

# Pathophysiologic Principles in the Management of Severe PAH

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In the face of tremendous advances in our understanding of the pathophysiology and new treatment options, for many patients, pulmonary arterial hypertension (PAH) remains a progressive condition. The often-relentless reduction in the cross-sectional area of the pulmonary vasculature leads to progressive increase in right ventricular (RV) afterload. Although the right ventricle can adapt to an increase in afterload, progression of the pulmonary vasculopathy in PAH causes many patients to develop progressive RV failure.<sup>1</sup> Alternately, for those with other forms of pulmonary hypertension, worsening lung disease or cardiac disease may destabilize the RV function. Acute RV decompensation may be triggered by disorders that lead to either an acute increase in cardiac demand (such as sepsis, surgery, or pregnancy), or an increase in ventricular afterload (such as an interruption in medical therapy or pulmonary embolism), or destabilization of a compensated RV (such as arrhythmia or volume overload). The poor reserve of the RV, RV ischemia, and adverse RV influence on left ventricular filling may lead to a global reduction in oxygen delivery and multi-organ failure.<sup>2</sup> The goals of this article are to provide an approach to right heart failure in the context of an increase in its afterload. This article will focus on pathophysiologic principles on which to build an approach to medical therapies. Mechanical and surgical strategies will be the focus in the accompanying article by Dr de Perrot.

## CAUSES OF WORSENING RIGHT VENTRICULAR FAILURE

The identification of potentially reversible causes should be the first priority in evaluating a patient with right ventricular (RV) failure.<sup>3,4</sup> In a French cohort study of 46 patients with pulmonary arterial hypertension (PAH) admitted to a critical care unit for RV failure, 19 (41%) had an identifiable triggering factor.<sup>5</sup> These factors 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). The presence of an infection during hospitalization was the strongest predictor of death.

Arrhythmias are often a harbinger of worsening RV function. Patients appear to be more susceptible to atrial as opposed to ventricular arrhythmias. Two retrospective series provide us with some insight into the importance of this complication. In one cohort study, 31 supraventricular tachycardia (SVT) 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.<sup>6</sup> Atrial fibrillation (n=13) and flutter (n=15) were more common than atrioventricular (AV) nodal re-entry tachycardia (n=3). Importantly, the failure to restore sinus rhythm was associated with poor outcome. Nine of 11 patients with sustained atrial fibrillation died, compared to only 1 death in patients who had restored sinus rhythm. In a more recent cohort of 239 patients with pulmonary hypertension (PH) (PAH=157, chronic thromboembolic pulmonary hypertension [CTEPH]=82), the cumulative incidence over a 5-year period of observation was 25% (95% CI of 14%, 35%).<sup>7</sup> The onset of atrial arrhythmia was associated with death, particularly for those in whom sinus rhythm could not be restored. This may in part relate to the diastolic dysfunction that characterizes the left ventricle (LV) and RV in PAH.<sup>8,9</sup> As a result, 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 adversely affected by the loss of atrial contribution to ventricular filling.

It is unclear whether rate control is sufficient; however, case series seem to support the notion that a return to sinus rhythm is associated with improved outcome. Therefore, it would seem that an attempt to restore normal sinus rhythm should be made. Correction of electrolyte imbalance, careful magnesium administration (rapid bolus may lead to hypotension), antiarrhythmics, and/or electrical cardioversion remain the preferred treatments in patients with acute RV decompensation.<sup>3</sup> The use of beta-blocking agents and calcium channel blockers should be cautiously considered, as both classes of agents may directly impair RV contractility. In the case series reported to date, patients were treated with various modalities including antiarrhythmics, electrical cardioversion, and radiofrequency ablation.<sup>6,7</sup>

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

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underwent lung transplantation. Tachypnea ( $>20$  breaths/min), renal dysfunction ( $\text{GFR} < 45$  mL/min), hyponatremia (serum sodium  $< 136$  mEq/L), and severity of tricuspid regurgitation were associated with a poor outcome.<sup>10</sup> The outcome of patients who require intensive care unit (ICU) admission is worse, with a reported mortality ranging from 30% to 40% in 2 series.<sup>5,11</sup> Systemic hypotension, Acute Physiology and Chronic Health Evaluation score, preexisting treatment with a prostanoid, serum levels of creatinine, brain natriuretic peptide, and C-reactive protein were associated with poor ICU outcome.<sup>5,11</sup> Therefore, the management of these patients requires a committed team with expertise and access to mechanical circulatory support and transplantation.

## PATHOPHYSIOLOGY OF RV FAILURE

The RV is highly efficient and well adapted to eject into a high capacitance, low impedance, low resistance circuit that is able to accommodate large increases in blood flow with (relative to the systemic circulation) small changes in pressure. In the face of these differences, the RV and LV are mechanically interrelated by the shared interventricular septum and pericardium. Although the RV is highly efficient, it is ill adapted to sudden increases in afterload. As such, 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 progressive 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 LV with an increase in RV elastance and a reduction in diastolic compliance.<sup>12</sup> However, in the face of a progressive or sudden worsening in RV afterload, these compensatory mechanisms can be overwhelmed.<sup>2</sup> In addition to rate of progression in RV afterload, the differences in the ability of the RV to compensate for an increase in afterload likely relate further to several factors. These factors include the age of the

patient and 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.<sup>13–15</sup> Indeed, persistence of the fetal phenotype may impart the improved prognosis in patients with post-tricuspid valve septal cardiac defects (eg, ventricular septal defect or patent ductus arteriosus). The cause(s) of the increase in afterload, and in a related manner, the location of the pulmonary arterial occlusion (proximal vs distal) may also affect the ability of the RV to adapt chronically. For example, there may be differences in RV adaptation in the setting of proximal (pulmonary artery banding or pulmonic stenosis) as opposed to more distal pulmonary vascular occlusion (PAH).<sup>14</sup> Finally, the chronically dilated or volume overloaded RV may adapt differently,<sup>16</sup> and may be less capable of compensating for an increase in RV afterload.

Clinically, RV failure is 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 ascites. A drop in a reduced cardiac output (ie, cardiac index  $< 2.5$  L/min/m<sup>2</sup>) will eventually lead to an impairment of systemic oxygen delivery to metabolically active tissues. The development of systemic hypotension and renal insufficiency portend a worrisome prognosis.<sup>17</sup>

## MONITORING RV FUNCTION IN THE ICU

Although there is some rationale for the use of invasive pulmonary hemodynamic monitoring, it is unclear whether an approach guided by changes in pulmonary hemodynamics will lead to an improvement in outcome.<sup>3</sup> In addition to concerns around the development of arrhythmias during insertion, there are both practical and theoretic limitations to the use of pulmonary hemodynamics to guide treatment. In addition, the severity of PH cannot be reliably assessed by the degree of elevation in pulmonary pressures, as a failing ventricle will produce lower pressures. Furthermore, the reliance on pulmonary

vascular resistance (PVR) as a measure of disease severity or prognosis may also be problematic.<sup>2</sup> Although a high PVR has been associated with a worse outcome, a recent study emphasized that prognosis is more strongly correlated to RV function,<sup>18</sup> and that changes in PVR are not consistently related to changes in RV ejection fraction (RVEF). These investigators also illustrated that despite medical therapy for PAH, RV dysfunction could progress with a decrease in PVR. Although this was a study in the outpatient setting, there is no reason to believe that these findings would not apply to the acute care setting and illustrates the need to incorporate modalities to directly evaluate RV function.

Although there are several echocardiographic measures of RV performance that have correlated with prognosis, it is unclear whether these can be used in the acute setting. Tricuspid annular displacement during RV systole (TAPSE), Tei index, and eccentricity index have all been correlated to RV function and prognosis in the outpatient setting.<sup>19–21</sup> However, these measurements have not been validated in the critical care setting.<sup>2</sup> Additionally, obtaining accurate images in the ICU setting may be limited. The same limitations in using estimates of pulmonary arterial pressures via direct hemodynamic methods apply to echocardiographic methods to estimate pulmonary artery pressures as a marker of RV function and as a treatment goal in the acute care setting. Although MRI is considered the gold standard of evaluating RV function, it is not practical in unstable patients.

Conventional estimates of the adequacy of tissue oxygenation such as mixed venous or central venous oxygen saturation, arterial lactate, and markers of end-organ function might provide some value in following the effects of various interventions. Although markers of end-organ function may not provide sufficient fidelity to gauge acute effects related to changes in treatment or pharmacological interventions, they likely do signal clinically relevant changes that occur over time. Similarly, levels of brain natriuretic peptide may not provide sufficient reliability 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 and be an undesired side effect of medical therapy.

## GENERAL PRINCIPLES OF MANAGING RV FAILURE

In addition to the reduction in RV output, an increase in RV wall tension will result in imbalance in myocardial oxygen consumption and delivery. An increase in wall tension and RV size may also worsen RV-LV interdependence and contribute to the spiraling decrease in cardiac function. The main objective of treatment 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. The focus of treatment should be to search for and address reversible causes, reduce RV wall tension, restore RV output, and reduce the adverse influence of a dilated/pressurized RV on LV filling.<sup>3</sup> These goals are obtained through the traditional approach in optimizing cardiac function through manipulating preload, afterload, and contractility without undue side effects from treatment—specifically tachycardia and systemic hypotension.

The general principles of ICU care also apply and include prophylaxis to prevent hospital-acquired infections, venous thromboembolism, and stress ulcers.<sup>3</sup> Although patients presenting with progressive RV failure generally require diuresis, 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.<sup>22,23</sup> In general, in established PH with demonstrable RV overload, fluid administration may worsen the severity of RV failure.

## REDUCE ADVERSE RV-LV INTERDEPENDENCE: THE IMPORTANCE OF RV PRELOAD

A reduction in oxygen delivery in PAH is mediated through 2 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.<sup>3</sup> Second, cardiac output may be reduced via leftward displacement of the intraventricular (and intra-atrial) septum. This septal displacement in turn will lead to a reduction in diastolic compliance and cause a reduction in LV filling.<sup>24</sup> This effect was elegantly demonstrated by Kasner and colleagues,<sup>8</sup> where 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 LV end-diastolic pressure (LVEDP). Importantly, this reduction in RV preload led to an improvement in cardiac output. Their observations are important for several reasons. First, they illustrate the importance of diuresis in improving cardiac function in patients with PAH. Second, their observations illustrate the potential pitfalls in volume loading these patients. Specifically, these patients may paradoxically have a reduction in LV filling with fluid administration. Finally, their study also illustrated the concerns about the effect of tachycardia, as the adverse LV filling was compounded during rapid atrial pacing.

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.<sup>25</sup> This prolongation causes RV contraction to continue beyond LV contraction, with resultant RV systolic encroachment upon LV filling. This prolongation of RV ejection has stimulated interest in RV pacing. In theory, 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. Recently dual-chamber (RA-RV) sequential pacing led to an improvement in LV function in 14 CTEPH patients.<sup>26</sup> Whether RV pacing will play a role in chronic or decompensated RV failure in patients with PAH remains to be determined.

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. RV preload may be reduced by diuresis or, in the setting of renal insufficiency, ultrafiltration. The use of venodilators is generally not recommended due to potential adverse effects on systemic blood pressure. Although 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,<sup>27,28</sup> the procedure is dangerous in unstable or hypoxicemic patients.

## REDUCING RV AFTERLOAD

The failing RV is likely benefited by 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) an increase in RV stroke volume, and 5) improved LV filling through a reduction in RV septal shift.<sup>2</sup> One of the most important interventions to reverse RV failure is to reduce RV afterload using pulmonary vasodilators or PAH-targeted therapies. An ideal pulmonary vasodilator would have selectivity for pulmonary circulation, avoid systemic hypotension, and not worsen intrapulmonary shunt. In general, this profile is afforded by inhaled medications such as nitric oxide (NO), prostanooids, or phosphodiesterase (PDE) type 5 or PDE3 inhibitors. The limitations of systemic vasodilators include systemic hypotension and potentially worsening of intrapulmonary shunt. Currently 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 failure or pulmonary embolism.<sup>3,29,30</sup> The use of PDE5 inhibitors in combination with NO is particularly attractive, but the additive effects are not consistently seen in a given patient. Once the patient is stabilized, the choice of definitive PAH-targeted therapies depends to some extent on previous treatment. However, in general, parenteral intravenous prosta-



cyclin derivatives (epoprostenol, treprostinil, iloprost) are the initial treatments of choice. It is worth emphasizing that intravenous epoprostenol remains the only PAH therapy that has been shown to improve survival (in outpatients) within the confines of a randomized, controlled clinical trial.<sup>31</sup>

### RESTORING CONTRACTILITY

Contractility may be improved through direct (inotropes) and indirect (maintaining systemic blood pressure and coronary perfusion) strategies. Indeed, a reduction in RV preload as discussed may lead to a reduction in wall tension with an attendant increase in regional myocardial perfusion and reduction in myocardial oxygen consumption. Both effects, in theory, should lead to an increase in contractility.

To directly increase contractility, inotropic agents may be used. These include  $\beta$  agonists, PDE inhibitors, and calcium channel sensitizers; however, as nicely summarized by Price et al, no study of any agent has evaluated more relevant outcomes or conclusively demonstrated superiority of one agent over another.<sup>30</sup> The  $\beta$ 1-agonist dobutamine augments myocardial contractility and reduces PVR, making it an attractive agent in RV failure.<sup>30</sup> However, it may also lead to a reduction in systemic vascular resistance (SVR) and require the concomitant use of a systemic vasoconstrictor. The use of dobutamine is also limited by the development of tachycardia. Agents that have less of an effect on heart rate such as PDE5I inhibitors may be preferable in some patients. PDE3 inhibitors may have direct inotropic effects by increasing levels of endogenous cAMP and indirectly augment cardiac function by reducing afterload.<sup>3</sup> More recently, PDE5 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.<sup>32,33</sup> However, due to systemic effects, PDE 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.

### 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.<sup>34</sup> Additionally, an increase in heart rate and RV afterload (and presumably wall tension)<sup>35</sup> also leads to an increase in myocardial oxygen consumption. The degree to which a mismatch in oxygen delivery and consumption contributes to worsening chronic RV function is uncertain. 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.<sup>36</sup> 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.<sup>2</sup> Consequently, either avoiding these agents or mitigating their effects using systemic vasoconstrictors is typically required. To avoid tachycardia, agents with predominate alpha-receptor effects (such as

noradrenaline or phenylephrine) are recommended. Noradrenaline is generally the preferred agent, as it also has some beta-receptor effects and may enhance RV contractility.<sup>3,29,30</sup> The use of vasopressin is attractive as it may augment the effects of exogenous vasopressors. However, caution must be applied as the effects on coronary perfusion and RV function have varied in experimental studies.

### OXYGEN AND MECHANICAL VENTILATORY SUPPORT

Adequate oxygenation should be maintained, though 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 prior to anesthesia should

Table 1: Principles of Managing Patients with PH and Acute RV Failure (Granton J, Mercier O, De Perrot M. Management of severe pulmonary arterial hypertension. *Semin Respir Crit Care Med*. 2013;34:700-713. © Georg Thieme Verlag KG, reproduced with permission.)

Variable	Treatment	Goal/effect
<b>Identify reversible causes for acute RV decompensation</b>	Depends on cause (eg, atrial arrhythmia, infection, pulmonary embolism)	Reduce RV demand
<b>Reduce RV afterload</b>	Pulmonary vasodilators (NO, prostanoids, PDE inhibitors) Control PaCO <sub>2</sub> Reduce alveolar hypoxemia/atelectasis Extracorporeal support Lung transplantation	Reduce RV wall tension Reduce RV-LV influence Improve RV output
<b>Reduce RV preload</b>	Diuretics Ultrafiltration Atrial septostomy	Reduce RV wall tension Reduce RV-LV influence
<b>Improve RV contractility</b>	Inotropic agents (PDE inhibition, $\beta$ -1 agonists, levosimendan)	Improve RV output
<b>Avoid tachycardia</b>	Caution re use of $\beta$ agonists	Preserve LV and RV diastolic filling
<b>Maintain systemic blood pressure</b>	Alpha receptor agonists Vasopressin	Maintain coronary perfusion Reduce RV-LV influence

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 minimal negative inotropic effects.<sup>37,38</sup> 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.<sup>39</sup> Treatment of atelectasis through alveolar recruitment led to an improvement in RV function. Whether the development of atelectasis in PAH patients will have the same deleterious effect on the decompensated RV needs to be established. It is clear that high levels of PEEP can have adverse effects on RV function. To the extent that alveolar recruitment occurs and hypoxic pulmonary vasoconstriction is reduced, the cautious application of PEEP may be associated with an improvement in RV function. 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.

## CONCLUSION

The approach outlined in Table 1 is limited by the absence of properly conducted clinical trials and is admittedly based on physiological principles, often derived from experimental observations in animal models or small case series in humans. In treating unstable patients, it is imperative to recognize the need to identify potentially reversible causes of RV failure and ensure that the systemic blood pressure is preserved. Thereafter, efforts can focus on optimizing RV preload and afterload. There should be consideration regarding the importance of RV-LV interactions and the influence that modifications in RV preload and afterload have on RV performance, LV filling, and end-organ function. Equally, it is incumbent on 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 lung or heart-lung transplantation. Sadly, in patients with advanced PAH where a treat-to-recovery goal is not a realistic endpoint and transplantation is not an option, palliative intent of treatments should be the focus of discussions with the patient and family.

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