Therapeutic strategies for pulmonary hypertension

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Introduction

There has been a significant advance in the understanding and treatment options for patients with pulmonary arterial hypertension. Anesthetists may be faced with management of these patients when they are being considered for elective or urgent surgery. They may also be faced with a patient who presents with severe de novo or with progressive / refractory disease in the intensive care setting. It is important to understand the broader concept of pulmonary hypertension and importance that an increase in right ventricular afterload has on a marginalized right ventricle.
**Diagnosis and classification**

**Diagnosis**

Pulmonary hypertension is defined as a mean pulmonary arterial pressure greater than 25 mm/Hg at rest. With advancing age both resting and exercise systolic pulmonary arterial pressures increase. Both systolic blood pressure and peak pulmonary systolic pressure with age show age-associated increases in both systolic blood pressure and right ventricular systolic pressure\(^1\). This is relevant as peak systolic pressures measured using echocardiography is the measure that typically causes concern\(^2\). Additionally many older patients may have underlying diastolic dysfunction. Patients with reduced left ventricular compliance can experience dramatic increases in pulmonary pressure with even trivial levels of exercise\(^3\). The relevance of this observation is relevant in situations where volume overload and increase in cardiac output or heart rate may have a dramatic influence on left atrial pressure and, in turn pulmonary pressures.

**Classification**

The classification of PH is divided into 5 groups as outlined in the most recent World Health Organization (WHO) Guidelines\(^4\). The WHO classification divides etiologies into five groups. Group 1 is perhaps the more familiar pulmonary arterial hypertension, divided into idiopathic pulmonary hypertension or familial pulmonary hypertension. This important group also includes pulmonary arterial hypertension related to connective tissue diseases, HIV, portal hypertension, congenital heart disease and other drugs such as anorexigens or illicit use of methamphetamines.

WHO group 2 encompasses pulmonary hypertension resulting from left heart disease, including both systolic and diastolic dysfunction (impaired ejection fraction with normal contractility) and patients with valvular heart disease. WHO category, group 3, includes patients with respiratory disease or hypoxemia; for example, chronic obstructive pulmonary disease, interstitial lung disease, or sleep apnea. In the ICU setting, this category certainly applies to patients who may have worsened pulmonary vascular tone due to hypercapnia or regional alveolar hypoxemia as might occur with atelectasis. WHO group 4 is the important category of chronic thromboembolism. This is one of the few conditions that actually can be cured surgically by pulmonary thromboendarterectomy. Finally, WHO group 5 is a miscellaneous category, with a variety of causes, including Gaucher’s disease and sarcoidosis.

**Relevant scenarios**
In the ICU setting, many patients arriving for surgery may present with known pulmonary hypertension. These patients may be admitted with a new diagnosis and present with right heart failure or represent progression of refractory disease. Patients with known PH may also be admitted post-operatively from either urgent or elective surgery. Surprisingly, there is very little information in the literature about the outcome of this patients or risk stratification prior to surgery\textsuperscript{5-7}. However, the outcome of these patients is, in general poor. In study of 28 consecutive patients with PH it even patients with mild disease could had significant postoperative morbidity and mortality\textsuperscript{8}. In this small series, there were two deaths in the perioperative phase, as well as about a 30% rate of perioperative morbidity related to right heart failure in patients who were previously well compensated. In their analysis, Emergency procedures, major surgery and longer operative time were associated with increased risk for a poor outcome.

Pregnant women constitute another group that may be encountered. These patients require close observation during pregnancy and peripartum. They constitute one of the most challenging patients to manage and often require intensification of their pulmonary hypertension therapy including the empiric use of parenteral prostanoids. ICU admission for more close observation to facilitate early intervention should be considered. However mortality rates in pregnant patients may be improving. When a cohort from 1997–2007 compared with historical published data (between 1978 and 1996) from about 38% to about 25%. Importantly, patients frequently encounter difficulty not at the time of delivery, but within about three weeks of delivery\textsuperscript{9}. This late morbidity and mortality likely relates to the marginalized right ventricle’s inability to accommodate the massive fluid shifts that occur after pregnancy. This latter point emphasizes the need to closely monitor patients beyond what would be considered a traditionally safe period of observation.

Right ventricular failure

The outcome of patients with pulmonary hypertension relates to the ability of the right ventricle (RV) to accommodate to an increase in afterload. Therefore an understanding of an approach to RV failure may be of value and help place the treatment options available to anaesthetists in perspective.

Pathophysiology of right ventricular failure

The RV is embryologically, morphologically, and functionally distinct from the left LV. The RV and LV are inter-related by the shared interventricular septum. RV-LV interaction, under normal conditions, allows the ejection of the RV to be augmented by left ventricular ejection. Although highly efficient, the naïve RV poorly adapts to sudden increases in afterload. Additionally RV
dilation may adversely affect LV filling\textsuperscript{10}.

Factors triggering right ventricular failure in patients with pulmonary hypertension

RV failure is frequently encountered as manifestation of disease progression despite therapy. In some cases factors causing or aggravating RV failure can be identified;

- infections,
- anemia,
- trauma,
- surgery, pregnancy,
- non-compliance with vasodilator or diuretic therapy
- pulmonary embolism
- arrhythmias

Management of RV failure in patients with pulmonary arterial hypertension

The initial focus of care should center upon addressing any potential reversible case of acute RV decompensation and a strategy to improve RV function\textsuperscript{11}. The principles of care focus upon

- Reduce RV-LV adverse interaction,
- Improve contractility
- Reduce RV afterload
- Maintenance of systemic pressure (to preserve coronary perfusion)
- Avoid tachycardia

Reducing RV afterload

It is important to understand that factors that govern RV afterload include the conventional notion of pulmonary vascular resistance, but also elastance and left atrial pressure\textsuperscript{12}. In the setting of an elevated transpulmonary gradient and normal left atrial pressures a pulmonary vasodilator may afford a reduction in RV afterload. The ideal pulmonary vasodilator would have a rapid onset of action, short half-life and selectivity for the pulmonary circulation. Unfortunately most pulmonary vasodilators do not have these features.

Pulmonary vasodilators

- Phosphodiesterase inhibitors
- Endothelin inhibitors
- Prostanoids
• Nitric oxide

Goals in management

Evaluation of cardiac function as well as end-organ function is critical in managing patients with RV failure (table 1). Measurements of renal, liver, and neurological function will provide some information about the adequacy of cardiac function and tissue perfusion. Echocardiography may be useful in the acute setting, however the asymmetrical shape of the RV challenges the reproducibly of assessing RV contractility or volume. Other echocardiographic measures including tricuspid annular plane excursion (TAPSE) or the TEI index have been shown to be potentially valuable measures in following patients with PAH, however their role in acute management have not been validated.

For patients with severe PH and RV failure the measurement of right atrial (RA) pressure, left atrial pressure, cardiac output and mixed-venous oxygen saturation (SvO₂) may assist care of patients in shock. Measurement of pulmonary vascular resistance is a composite index of pulmonary pressure and cardiac output and may be useful to follow. However PVR may not fully reflect right ventricular afterload.

Ultimately the effects of a treatment strategy should be guided by the adequacy of tissue oxygenation. Tissue oxygenation may be estimated by measurements such as SvO₂ or central venous oxygen saturations (ScvO₂). Plasma lactate levels should be monitored closely as elevated and/or increasing levels may signal progressive RV failure. The use of brain natriuretic peptide (BNP) measurements to guide care may be of value to document trends in the adequacy of cardiac function overtime, but may not provide sufficient real-time information to inform decisions about treatment in an unstable patient.
Table 1: Monitoring of the critically ill patient with severe pulmonary arterial hypertension.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Modality</th>
<th>Treatment goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal function</td>
<td>Urinary catheter</td>
<td>Maintain kidney function and diuresis. In general a net negative fluid balance is required.</td>
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<tr>
<td></td>
<td>Serum creatinine</td>
<td></td>
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<tr>
<td>Liver function</td>
<td>AST, ALT, bilirubin</td>
<td>Reduce hepatic congestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintain hepatic perfusion</td>
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<tr>
<td>Cardiac function</td>
<td>Central venous line (central venous pressure, ScvO₂)</td>
<td>Improvement in cardiac function demonstrated by an increase in cardiac output with improvement (reduction) in right atrial pressures</td>
</tr>
<tr>
<td></td>
<td>Pulmonary arterial catheter (RA pressure, cardiac index, PAPm, PVR, SvO₂)</td>
<td>ScvO₂ &gt;70%</td>
</tr>
<tr>
<td></td>
<td>Echocardiography</td>
<td>SvO₂ &gt;65%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improve LV filling</td>
</tr>
<tr>
<td>Tissue perfusion/oxygenation</td>
<td>Lactate</td>
<td>&lt; 2.0 mmol / L</td>
</tr>
<tr>
<td>Neurohormonal markers</td>
<td>Brain Natriuretic Peptides (BNP or NT-proBNP)</td>
<td>Reduction in BNP levels</td>
</tr>
<tr>
<td>Myocardial perfusion</td>
<td>Systemic blood pressure (non-invasive or invasive)</td>
<td>Ensure adequate systemic diastolic pressure (&gt;60 mmHg)</td>
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<td></td>
<td>ECG</td>
<td>Avoid/treat tachycardia/tachyarrhythmia</td>
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<tr>
<td></td>
<td>Troponin</td>
<td>Optimize myocardial perfusion (negative troponin)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AST, aspartate aminotransferase; ALT, alanine aminotransferase; RA, right atrial; PAPm, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; ScvO₂, central venous oxygen saturation; SvO₂, mixed venous oxygen saturation; LV, left ventricle; BNP, brain natriuretic peptide, NT-proBNP, N-terminal fragment of brain natriuretic peptide; ECG, electrocardiogram