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Management of Severe Pulmonary Arterial Hypertension

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Abstract and Introduction

Abstract

Despite advances in medical therapies, pulmonary arterial hypertension (PAH), continues to cause significant morbidity and mortality. Although, the right ventricle can adapt to an increase in afterload, progression of the pulmonary vasculopathy that characterizes PAH causes many patients to develop progressive right ventricular (RV) failure. Furthermore, acute RV decompensation may develop from disorders that lead to either an acute increase in cardiac demand or an increase in ventricular afterload including interruptions in medical therapy, arrhythmia, or pulmonary embolism. The poor reserve of the right ventricle, RV ischemia, and adverse RV influence on left ventricular filling may lead to a global reduction in oxygen delivery and multiorgan failure. The authors present an approach to patients with advanced PAH focusing on both medical and surgical strategies to improve RV function based upon current evidence and physiological principles.

Introduction

Pulmonary arterial hypertension (PAH) remains a devastating condition. In the face of tremendous advances in our understanding of the pathophysiology and newer treatment options, many patients continue to experience progression of their disease. In these patients the relentless reduction in the cross-sectional area of the pulmonary vasculature leads to progressive right ventricular (RV) failure. Patients may present either de novo or while receiving treatment, with refractory symptoms, progressive reduction in exercise capacity or a sudden clinical decompensation. The severity of PAH (and indeed any form of pulmonary hypertension [PH]) is best defined from the perspective and function of the RV. RV failure is the most common cause of death in patients with PH and RV function is the major determinant of morbidity and mortality in this patient population.[1]

Pathophysiology of Right Ventricular Failure

The RV is embryologically, morphologically, and functionally distinct from the left ventricular (LV).[2,3] The metabolic and genetic profile in response to an increase in afterload also differ.[4] Before the birth the RV is the dominant ventricle and is well suited to eject blood into the systemic circulation via a patent ductus arteriosis. After birth and following normal lung inflation it rapidly assumes the adult phenotype of a relatively thin-walled, oddly crescent-shaped structure (Fig. 1). Despite these changes it is highly efficient and well adapted to eject into the pulmonary circulation; a circuit that is able to accommodate large increases in blood flow with little change in pressure owing to high vascular reserve, high compliance, and low impedance. The RV and LV are mechanically interrelated by the shared interventricular septum and pericardium. Although, RV contraction contributes to pulmonary blood flow, ejection of the RV is significantly augmented by LV contraction.[5,6] Though the RV is highly efficient, it is ill adapted to sudden increases in afterload. When presented with an acute increase in afterload, cardiac output is likely preserved through an increase in RV end-diastolic volumes via a Frank-Starling mechanism as well as a homeometric mechanism that is characterized by an increase in work and more rapid development of pressure at a given end-diastolic volume.[7,8] However, a severe and sudden increase in RV afterload may overwhelm the contractile capability of the RV and lead to hemodynamic collapse. In patients with chronic pulmonary vascular disease, manifested by a more gradual increase in RV afterload, there is a change in the mechanical characteristics of the RV as it starts to assume a similar pattern of ejection to that of the left ventricle with an increase in RV elastance and a reduction in diastolic compliance.[9] However, in the face of a progressive or sudden worsening in RV afterload these compensatory mechanisms are overwhelmed. In addition to the rate of progression in RV afterload, differences in the ability of the RV to compensate for an increase in afterload likely relate to age of the patient (or age at onset of the RV pressure load). Early in life the fetal RV is well adapted to high afterload making it well suited to situations where it may assume the role as the systemic ventricle.[10–12] Additionally, there may be differences in RV adaptation in the setting of proximal (pulmonary artery [PA] banding or pulmonic stenosis) as opposed to more distal pulmonary vascular occlusion (PAH).[11] Finally, the chronically dilated or volume overloaded RV may adapt differently[13] and may be less capable of compensating for an increase in RV afterload.[14]

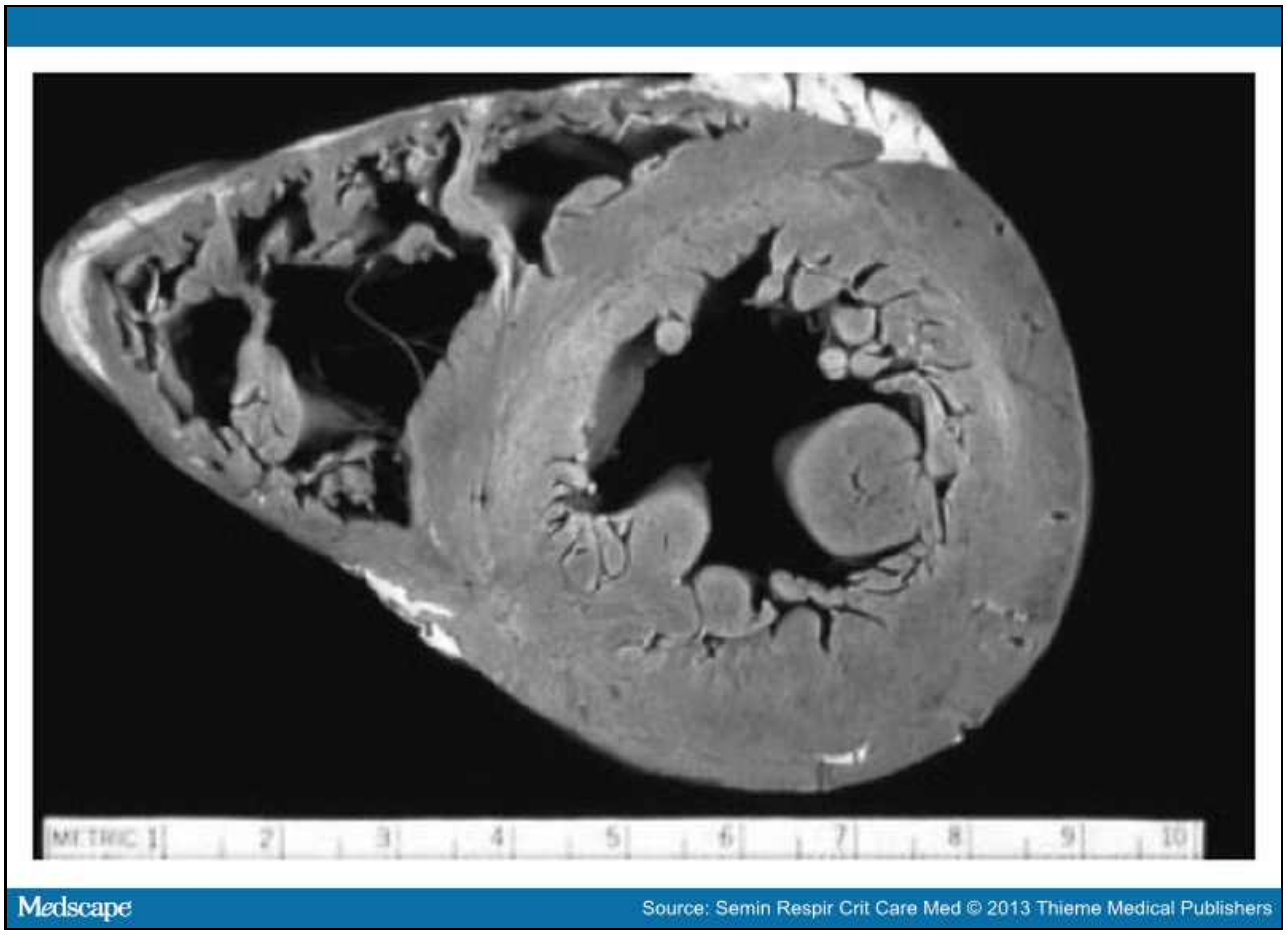

Figure 1.

Cross-sectional view of the normal heart contrasting the differences in the shape of the right and left ventricles. The right ventricle is thin walled, crescented in shape, and shares the muscular intraventricular septum. Image courtesy of Dr. Jagdish Butany.

Physiologically, RV failure represents the point at which there is dissociation between ventriculoarterial coupling. This coupling is a major determinant of RV function as it relates RV end-systolic elastance (a load-independent measure of contractility) relative to pulmonary arterial elastance (difference in end-systolic and end-diastolic RV pressure relative to stroke volume).[15] Normal coupling represents a point at which there is adequate output at the lowest energy cost. In addition to the reduction in RV output, an increase in RV wall tension with resultant imbalance in myocardial oxygen consumption and delivery as well as adverse RV-LV interdependence may also contribute to the spiraling decrease in cardiac function and must be emphasized as important therapeutic targets in treating patients with RV failure (vide infra).[16,17]

The clinical sequelae of RV failure is more familiar, and characterized by a reduction in cardiac output with resultant increase in venous pressure and signs/symptoms of venous congestion such as jugular venous distention, hepatomegaly, peripheral edema, and ascities. A reduction in a reduced cardiac output (i.e., cardiac index < 2.5 L/min/m^2) will eventually lead to an impairment of systemic oxygen delivery to tissues. Indeed the development of systemic hypotension and renal insufficiency are ominous prognostic signs.[18,19]

Monitoring of Right Ventricular Function in the ICU

There is no gold standard method of monitoring RV function in the intensive care unit (ICU). Although, many advocate for the use of invasive pulmonary hemodynamic monitoring it is unclear if an approach guided by changes in pulmonary hemodynamics translates into improved outcomes.[20] In addition, there are both practical and theoretical limitations to the use of pulmonary hemodynamics to guide treatment. The measurement of thermodilution cardiac output in the setting of severe tricuspid insufficiency may be problematic.[21–23] Additionally, the use of the indirect Fick method (using an assumed value for oxygen consumption) may be inaccurate as it will not incorporate changes in oxygen consumption with changes in treatment or metabolic rate. The severity of PH cannot be reliably assessed by the degree of elevation in pulmonary pressures as a failing ventricle will produce lower pressures as it fails. Furthermore, the reliance on pulmonary vascular resistance (PVR) as a measure of disease

severity or prognosis may also be problematic. A recent study demonstrated that although a high PVR at baseline was associated with outcome, the prognosis was primarily determined by right ventricular ejection fraction (RVEF).[24] Furthermore, the changes in PVR were not strongly related to the changes in RVEF. They also illustrated that despite medical therapy; RV dysfunction could progress in the face of a decrease in PVR. Disturbingly in their cohort, 25% of the treated patients did not experience an improvement in RVEF. This fact and the relentless mortality in many patients with advanced functional class emphasize the need for greater vigilance and attention to the response of the right ventricle to therapy.

Although, there are several echocardiographic measures of RV performance that have correlated with prognosis, it is unclear if these can be used in the acute setting. Tricuspid annular displacement during RV systole, Tei index, and eccentricity index have all been correlated to RV function and prognosis in the outpatient setting.[25–27] However, test characteristics such as reliability, reproducibility, and diagnostic accuracy as a maker of RV function have not been formally evaluated in the critical care setting. Additionally, practical limitations may preclude obtaining accurate images to make these measurements. Similar to the caveat with following pulmonary arterial pressures, there are pitfalls to the use of right ventricular systolic pressure as a marker of RV function and as a goal of treatment in the acute setting. Although, magnetic resonance imaging is considered the gold standard of evaluating RV function it is not practical in unstable patients. Whether newer echocardiographic modalities of measuring RV volume and RVEF can be used in the critical care environment needs to be evaluated (Fig. 2).

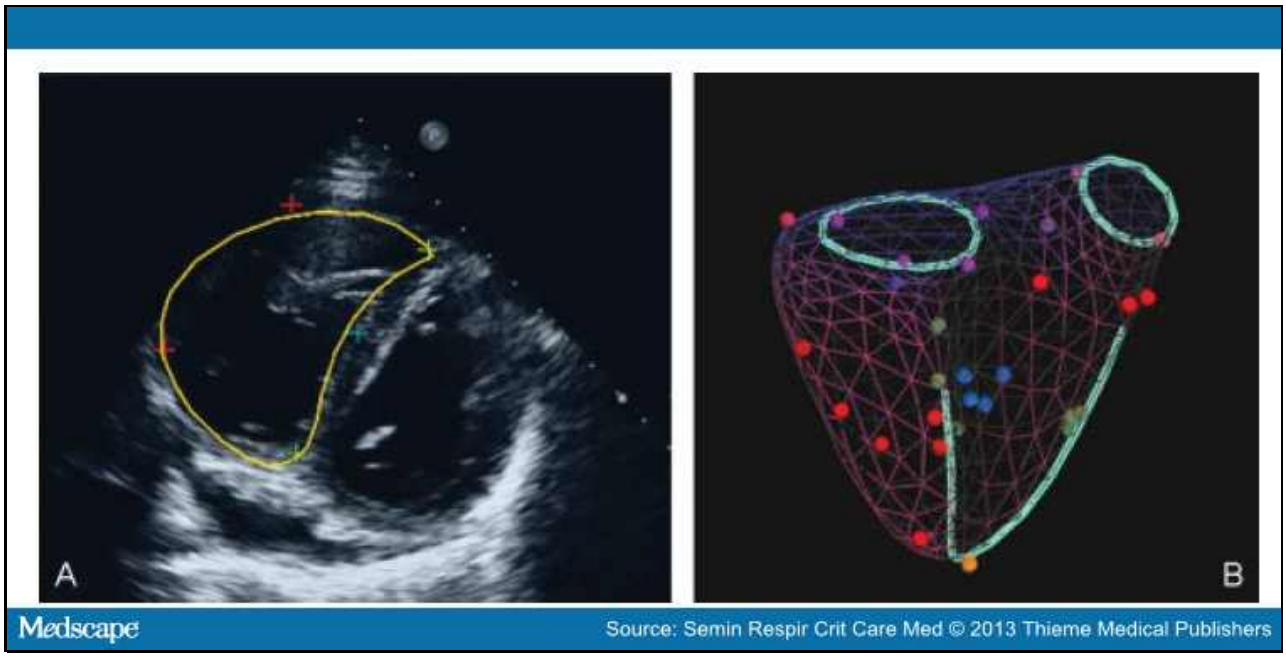

Figure 2.

Echocardiogram of a patient with severe pulmonary hypertension. (A, B) A short axis view with point placement and outline of the right ventricular (RV) free wall and septum to allow for a knowledge-based three-dimensional reconstruction of the RV using the method developed by VentriPoint (Seattle, WA) to estimate RV volume and ejection fraction.

It is the authors' preference to use the traditional markers of the adequacy tissue oxygenation such as mixed venous or central venous oxygen saturation, arterial lactate, and markers of end-organ function. Admittedly however, markers of end-organ function may not provide sufficient fidelity to gauge acute effects related to changes in treatment or pharmacological interventions. Similarly, though changes in levels of brain natriuretic peptide (BNP) relate to prognosis its measurement may also not provide sufficient fidelity or accuracy in a critically ill patient who may also have renal impairment. Heart rate is an important feature to follow as tachycardia may reflect worsening RV function as well as be an undesired side effect of medical therapy.

Principles of Managing Right Ventricular Failure

Several general principles apply in treating patients with advance RV failure, both as it relates to goals of therapy, but also pitfalls to avoid (). The main objective is to restore RV function to the point where either the patient can be stabilized for definitive treatment with traditional oral or parenteral pulmonary vasodilators or undergo lung or heart-lung transplantation (LTx). To achieve this end, the focus of treatment should be to search for and address reversible causes, reduce RV wall tension, restore RV output, reduce the adverse influence of a dilated, pressurized RV on LV filling.[20] These goals are obtained through the more familiar/traditional methods of improving cardiac function through manipulating preload, afterload, and contractility without undue

side effects from treatment—particularly tachycardia and systemic hypotension.

Table 1. Principles of managing patients with pulmonary hypertension and acute right ventricular failure

Variable	Treatment	Goal/effect
Identify reversible causes for acute RV decompensation	Depends on cause (e.g., atrial arrhythmia, infection, pulmonary embolism)	Reduce RV demand
Reduce RV afterload	Pulmonary vasodilators (nitric oxide, prostanoids, phosphodiesterase inhibitors) Control $PaCO_2$ Reduce alveolar hypoxemia/atelectasis Extracorporeal support Lung transplantation	Reduce RV wall tension Reduce RV-LV influence Improve RV output
Reduce RV preload	Diuretics Ultrafiltration Atrial septostomy	Reduce RV wall tension Reduce RV-LV influence
Improve RV contractility	Inotropic agents (phosphodiesterase inhibition, β-1 agonists, levosimendan)	Improve RV output
Avoid tachycardia	Caution reuse of B-agonists	Preserve LV and RV diastolic filling
Maintain systemic blood pressure	α-receptor agonists Vasopressin	Maintain coronary perfusion Reduce RV-LV influence

Abbreviations: LV, left ventricular; RV, right ventricular.

The outcome of patients with PAH admitted to hospital with RV failure is poor. In a retrospective review of 119 patients (207 hospital admissions) in a single center 34 patients either died or underwent LTx. Tachypnea (> 20 breaths/min), renal dysfunction (glomerular filtration rate < 45 mL/min), hyponatremia (serum sodium < 136 mEq/L), and severity of tricuspid regurgitation were associated with a poor outcome.[28] The outcome of patients who require ICU admission is worse with a reported mortality ranging from 30 to 40% in two series.[29,30] Systemic hypotension, acute physiology and chronic health evaluation score, preexisting treatment with a prostanoid, serum levels of creatinine, BNP, and C-reactive protein were associated with poor ICU outcome.[29,30] Therefore, the management of these patients requires a committed team with expertise and access to mechanical circulatory support and transplantation.

Factors Triggering Right Ventricular Failure in Patients With Pulmonary Hypertension

The identification of potentially reversible causes should be the first priority.[20,31] In the French series described above, of the 46 patients with PAH admitted to the ICU for RV failure 19 (41%) had an identifiable triggering factor.[30] This included unanticipated withdrawal of PAH-targeted therapy (*n* = 3) or diuretics (*n* = 1), pregnancy (*n* = 1), septicemia (*n* = 7), pneumonia (*n* = 3), and arrhythmia (*n* = 3). Importantly, the presence of an infection during the ICU stay was the strongest predictor of death. The general principles of ICU care apply and include prophylaxis to prevent hospital acquired infections, venous thromboembolism, and stress ulcers. Although, patients present with progressive RV failure generally require diuresis (see below), those who present with sepsis, or hypovolemia may require judicious fluid administration. The fluid strategy in patients with acute pulmonary embolism is controversial with conflicting reports regarding the hemodynamic effects of fluid administration.[32,33] In general, in established PH with demonstrable RV overload, fluid administration may worsen the severity of RV failure (see below).

Patients with PAH appear to be more susceptible to atrial as opposed to ventricular arrhythmias. In a rat monocrotaline model, Benoist et al demonstrated that the RVs in pulmonary hypertensive animals were characterized by structural and electrical changes and structural and functional disarray of calcium handling by the sarcoplasmic reticulum—features that they concluded predisposed to electrical alternans.[34] In a mapping study, Medi et al described the electrophysiological and structural electrical changes in the right atrium in eight PAH patients.[35] The degree to which these electrical and structural changes interrelate with the neurohormonal activation seen in PAH to produce atrial arrhythmias is uncertain.[36,37] Two retrospective series from the group in Hannover, Germany have provided insight into the importance of this complication. In one study, 31 supraventricular tachycardia events were identified in 27 patients (of 231 patients followed over 6 years) for a cumulative incidence of 12% and an annual risk of 2.8% per patient.[38] Atrial fibrillation (*n* = 13) and flutter (*n* = 15) were more common than atrioventricular nodal reentry tachycardia (*n* = 3). Importantly the onset of tachycardia was associated with RV failure. Failure to restore sinus rhythm was associated with poor outcome as 9 of 11 patients with sustained atrial fibrillation died compared with only 1 death in patients who

had restored sinus rhythm. In a more recent cohort of 239 patients with PH, (PAH = 157, chronic thromboembolic pulmonary hypertension, CTEPH = 82) the cumulative incidence over a 5-year period of observation was 25% (95% confidence interval of 14%, 35%).[39] The onset of atrial arrhythmia was associated with death, particularly in those in whom sinus rhythm could not be restored. The notion that atrial fibrillation is more than a marker of severe disease and that it directly contributes to mortality is supported by these studies. Owing to the diastolic dysfunction that characterizes the LV and RV in PAH, these patients are particularly susceptible to tachycardia due to an adverse influence of a reduction in ventricular filling time on LV and RV output. Similarly, they are likely to be adversely affected by the loss of atrial contribution to ventricular filling.

The management of supraventricular tachyarrhythmia in patients with PH has not been systematically evaluated. It is unclear if rate control is sufficient or not, however the case series cited earlier seem to support the notion that a return to sinus rhythm is associated with improved outcome. Antiarrhythmics and/or electrical cardioversion remain the preferred treatment in patients with acute RV decompensation. Careful consideration for the use of β-blocking agents and calcium channel blockers should be undertaken in this group of patients as both class of agents may directly impair RV contractility. In the case series reported patients were variably treated with medication, electrical cardioversion, and radiofrequency ablation.[38,39]

Reduce the Adverse Influence of the RV on LV Filling—Adverse Interdependence

A reduction in oxygen delivery in PAH may be mediated through two mechanisms. First, it may result from a decrease in LV filling directly as a result of a reduction in pulmonary blood flow and pulmonary venous return to the LV—a series effect. More recent attention however has focused on a parallel effect, specifically the compressive effect of an enlarged, pressurized RV on LV filling.[40,41] Second, a The resultant leftward displacement of the intraventricular (and intraatrial) septum will lead to a reduction in diastolic compliance and cause a reduction in LV filling (Fig. 3).[42] This effect was elegantly demonstrated in a recent study by Kasner et al.[43] In contrast to controls, or patients with impaired LV diastolic function, a temporary reduction in RV preload (by balloon occlusion of the inferior vena cava) in patients with PAH was associated with an improvement in LV end-diastolic volume and a reduction in left ventricular end-diastolic pressure (Fig. 4)—an improvement in LV diastolic compliance. Importantly this reduction in RV preload led to an improvement in cardiac output. This observation is important for two reasons. First, it illustrates the importance of diuresis in improving cardiac function in patients with PAH. Second, it illustrates the potential pitfalls in volume loading these patients—who may paradoxically have a reduction in LV filling with fluid administration. This study also illustrated the importance of tachycardia as the effect on LV filling was compounded during rapid atrial pacing. Although, the pericardium may augment the compressive effect of a dilated RV on LV filling,[44] in the chronic situation the pericardium likely becomes more compliant and RV wall tension likely plays a more significant role. This adverse ventricular interaction may be further enhanced through prolongation of RV contraction. Indeed an increase in RV wall tension is associated with a longer duration of RV ejection.[45] This prolongation of RV contraction causes RV contraction to continue beyond LV contraction leading to RV systolic encroachment upon LV filling.

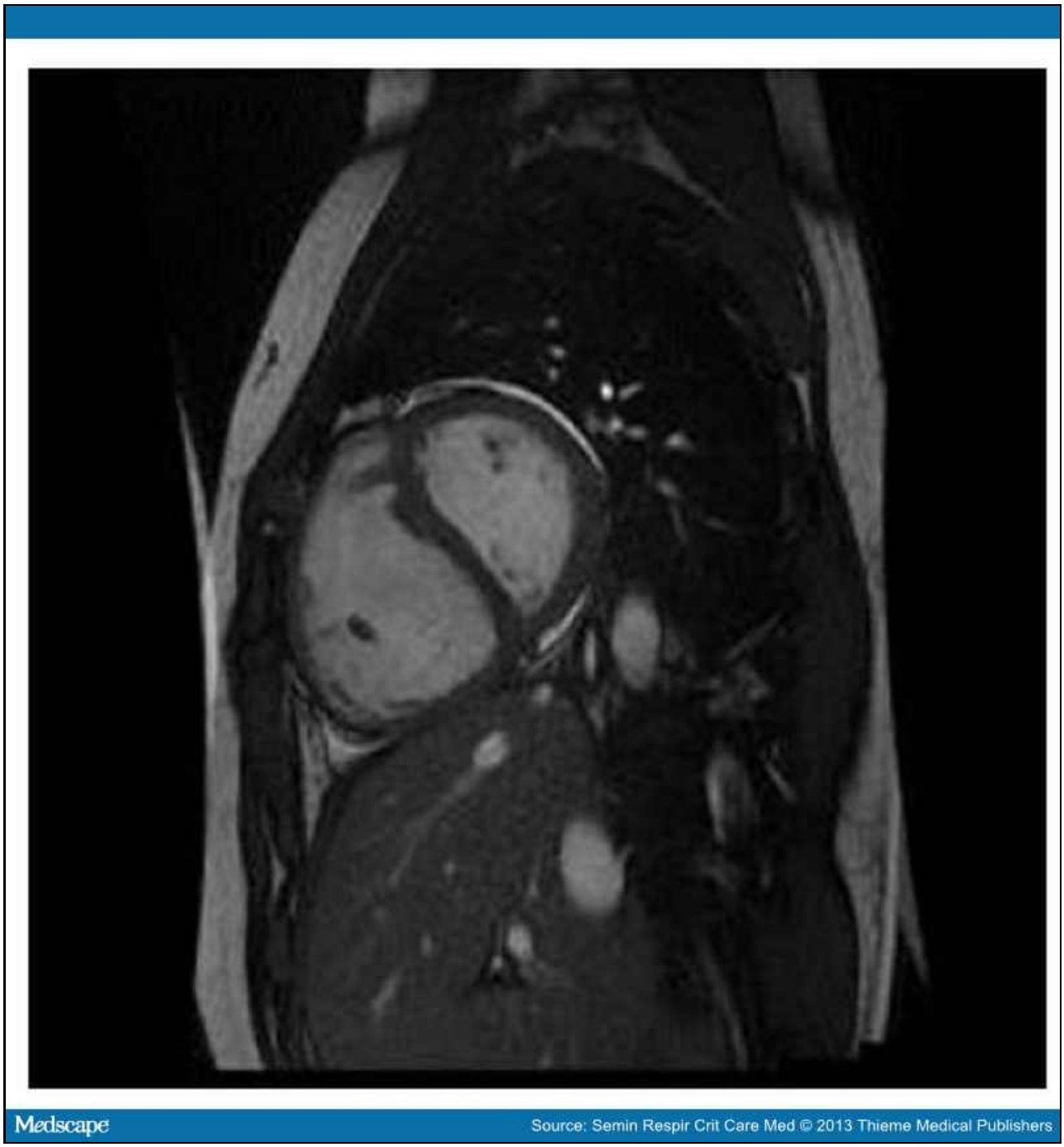

Figure 3.

Magnetic resonance image of a patient with severe idiopathic pulmonary hypertension. Leftward shift of the intraventricular septum in early left ventricular diastole is shown (arrow).

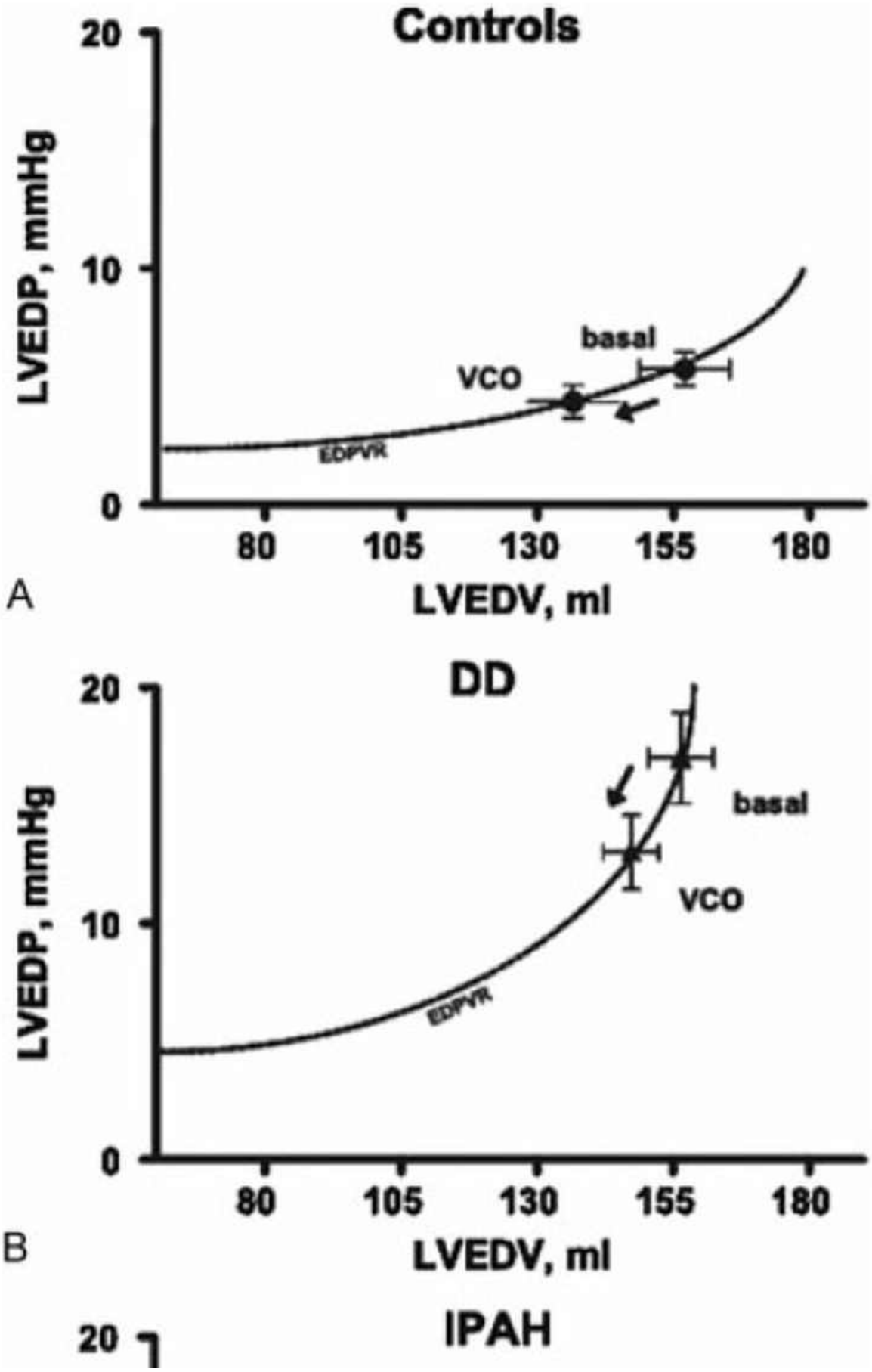
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Figure 4.

Changes in end-diastolic pressure volume relationship (EDPVR) indicated by left ventricular (LV) stiffness during preload reduction obtained by vena cava occlusion (VCO). (A) Control subjects show a regular EDPVR as indicated by a normal end-diastolic pressure and expected downshift to the left during preload reduction. (B) Patients with diastolic dysfunction (DD) show a steeper EDPVR curve than control subjects, indicating an increased LV stiffness. (C) Patients with idiopathic pulmonary hypertension (IPH) show a EDPVR pattern under basal conditions similar to the patients with DD, but during preload reduction and reducing the effect of external constraint they reveal an initial (first three to four beats) LV volume expansion and downshift to the right of EDPVR on the level observed by control subjects. LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume. Printed with permission from Kasner et al.[43]

This prolongation of RV ejection has stimulated interest in RV pacing. Theoretically if the RV is paced to facilitate ejection earlier it may allow for better mechanical coupling between the RV and LV and allow for improved LV filling. Indeed in an isolated heart, RV pacing was found to improve RV ejection, synchronize the time of RV and LV peak pressure, and reduce adverse diastolic influence of the RV on LV filling.[46] More recently dual chamber (RA-RV sequential pacing) led to an improvement in LV function in 14 CTEPH patients.[47] Whether RV pacing will play a role in chronic or decompensated RV failure in patients with PAH remains to be determined.

Patients with advanced PAH may also present with large pericardial effusions. Although, associated with a poor prognosis the hemodynamic relevance of these effusions as it relates to RV-LV influence is uncertain. Unfortunately, the echocardiographic features of tamponade are often lost, as the pressurized RV and right atrium (RA) do not collapse as they would in the normal setting of tamponade. Although it is tempting to drain these effusions, this should be undertaken cautiously.[48] Indeed in one series the drainage of the effusion was associated with high mortality.[49]

At present the mainstay of reducing adverse RV-LV diastolic influence has been on optimizing RV afterload and preload; a reduction in either or both will result in a reduction in wall tension. Strategies to reduce RV afterload are discussed below. RV preload may be reduced by diuresis or, in the setting of renal insufficiency, ultrafiltration. The use of venodilators is generally not recommended owing to potential adverse effects on systemic blood pressure. Atrial septostomy has several potential beneficial effects including: (1) a reduction in RV wall tension, (2) an increase in LV filling, (3) reduction in sympathetic hyperactivity, and (4) an increase in systemic oxygen delivery (the increase in blood flow offsetting the resultant reduction in arterial saturation).[50–52] In selected patients atrial septostomy has been shown to improve cardiac function and symptoms of RV failure, survival and has been used as a bridge to transplantation.[53,54] Of concern however, is the observation that venous saturation may not increase after septostomy (as it should if cardiac oxygen delivery is improved). Additionally, the optimum size of the septostomy has not been defined and progressive dilations are usually required.[55,56] A defect which is too large may produce significant arterial hypoxemia. All these factors make the procedure dangerous in unstable or hypoxemic patients.

Preserve Coronary Perfusion

With a progressive increase in RV volume and RV afterload, RV wall tension increases. This increase in wall tension may lead to a reduction in coronary blood flow.[57] Additionally, an increase in the heart rate and RV afterload (and presumably wall tension)[58] also leads to an increase in the myocardial oxygen consumption. The degree to which a mismatch in oxygen delivery and consumption contributes to worsening chronic RV function is uncertain. An early study in 23 patients correlated the presence of ischemia seen using RV myocardial scintigraphy with RV dysfunction. It is possible that acute increases in wall tension may lead to RV ischemia and hemodynamic collapse. More sustained regional ischemia may lead to focal fibrosis, particularly at the insertion sites of the RV free wall onto the interventricular septum.[59] In addition to reducing wall tension, it is important to consider that some of the pharmacological therapies may adversely affect coronary perfusion through a reduction in systemic blood pressure. Consequently, either avoiding these agents or mitigating their effects through the use of systemic vasoconstrictors is typically required. To avoid tachycardia, agents with predominate α-receptor effects (such as noradrenaline or phenylephrine) are recommended. Noradrenaline is generally the preferred agent as it also has some β-receptor effects and may also enhance RV contractility.[20,60,61] Concerns about adverse effects on PVR have not been validated when used at lower doses.[62] The use of vasopressin is attractive as it may augment the effects of exogenous vasopressors. However, caution needs to be applied as the effects on coronary perfusion and RV function have varied in experimental studies.[63–66]

The use of systemic vasopressors may also have an unintended advantage of reducing the adverse influence of RV dilation on LV filling. In an early experiment aortic banding in a model of acute PH led to an improvement in cardiac function independent to changes in coronary blood flow. The authors concluded that this was due to improved ventricular interaction. These observations were supported in a more recent study of aortic banding and also suggested a beneficial effect on chronic RV remodeling.[67]

Maintaining Cardiac Output

Systolic RV failure may require a strategy to directly augment contractility to stabilize blood pressure and cardiac output. Broadly the agents used are β-agonists, phosphodiesterase (PDE) inhibitors, and calcium channel sensitizers. The relative merits of different agents were nicely presented in a systematic review by Price et al.[61] However, no study of any agent has evaluated more relevant outcomes or conclusively demonstrated superiority of one agent over another. The β1-agonist dobutamine augments myocardial contractility and reduces PVR making it an attractive agent in RV failure.[61] However, it may also lead to a reduction in systemic vascular resistance and require the concomitant use of a systemic vasoconstrictor. The dose of dobutamine used is often limited by tachycardia. Consequently agents that are devoid of effects on heart rate such as PDE-3 inhibitors may be preferable in some patients. PDE-3 inhibitors may have direct inotropic effects by increasing levels of endogenous cyclic adenosine monophosphate and indirectly augment cardiac function by reducing the afterload.[20] Although, these agents received a high recommendation in the systematic review by Price et al, most of the referenced studies were completed in patients with PH secondary to LV failure, postventricular assist or cardiac transplant.[61] More recently PDE-5 inhibitors have been evaluated in the treatment of RV failure. In addition to their role as pulmonary vasodilators these agents may have a direct inotropic effect on the failing RV.[68,69] Despite potential advantages of these agents, systemic vasodilation is often dose limiting. Phosphodiestrase inhibitors may also require concomitant administration of a systemic vasoconstrictor.

Levosimendan, a calcium-sensitizing agent with positive inotropic and vasodilatory effects, holds promise for patients with PH and RV failure but it has not yet been thoroughly investigated in these patients. A recent study found that levosimendan was superior to dobutamine in the treatment of PH following cardiac surgery in children.[70] However, there was no control group and the relative improvement in cardiac index was minimal and of uncertain clinical relevance.

Oxygen and Ventilator Support

Adequate oxygenation should be maintained, thought patients with chronic pulmonary to systemic shunts may tolerate severe arterial hypoxemia. Anemia should be treated as it may contribute to an increase in cardiac demand. Furthermore, relative anemia in patients with chronic pulmonary to systemic shunts and hypoxemia may need to be treated to ensure adequate oxygen delivery to the systemic circulation.

For patients with refractory hypoxemia continuous positive airway pressure or noninvasive ventilation should be considered before intubation. If intubation and mechanical ventilation are deemed necessary, hypotension and loss of RV contractility must be prevented and the administration of catecholamines before anesthesia should be considered. Despite the lack of controlled clinical trials, etomidate and ketamine are the preferred drugs for induction of general anesthesia given their relatively beneficial hemodynamic profiles, pulmonary vasodilation, and little negative inotropic effects.[71,72] The potential adverse effects of positive end-expiratory pressure (PEEP) on RV afterload are well described. However, equally, atelectasis may have adverse effects on RV function. In a rat model of acute lung injury the development of atelectasis was associated with echocardiographic evidence of severe RV dilation.[73] Treatment of atelectasis through alveolar recruitment led to an improvement in RV function. Interestingly, the mortality in the atelectatic group of animals was 40%. There were no deaths in the recruited population. The development of atelectasis in patients may have the same deleterious effect on the decompensated RV. Therefore, in the presence of atelectasis judicious application of PEEP may be associated with an improvement in RV function to the extent that alveolar recruitment occurs and hypoxic pulmonary vasoconstriction in reduced. In general, however, airway pressures should be kept to a minimum while at the same time hypercapnia avoided because of its deleterious effects on pulmonary hemodynamics.

Reducing Right Ventricular Afterload

Similar to the LV, the failing RV is likely benefited through even minor changes in RV afterload. Reduction in RV afterload may lead to an improvement in cardiac function through a variety of mechanisms including: (1) a reduction in RV wall tension, (2) reduced myocardial oxygen consumption, (3) improved coronary macrovascular and microvascular perfusion, (4) lead to an increase in RV stroke volume, and (5) improve LV filling through a reduction in adverse RV-LV interaction. One of the most important interventions to reverse RV failure is to reduce RV afterload through the use pulmonary vasodilators or PAH-targeted therapies. The properties of an ideal pulmonary vasodilator are provided in . An ideal agent would have selectivity for pulmonary vasodilation and avoid systemic hypotension or dilation of pulmonary vessels that are not adequately ventilated to reduce effects on intrapulmonary shunt. In general this profile is afforded by inhaled medications such as nitric oxide, prostanoids, or phosphodiesterase inhibitors. At present no agent has demonstrated clinical superiority over another. Most of the trials relate to comparing the relative hemodynamic effects of one agent over another, often in postsurgical cardiac patients, PH secondary to LV heart failure, pulmonary embolism.[20,60,61] No studies have demonstrated superiority over another agent in patients with PAH. The authors approach is to first stabilize patients on a relatively selective pulmonary vasodilator given by inhalation and then add in a conventional pulmonary vasodilator. The choice of PAH-targeted therapies depends to some extent on previous treatment. However, in general parenteral intravenous prostacyclin derivatives (epoprostenol, treprostinil, iloprost) are the initial treatment of choice. It is worth emphasizing that intravenous epoprostenol remains the only PAH therapy that has been shown to improve survival within the confines of a randomized, controlled clinical trial.[74] The use of PDE-5 inhibitors in combination with nitric oxide (NO) is particularly attractive, but the additive effects are not always apparent. The limitations of systemic vasodilators include systemic hypotension, worsening of intrapulmonary shunt and in the case of prostanoids unwanted side effects such as flushing,

headache, nausea, and vomiting. In general the use of endothelin antagonists has not been evaluated in patients with acute RV decompensation. Indeed one study in isolated perfused RVs from a monocrotoline rat model of PH, suggests that these agents may have direct negative inotropic effects on the hypertrophied RV. It is unclear if this effect would offset the potential benefits in PVR in the setting of acute RV failure in humans.[75]

Table 2. Desired properties of pulmonary vasodilator

Property	Variable to monitor
Pulmonary selectivity	PVR/SVR ratio Systemic blood pressure Venous admixture (intrapulmonary shunt)
Half life	
Rapid onset of action	
Avoidance of tachycardia	Heart rate
Cost	Your budget

Abbreviations: PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

Lung Transplantation

Traditionally double lung transplantation (DLTx) or heart-lung transplantation (HLTx) represents the gold standard of treatment for patients with advanced disease. Bilateral sequential LTx remains the most common modality, however practice varies from center to center.[76] When appropriate, lung transplant referral should occur before the patient develops severe RV failure. In general patients should be counseled about lung transplant early in their diagnosis.[77] The authors routinely refer patients for lung transplant assessment when they are started on parenteral therapy and refer them for active listing when they have failed to achieve their therapeutic endpoints. Specifically those that continue to have the New York Heart Association (NYHA) class IV or class III symptoms with any other marker of poor prognosis. Recommendations for listing developed by the International Society of Heart Lung Transplantation include: (1) persistent NYHA class III or class IV on maximal medical therapy, (2) a low (< 350 m) or declining six-minute walk test, (3) failing therapy with intravenous epoprostenol, or equivalent, (4) a cardiac index of less than 2 L/min/m^2, or (5) a right atrial pressure > 15 mm Hg.[78] At present it is unclear if prognostic scoring systems such as those developed by the REVEAL registry investigators has sufficient fidelity to be used to guide clinicians in assessing the timing of LTx.[18,79] The timing of patients with Eisenmenger physiology is particularly challenging as these patients have prolonged survival in the face of often supersystemic pulmonary arterial pressures and severe hypoxemia.[80,81] Additionally, these patients more commonly require HLTx—an intervention associated with a longer waiting list.[76] The timing of transplantation to thwart the demise of patients for complications that may lead to sudden death requires clairvoyance. In general it is important to quickly identify patients with persistent evidence of RV failure in the presence of maximal medical treatment before they develop irreversible end organ injury. If appropriate these patients should be considered for extracorporeal/mechanical bridging to LTx. This is particularly relevant given the higher incidence of early death posttransplantation in patients with PAH compared with other lung diseases.[76] Circulatory support may provide an opportunity to stabilize patients, improve organ function, and increase the chances of survival.

Bridge to Transplantation

Over the past decade, extracorporeal life support (ECLS) has seen dramatic technological improvements; providing an opportunity to deal with refractory disease and RV failure. Ultimately it has provided patients with an opportunity to benefit from DLTx or HLTx who would have otherwise succumbed. This support has likely contributed to an improvement in the historical waiting list mortality rate (historically reported as high as 20–30%) with good long-term posttransplantation results.[82,83]

Indications

ECLS should be considered in PH patients in the setting of persistent RV failure despite optimal medical management. Of importance, bridge to transplant could achieve good long-term results after transplantation provided no additional organ failure occurred.[84–89] It is generally felt that mortality in transplant patients supported with ECLS is often related to the degree of organ dysfunction. Hence, bridge therapy should be initiated earlier in the course of RV heart failure before secondary organ injury. Parameters known to be associated with high ICU mortality in PAH patients requiring inotropic support include low systemic blood pressure, elevated creatinine, hyponatremia, high BNP, and increasing inotrope requirements.[30] These risk factors may serve to guide decision-making and ensure the appropriate timing for initiating ECLS.

Modes of Extracorporeal Life Support

ECLS as a bridge to DLTx has been first described for patients who presented a rapid deterioration in their chronic lung disease

while on the waiting list or during the lung transplant evaluation process. United Network for Organ Sharing (UNOS) reported that between 1987 and 2008, 51 patients (0.3% of all LTx) underwent ECLS as a bridge to transplantation with a 1 and 2 year survival of 50 and 45% as compared with 79 and 70%, respectively without pretransplantation support.[89] Since then, improvement of ECLS material and high selection of patients have improved these results.

For the reason that PAH patients on waiting list are dying of RV failure rather than lung failure, the ECLS configuration used as a bridge to LTx, needs to support the heart without compromising oxygenation. Hence, the pulmonary artery-left atrium (PA—LA, Novalung, Heilbronn, Germany) and venoarterial extracorporeal membrane oxygenator (VA-ECMO) have been used to bridge PH patients to transplantation.[84,87,89–95] Three main technological innovations have proven valuable for ECLS therapy over the last few years: (1) long-term use, low-resistance, and low-volume polymethylpentene oxygenator membrane, (2) heparin coated circuits, and (3) new centrifugal pumps. The Novalung is a newly designed oxygenator with very low resistance that can accommodate a flow of 0.5 to 4.5 mL/min. The pressure gradient is only 6 mm Hg at a flow of 1.5 L/min and the surface area is 1.3 m^2. When implanted between the PA and LA (PA-LA ECLS),[90,95,96] it creates a parallel circuit to the lungs, thereby unloading the RV and providing oxygenation and carbon dioxide removal through the newly established right to left extracardiac shunt (Fig. 5). This pumpless ECLS mode results in immediate hemodynamic stabilization of the patients in RV failure by reducing the RV filling pressure and restores LV filling (Figs. 6 and 7). The degree to which this mitigates the reported LV dysfunction after LTx in patients with advanced RV failure is a theoretical benefit that has not been evaluated. The implementation of these new oxygenators along with new centrifugal pumps, heparin coated circuits, and new cannulas have improved the long-term use of VA-ECMO, which is the second ECLS option for PH patients. Both options of support can currently be used for several weeks until RV recovery and transplant. In the authors' experience, long-term support waiting for transplant is possible provided the oxygenator is changed when needed (i.e., every 2–4 wk).

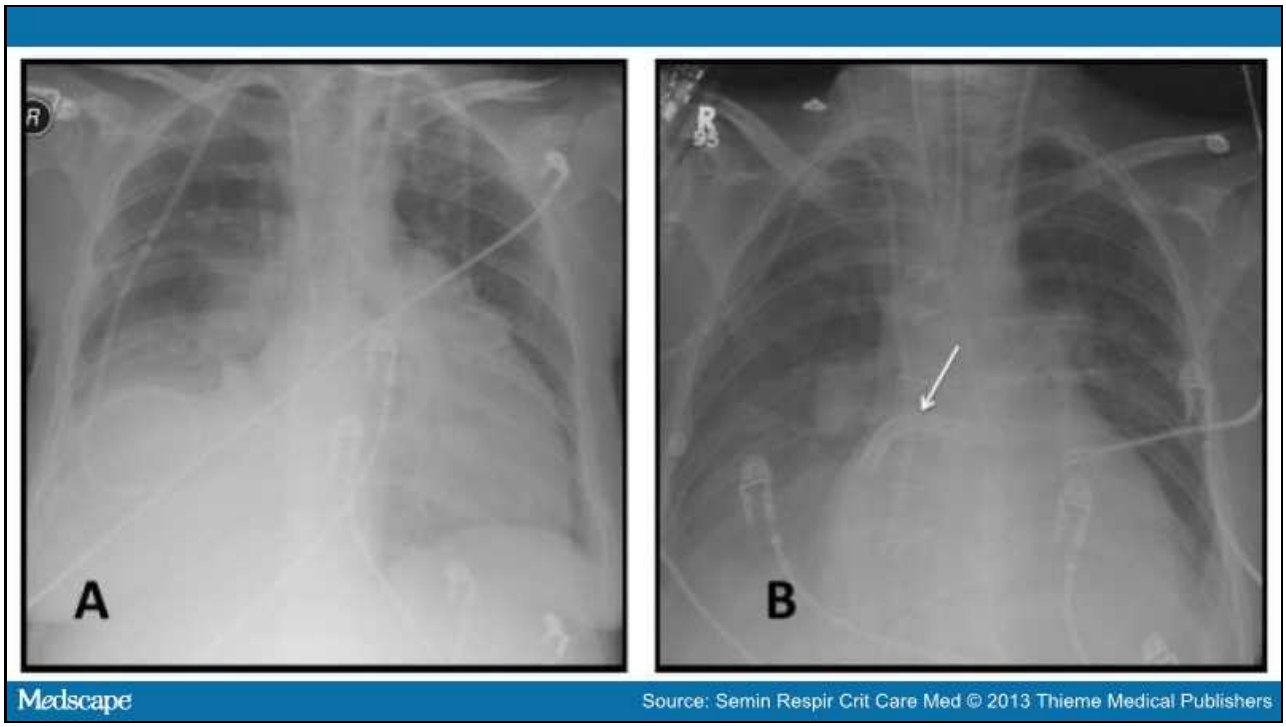

Figure 5.

Anteroposterior chest X-ray before (A) and after (B) implantation of a pumpless extracorporeal life support between the pulmonary artery and the left atrium in a pulmonary hypertension patient with right heart failure awaiting for double lung transplant. White arrows show the reduced right ventricle filling allowing recovery before transplant. Solid arrow points to the left atrial cannulation and the dashed arrow the pulmonary artery cannulation.

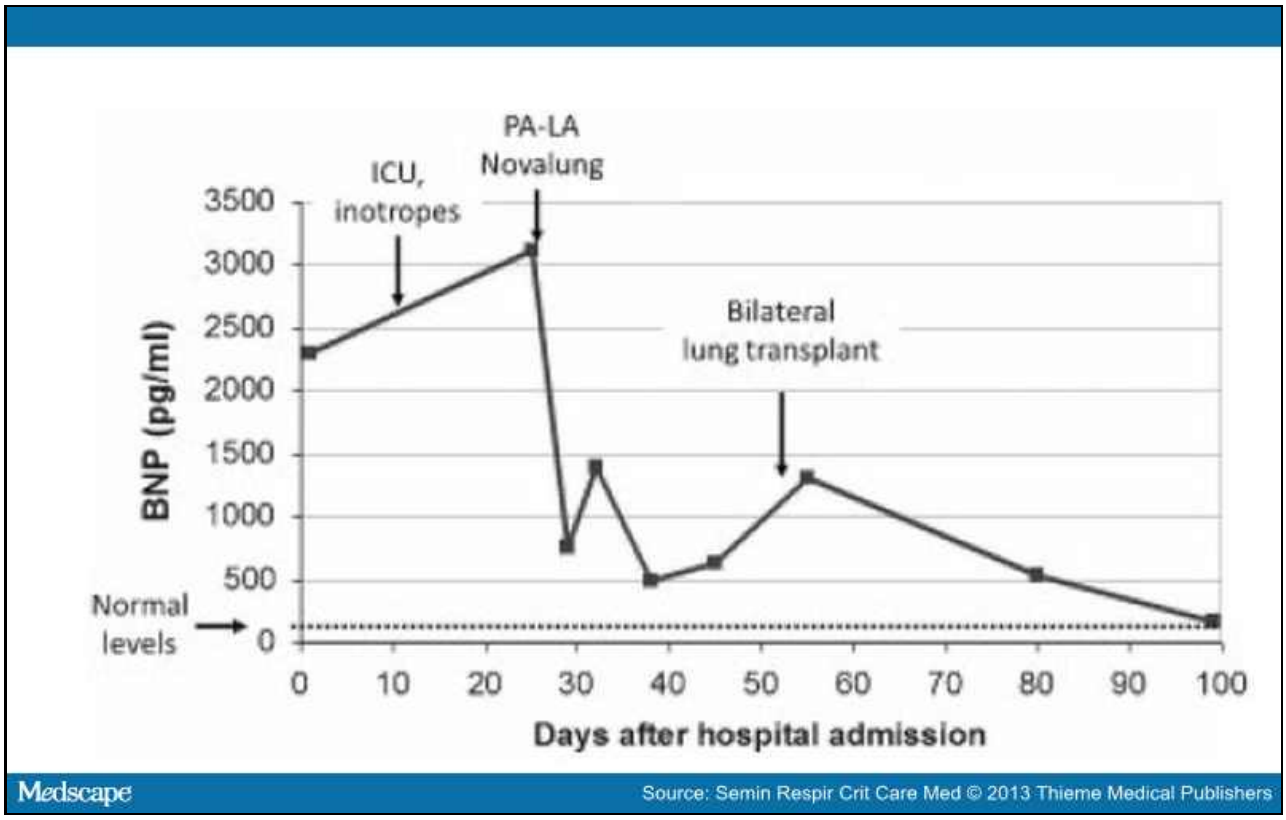

Figure 6.

Progression of brain natriuretic peptide (BNP) after hospital admission for right ventricular heart failure while waiting for double lung transplant. With placement on pulmonary artery-left atrium Novalung there was a significant and sustained reduction in serum BNP. The patient underwent transplantation 27 days later.

The main disadvantage of the PA-LA Novalung is that a sternotomy is required while VA-ECMO cannulas are inserted under local anesthesia. The central cannulation, however, offers the advantage of allowing patients to start ambulating once they are extubated. This is a major advantage compared with femoral cannulation and VA-ECMO, which confines patients in bed until the transplant even though they can be awake and spontaneously breathing.[94] Upper body cannulation through axillary and jugular vessels seems to be an interesting option for VA-ECMO when possible since it could allow conditioning before transplant. Strengths and weaknesses of these two bridge options are summarized in . PA-LA would be preferred for long predicted waiting time and pediatric patients with small peripheral vessels, whereas VA-ECMO would be for adult recipients with short predicted waiting time or emergency cases.

Table 3. Main characteristics of the two extracorporeal life support options for bridging pulmonary hypertension patients to transplant

Characteristics	VA-ECMO	PA-LA
Strengths	Local anesthesia Safe and fast Awake patients Low heparin dose Can be maintained after Tx	Pumpless Long term bridge Easy to change Allow mobilization and exercises
Weaknesses	Arterial complications No mobilization	General anesthesia Sternotomy needed Normal LV function needed
Improvements	Cannula on the upper limb to allow mobilization	
Indications	Predicted short waiting time Adult recipients Emergency cases	Pediatric or small recipients Long predicted waiting time (size, antibodies, etc)

Abbreviations: LV, left ventricle; PA-LA, pulmonary to left atrial Novalung; Tx, transplant; VA-ECMO, venoarterial extracorporeal membrane oxygenator.

Outcomes

Several centers have reported a success rate of 76 to 100% in bridging and successfully transplanting PH patients on ECLS.[84,86,87,89-95] In the era of modern ECLS, 1-year survivals after transplant in bridged PH patients have been calculated between 50 and 96% ( ). Hence, the authors assume that bridge therapy may lead to decreased mortality on waiting list without hampering the survival results of lung transplant.[85] However, the limitation of ECLS support is due to the deconditioning that the patients experienced during the prolonged immobilization. Hence, emphases have been placed on their ability to extubate and mobilize the patients while on ECLS. While physiotherapy is possible and promoted on PA-LA Novalung, upper body cannulation sites are increasingly being used to allow mobilization of the patients while on VA-ECMO.[97,98] Interestingly, weaning the patient from the ventilator while on ECLS avoids not only deconditioning but also decreases the rate of pneumonia, infectious complications, or skin breakdown/ulcers; in turn helping the patient reach transplant in better condition. As a result, awake patients on ECLS have been reported to have lower postoperative morbidity, faster postoperative recovery, and higher 1-year survival rate compared with nonawake patients (85.7 vs. 50%, respectively).[86,87,88,98] The duration of bridge on ECLS is another relevant cofactor for mortality and morbidity. In general, the shorter is the duration on ECLS, the better are the posttransplant outcomes.[85,89] However, for patients with advanced PAH, ECLS duration may not carry the same level of adverse impact if it allows for some restoration in RV function and improvements in distal organ function. Indeed, new generation ECLS are well tolerated and allow exercise while right ventricle recovers from failure. ECLS has been reported to have been used for up to 107 days as a bridge to transplantation[99] and in the authors' own center's experience they have supported a patient up to 174 days with a PA-LA Novalung with a good result after double lung transplant (Fig. 7). Long-term bridge is particularly useful in children, small recipients or patients with rarer blood types for whom the waiting time may be prolonged.

Table 4. Experience with bridge to transplantation in pulmonary hypertension patients

Study		n	PH (n)	Duration of ECLS	Mode of ECLS	Successful bridge (%)	30-d survival (%)	1-y survival (%)
Strueber et al	2009	4	4 (100%)	17	PA-LA	100	100	75
Olsson et al	2010	5	5 (100%)	21	VA-ECMO	80	100	–
Hämmäinen	2011	16	3 (18%)	16.8 ± 19.2	VA-ECMO	81	100	92
de Perrot	2011	6	6 (100%)	22 (1–69)	VA/PA-LA	100	83	50
Fuehner et al	2012	26	11 (42%)	11 (1–45)	VA-ECMO	77	–	80
Lang et al	2012	34	4 (11%)	5.5 (1–63)	VA/PA-LA/both	76	–	60
Hoopes et al	2013	31	5 (16%)	15 (2–28)	VA/PA-LA/central	–	–	93
Toyoda et al	2013	24	1 (4%)		VA-ECMO	77	–	96

Abbreviations: d, day; ECLS, extracorporeal life support; PA-LA, pulmonary to left atrial Novalung; VA-ECMO, venoarterial extracorporeal membrane oxygenator; y, year.

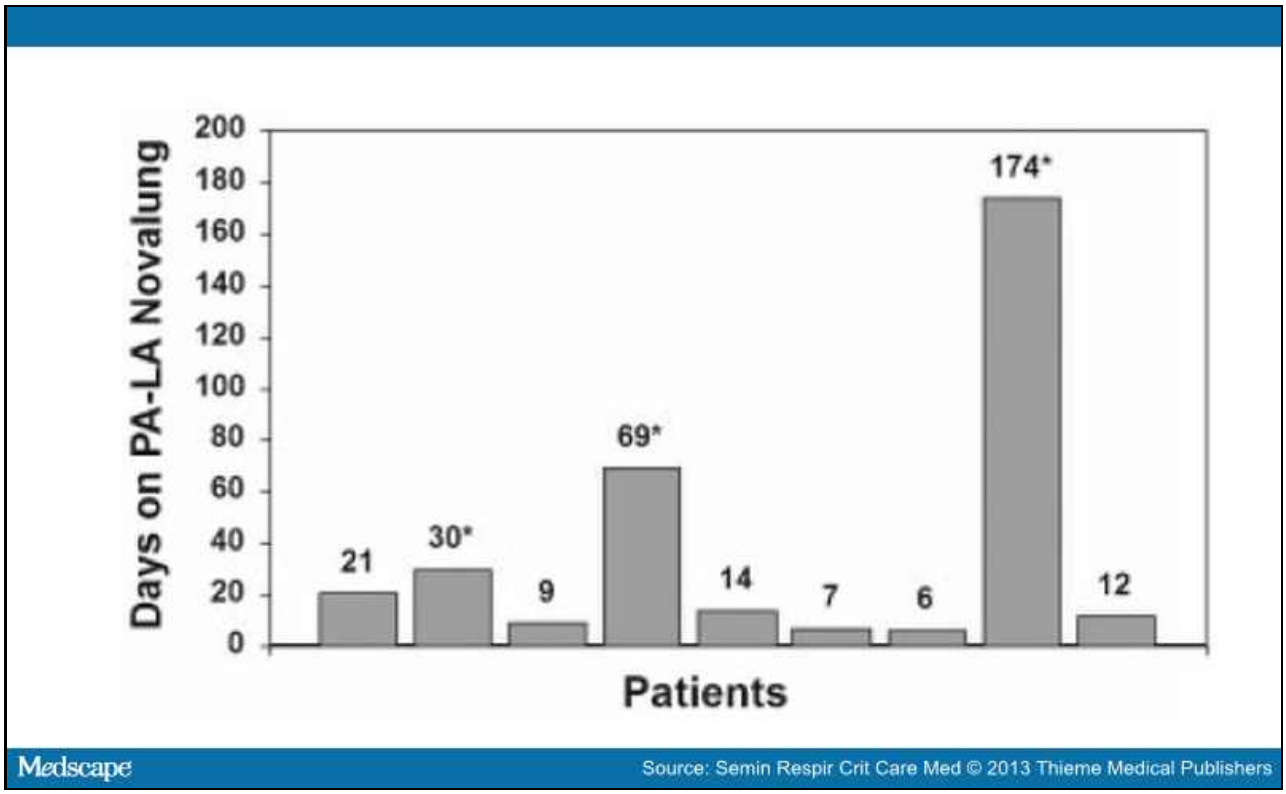

Figure 7.

Toronto general hospital experience with pulmonary artery-left atrium Novalung as a bridge to transplant. The time duration of support for the nine patients was between 2006 and 2010. *Pediatric patients.

Complications

The most common complications during ECLS include hemorrhage, infection at the cannulation site, renal failure, neurological complications, and peripheral vessels lesions. ECLS as a bridge to transplant is an effective tool to reduce mortality of PH patients on waiting list but remain a complex treatment carrying specific morbidity and mortality requiring high selection of patients.

Summary

Despite an increase in awareness of PAH patients continue to present with advanced disease. Additionally, in the face of an improvement in treatment options, many patients with PAH experience progressive RV failure or develop an acute complication that precipitates RV failure. Unfortunately, there are no studies that have systematically evaluated treatment strategies in patients with advanced RV failure. Recommendations and strategic approaches are often based upon case series that have focused on hemodynamic endpoints. There are no studies that have evaluated more relevant outcomes such as ICU or hospital survival. Therefore, the principles of treatment must be based upon physiological principles, often derived from experimental observations in animal models or small case series in humans. In treating unstable patients, it is critically important to recognize the importance of RV-LV interactions and the influence that modifications in RV preload and afterload have on RV performance and end organ function. Equally it is incumbent upon teams to recognize when medical treatments are not achieving their goals and consider extracorporeal support for those who are eligible for destination therapy such as LTx or HLTx. In patients with advanced PAH and RV failure a treat to recovery goal is usually not a realistic endpoint.

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Note

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