Title: Right ventricular dysfunction in patients implanted with left ventricular assist devices

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New findings

- Incidence of right heart failure post left ventricular assist device (LVAD) implantation is improving, as the understanding of LV-RV physiology improves. Yet, it remains one of major adverse events affecting LVAD patients.
- Assessment of RV failure in the context of LVAD physiology should consider its unique anatomical and physiological peculiarities which may advance our understanding of RV function in general.

Abstract

The adaptation of the right ventricular (RV) output to a left ventricular assist device (LVAD) often determines the fate of patients with pulmonary hypertension secondary to left heart failure. Pre-existing right heart dysfunction in patients with advanced left heart failure is the consequence of increased (arterial) afterload and not the mere consequence of a myocardial disease. If unaccounted for, it has the potential of accelerating into right heart failure post LVAD, leading to significant morbidity and mortality. Following LVAD implant, the RV has to face increased flow generated by the LVAD, cardiac arrhythmias and exaggerated functional interactions between both ventricles. Understanding the key pathophysiology mechanisms of RV dysfunction in patients with end-stage heart failure, will allow us to predict and hence prevent RV failure post LVAD.

Introduction

Most patients with advanced left heart failure (HF) requiring left ventricular assist device (LVAD) placement have some degree of right ventricular (RV) dysfunction (Lampert & Teuteberg, 2012). In fact, outcomes of LVAD patients are critically dependent on RV function, since the RV needs to provide sufficient flow through the pulmonary vasculature, fill the LVAD and hence, ensure an optimal performance. In recent years, there has been increasing emphasis on appropriate patient selection and optimization of the right heart before LVAD implantation to avoid post LVAD RV failure.(Drakos et al., 2010; Kormos et al., 2010; Loghmanpour et al., 2016) Unfortunately, patients receiving continuous-flow LVAD continue to demonstrate RV failure in 10-40% implants, many requiring biventricular VAD support.(Kirklin et al., 2017) This has a direct effect on mortality and is associated with prolonged length of intensive care unit and hospital stay post LVAD implant.(Dang et al., 2006)

It is key to recognize that both ventricles work functionally in series within the circulation, differ in anatomy and physiology, and fail and/or respond to LVAD therapy in ways distinct from each other.(Lampert & Teuteberg, 2012) In patients with advanced left HF, RV dysfunction may occur secondary to increased RV afterload from postcapillary pulmonary hypertension (PH), volume overload and arrhythmias, in addition to the underlying myocardial disease. In fact, it is the pre-existing RV impairment that commonly gets unmasked with the increase in right-sided preload afforded by LVAD perfusion, resulting in RV failure. In this report, we analyze the key physiological insights into RV failure in patients with left HF, requiring LVAD therapy.

Normal RV anatomy and physiology: more than a sum of its parts

The RV is coupled to the systemic venous return (preload) and the pulmonary circulation (afterload). Its muscle fibers are arranged in 2 layers: superficial layers arranged circumferentially and deep layers aligned longitudinally.(Dell'Italia, 1991) This differs from the LV, where oblique fibers are present in the subendocardium and subepicardium, with additional circumferential fibres in the midwall and some transverse fibers that contribute to auxotonic and unloading forces.(references).~~(Haddad, Hunt, Rosenthal, & Murphy, 2008)~~ Normal RV function is governed by systemic venous return, pulmonary artery load, pericardial

compliance, and native contractility of the RV free wall and inter-ventricular septum. Systolic ventricular interdependence is primarily mediated through the interventricular septum (IVS) and diastolic interdependence through the pericardium.(Vonk Noordegraaf et al., 2019) In fact, 30% of RV output results from LV contraction.(Feneley et al., 1985)

The ventricular pressure–volume loop analysis is central in understanding right ventricular physiology, while pressure–flow analysis is central in understanding pulmonary hemodynamics.(Vonk Noordegraaf et al., 2019) Understanding the intrinsic characteristics of this cardiopulmonary unit allows us to appreciate how the global cardiac function is consequence of their interplay. The performance of both ventricles is intricately linked with each other, whereby alterations of one ventricle affect the size, shape, and function of the other (Kukucka et al., 2011). The RV is much more compliant than the LV, allowing it to accommodate large variations in venous return without altering end-diastolic pressure.(Haddad et al., 2008) Additionally, both ventricles respond variably to change in afterload, based on their underlying physiology.

RV anatomy and physiology in patients with pulmonary hypertension in left heart disease

RV failure in left heart disease is the consequence of increased afterload, altered contractility, ventricular interdependence and rhythm alterations.(Haddad et al., 2008) The underlying myopathy that ails the LV often affects the RV myocardium as well. Within physiological limits, an increase in RV preload improves myocardial contraction per the Frank-Starling mechanism. However, excessive RV volume loading can compress the LV and impair global ventricular function through the mechanism of ventricular interdependence.(Chin, Kim, & Rubin, 2005) Patients with advanced left HF suffer from a from a gradual increase in RV afterload from chronic volume overload, made further worse by secondary tricuspid regurgitation. Long-standing pressure or volume overload imposed on the RV initially promotes compensatory myocyte hypertrophy and fibrosis analogous to the remodeling that occurs in LHF. If the load persists, then the RV transitions from a compensated to decompensated phenotype characterized by myocyte loss and replacement/fibrosis.(Vonk Noordegraaf et al., 2019) This results in increased sensitivity of the RV to changes in afterload.(MacNee, 1994) While an increase on the left side leads to only a slight decrease in stroke volume, the same increase in the RV results in a marked fall in stroke volume.   This

leads to further RV dilatation to preserve stroke volume. Because of the right ventricle's thinner wall and higher dependence on coronary perfusion pressure, it is more vulnerable to an increase in RV size (intramural pressure) and systemic hypotension. Additionally, the pericardium imposes greater constraints on the thinner, more compliant RV.(Dell'Italia, 1991)

RV failure results in elevated central venous pressure (CVP), which adversely affects renal, hepatic, and gastrointestinal function in these already sick patients. Increased systemic venous pressure impedes lung lymphatic drainage, decreasing lung fluid clearance and exacerbating pulmonary edema. Thus patients with a CVP that approaches the left-sided filling pressure before LVAD might represent the group at highest risk for right heart failure after LVAD implantation.(Kormos et al., 2010)

Influence of LVAD on RV function: multiple-hit mechanisms

As the LVAD decompresses the LV, and reduces LV end-diastolic pressure, pulmonary artery pressure should decrease, resulting in improved RV function. However, unloading of the LV via an LVAD influences RV function in several ways.(Sack et al., 2018) On the one hand, LVAD directly reduces the LV filling pressures as manifested by a reduction of pulmonary capillary wedge pressure (PCWP). This decrease in PCWP acts as a mechanical afterload reduction on the RV aiding its ability to eject blood and maintain a normal CVP. In fact, there was a marked immediate improvement of RV geometry and function after implantation of LVAD that seems to result from the relief of LV congestion and the concomitant reduction in RV afterload in a patient specific finite-element model of chronic, dilated heart failure.(Sack et al., 2018) On the other hand, implantation of an LVAD increases venous return and causes a leftward shift of the interventricular septum. This overwhelms a functionally impaired RV, leading to potential RV dilatation, worsening tricuspid regurgitation and clinical RV failure.

As mentioned above, patients with end-stage LV failure have pre-existing RV impairment that gets unmasked with the increase in right-sided preload afforded by LVAD perfusion. Those who have a lack of RV contractile reserve from long standing PH might have more septal shift and increased venous return, which outweighs any benefits of LV unloading. It is key to recognize that the mechanical interplay between the two ventricles due to septal interdependence is altered significantly due to LVAD placement. Excessive left- ward shift of the IVS, particularly with overly aggressive LV decompression with continuous-flow (CF)

LVADs, may also decrease septal contribution to RV contraction, leading to RVF. Detection of excessive LV unloading and distortion of normal ventricular interaction by echocardiography and its consecutive correction by pharmacological support and adjustment of the LVAD flow rate may be pivotal for the preservation of RV function and geometry in these patients.(Kukucka et al., 2011)

The impact of different LVAD operating speeds on the RV in a chronic heart failure model was demonstrated by Sack et al. LVAD speed-dependent reductions in LV filling pressure, pressure generation allowed a progressive transformation of the PV loop from trapezoidal shape to triangular shape.(Sack et al., 2018) This is a result of CF-LVADs removing volume from the LV throughout the cardiac cycle, thus eliminating isovolumic contraction phases.(Wang et al., 2014) With LVAD-induced LV unloading, the RV PV-loop shifted toward larger volumes and higher pressures, indicating that the RV end-diastolic pressure-volume loop was shifting rightward. This RV-LV interaction results in increased RV diastolic compliance reduction in RV systolic pressure. If the LVAD is operated on a high speed, it would eventually result in the LV being unloaded at a rate faster that it is being filled.(Sack et al., 2018) This is turn generates worsening cardiac arrhythmias and RV failure, further impairing LV filling, pulling the septum farther left wards.

These aspects are now being routinely considered at the time of LVAD and when deciding on device settings.(Raina & Patarroyo-Aponte, 2018) Perioperative management now focuses on minimization of intraoperative RV ischemia, maintenance of appropriate filling pressure monitored with hemodynamic catheters, supportive therapy with pulmonary vasodilators and inotropes, and early surgical interventions implantation RV assist devices in select cases.(Marzec & Ambardekar, 2013) It is recommended that patients undergo hemodynamic and imaging driven ramp study to choose the optimal speed which allows for allowing the septum stay central and minimizing RV distortion while adequately unloading the LV.(Uriel et al., 2016) These considerations, along with ongoing understanding of RV physiology will hopefully shift the focus of discussion from treatment of RV failure to anticipation and prevention of this devastating adverse event.

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