortening, a pattern indistinguishable from the normal LV. In the end, the relative increase in RV afterload is much greater in pulmonary arterial hypertension (PAH) than the increase in LV afterload in systemic hypertension, implying that the RV can maintain function and adequate output in the face of systemic pressure over prolonged periods(62). Some of these changes are almost certainly beneficial, but progressive RV dilation and dysfunction often occur(77). Furthermore, hypertrophy also increases the oxygen demand of the ventricle while the higher chamber pressure limits coronary blood flow to diastole leading to a chronic oxygen demand-supply mismatch(55,59).

The adaptations to chronically increased afterload are reflected in the RV pressure-volume loop. A shift to a square shaped loop indistinguishable from the normal LV pressure-volume loop manifests increased contractility (higher E_{es}) that increases proportionally with increased arterial elastance (E_a , reflecting afterload) to maintain stroke volume. When end-systolic elastance increases less than arterial elastance, the E_{es}/E_a ratio decreases leading to ventricular-arterial uncoupling, which is regarded as a physiological sign of RV failure. When the RV ultimately fails, the ventricle dilates, diastolic function is impaired, and the pressure-volume loop shifts to the right, with a resultant decrease in end-systolic elastance and compromised cardiac output(59,62).

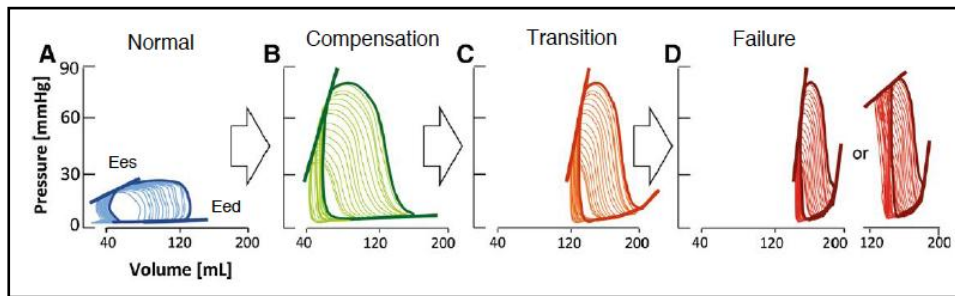


Image 5(59): Pathophysiology of the pressure-loaded RV. Typical pressure-volume loops from compensation to failure; Eed, end-diastolic elastance; Ees, end-systolic elastance; A, normal; B, increased systolic function (Ees) and RV dilatation (increased end-systolic volume); C, increased systolic function and impaired diastolic function (Eed); D, increased or pseudo-normalized systolic function (Ees) and further impaired diastolic function (Eed)

The Frank-Starling mechanism is often viewed as the primary means by which the heart adapts to an increase in demand. However, shape differences between the two ventricles alter how the Frank-Starling mechanism operates. In the RV, the increase in volume is mostly due to an increase in RV free wall septal dimension, with much less increment in RV free wall surface area and therefore the recruitment via the Frank-Starling mechanism is reduced, playing a smaller role in RV adaptation than it does in the LV. The Frank-Starling mechanism becomes more important only during a later stage when the RV becomes more cylindrical and dilated(56).

Furthermore, it is important to notice that in the resting state, and when pulmonary pressures are normal, there may be minimal evidence of right heart dysfunction, which may only be evident when there is an increased load on right ventricular ejection and, importantly, when there is a demand for increased flow(87).

6 RVF post-LVAD

Such a demand for increased flow occurs after LVAD implantation, when the increased LV output forces the RV to work harder. Unfortunately, many patients undergoing LVAD implantation also have some degree of RV dysfunction that may hamper this necessary increase in RV output and lead to failure(29,78). Despite improved outcomes and lower RVF rates with CF over PF LVADs, RVF in this early post-LVAD implantation period is still a common, poorly predictable, and often fatal complication(14,78). The reported incidence of RVF after LVAD ranges from 6% to 44%, varying mostly due to differences in RVF definition, different types of LVADs, and differences in patient populations(88).

6.1 Definition of post-LVAD RVF

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has adopted a definition of RVF following LVAD implantation to standardize reporting of outcome among different centers. Criteria include:

- Symptoms and signs of persistent RV dysfunction, central venous pressure (CVP) >18mmHg with a cardiac index (CI) <2.0l/min/m²
- Absence of elevated left atrial/pulmonary capillary wedge pressure >18mmHg, tamponade, ventricular arrhythmias or pneumothorax
- Requiring RVAD implantation, or requiring inhaled nitric oxide or inotropic therapy for duration of more than one 1 week at any time after LVAD implantation(89).

Most studies have used a variation of this definition combining clinical findings and hemodynamics(16).

In terms of severity, the INTERMACS has adopted the following grading scale

- Severe: Need for RVAD
- Moderate: Need for inotrope or intravenous or inhaled pulmonary vasodilator (e.g. prostaglandin E or inhaled nitric oxide)
- Mild: Meets 2 of the 4 clinical criteria listed below
 - ♦ CVP > 18mmHg or mean right atrial pressure > 18mmHg
 - ♦ CI < 2.3 l/min/m² (using a pulmonary artery catheter)
 - ♦ Ascites or evidence of moderate to worse peripheral edema
 - ♦ Evidence of elevated CVP by echo (dilated inferior vena cava without collapse), physical exam (signs of increased jugular venous pressure)(89)

6.2 Pathophysiology or The Importance of Ventricular Interdependence

The etiology of post-LVAD RVF is complex, multifactorial and not yet completely understood. The physiological changes following LVAD implantation immediately affect the factors determining RV output and function such as RV preload, afterload, and contractility(14,88).

RV preload acutely increases as a result of increased LV output and the administration of fluids and blood products during the perioperative period. The resulting overstretching of cardiac myofibrils beyond the point of optimal contractility based on the Frank Starling principle leads to decreased RV stroke volume. In addition, the increase in RV preload may lead to RV annular dilatation and tricuspid regurgitation further increasing the load placed on the RV(88).

Previous studies have demonstrated a reduction in pulmonary artery pressure after LVAD implantation in both PF and CF devices. The resulting reduction in afterload counterbalances the increased preload, and thereby conserves or even improves RV function. However, the speed of this reduction in pulmonary artery pressure is unpredictable, and the lack of afterload relief in the meantime, coupled with an increased preload may cause RVF(17).

RV contractility strongly depends on ventricular interdependence, a concept encompassing the complex interplay between the two ventricles, which is also affected through LVAD implantation. In order to better understand RVF post-LVAD and the importance of RV functional reserve discussed later, I will summarize the most important facts about ventricular interaction in the context of LVAD in the following paragraphs.

Despite their numerous differences discussed earlier, the two ventricles are anatomically conjoined, forming a continuous muscular “syncytium” enclosed within the pericardium. Muscle fibers extending from the free walls of both ventricles contribute to the IVS, while subepicardial fibers from the LV free wall are continuous with the RV free wall at the interventricular junction(90). Consequently, the function of the two ventricles is inextricably linked in both the structurally normal and abnormal heart through this aforementioned concept known as ventricular interdependence(62).

Ventricular interdependence is defined as the forces that are transmitted from one ventricle to the other through the myocardium and pericardium, independent of neural, hormonal, or circulatory effects(35). Thus, implying that the size, shape, and compliance of one ventricle may immediately affect the size, shape, and pressure-volume relationship of the other ventricle(57). In addition to the direct and immediate mechanical interactions (diastolic and systolic ventricular interdependence), the right and left hearts are connected in series (series effect). Therefore, except for a few beats, the left heart can only pump out what the right heart gives it(87).

Diastolic ventricular interaction refers to the competition for space within the indistensible pericardium(67). Increased distension of either ventricle during diastole alters the compliance and geometry of the opposite ventricle. Bemis(91), Elzinga(92), and Santamore(93) used isolated beating hearts to demonstrate that independent loading of one ventricle shifted the diastolic pressure-volume relationship of the contralateral ventricle upward and to the left (Image 6). This occurs even with the pericardium open, although coupling is stronger with it closed(35,94).

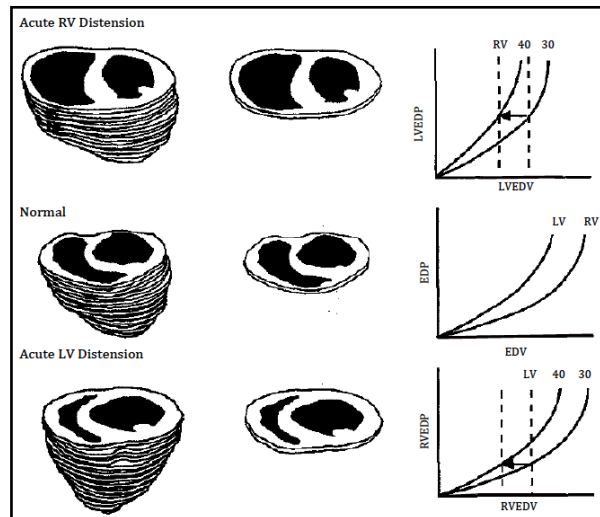


Image 6(35):Acute distension of one chamber directly affects the opposite chamber. EDP, end-diastolic pressure; EDV, end-diastolic volume; LV, left ventricle; RV, right ventricle

Systolic interaction refers to positive and immediate interactions between RV and LV contractions. It is mostly mediated via the IVS and the shared muscle fibers connecting the free walls of the ventricles and thereby permitting the transmission of forces generated by LV contraction to the RV free wall(67,77,90).

Several studies(95–97) suggested that the LV generates between 40 and 65% of the work of the normal RV. The importance of LV-to-RV myocardial cross-talk was elegantly demonstrated in an experimental study of intact explanted hearts in which electric but not mechanical continuity between the RV and LV was interrupted. RV pacing led to little detectable mechanical activity (measured by developed pressure) in the LV. Conversely, however, pacing-induced contraction of the electrically isolated LV was associated with the development of an almost normal RV pressure trace and pulmonary blood flow(62,95). Hoffman et al.(98)expanded on these observations in in vivo experiments (replacing RV myocardium with a non-contractile prosthesis) and were able to show virtually normal RV pressure generation as a consequence of normal LV shortening(62).

They further observed that intact RV geometry is crucial for normal LV mechanical performance. During gradual enlargement of the non-contractile RV free wall, there was a progressive

reduction in both RV and LV mechanical work(98). Progressive RV dilatation not only altered septal position and dimensions but also caused regional deformation in the LV free wall, thereby disturbing LV geometry and impairing LV filling and ejection(35). The resulting decrease of pulmonary emptying and increase in pulmonary pressure further increase the load on the RV and contribute to the downward spiral of RV function(87).

In addition, LV preload is diminished by reduced RV cardiac output (series effect), resulting in LV unloading and atrophy, particularly of the LV free wall. This in turn leads to a decreased contribution of the LV free wall to RV output (ventricular interdependence)(56,99).

In the context of LVAD implantation, the device prevents a decrease in pulmonary emptying, but an excessive leftward shift of the IVS following LV decompression may decrease septal contribution to RV contraction. Furthermore, the concomitant change in RV geometry results in decreased elastance and a change in distensibility(17,78,89). Following LVAD instauration, the now unloaded LV needs to generate less pressure, resulting in a decreased contribution of LV free wall to RV contraction. The following image summarizes the changes in preload, afterload and contractility after LVAD implantation.

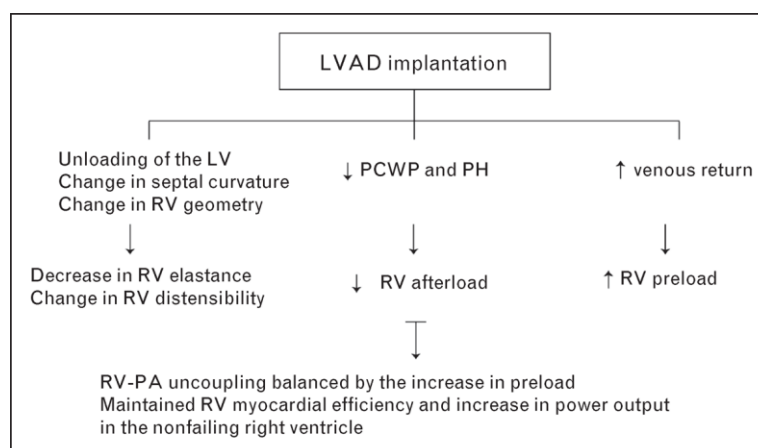


Image 7(89):Changes in RV physiology secondary to LVAD implantation. PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension

A further mechanism involved includes tachyarrhythmias. Atrial arrhythmias occur in more than 20% of LVAD patients and double the risk of RVF. In addition, ventricular fibrillation may quickly cause more than a 30% decrease in LVAD flow(17).

Finally, RV dysfunction may be accentuated by intraoperative RV injury due to poor cardioprotection, right coronary air embolus, and/or pulmonary hypertension related to cardiopulmonary bypass(29).

6.3 Post-Operative Outcome

The outcome after LVAD implantation depends on the RV's capacity to provide blood flow to fill the LVAD for optimal function(15,17). Therefore, RVF post-LVAD carries poor prognosis with higher mortality, greater risk of bleeding and/or re-operation, longer ICU or hospital stays, worse end-organ function, and lower success of BTT therapy(78). Although RVADs are available for short-term support, long-term mechanical circulatory support of the RV is still under development(14). Furthermore, RVAD implantation as a treatment option for RVF leads to increased morbidity secondary to increased infection risk, need for transfusion, and risk of device failure(88). Elective, planned biventricular support is feasible and leads to better outcomes compared with "bailout" RV support. Also, surgical series suggest that reduction of tricuspid regurgitation during LVAD surgery in patients with severe RV dysfunction may improve outcomes. Therefore, assessment of RVF risk using RVF risk prediction models is of paramount importance for patient selection and planning of surgical strategy, especially for DT implants(14,15).

6.4 Clinical Scores

The importance of RVF and its predictors in a setting of LVAD implantation has been recognized early, as evidenced by an abundant number of attempts to identify independent risk factors and to develop RVF predictor scores with the common purpose to improve patient selection and outcomes by recognizing potential need for biventricular assist device (BiVAD) at the time of LVAD implantation(88). Several clinical models have been developed, including the Michigan(19), Penn(20) and Utah(21) scores and, more recently, the Pittsburgh Decision Tree(23) and CRITT scoring(24). Kormos et al.(22)also reported on multivariable predictors of RVF, although without proposing a specific risk score. Table 2 summarizes their results, patient characteristics and the RVF definition used, as well as their limitations.

Most of available literature includes retrospective studies from single institutions that have similar limitations, including small sample size, lack of score validation, and for some earlier studies inclusion of patients receiving mostly PF LVADs, thus not fully representing the current LVAD population. Additional factors making evaluation and comparison of different predictor models and respective risk scores difficult are various definitions of RVF, heterogeneity of variables considered in construction of prediction models, and variability in inclusion of BTT and DT patients(16,17,88). Both older and newer risk score models have not been rigorously tested in populations outside those in which they were derived, and most existing RVF risk-scoring systems have not used quantitative imaging parameters to aid in risk stratification(15,29,31).

Table 2: Clinical Risk Prediction Scores for RVF in LVAD Recipients

Study	Patients	RVF Definition and Rate	Multivariable Predictors	Limitations
Predictors of severe RVF after implantable LVAD(18) 2002	245 patients PF 98% BTT	Need for RVAD RVF rate: 9%	Pre-op circulatory support (OR 5.3) Female gender (OR 4.5) Non-ischemic etiology (OR 3.3)	No echocardiographic parameters; Retrospective; PF only; Single institution
Michigan RV failure risk score (RVFRS)(19) 2008	197 patients 28 CF 94% BTT	Need for RVAD, ≥ 14 days inotropes, inhaled nitric oxide ≥ 48 hours RVF rate: 35%	Preoperative vasopressors (OR 3.9) AST ≥ 80 IU/liter (OR 2.1) Bilirubin ≥ 2.0 mg/dl (OR 2.4) Creatinine ≥ 2.3 mg/dl (OR 2.9)	Semi-quantitative echocardiographic parameters; Single institution; Mostly PF; RVF occurred in 20% of patients in lowest strata (RVFRS ≤ 3)
Penn RVAD risk score(20) 2008	266 patients 6 CF BTT vs DT not reported	Need for RVAD, including ITT RVAD RVF rate: 37%	Cardiac index ≤ 2.2 l/min/m ² (OR 5.7) RVSWI ≤ 0.25 mmHg/l/m ² (OR 5.1) Severe pre-op RV dysfunction (OR 5.0) Pre-op creatinine ≥ 1.9 mg/dl (OR 4.8) Previous cardiac surgery (OR 4.5) SBP ≤ 96 mmHg (OR 2.9)	Semi-quantitative echocardiographic parameters; Retrospective; Single institution; Mostly PF; Inclusion of ITTBiVAD
Utah RV risk score(21) 2010	175 patients 25 CF 58% BTT, 42% DT	Need for RVAD, ≥ 14 days inotropes, inhaled nitric oxide ≥ 48 hours RVF rate: 44%	DT (OR 3.3) IABP (OR 3.9) Peripheral vascular resistance - 1.8-2.7 Wood unit (OR 2.0) - 2.8-4.2 Wood unit (OR 3.0) - ≥ 4.3 Wood unit (OR 4.1) Inotrope dependency (OR 2.5) Obesity (BMI ≥ 30 kg/m ²) (OR 2.0) ACEI or ARB (OR 0.5) B-Blocker (OR 1.6)	Semi-quantitative echocardiographic parameters; Single institution
Kormos et al(22) 2010	484 patients All CF, 100% BTT	Need for RVAD, ≥ 14 days inotropes, late inotrope support starting >14 days after implant RVF rate: 20%	CVP/PCWP > 0.63 (OR 2.3) Pre-op ventilator support (OR 5.5) BUN > 39 mg/dl (OR 2.1)	No echocardiographic parameters; Retrospective
Pittsburgh Decision Tree(23) 2012	183 patients 40 CF BTT vs DT not reported	Need for RVAD RVF rate: 15%	Age, HR, transpulmonary gradient, right atrial pressure, INR, white blood cell count, ALT, number of inotropic agents	No echocardiographic parameters; Single institution; Retrospective
CRITT score(24) 2013	167 patients All CF 51 BiVADs BTT vs DT not reported	Need for BiVAD RVF rate: 23%	CVP >15 mmHg (OR 2.0) Severe RV dysfunction (OR 3.7) Pre-operative mechanical ventilation (OR 4.3); Severe TR (OR 4.1); HR > 100 (OR 2.0)	Semi-quantitative echocardiographic parameters; Single institution; Retrospective

ACEI, 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; CF, continuous flow; CRITT, central venous pressure-RV dysfunction-preoperative intubation-severe tricuspid regurgitation-tachycardia; CVP, central venous pressure; DT, destination therapy; HR, heart rate; 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; PF, pulsatile flow; 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.

Their limited clinical applicability was demonstrated in 2015 by Kalogeropoulos et al.(15), who assessed their individual performance for RVF prediction in a CF LVAD recipient population (Image 8). A common feature across scores was the higher specificity compared with sensitivity, with the exception of the Utah score. Moreover, all scores demonstrated a higher negative than positive predictive value. Thus, a low score more reliably ruled-out RVF than a high score predicted RVF. To their surprise, the Michigan score derived from a mostly PF pump recipient cohort, outperformed newer scores derived from CF pump populations, but still presented a positive predictive value below 60%.

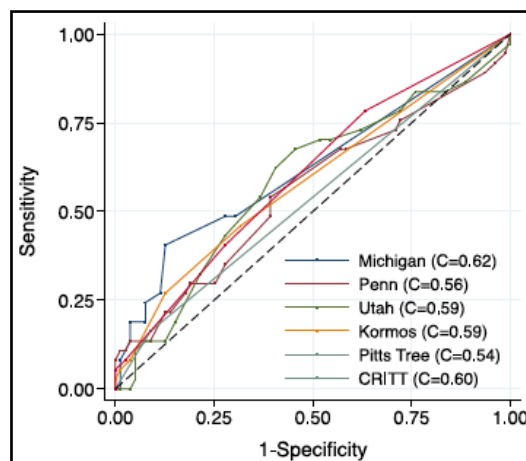


Image 8(15):Comparative receiver operating characteristic (ROC) curve plots with right ventricular failure (RVF) prediction as the outcome of interest for the scores evaluated. RVF was defined as: need for a right ventricular assist device; use of pulmonary vasodilators for ≥ 48 hours; multi-organ failure due to RVF; inotrope use for ≥ 14 days after implantation; or re-institution of inotropes after 14 days. The C statistics correspond to the area under the curve. The 45° diagonal dashed line represents prediction of no better than chance (C=0.5)

Despite their limited clinical applicability, these studies have identified numerous clinical, biochemical, and hemodynamic factors associated with RVF. Among them, the most consistent factors presenting high odds ratios (OR) include the following:

Preoperative circulatory support including intra-aortic balloon pump (IABP), vasopressors, inotropes, temporary heart assist devices, and heparin-coated extracorporeal membrane oxygenation (ECMO) was the most significant predictor for RVAD use in the multivariable logistic regression analysis by Ochiai et al.(18)(OR 5.3) and also reached with 3.9 the highest OR in the Michigan Right Ventricle Failure Risk Score (MRVFRS). IABP and inotrope dependency are also used in the Utah Risk Score and the number of inotrope agents used is present in the Pittsburgh Decision Tree. Although preoperative circulatory support does not figure within the final CRITT Score, it was more likely to be found in the BiVAD cohort during univariate analysis. Its importance was also confirmed in more recent studies(28,29,31)evaluating quantitative echocardiographic parameters for risk prediction and including a higher number of DT recipients. Thus, preoperative circulatory support has predicted RVF throughout different

studies with different devices and study populations, thereby endorsing its importance as a risk factor.

Preoperative mechanical ventilation was another predictor mentioned throughout different studies, reaching an OR of 5.5 in the study conducted by Kormos et al.(22). While it isn't included in the Pittsburgh Decision Tree, preoperative mechanical ventilation stands for the "I" (intubation) in the CRITT Score and has been predictive in univariate analysis in several studies(18–21). Similar to preoperative circulatory support, preoperative mechanical ventilation is also mentioned as a predictor in a newer study including echocardiographic parameters(29).

Almost constantly figures a *high preoperative creatinine* within either univariate or multivariate analysis, reaching ORs of 4.8(20) and 2.9(19) depending on the cut-off level and the study population considered. Further laboratory values to consider include elevated *bilirubin*(18–22), *aspartate aminotransferase*(18–22,24)and *white blood cell count*(19,20,22,24) as well as a low *albumin*(19,20,23,24)and *platelet count*(19–21,23,24).

When we look at the hemodynamic parameters, a low *CI*(19,20) and *right ventricle stroke work index* (RVSWI)(18–20,22,24) have been identified most frequently as predictors in the different studies and represent the two most important factors in the Penn Score.

6.5 Echocardiography

RV imaging is an attractive adjunct to clinical RV evaluation because it is non-invasive and may offer greater sensitivity to change than markers of pre-existing RVF(17,29). However, the structure and orientation of the RV in the anterior chest, as well as its unique shape, have made it challenging to fully characterize the RV by 2-dimensional echocardiography (2DE). There is no one echocardiographic view that is able to completely visualize the whole RV and therefore, different probe orientations are used to assess the RV in piecemeal fashion(100). Load dependence and inadequate standardization of the assessment further complicate proper evaluation(101). Despite these challenges, transthoracic echocardiography (TTE) is still the most available, feasible, affordable, and safe imaging modality for patients with advanced HF(16) and numerous ways have been developed to assess RV function. A paper published in 2015(100) summarizes the different measures used to quantitatively assess RV function, pointing out their limitations and strengths. Here, I will only discuss the most important parameters used in different studies as either individual risk predictors of RVF or in addition to clinical risk prediction scores (Table 3).

Table 3(16): Quantitative Right-Sided Parameters for Prediction of RVF

Study	Patients	RVF Definition and Rate	Univariate Echo Predictors	Multivariate Echo Predictors
Potapov et al.(25) 2008	N=54, mean age 52, male 91% CF 37; PF 17	≥2 within 48h in the absence of cardiac tamponade: mean arterial pressure ≤55mmHg, CVP ≥16mmHg, mixed venous saturation ≤55%, CI < 2l/min/m ² , inotropic support >20 units OR Need for RVAD RVF rate 17%	RV short/long axis ratio, RV EDD, RV EF, TR, LV EDD	RV short/long axis ratio TR grade III to IV
Puwanant et al.(26) 2008	N=33, mean age 54, BTT 67%, DT 21%, BTR 12% CF 26, PF 7	Need for inotropic support or pulmonary vasodilators for ≥14 days post-operatively RVF rate 33%	TAPSE, RV systolic pressure	Multivariate analysis not performed
Kukucka et al.(27) 2011	N=115, mean age 54, male 90%	≥2 within 48h in the absence of cardiac tamponade: mean arterial pressure ≤55mmHg, CVP ≥16mmHg, mixed venous saturation ≤55%, CI < 2l/min/m ² , inotropic support >20 units OR Need for RVAD RVF rate 13%	R/L EDD ratio	Multivariate analysis not performed
Topilsky et al.(28) 2010	N=83, mean age 63, male 81% BTT 33%, DT 67% CF 100%	Need for RVAD or inotropic support for more than 7 days post-operatively RVF rate 24%	TRDc, MPI, TR-RV ejection time	LV EDD, TRDc
Grant et al.(29) 2012	N=117, mean age 58, male 79%, BTT 67%, DT 33% CF 100%	Need for RVAD or inotropic support for >14 days RVF rate 40%	RV dysfunction (visual semi-quantitative), RV free-wall strain	RV free-wall strain
Kato et al.(30) 2012	N=111, mean age 56, male 78% CF 79, PF 32	Need for RVAD, nitric oxide inhalation >48h and/or inotropic support >14 days RVF rate 32%	LV EDD, LV ESD, LV EF, LA diameter to LV EDD (ratio)	LV EDD LV EF LA diameter to LV EDD
Raina et al.(31) 2012	N=55, mean age 54, male 71%, BTT 65%, DT 35% CF 39, PF 3	Need for RVAD or inotropic support ≥14 days RVF rate 29% 13 patients had initial BiVAD	RVFAC, RA pressure, LA volume	None
Kato et al.(32) 2013	N=68, mean age 63, 90% male CF 100%	Need for RVAD or inotropic support at 14 days after surgery or pulmonary vasodilator therapy 14 days after surgery RVF rate 35.3%	RVFAC, TAPSE, RV E/E', RV global strain	Multivariate analysis not performed
Vivo et al.(33) 2013	N=109, mean age 54, male 77%, BTT 49%, DT 49%, BTD 2%, CF 100%	Need for RVAD or ≥14 days of inotropic support RVF rate 22.9%	RV/LV diameter, RVSWI	Increased RV/LV diameter ratio
Kiernan et al.(34) 2015	N= 26, mean age 46, male 73% CF 100%	Need for BiVAD or >14 days of inotropic support RVF rate 46%	RVEDVI, RVESVI, RVEF	Multivariate analysis not performed

BTD, bridge to decision; BTR, bridge to recovery; BTT, bridge to transplantation; CF, continuous flow; CI, cardiac index; CVP, central venous pressure; DT, destination therapy; EDD, end-diastolic diameter; E/E', tricuspid early inflow velocity to early diastolic annular velocity ratio; EF, ejection fraction; ESD, end-systolic diameter; LA, left atrial; LV, left ventricular; MPI, myocardial performance index; PF, pulsatile flow; RA, right atrial; RV, right ventricular; RVEDVI, right ventricular end diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end systolic volume index; RVFAC, right ventricular fractional area change; RVSWI, right ventricular stroke work index; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TRDc, duration of TR corrected for heart rate; and VTI, velocity time integral.

For studies without BTT vs DT information, indication was not reported in the original publication.

A small retrospective study by Potapov et al.(25) showed that tricuspid incompetence and geometry of the RV may help to select patients who would benefit from biventricular support. Other investigators, such as Grant et al.(29), however, failed to reproduce the predictive value of tricuspid incompetence. Furthermore, tricuspid incompetence is more and more frequently corrected through valve repair (or replacement) at the time of LVAD implantation(16).

Puwanant et al.(26) evaluated tricuspid annular plane systolic excursion (TAPSE) in 33 patients with LVAD placement and found significantly lower values in patients who developed RVF. TAPSE is a simple approach in order to evaluate longitudinal shortening, a major contributor to RV function(16). However, TAPSE was not significantly different in other studies(27,31,33). This was explained by the fact, that TAPSE is only a regional marker of RV function and assumes that the motion of the RV free wall base represents the function of other segments(102). Furthermore, the value of TAPSE is uncertain in patients who have had previous cardiac surgery, as it is the case in many patients evaluated for LVAD(31).

Reduced RV fractional area change (RVFAC) was used as a feasible quantitative alternative to evaluate RV systolic function and correlates well with cardiac MRI measurements (current “gold standard” for RV assessment)(16,34). RVFAC has the benefit of accounting for both longitudinal and transverse shortening of the RV, resulting in a more balanced overall assessment of RV function(31). An RVFAC <35% is considered abnormal and a >10% reduction in RVFAC at 1 month was associated with worse quality of life and poor exercise capacity in patients with an LVAD(16). In a small retrospective study lower RVFAC predicted RVF(31), however, this could not be confirmed in other retrospective studies(16,26,27,29). The drawback of this measure is that it requires appropriate endocardial definition to circumscribe RV end-systolic and end-diastolic areas from the apical 4-chamber view, which can be technically difficult in critically ill and mechanically ventilated patients(31).

Kukucka et al.(27) suggested that increased RV/LV diameter ratio is a strong predictor of RVF after LVAD, based on prospective preoperative transesophageal echocardiography (TEE) measurements. This finding had already been mentioned by Potapov et al.(25) and was later confirmed in another study(33) based on analysis of patients implanted with CF LVADs that included 26 TTE parameters. Other studies, however, failed to confirm this finding(29,31). Furthermore, TEE is an invasive procedure, which is often not performed until the patient is already in the operating room under general anesthesia, when loading conditions are different than in the pre- and postoperative setting(31).

Tissue Doppler Imaging (TDI) is an attractive alternative to TAPSE because myocardial velocities are easy to obtain and reproduce. Although systolic velocity of the tricuspid annulus reflects longitudinal RV function, the velocities depend on insonation angle and loading

conditions. 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(16). A study of 68 recipients with LVAD could not identify systolic tricuspid annular velocity as a predictor of RVF(32).

Raina et al.(31)demonstrated that lower left atrial volume, indexed for body surface area, was significantly predictive for patients with RVF compared with those without RVF. This reflects the fact that patients with larger left atria have had more chronic and/or severe left atrial congestion and LV diastolic dysfunction, which would be ameliorated with LVAD placement, leading to improvement or preservation of RV function. Where as patients with smaller left atria may derive less benefit after left-sided decongestion and the increased preload is less counterbalanced by the benefit of reduced left-side congestion.

Another echocardiographic variable identified as a significant predictor of survival or RVF following LVAD includes early systolic equalization of RV and right atrial pressure demonstrated as decreased time interval between onset and cessation of tricuspid regurgitation flow corrected for heart rate (TRDc)(28,88).

It can sometimes be technically challenging to obtain standardized RV images that allow quantitative assessment from patients with advanced HF, particularly if patients are severely congested, intubated, and/or have a markedly enlarged LV that obscures the RV. Therefore, Kato et al.(30)focused on LV parameters to create a simple scoring system to predict post-LVAD RVF. Smaller LV end-diastolic dimension (LVEDD), greater LV ejection fraction, and large left atrial diameter relative to LV cavity size were found to be associated with RVF development. In another study(33), however, isolated LV echocardiographic parameters were not predictive of adverse events.

As acquisition of RV physiology improves, the aforementioned descriptions of RV function may become obsolete. RV strain and 3-dimensional echocardiography (3DE) are two promising approaches to evaluate RV function and may perform even better once they become more advanced and adopted(100).

Strain is a measurement of tissue deformation as the myocardium contracts in systole as a result of sarcomere shortening. The myocardial tissue deforms as the myocardial tissue changes 3D shape, with longitudinal shortening, circumferential shortening, and radial thickening. Strain is expressed as the percent change from the initial length in end-diastole or onset of the cardiac cycle, whereas strain rate is the rate of deformation over time. Strain and strain rate, collectively termed ventricular mechanics, reflect myocardial performance and provide a direct assessment of myocardial contractility and may help delineate more subtle abnormalities of RV contractility

than other echo variables, such as subjective RV function or RVFAC(16,29,100). Longitudinal shortening resulting in a negative strain can be measured with DTI in the apical 4-chamber view, and circumferential shortening strain, which is also a negative strain, is obtained in the short-axis view but is less standardized than longitudinal strain in the acquisition methods. Color DTI strain is limited by different ranges of “normal” provided by different echocardiogram vendors and is dependent on complex post-processing, image acquisition, frame rate, and angle of acquisition(100).

Speckle tracking is a technique where the unique speckled backscatter of the reflected ultrasound beam in the myocardium is followed frame by frame. The use of algorithms to identify and follow speckles and its angle independency make it a more reliable measure of RV strain than DTI(16,17,100). However, it is still dependent on image quality and frame rate, and the normal values still vary, depending on the vendor providing the strain software, which makes comparison between centers difficult(100).

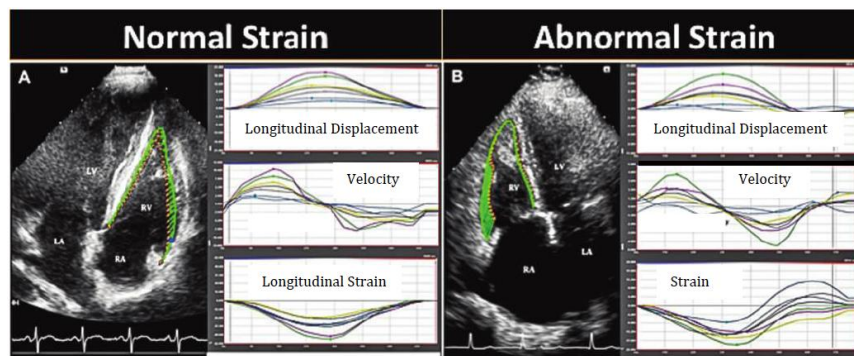


Image 9(100):Velocity vector imaging (a variant of speckle tracking using standard Digital Imaging and Communications in Medicine images¹⁸) showing normal (A) and abnormal (B) segmental patterns of longitudinal displacement, velocity, and strain. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle

A recent report by Grant et al.(29)indicated that decreased RV peak longitudinal strain was a novel predictor of RVF, more powerful than any other echocardiographic parameter studied and significantly refined prediction when added to the Michigan score (*C* statistic = 0.77 vs 0.66). Kato et al.(32)also investigated the utility of serial TDI and speckle tracking echocardiography to measure RV strain as risk predictor and pointed out their high reproducibility and their advantage of reflecting both systolic and diastolic ventricular function. Other groups have recently reported similar findings(14,103). Unfortunately, this method remains unsuitable for patients with poor acoustic windows or very large RVs because the measurements are difficult in the thin-walled RV(29).

3DE has the ability to quantitatively assess RV volumes similar to cardiac MRI but without its contraindications, time and cost burden(34). Currently, in order to acquire 3D volumes of the RV, tracings of anatomical landmarks are made at the end of diastole, and then, akin to speckle tracking, these sites are followed over the course of systole in order to reconstruct the 3D

images(100). Kiernan et al.(34)used 3DE to measure preoperative RV volumes and RVEF for risk stratification of LVAD patients. RV end diastolic volume index and RV end systolic volume index were the strongest preoperative determinants of RVEF, independently from known hemodynamic correlates of RV function such as RVSWI. Their findings thereby support the concept that volumetric quantification of RV size and function may be the best method of RV functional assessment.

One limitation to this technique is the need to obtain 3-6 cardiac cycles to create full-volume imaging, and therefore this can be subject to increased error in the setting of arrhythmia. Otherwise, this method does facilitate imaging of the entire RV and can therefore measure RV volumes. These volume acquisitions and subsequent RVEF measurements have been validated compared to in vivo volumes and function, and have demonstrated minimal interobserver variability(100).

7 Future directions

The inconsistency of parameters across different studies and the often divergent outcomes might be frustrating. But the value of these studies lies in the fact that they provide a wide range of key factors to take into account in clinical decision making, rather than to replace clinical judgment. A new combination of the most persistent factors might be interesting to test in a new cohort, but there are several limitations to this approach. First of all, the use of hemodynamic and laboratory markers as surrogates (“proxies”) of RVEF instead of direct RV function assessment adds to their limited clinical applicability, because end-organ dysfunction is multifactorial(15). Second, even if the RV is assessed directly with echocardiography prior to surgery, we don’t deal with the same RV after LVAD implantation. Hemodynamic and ventricular interaction change immediately after surgery and intraoperative events such as blood transfusions and air embolism may further influence outcome. The resulting demand for increased RV blood flow in a setting of reduced ventricular systolic assistance may unmask RV dysfunction gone until then unnoticed. Third, there has been an increase in concomitant procedures during LVAD implantation. For example, concomitant tricuspid valve repair (or replacement) for severe TR results in improved RV function post implantation influencing risk prediction(16). Forth, the utility and feasibility of complexly calculated risk scores has been questioned, and even the Michigan group neither systematically calculates their own risk score nor presents it to their patients(24).

Although newer studies such as the CRITT score and the Pittsburgh decision tree have proposed easier models to predict RVEF, they still face several limitations and have not been proven to outperform older risk scores.

Therefore, instead of combining several factors into a new and easily applicable score, I simply propose to divide the clinical, hemodynamic and laboratory parameters discussed above into major and minor risk factors.

Major Risk Factor	Minor Risk Factor
Preoperative circulatory support	AST ≥ 80 IU/liter
Preoperative mechanical ventilation	Bilirubin ≥ 2.0 mg/dl
Cardiac Index ≤ 2.2 l/min/m ²	Albumin ≤ 3.0 g/dl
RVSWI ≤ 0.25 mmHg/l/m ²	White blood cell count ≥ 12.2 k/mm ³
Creatinine > 1.9 mg/dl	Platelet count ≤ 120 k/mm ³

Their presence, especially if multiple factors are combined, clearly indicate severely ill patients at high risk of RVF but also other complications. However, they don't provide information about the RV's capacity to increase function and tolerate increased workload. This capacity known as ventricular functional reserve is crucial in the early postoperative period, when the increased preload and decreased LV and IVS contribution to RV contraction are not yet balanced by a decrease in afterload. Testing the RV's capacity to increase contractility might best simulate the postoperative period and thereby uncover an otherwise asymptomatic RV dysfunction.

The concept of using stress, whether during exercise or pharmacologically induced, to evaluate this ventricular functional reserve is not new and is frequently applied in aortic stenosis to predict LV recovery(100). The same concept has recently been introduced to evaluate RV functional reserve in a few disease states, but there are no established and standardized methods(100,101). In PAH, for example, the exercise induced increase in CI(104) or systolic pulmonary artery pressure (sPAP)(101) were used to measure right ventricle reserve and both predicted better prognosis in their respective study.

In a similar fashion, Deswarte et al.(105)evaluated RV functional reserve in LVAD recipients by continuous dobutamine infusion increasing the dose every 15 minutes by 5 μ g/kg/min until the maximal dose of 15 μ g/kg/min was reached. In their study, dobutamine-induced changes in TAPSE and sPAP predicted RVF within 30 days of LVAD implantation in end-stage ambulatory congestive HF patients with biventricular dysfunction. None of their patients with a change in TAPSE greater than 40% or a change in sPAP greater than 30% experienced RVF within 30 days after surgery, giving these thresholds a high (100%) sensitivity and specificity to predict post-operative RVF. However, their study included only 14 patients, out of which 6 underwent dobutamine testing and 3 of them later developed RVF.

When we consider the pathophysiology behind post-LVAD RVF, it is obvious that RV dysfunction prior to surgery puts the patient at risk for RVF. But the study done by Deswarte et al.(105), suggests that patients with moderate RV systolic dysfunction could still undergo successful LVAD implantation, if they show a RV functional reserve assessed by dobutamine-induced increase in sPAP and TAPSE. Therefore, this test not only tries to uncover an otherwise silent RV

dysfunction, but also tells us, whether a patient with RV dysfunction can still undergo LVAD implantation successfully. Further testing of this approach might produce a very valuable tool to help decide on the best surgical strategy and I consider the RV functional reserve as the most important factor to evaluate.

On these grounds, I propose to adapt a similar approach as Deswarte et al.(105)and assess dobutamine-induced changes in echocardiographic parameters. I suggest echocardiography rather than cardiac IRM because of its feasibility, its cost and time efficiency and its lack of major contraindications. Regarding the parameters, I recommend continuing testing sPAP in other patients, since it has performed well in their study, as well as in the experience conducted by Grünig et al.(101). However, sPAP doesn't directly reflect how the RV contracts, but how the pressure generated in the RV is transferred to the pulmonary circulation. Since dobutamine also stimulates the LV, some of the generated pressure in the RV might be due to the increased LV contraction. Therefore, I propose to add another parameter that focuses more on the RV myocardium itself as comparison.

RV strain obtained by speckle tracking seems to be the most promising choice for this second parameter, as it presents several advantages, such as load and angle independency, and evaluation of global RV function. Also, the consistency of findings on the predictive value of longitudinal RV mechanics for RVF across different research groups is promising(14,29,32,103).Therefore, it would be interesting to test, if a certain dobutamine-induced change in RV longitudinal strain can predict favorable outcome after LVAD implantation on it's own or in combination with several of the risk factors mentioned earlier.

Its dependency on image quality and the difficult measurement of RV strain in a thin-walled RV may represent major obstacles to this approach, however, every one of the above mentioned echocardiographic parameter has its limitations. Furthermore, HF is multifactorial and the patient population receiving an LVAD is extremely diverse. Like there is no single LVAD that fits all, there might not be a single investigation that can predict RVF in all patients. Further evaluation of dobutamine-induced changes in several other parameters might provide a set of possible methods to choose from and enable a more complete coverage of this heterogeneous LVAD recipient population.

8 Conclusion

Anatomy and physiology paint a picture of two unequal but interdependent sides of the heart that influence each other on a beat-to-beat basis. Implantation of an LVAD plays with this interdependence and the experience with these devices has clearly shown that the LV needs a RV strong enough to tolerate surgery and to adapt to the important hemodynamic changes following surgery. Every intervention on the left side of the heart also has an impact on the right side and therefore demands the implication of the RV in the treatment plan. The best way to know whether or not the RV can handle a LVAD implantation is to simulate the post operative situation; in this case, a demand for improved right cardiac output with a decreased LV contribution. Therefore, we have to evaluate the RV's functional reserve.

The constant ventricular interaction, however, also interferes with the evaluation of the RV's functional reserve. Since uncoupling of the two ventricles to reduce LV contribution to the RV output is not possible, we have to evaluate the RV's functional reserve by the methods that best reflect the RV's contractility itself. By focusing on RV wall deformation, RV strain measured by speckle tracking differentiates between active and passive wall motion and thereby assesses RV contractility more accurately than other imaging techniques. Further development of this method may considerably improve patient selection and indicate the patients in need for direct BiVAD implantation.