Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Intensive care management of pulmonary hypertension

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Abstract:

Pulmonary hypertension (PH) in the Intensive Care Unit (ICU) may be due to preexisting pulmonary vascular lung disease, liver disease, or cardiac diseases. PH also may be caused by critical illnesses, such as acute respiratory distress syndrome (ARDS), acute left ventricular dysfunction and pulmonary embolism, or may occur after cardiac or thoracic surgery.

Regardless of the underlying cause of PH, the final common pathway for hemodynamic deterioration and death is RV failure, which is the most challenging aspect of patient management. Therapy is thus aimed at acutely relieving RV overload by decreasing PVR and reversing RV failure with pulmonary vasodilators and inotropes.

Key words:

Hemodynamics, intensive care unit, pulmonary hypertension, Saudi association for pulmonary hypertension guidelines

Pulmonary hypertension (PH) in the intensive care unit (ICU) may be due to preexisting pulmonary vascular lung disease, liver disease, or cardiac diseases. PH also may be caused by critical illnesses, such as acute respiratory distress syndrome (ARDS), acute left ventricular dysfunction and pulmonary embolism, or may occur after cardiac or thoracic surgery.

Idiopathic pulmonary arterial hypertension (IPAH) is the result of increased vasoconstriction, pulmonary vascular remodeling, and *in situ* thrombosis triggered by endothelial dysfunction, smooth muscle proliferation, and neointimal formation in the precapillary arteries and arterioles.[1-3] In acute lung injury, both hypoxemia and the accumulation of intravascular fibrin and cellular debris contribute to subsequent vascular obliteration and PH. The consequence of these aberrant cellular and molecular pathways is an increase in pulmonary vascular resistance (PVR) and impedance of flow, causing right ventricular (RV) strain that impairs filling and leading to RV volume and pressure overload. The RV then dilates and eventually hypertrophy develops, encroaching on the left ventricle and decreasing preload, cardiac output, and coronary perfusion. Increased RV wall stress results in RV ischemia, which lead to RV dysfunction and portends a poor prognosis.[4]

Right Ventricular Dysfunction in Pulmonary Hypertension

Compared with the left ventricle, the RV demonstrates a heightened sensitivity to changes in afterload. RV stroke volume decreases proportionately to acute increases in afterload.[5] RV systolic dysfunction, severe tricuspid regurgitation, arrhythmias, and left ventricular dysfunction caused by ventricular interdependence may contribute to low cardiac output and hypotension in patients with PH. Ventricular interdependence refers to the concept that the size, shape, and compliance of one ventricle may affect the size, shape, and pressure–volume relationship of the other ventricle. In the presence of RV volume or pressure overload, the interventricular septum shifts toward the left and limits left ventricular filling and output. This has direct implications for the management of patients with PH and acute RV failure.

In fact, the challenge is to find the optimal preload to avoid the detrimental effects of ventricular interdependence.[6] Another consequence of RV failure in the setting of PH is the opening of the foramen ovale and development of right to left shunting that can cause or aggravate hypoxemia. Neurohormonal activation is important in acute and chronic right-sided failure. Atrial and B-type natriuretic peptide levels recently have been described to be elevated in patients with RV

failure and PH.[7] These markers appear to be important in the pathogenesis of the disease. Atrial and B-type natriuretic peptides are cardiac peptides that not only promote diuresis, but also inhibit pulmonary vasoconstriction.

Diagnostic Tools in the Intensive Care Unit

Laboratory evaluation is undertaken to identify reversible causes of PH. In the ICU, however, many laboratory derangements result from critical illness itself.

Electrocardiography (ECG) is an insensitive measure of RV hypertrophy, but the findings of right axis deviation, R/S wave >1 in V1 with R wave >0.5 mV, and P pulmonale are >90% specific.[8] ECG changes reflecting RV abnormalities are significant predictors of mortality in patients with IPAH.[9]

Although these ECG findings have not been used for prognosis in the ICU, they provide evidence of advanced disease that may be difficult to manage in critically ill patients.

Plain chest radiography is of limited utility in diagnosing PH in the ICU, but may help define an underlying cause. Typical findings of RV hypertrophy, right atrial enlargement, and obscuring of the aortopulmonary window by enlarged pulmonary arteries are less obvious on portable radiographs. Nonetheless, diffuse severe pulmonary parenchymal abnormalities may suggest an underlying cause of PH. Computerized tomographic angiography, ventilation-perfusion scanning, or pulmonary angiography may identify thromboembolic disease as the cause of PH.[10]

Echocardiography is useful for diagnosing and determining the degree and significance of PH.[10] Echocardiography can estimate right atrial and pulmonary arterial pressures (PAP), evaluate the degree of RV dysfunction, and reveal potential causes of PH such as left ventricular systolic or diastolic dysfunction, mitral stenosis or regurgitation, and certain intra-cardiac shunts. Although images may be suboptimal in critically ill patients because of limitations of patient positioning, interference by dressings, or positive pressure ventilation, a transthoracic echocardiogram should be obtained as a screening test.[10] Echocardiographic signs of significant PH include RV dilation and hypertrophy, septal bowing into the left ventricle during late systole to early diastole (D-shaped left ventricle), RV hypokinesis, tricuspid regurgitation, right atrial enlargement, and a dilated inferior vena cava.[11-13] Demonstration of septal dyskinesia and RV enlargement indicate RV systolic and diastolic overload, respectively.[12,13]

Right heart or pulmonary artery (PA) catheterization is the gold standard for the diagnosis of PH.[11,14] In patients with significant PAH, the most useful information is obtained in the cardiac catheterization laboratory. Precise analysis of mixed venous oxygen saturations during insertion and passage of the PA catheter through the cardiac chambers can allow diagnosis of intra-cardiac shunts. A pulmonary artery wedge pressure (PAWP) <15 mmHg helps in ruling out left ventricular and pulmonary venous diseases.[11] Observation of real-time mean PAP (mPAP), cardiac output, and PVR allows immediate evaluation of response to vasodilator therapy. Although the definition of a substantial response to therapy remains controversial, the most recent definition requires a reduction in mPAP of at least 10 mmHg to <40 mmHg with an increased or unchanged cardiac output.[15] Because increased pulmonary arterial blood flow can elevate mPAP, documentation of the response to therapy also should include the change in PVR. Regardless of the parameters used, the presence of vasoreactivity may suggest a better prognosis and ultimately can help determine medical therapy.[16]

Despite current controversies regarding the utility of PA catheters in the ICU, hemodynamic data are valuable in the care of critically ill patients with PH. In this setting, technical and interpretive limitations must be recognized. Severe tricuspid regurgitation and elevated PAP often make placing a PA catheter challenging, and may necessitate the use of fluoroscopy. Accurate determination of cardiac output by thermodilution may be limited in patients with tricuspid regurgitation or low cardiac output.[17] The Fick method may be more accurate, but requires determination of oxygen consumption, which is challenging in critically ill patients. Complications of PA catheterization are particularly dangerous in patients with PH and RV strain. Tachyarrhythmias have potentially life-threatening consequences of decreased stroke volume due to shortened filling time, or deterioration into fatal arrhythmias. Obtaining a PAWP also may be difficult in patients with markedly elevated pulmonary pressures.

Recommendations

1. Echocardiography should be used as the screening tool to detect PH in critically ill patients (class of recommendation I; level of evidence C).
2. Echocardiography may provide additional information about the causes of PH and evaluate the RV function (class of recommendation I; level of evidence B).
3. Right hear (PA) catheterization should be performed to confirm the diagnosis before commencing therapy (class of recommendation I; level of evidence C).

Management of Pulmonary Hypertension in the Intensive Care Unit

When managing a critically ill patient with PH in the ICU, primary considerations include:

1. The diagnosis and treatment of specific causes of PH
2. The application of PAH-specific therapies only when appropriate
3. The determination of the degree of RV failure and its appropriate therapy.

Patients with decompensated PH often require an aggressive combination of therapies for RV failure, including pulmonary vasodilators and inotropes. In patients with pulmonary venous hypertension, optimization of left-sided heart failure and valvular disease management is the most important facet of therapy. In patients with PH secondary to various causes of parenchymal lung disease and/or hypoxemia, primary therapy consists of treating the underlying cause. Patients with PH resulting from critical illness or chronic lung disease are less likely to suffer from significant underlying pulmonary vascular disease,[18] and their treatment should address the primary cause of their hemodynamic deterioration, such as sepsis or left ventricular

dysfunction. These patients usually do not require treatment with pulmonary vasodilators.

Aggressive fluid balance management is critical in patients with decompensated PH and RV failure. Hypovolemia and hypervolemia can lead to suboptimal preload and decreased cardiac output. In the hemodynamically unstable patient, initiation of inotropic therapy may be necessary.[19]

Effects of Mechanical Ventilation

In patients with PH and respiratory failure, mechanical ventilation may have untoward hemodynamic effects. Increases in lung volume and decreases in functional residual capacity can increase PVR and RV afterload.[19] However, in patients with preexisting or impending RV failure, lung hyperinflation and either inadequate or excessive positive end-expiratory pressure can fatally reduce cardiac output.[19-21] Data suggest that the optimal ventilator management of patients with PH may be with low tidal volumes and relatively low positive end-expiratory pressure. This strategy of low tidal volume ventilation is similar to the strategy used to ventilate patients with ARDS, but care should be taken to avoid permissive hypercapnia, which may have untoward hemodynamic effects.[22]

Oxygen

Oxygen inhalation has been shown to reduce PA pressure and improve cardiac output in patients with PH, regardless of the underlying cause.[23] In addition, hypoxic pulmonary vasoconstriction may contribute to PH in critically ill patients.[24] Thus, supplemental oxygen should not be overlooked as a key component of PH therapy in the ICU.

Pharmacologic Therapy of Pulmonary Hypertension

Hemodynamic goals in patients with RV failure due to PH are to reduce PVR, augment cardiac output, and resolve systemic hypotension, while avoiding tachyarrhythmias. Most traditional vasopressors and inotropes are suboptimal in reducing PVR. Only a few small human studies address hemodynamic support in patients with PAH, RV failure, and hypotension, and most of the common vasopressors and inotropes have not been studied.

Vasopressors and inotropes

The use of vasopressors and inotropes in patients with PH must therefore be guided by knowledge of their effects on PVR and cardiac output, and must be individualized based on patient response. In many cases, combination therapy is required.

Dobutamine

Dobutamine is an inotrope that acts primarily through β1-adrenergic receptors to augment myocardial contractility and reduce left ventricular afterload.[25] When combined with inhaled nitric oxide in both animal and human studies of acute and chronic PH, dobutamine improved cardiac index, decreased PVR indices, and significantly increased PaO_2/FIO_2.[26] These studies suggest that dobutamine doses in both acute and chronic PH should be maintained at <5 mcg/kg/min, and should be combined with pulmonary vasodilators such as inhaled nitric oxide when possible. However, dobutamine may cause systemic hypotension in some patients because of its β peripheral-adrenergic effects and may necessitate the use of norepinephrine or a peripheral vasoconstrictor. Therefore, dobutamine should be titrated in individual patients.

Norepinephrine

Norepinephrine stimulates α1 and β1-adrenergic receptors. When used in animal and human studies of both acute and chronic PH, it has been shown to increase mPAP and PVR.[27,28] Unlike dobutamine, norepinephrine has vasoconstrictive effects that are much more pronounced than the chronotropic and inotropic effects.[28] Although norepinephrine may be useful in hypotensive patients and cause less tachycardia, dobutamine remains a superior choice in the setting of PH and RV failure.

Dopamine

Dopamine is an adrenergic and dopaminergic agonist that increases blood pressure and cardiac output. The augmented cardiac output comes at the price of significant tachycardia that may decrease left ventricular preload and worsen demand ischemia.[29]

Isoproterenol

Isoproterenol is primarily a β1 and β2-adrenergic agonist that has historically been used to treat PH during surgery. Because it is a stronger chronotropic agent than dobutamine, the use of isoproterenol is associated with significant tachyarrhythmias. Although it improves cardiac output and PVR,[28] the utility of isoproterenol in animal models of acute PH has been limited by the induction of arrhythmias and the lack of effect on PAP.[30]

Epinephrine

Although commonly used to improve cardiac output and increase systemic vascular resistance in hypotensive patients in the ICU, epinephrine, a potent α- and β-adrenergic agent, has not been studied in the setting of PH.

Pulmonary vasodilators

Pulmonary vasodilators can be classified into two main categories: Those that increase production of cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP), such as nitric oxide and prostanoids, respectively; and those that decrease the breakdown of cGMP, such as sildenafil,[31] and of cAMP such as milrinone.

Nitric oxide

Nitric oxide is a potent vasodilator that, when inhaled, dilates pulmonary vasculature in ventilated lung units, thereby improving oxygenation, reversing hypoxic pulmonary vasoconstriction, and reducing PAP. Nitric oxide is quickly inactivated by reaction with hemoglobin in the pulmonary capillaries, and has no systemic vasodilatory effects. Inhaled nitric oxide has been studied in PH of various etiologies.[32,33] Although ARDS patients without sepsis initially improve oxygenation with inhaled nitric oxide, there is no evidence that outcomes are improved.[34,35]

Abrupt withdrawal of nitric oxide has been associated with rebound PH and hemodynamic collapse in up to 48% of patients evaluated.[35,36] In spite of its limitations, inhaled nitric

oxide is a useful agent to treat PH in the ICU, particularly in combination with other agents, such as dobutamine or milrinone.

Prostaglandins

Recent studies have demonstrated the efficacy of both inhaled and intravenous prostacyclin in managing PH.[37-39] In a retrospective study of 33 adult ICU patients with hypoxemia and PH from cardiac and noncardiac causes, inhaled prostacyclin improved mPAP and hypoxemia.[40] Other studies and case reports have demonstrated the utility of inhaled prostacyclin and of the prostacyclin analog, iloprost, in reducing PAP and improving cardiac output,[41-43] although prospective studies in critically ill patients with PH are lacking.

In patients with PAH and RV failure, chronic therapy with intravenous epoprostenol may be lifesaving. Epoprostenol has an elimination half-life of 3-6 min and is typically started at a dose of 1-2 ng/kg/min, titrated upward at a rate of 0.5-1.0 ng/kg/min at intervals of 15-30 min or more. An increase in cardiac output with a decrease in PAP and PVR is considered a favorable response. The use of epoprostenol to reduce PA pressures acutely is limited by dose dependent systemic side-effects,[43] particularly systemic hypotension. In conscious patients, headache, nausea, vomiting, and diarrhea also may limit rapid titration of epoprostenol.

Milrinone

Milrinone is a selective phosphodiesterase-3 inhibitor with inotropic and vasodilatory effects. In animal models of both acute and chronic PH, milrinone significantly reduced PVR and improved RV function.[44,45] In combination with inhaled nitric oxide, milrinone produces selective and additive pulmonary vasodilatation in pediatric patients after repair of congenital heart defects,[46] and after cardiac surgery in animal studies.[43]

Milrinone may have some utility in the treatment of hemodynamic instability in patients with PH, although systemic hypotension often limits its use. Further studies are needed to verify the effects of milrinone in patients with PH.

Sildenafil

Sildenafil is a specific phosphodiesterase-5 inhibitor with acute and chronic hemodynamic effects in patients with PH.[47-50]

However, there are only case reports or small case series describing its use in critically ill patients. A retrospective case review of eight adults with PH after mitral valve repair or placement of a left ventricular assist device showed that sildenafil significantly reduced mPAP and reduced PVR with only a minimal drop in mean arterial pressure, thus facilitating weaning of inhaled and intravenous pulmonary vasodilators.[50]

In stable patients, sildenafil alone or in combination with inhaled nitric oxide or epoprostenol reduces mPAP and PVR and increases cardiac output.[51-53] In patients with IPAH, sildenafil also can significantly improve cardiac output.[49] Furthermore, limited human and animal data suggest that sildenafil may augment and maintain the effects of inhaled nitric oxide[47,54,55] and iloprost[53] and minimize rebound PH after withdrawal of these agents.[56,57]

The hemodynamic effects of sildenafil start within 15 min of administration and last up to several hours, although peak hemodynamic effects are seen within 30-60 min. The relatively rapid onset of action, its diminution during 3-4 h, and the accompanying systemic hypotension suggest caution in critically ill patients. Sildenafil is contraindicated in patients receiving nitrates because of the potential for severe systemic hypotension.

Diuretics

Diuretics have long been conventional therapy for PH, whether caused by pulmonary vascular disease or left ventricular failure. The goal of diuretic use is to decrease volume load on the distended, failing right ventricle in advanced PH without compromising preload. Optimization of diuresis in this setting is complex and should be adjusted according to hemodynamic response.

Recommendations

1. Critically unstable patients with decompensated PH often require an aggressive combination of therapies (class of recommendation I; level of evidence C).
2. The treatment should be directed towards the specific causes of PH (class of recommendation I; level of evidence C).
3. The determination of the presence and the degree of RV failure should direct the line of therapy (class of recommendation I; level of evidence C).
4. The use of vasopressors and inotropes in PH patients in the ICU must be guided by knowledge of the effect of each drug on PVR and cardiac output, and must be individualized based on patient response (class of recommendation I; level of evidence C).
5. The application of PAH-specific therapies should be carefully applied only when appropriate (class of recommendation I; level of evidence C).

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