Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Perioperative management in patients with pulmonary hypertension

Adriano R. Tonelli, Omar A. Minai

Department of Pulmonary Medicine, Respiratory Institute, Cleveland Clinic, Ohio, USA

Address for correspondence:
Dr. Omar A. Minai, MD, Associate Professor of Medicine, Respiratory Institute, Cleveland Clinic, Ohio, 9500 Euclid Avenue A-90, Cleveland, Ohio, 44195, USA.
E-mail: minaio@ccf.org

Abstract:

Patients with pulmonary hypertension (PH) are being encountered more commonly in the perioperative period and this trend is likely to increase as improvements in the recognition, management, and treatment of the disease continue to occur. Management of these patients is challenging due to their tenuous hemodynamic status. Recent advances in the understanding of the patho-physiology, risk factors, monitoring, and treatment of the disease provide an opportunity to reduce the morbidity and mortality associated with PH in the peri-operative period. Management of these patients requires a multi-disciplinary approach and meticulous care that is best provided in centers with vast experience in PH.

In this review, we provide a detailed discussion about oerioperative strategies in PH patients, and give evidence-based recommendations, when applicable.

Key words:

Heart failure, perioperative management, pulmonary hypertension, surgery, Saudi association for pulmonary hypertension guidelines

Patients with pulmonary hypertension (PH) are being encountered more commonly in the perioperative period and this trend is likely to increase as improvements in the recognition, management, and treatment of the disease continue to occur. Management of these patients is challenging due to their tenuous hemodynamic status. Recent advances in the understanding of the pathophysiology, risk factors, monitoring, and treatment of the disease provide an opportunity to reduce the morbidity and mortality associated with PH in the perioperative period. Management of these patients requires a multi-disciplinary approach and meticulous care that is best provided in centers with vast experience in PH.[1] Current management is aimed at minimizing risk factors, optimizing hemodynamics (right ventricular [RV] preload, afterload, and contractility), and aggressively treating complications.[1,2]

The number of patients with PH has increased because of increased awareness, better diagnostic techniques, and longer survival with the development of more effective treatment options.[3-5] Thus, more patients with PH are likely to require elective or emergency surgery. Notably, surgeries in PH patients carry higher morbidity and mortality.[1,6] In fact, PH represents one of the most important risk factors for complications during the perioperative or peripartum period.[7-12]

In spite of this increased risk, little information exists on the appropriate risk assessment and management of PH (including disease-specific therapies) in the perioperative period.[1] Controlled trials are lacking and most recommendations are based on case series or expert opinion.[13] In this review, we will summarize the scope of the problem and available evidence, as well as propose recommendations regarding the management of PH in the perioperative period.

Definition

Pulmonary hypertension is a disease characterized by an increase in pulmonary pressures caused by different etiologies that can lead to RV failure and death.[14] The 4th World Symposium on PH defined the presence of this condition when the mean pulmonary artery pressure (mPAP) is ≥25 mm Hg during right heart catheterization (RHC).[15,16]

In order to make the diagnosis of PH a high level of suspicion is of outmost importance. The Registry to Evaluate Early and Long-term pulmonary arterial hypertension (PAH) Disease Management found that 21% of PH patients experienced a diagnostic delay of >2 years. This delay in PH diagnosis predominantly occurred in younger patients and those who had concomitant

respiratory diseases, less severe RV dysfunction, or covered <250 m during the 6-min walk testing.[17]

Need for Surgery in Pulmonary Hypertension Patients

As it occurs in the general population, PH patients may require a variety of cardiac or noncardiac surgeries that are associated with a broad range of inherent morbidity and mortality risks. In addition, female patients with PH may become pregnant and opt for delivery. Although PH patients have traditionally been counseled against having elective surgeries or becoming pregnant, it is not uncommon, in recent years, to evaluate and manage PH patients before, during, and after surgical interventions.

There are other surgical interventions that are specifically indicated for certain groups of PH patients such as thromboendarterectomy (for individuals with chronic thromboembolic PH) or lung transplantation (for those patients with advanced PH nonresponsive to PH-targeted therapies).

Pathophysiologic Considerations

Normal resting mPAP is 14 ± 3 mm Hg with the upper limit of normal of 20.6 mm Hg.[15] The normal pulmonary vascular resistance (PVR) (0.8 ± 0.4 Wood units) is 80-90% lower than the resistance observed in the systemic circulation. In PH, the chronic elevation of the pulmonary pressures leads to progressive dilation and hypertrophy of the RV that generates higher wall stress and limits the myocardial perfusion in diastole, increasing the risk of RV ischemia and failure in the presence of systemic hypotension.[18]

In PH, the RV does not appropriately tolerate acute increases in afterload, as a consequence the RV dilates and the stroke volume decreases due to its limited ability to increase preload or contractility.[18,19] RV dilation can lead to a paradoxical shift of the interventricular septum toward the left ventricle (LV), compromising LV filling and reducing systemic cardiac output and coronary perfusion pressure due to ventricular interdependence. The elevated venous pressure, coupled with low systemic perfusion pressure can markedly reduce the blood supply to vital organs (kidney, liver, gastrointestinal tract, brain, etc.) leading to multiple organ system failure.[20] Patients with PH can also develop acute tricuspid regurgitation with further reduction in RV output and LV preload. In addition, the elevated RV end-diastolic pressure associated with RV failure may open a patent foramen ovale leading to right-to-left shunt and deterioration of the underlying hypoxemia. These events could in turn worsen RV myocardial ischemia and right heart failure.[18,21]

Factors that impair RV contractility, RV preload, or RV afterload can precipitate right-sided circulatory failure during the perioperative or peripartum period. RV contractility can be affected by ischemia or medications used during surgery. RV preload can be reduced by arrhythmias, positive intrathoracic pressure during mechanical ventilation, and excessive use of diuretics or fluid restriction. Increases in RV afterload may be precipitated by sympathetic stimulation (e.g., pain and endotracheal intubation), hypoxemia,

hypercapnia, hypothermia, acidemia, or high airway pressures in mechanically ventilated patients.[21-26] PH can also be aggravated by the occurrence of thromboembolism, carbon dioxide or fat embolism, use of protamine, or extracorporeal circulation.[27]

Marked cardiopulmonary changes occur during pregnancy and puerperium. During pregnancy the intravascular volume and cardiac output increase by approximately 50%. Cardiac output may increase even further during labor and the immediate postpartum period,[28,29] meanwhile the return to baseline values may take up to 6 months after delivery.[29] These large hemodynamic changes in PH patients are poorly tolerated, since they have a fixed resistance of the pulmonary vasculature with limited ability to compensate. Increases in heart rate and circulatory volume can lead to RV failure, especially when associated with hypoxemia, hypercapnia, and acidemia.[29,30] In addition, an increase in venous return following delivery (uterine contraction and relief of the inferior vena cava compression) as well as pulmonary embolism can worsen PH during pregnancy and the postpartum period.

Pulmonary Hypertension in Noncardiac Surgery

Pulmonary hypertension is a risk factor for worse outcomes in noncardiac surgery predominantly in the early postoperative period.[1,31,32] However, the guidelines on perioperative cardiovascular evaluation for noncardiac surgery from the American College of Cardiology and American Heart Association (2007) do not include PH in the risk stratification of these patients. These guidelines emphasize that most experts agree that PH poses an increased risk for noncardiac surgery; however, no major study has been performed to prove this concept.[33] We summarized the studies on PH in noncardiac surgery, as shown in Table 1.[9-12,34]

It is important to mention that the results presented in this table are applied to PH patients that underwent surgeries in referral centers. It is unclear if similar outcomes will be observed in centers with less experience in the management of this disease.

Kaw et al. described that PH patients undergoing noncardiac surgery were more likely to develop heart failure, hemodynamic instability, sepsis and respiratory failure when compared with patients without PH on RHC. Furthermore, the authors noted that PH patients needed longer mechanical ventilatory support, intensive care unit (ICU) stay, and had more 30-day hospital readmissions.[10] A recent international prospective survey found that the risk factors for major complications in noncardiac nonobstetric surgery in patients with PAH were an elevated right atrial pressure (>7 mm Hg), a 6-min distance walked <399 m, the perioperative use of vasopressors and the need for emergency surgery.[35]

Factors reported to increase the operative risk in PH patients are summarized in Table 2. High-risk surgery is defined as a procedure with significant perioperative systemic inflammatory response, rapid blood loss, risk of venous air, CO_2, fat or cement emboli, loss of pulmonary vasculature, or exposure to factors that can acutely increase PVR.[20] At present, no study was able to determine whether the anesthetic approach (regional versus general), type of anesthetic used and

Table 1: Studies of outcomes of noncardiac and nonobstetric surgery in patients with PH

Author, year (Reference)	Type of study and timeframe	n	n° procedure	Predominant type of PH disease	PH diagnosed by	NYHA functional class %	Advanced PH therapies %	Type of surgery %	Anesthesia %	Perioperative morbidity* %	Mortality %
Ramakrishna et al., 2005[9]	Retrospective 1991-2003	145	145	PAH	Echo	I/II: 73 III/IV: 27	14	Major: 79	100 general	42	7
Minai et al., 2006[12]	Retrospective 1996-2002	21	28	PAH	RHC	I/II: 38 III/IV: 62	76	Major 86	79 general	19	18
Lai et al., 2007[11]	Retrospective, case-control 1999-2004	62	62	PVH	Echo	N/A	0	Major: 65	58 general	24	9.7
Price et al., 2010[34]	Retrospective 2000-2007	28	28	PAH	RHC	I/II: 75 III/IV: 25	57	Major: 57	50 general	29	7
Kaw et al., 2011[11]	Retrospective 2002-2006	96†	96	Mixed PH	RHC	N/A	N/A	Major: 100	100 general	26	1

*Perioperative morbidity was defined differently depending on the study, †Patients with PH were 96, out of 173 individuals included in the study, #Patients had a combination of pulmonary arterial and venous hypertension. Echo = Echocardiography, N/A = Not available, NYHA = New York Heart Association, PAH = Pulmonary arterial hypertension, PH = Pulmonary hypertension, PVH = Pulmonary venous hypertension, RHC = Right heart catheterization

treatment with advanced PH therapies have an impact in the perioperative morbidity or mortality.

Pulmonary Hypertension in Cardiac Surgery

Pulmonary hypertension is a recognized risk factor for morbidity and mortality in cardiac surgery.[1,36] Among 2,149 patients that underwent coronary artery bypass grafting, PH was an independent predictor for postoperative mortality.[7] Similarly, PH was an independent risk factor for mortality in patients that underwent heart surgery in the EuroSCORE study.[37] Other studies have also shown that a mPAP ≥25 or >30 mm Hg is a useful predictor of perioperative morbidity, mortality, and ICU length of stay in patients undergoing cardiac surgery.[38,39] Similarly, the risk of mitral valve replacement is increased in patients with PH, especially when the pulmonary pressures are above systemic levels.[40,41] Even though the early mortality is high, the long-term results are comparable to patients without PH.[41] PH has also been found to be a strong and independent predictor of mortality in severe aortic stenosis.[42-44] In fact, aortic valve replacement in PH patients is associated with higher mortality; nevertheless, it is associated with a marked survival benefit when compared to conservative management, since the latter has a dismal prognosis.[42,45,46] Interestingly, persistent moderate or severe PH after aortic valve replacement is associated with reduced long-term survival.[43]

A lower mean systemic-to-pulmonary artery pressure (PAP) ratio after anesthesia induction predicts hemodynamic complications after surgery.[1,47] A favorable response to inhaled nitric oxide (iNO) may identify patients at low risk for perioperative complications. Those PH patients with a ratio of pulmonary over systemic vascular resistance (on ~100% oxygen and iNO) <0.33, or a decrease of 20% when compared to baseline had a lower risk of complications.[48]

Pulmonary Hypertension in Pregnancy

The estimated overall maternal mortality for individuals with PH (≥25 mm Hg) has traditionally been between 30% and 56%. Most of the maternal fatalities occur in the early postpartum

Table 2: Risk factors for perioperative morbidity and mortality in PH

Surgical procedure	Comorbidities	PH
Emergency surgery	History of pulmonary embolism	NYHA class ≥II
Major surgery	Obstructive sleep apnea	RV hypertrophy
High risk surgery	Coronary artery disease	RV systolic pressure/systolic arterial blood pressure ≥0.66
Long operative time (>3 h)		RV myocardial performance index ≥0.75*
Vasopressor use		Right axis deviation
		Right atrial dilation
		Higher systolic PAP or PVR
		Lower LV ejection fraction

*RV performance index = RV isovolumic relaxation and contraction times divided by the ejection time interval. PH = Pulmonary hypertension, RV = Right ventricular, NYHA = New York Heart Association, LV = Left ventricle

period (1st month) and are due to sudden or progressive heart failure.[30,49] Mortality depends on the etiology of PH, time to recognition, and medical treatment received during pregnancy, delivery, and postpartum.[32,49,50] Patients with Eisenmenger's syndrome have higher maternal mortality (40-52%) than other groups, although most of the evidence comes from studies performed before the introduction of PH-specific therapies.[51,52] A late diagnosis and delayed hospitalization are strong predictors of maternal mortality.[49]

Recent studies using advanced PH therapies and a multi-disciplinary approach showed a lower maternal mortality (11-33%) than historical controls.[30,53,54] Nevertheless, maternal mortality remains prohibitively high especially in those with uncontrolled PH.[30,32,54] Thus, pregnancy is discouraged and contraception advice becomes critical in women of child bearing potential who have PH.[32] In pregnant women with PH, the risks of pregnancy should be carefully discussed with the patient including the option of early termination of pregnancy, especially in the event of PH deterioration.[32,55] If the pregnancy is to be continued, early hospitalization with careful multi-disciplinary management is the standard of practice.

The main goals are to recognize and manage PH, prevent its progression, and minimize side-effects of various therapies.[56] The optimal mode of delivery (vaginal versus caesarean section) and best anesthetic approach (epidural versus general) remain controversial.[30,32,50,53-55,57] Although promising, the effects of advanced PH therapies on pregnancy outcomes remain largely unknown.[30] Endothelin receptor antagonists (including bosentan, ambrisentan and macitentan) are contraindicated during pregnancy due to potential teratogenic effects.[58] Similarly, riociguat, a soluble guanylate cyclase stimulator showed evidence of fetal abnormalities in animal reproduction studies, therefore its use is contraindicated in women how are or may become pregnant. Although the data are insufficient, epoprostenol and sildenafil appear to be well tolerated during pregnancy without any reported adverse consequence to the fetus.[29,57,59] NO has also been used effectively in the peripartum management of patients with PH.[60] Pregnancy in PAH patients who are long-term responders to calcium channel blockers appears to have a particularly good outcome.[54]

In patients who desire to become pregnant despite the recommendation against it, a year of successful PH therapy with the goal of improving the RV function to near-normal is usually suggested.[57]

Management

Preoperative
Preoperative evaluation starts by obtaining a thorough history and physical examination with special attention to symptoms of PH.[1,61] Complementary studies may show signs of RV hypertrophy on electrocardiogram or dilated pulmonary arteries on imaging studies. The best initial screening modality when PH is clinically suspected is echocardiography, but a definitive diagnosis requires RHC.[15] In addition, RHC narrows potential etiologies, provides prognostic information, and guides the therapeutic decisions.[16]

The presence of PH (mPAP ≥25 mm Hg) should prompt a re-evaluation of the need for surgery. The risk assessment should take into account the type of surgery, co-morbidities and PH severity [Table 2].[6,62] In patients with unacceptably high-risk for the surgical intervention, it is essential to consider other alternatives to surgery or the administration of advanced

PH therapies.[63] If the decision is to proceed with surgery, a multi-disciplinary approach in a center with experience in the management of PH is recommended.

The preoperative management encompasses general measurements and consideration of advanced PH therapies. Oxygen is indicated when the oxygen saturation is below 90%.[64] Diuretics are considered in the presence of RV volume overload, but they should be used judiciously, as excessive diuresis can hazardously reduce RV preload.[22] Digoxin may modestly improve cardiac output in patients with PH and RV failure; however, limited data is available.[65]

Bridging with heparin is recommended in patients with indications for oral anticoagulation beyond PAH.[66]

Calcium channel blockers (diltiazem, nifedipine and amlodipine) need to be continued in PAH patients who are vasoreactive and have a long-term response to these medications.[67] Calcium channel blockers are contraindicated in subjects with hemodynamic instability, heart failure (cardiac index below 2 L/min/m² and right atrial pressure above 20 mm Hg) or previous adverse reactions to the medication.[67]

Advanced PH therapies should be continued in the perioperative period. If the patient is "nil per mouth," sildenafil can be given in intravenous (IV) form. Patients treated with subcutaneous treprostinil may continue the infusion for short procedures, however for prolonged interventions this medication should be converted to IV treprostinil or epoprostenol.[63] Similarly, in patients that cannot continue inhaled iloprost or treprostinil, like those requiring mechanical ventilation, iNO, IV or nebulized epoprostenol should be considered.[6]

Intraoperative
The main goals for the intraoperative management of patients with PH [Table 3] are based on:
1. Maintenance of adequate systemic perfusion, RV preload, and optimal contractility.[1]
2. Aggressive control of PH triggers and prevention of the PH crisis and RV failure.[1,66] Careful monitoring is critical to avoid and correct PH triggers such as hypoxia, hypercapnia, acidosis, hypothermia, sympathetic activation, and hyperinflation.

Table 3: Recommendations on the perioperative management of patients with PH (class of recommendation; IIb and level of evidence: C)

Preoperative	Intraoperative	Postoperative
Identify the presence of PH	Careful monitoring	Careful monitoring predominantly during first 48 h
Determine the severity of PH	Maintain adequate systemic perfusion, RV preload and optimal RV contractility	Provide appropriate analgesia
Evaluate need and type of surgery after considering risks/benefits of the intervention	Do not change dose of PH-specific therapies unless absolutely necessary	Do not change dose of PH-specific therapies unless absolutely necessary
Multidisciplinary approach in a center with experience in the management of these patients	Avoid/correct PH triggers	Avoid/correct PH triggers
Start/optimize PH-specific therapy with goal of improving RV function	Regional anesthesia should be considered when appropriate	
Evaluate need to convert to other PH-specific therapies depending on the type/duration of the intervention	Avoid lung hyperinflation or high levels of PEEP	

PH = Pulmonary hypertension, RV = Right ventricular, PEEP = Positive end-expiratory pressure

There are no validated data to help define the best monitoring approach for PH patients undergoing surgery, thus the extent of monitoring required should be determined on a "case by case" basis. Most patients with PH benefit from arterial and central venous catheters, to allow continuous blood pressure monitoring, frequent arterial blood gases analysis, and assessment of fluid volume status. The need for perioperative insertion of a pulmonary arterial catheter is controversial due to lack of evidence on improving outcomes and concern for potential complications.[68] An approach to systemic hypotension using information derived from the pulmonary artery catheterization is shown in Figure 1. Trans-esophageal echocardiography is a promising diagnostic modality to evaluate preload and ventricular function in this group of patients.

Various anesthetic techniques have been used in patients with PH, including regional (limited or neuroaxial) and general anesthesia. Limited regional anesthesia using nerve blocks should be considered when appropriate. Regional anesthesia using a low epidural dose and slow titration is well tolerated in PH patients since it minimizes the hemodynamic compromise associated with systemic afterload reduction. However, this anesthetic approach may not be appropriate for many surgeries or when cessation of anticoagulation is not possible.[34] It is uncertain if neuroaxial anesthesia is safe in patients treated with prostacyclin analogs, since these medications have antiplatelet effects, nevertheless there are no data suggesting increased risk of epidural bleeding in association with these medications.[22] Spinal anesthesia should be avoided as it may cause sudden and poorly tolerated hemodynamic changes at induction and during recovery from the block.[22]

General anesthesia can increase PVR by sympathetic tone activation during airway instrumentation, use of certain anesthetic agents, positive pressure mechanical ventilation, hypoxemia, hypercapnia, and acidemia.
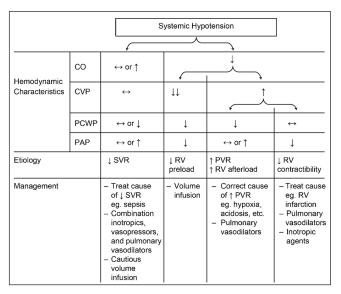
During intubation, opioids and lidocaine can be used to block the cardiorespiratory response. Propofol, pentothal, and etomidate are appropriate induction medications.[6,22] Concern existed regarding the use of ketamine in PH patients as it may increase PAP;[69] however, a recent retrospective study looking at perioperative complications in children with PH undergoing general anesthesia with ketamine, found similar rates of complications when compared to other medications.[70]

Dexmedetomidine, an alpha 2-agonist that reduces central sympathetic outflow and induces sedation, may be beneficial in PH patients.[71,72] Volatile anesthetic agents, regularly used for anesthesia maintenance, may adversely affect RV preload, contractility, and afterload, leading to RV dysfunction.[73,74]

Nevertheless, the effects on the pulmonary vasculature have been conflicting and no specific agent has been proven superior.[74-77] Nitrous oxide should generally be avoided as it may increase PVR and produce postoperative myocardial ischemia.[78-80] Volatile agents can also decrease systemic arterial pressure, resulting in RV ischemia. High dose opioids can blunt the cardiovascular response to surgical stimulation and reduce the dose of volatile anesthetics, limiting their potential adverse effects.[66]

Endotracheal intubation should be avoided when possible, especially in patients with evidence of RV failure.[81] In patients requiring mechanical ventilation, hyperinflation, high plateau pressure and the use of high levels of positive end-expiratory pressure (PEEP) should be avoided as they may reduce RV preload and increase PVR.[82,83] It might be reasonable to use high FiO_2, moderate tidal volumes (8 mL/kg) with low levels of PEEP (<12 mm Hg) and relatively high respiratory rates to prevent hypoxemia and hypercapnia.[63,83]

Postoperative

Most PH patients that die in the perioperative period do so in the first few days after surgery.[1] Price *et al*. in their study have reported that 92% of the perioperative complications in PH patients occurred in the first 48 h following surgery. Meanwhile, no significant clinical or hemodynamic deterioration was observed in survivors for up to a year of postoperative follow-up.[34] Therefore, it is particularly important to closely follow individuals during the first few days after surgery to promptly detect sudden worsening of PH and RV failure [Table 3], predominantly when anesthetics wear off.

Extubation should be considered when the FiO_2 requirement is ≤40% and patients have appropriate ventilation on minimal ventilator settings. Patients should receive adequate analgesia and be hemodynamically stable. Extubation is usually performed in the ICU; however, for less invasive surgeries without complications, extubation can be done in the operating room.[12] If started intraoperatively, inotropic agents, vasopressors and pulmonary vasodilators should be weaned off gradually. Pulmonary artery catheter monitoring is removed when the patient becomes hemodynamically stable. Sildenafil has been used successfully in the postoperative management of PH after heart transplantation and congenital heart surgery.[84,85]

Hemodynamic Characteristics		Systemic Hypotension			
	CO	↔ or ↑		↓	
	CVP	↔	↓↓		↑
	PCWP	↔ or ↓	↓	↓	↔
	PAP	↔ or ↑	↓	↔ or ↑	↓
Etiology		↓ SVR	↓ RV preload	↑ PVR ↑ RV afterload	↓ RV contractility
Management		– Treat cause of ↓ SVR eg. sepsis – Combination inotropics, vasopressors, and pulmonary vasodilators – Cautious volume infusion	– Volume infusion	– Correct cause of ↑ PVR eg. hypoxia, acidosis, etc. – Pulmonary vasodilators	– Treat cause eg. RV infarction – Pulmonary vasodilators – Inotropic agents

Figure 1: Management of systemic hypotension based on determinations obtained from right heart catheterization (figure obtained with permission from Minai *et al*.[1]). CO = Cardiac output, CVP = Central venous pressure, PAP = Pulmonary artery pressure, PCWP = Pulmonary capillary wedge pressure, RV = Right ventricle, SVR = Systemic vascular resistance

Management of right ventricular failure

Right ventricular failure continues to be a common cause of death and RV function is a major determinant of morbidity and mortality in PH patients.[1,86,87] Acute decompensation during the perioperative period has a poor prognosis and often occurs as a result of acute RV failure.[9,22] Therefore, it is critical to promptly identify this commonly misdiagnosed complication.

The management of acute RV failure is challenging and requires a multi-disciplinary approach [Table 4].

In patients with acute RV failure experts advocate the placement of a pulmonary artery catheter to allow measurement of right atrial pressure, cardiac output, PVR and mixed-venous oxygen saturation.[88] Factors causing a negative effect on pulmonary hemodynamics need to be corrected, such as inadequate mechanical ventilatory support or hypothermia.

Anemia may worsen RV function; hence some authors suggest a hemoglobin level of ≥10 g/dL.[88,89] Systemic hypotension during the perioperative period should not be managed by downtitrating the PH-specific therapies.[6] Volume loading may paradoxically lead to a reduction in the left ventricular preload and worsen hypotension. On the other hand, diuresis may improve left ventricular preload and cardiac output through a reduction in the leftward septal displacement.[88,90]

Vasopressors may need to be added to prevent or treat RV ischemia, particularly when systemic hypotension develops despite optimization of the fluid status, ventilator settings, and medications.[91,92] It has been suggested that an increase in left ventricular afterload may optimize the ventricular interdependence.[88] Vasopressors that can potentially be used include norepinephrine and vasopressin.[93-95] Norepinephrine decreases the ratio of PAP over systemic blood pressure without a change in cardiac output; meanwhile vasopressin, which may lead to a decrease in PVR by way of releasing NO, has been used successfully in a limited number of PH patients.[93,94,96-98] Dopamine and epinephrine are not ideal as they tend to increase heart rate and myocardial oxygen consumption more than norepinephrine.[11,92] It is unknown whether these differences could have a clinically significant impact in the perioperative outcomes of PH patients. Dobutamine and milrinone are the preferred inotropic agents since they have vasodilator properties, thereby increasing RV function and reducing PVR.[99-102]

Pulmonary vasodilators including iNO and other PH-specific therapies may also be initiated. iNO reduces PAPs and

pulmonary vascular resistance, while it does not produce systemic vasodilation, since it is rapidly inactivated by hemoglobin binding.[67,103-107] PH-specific therapies, used in the perioperative period, include oral or IV sildenafil,[13,108,109] IV or inhaled epoprostenol,[110-115] inhaled iloprost,[116-118] and IV treprostinil.[119] Endothelin receptor antagonists have a limited role in the acute setting as they are considered long-term therapies for PH.[120,121] There is lack of data to recommend any particular PH-targeted strategy. Inhaled agents are especially attractive since they are short acting and predominantly produce pulmonary vasodilation without other systemic hemodynamic effects. Nonspecific vasodilators such as calcium channel blockers should be avoided in RV failure as they may cause profound systemic hypotension leading to death.[67]

Data are promising for the use of other therapies such as inhaled milrinone (less systemic effects than the IV form),[122-124] inhaled nitroglycerin (more selective pulmonary vasodilatory effects),[125,126] IV iloprost,[127] inhaled sildenafil,[128] and IV levosimendan (myocardial calcium sensitizer and pulmonary vasodilator).[73,129,130] Further studies are needed before specific recommendations regarding these therapies can be provided.

When prior therapies fail, patients may benefit from mechanical support such as veno-arterial extracorporeal membrane oxygenation (ECMO) as a bridge to recovery or transplantation.[131,132] ECMO decompresses the RV and improves the perfusion to other organs, especially bowel, liver, and kidneys.[88] Ideally, this mechanical support should be provided before intubation to avoid hemodynamic instability associated with the airway manipulation and mechanical ventilation.[88] Another potential intervention in severe cases is atrial septostomy, which allows decompression of the right heart chambers, decreasing wall tension and improving contractility.[18,133] However, this intervention is discouraged as an emergency procedure in patients with RV failure, due to a higher risk of fatal complications.[134] Lung transplantation is usually not an option as patients are often unsuitable candidates due to comorbidities.

Conclusions

As PH patients live longer and their disease is under better control, it is likely that more patients with this condition will be encountered in the perioperative setting. Management of these patients is challenging due to their tenuous hemodynamic and respiratory status. Better understanding of the pathophysiology, risk factors, monitoring, and treatment of the disease are expected to improve the outcomes of surgical interventions. The perioperative management of PH patients requires a thorough multi-disciplinary approach and meticulous care that is best provided in centers that specialize in PH management.

Table 4: Principles of management of RV failure in the perioperative period

Management of right ventricular failure perioperatively

Treat known triggers that worsen pulmonary hemodynamics including hypoxemia, hypercarbia, acidosis, and hypothermia

Look for and treat co-morbidities such as pulmonary embolism, arrhythmias, etc

Maintain systemic blood pressure by administration of fluids or vasopressors as needed

Reduce RV afterload by initiation of pulmonary vasodilators

Consider initiation of mechanical support (RV assist device and extracorporeal membrane oxygenation) as needed

RV = Right ventricular

References

1. Minai OA, Yared JP, Kaw R, Subramaniam K, Hill NS. Perioperative risk and management in patients with pulmonary hypertension. Chest 2013;144:329-40.
2. Tonelli AR, Minai OA, Dweik RA. Perioperative management of the patient with pulmonary hypertension. In: Mandell BF, editor.

Perioperative Management of Patients with Rheumatic Disease. New York: Springer Science, LLC; 2013.

3. Galiè N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 2009;30:394-403.

4. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: Insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL). Circulation 2010;122:164-72.

5. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010;122:156-63.

6. Pritts CD, Pearl RG. Anesthesia for patients with pulmonary hypertension. Curr Opin Anaesthesiol 2010;23:411-6.

7. Reich DL, Bodian CA, Krol M, Kuroda M, Osinski T, Thys DM. Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. Anesth Analg 1999;89:814-22.

8. Reich DL, Wood RK Jr, Emre S, Bodian CA, Hossain S, Krol M, et al. Association of intraoperative hypotension and pulmonary hypertension with adverse outcomes after orthotopic liver transplantation. J Cardiothorac Vasc Anesth 2003;17:699-702.

9. Ramakrishna G, Sprung J, Ravi BS, Chandrasekaran K, McGoon MD. Impact of pulmonary hypertension on the outcomes of noncardiac surgery: Predictors of perioperative morbidity and mortality. J Am Coll Cardiol 2005;45:1691-9.

10. Kaw R, Pasupuleti V, Deshpande A, Hamieh T, Walker E, Minai OA. Pulmonary hypertension: An important predictor of outcomes in patients undergoing non-cardiac surgery. Respir Med 2011;105:619-24.

11. Lai HC, Lai HC, Wang KY, Lee WL, Ting CT, Liu TJ. Severe pulmonary hypertension complicates postoperative outcome of non-cardiac surgery. Br J Anaesth 2007;99:184-90.

12. Minai OA, Venkateshiah SB, Arroliga AC. Surgical intervention in patients with moderate to severe pulmonary arterial hypertension. Conn Med 2006;70:239-43.

13. Hill NS, Roberts KR, Preston IR. Postoperative pulmonary hypertension: Etiology and treatment of a dangerous complication. Respir Care 2009;54:958-68.

14. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54 1 Suppl:S43-54.

15. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54 1 Suppl:S55-66.

16. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: Developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. Circulation 2009;119:2250-94.

17. Brown LM, Chen H, Halpern S, Taichman D, McGoon MD, Farber HW, et al. Delay in recognition of pulmonary arterial hypertension: Factors identified from the REVEAL Registry. Chest 2011;140:19-26.

18. Piazza G, Goldhaber SZ. The acutely decompensated right ventricle: Pathways for diagnosis and management. Chest 2005;128:1836-52.

19. McIntyre KM, Sasahara AA. Determinants of right ventricular function and hemodynamics after pulmonary embolism. Chest 1974;65:534-43.

20. Strumpher J, Jacobsohn E. Pulmonary hypertension and right ventricular dysfunction: Physiology and perioperative management. J Cardiothorac Vasc Anesth 2011;25:687-704.

21. Zamanian RT, Haddad F, Doyle RL, Weinacker AB. Management strategies for patients with pulmonary hypertension in the intensive care unit. Crit Care Med 2007;35:2037-50.

22. Blaise G, Langleben D, Hubert B. Pulmonary arterial hypertension: Pathophysiology and anesthetic approach. Anesthesiology 2003;99:1415-32.

23. Bristow MR, Zisman LS, Lowes BD, Abraham WT, Badesch DB, Groves BM, et al. The pressure-overloaded right ventricle in pulmonary hypertension. Chest 1998;114 1 Suppl:101S-6.

24. Moudgil R, Michelakis ED, Archer SL. Hypoxic pulmonary vasoconstriction. J Appl Physiol (1985) 2005;98:390-403.

25. Balanos GM, Talbot NP, Dorrington KL, Robbins PA. Human pulmonary vascular response to 4 h of hypercapnia and hypocapnia measured using Doppler echocardiography. J Appl Physiol (1985) 2003;94:1543-51.

26. Jardin F, Brun-Ney D, Cazaux P, Dubourg O, Hardy A, Bourdarias JP. Relation between transpulmonary pressure and right ventricular isovolumetric pressure change during respiratory support. Cathet Cardiovasc Diagn 1989;16:215-20.

27. Winterhalter M, Antoniou T, Loukanov T. Management of adult patients with perioperative pulmonary hypertension: Technical aspects and therapeutic options. Cardiology 2010;116:3-9.

28. van Oppen AC, Stigter RH, Bruinse HW. Cardiac output in normal pregnancy: A critical review. Obstet Gynecol 1996;87:310-8.

29. Madden BP. Pulmonary hypertension and pregnancy. Int J Obstet Anesth 2009;18:156-64.

30. Bédard E, Dimopoulos K, Gatzoulis MA. Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 2009;30:256-65.

31. Memtsoudis SG, Ma Y, Chiu YL, Walz JM, Voswinckel R, Mazumdar M. Perioperative mortality in patients with pulmonary hypertension undergoing major joint replacement. Anesth Analg 2010;111:1110-6.

32. Bonnin M, Mercier FJ, Sitbon O, Roger-Christoph S, Jaïs X, Humbert M, et al. Severe pulmonary hypertension during pregnancy: Mode of delivery and anesthetic management of 15 consecutive cases. Anesthesiology 2005;102:1133-7.

33. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. Circulation 2007;116:1971-96.

34. Price LC, Montani D, Jaïs X, Dick JR, Simonneau G, Sitbon O, et al. Noncardiothoracic nonobstetric surgery in mild-to-moderate pulmonary hypertension. Eur Respir J 2010;35:1294-302.

35. Meyer S, McLaughlin VV, Seyfarth HJ, Bull TM, Vizza CD, Gomberg-Maitland M, et al. Outcomes of noncardiac, nonobstetric surgery in patients with PAH: An international prospective survey. Eur Respir J 2013;41:1302-7.

36. Kuralay E, Demírkiliç U, Oz BS, Cíngöz F, Tatar H. Primary pulmonary hypertension and coronary artery bypass surgery. J Card Surg 2002;17:79-80.

37. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, et al. Risk factors and outcome in European cardiac surgery: Analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15:816-22.

38. Bernstein AD, Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery. Ann Thorac Surg 2000; 69:823-8.

39. Tuman KJ, McCarthy RJ, March RJ, Najafi H, Ivankovich AD. Morbidity and duration of ICU stay after cardiac surgery. A model for preoperative risk assessment. Chest 1992;102:36-44.

40. Mubeen M, Singh AK, Agarwal SK, Pillai J, Kapoor S, Srivastava AK. Mitral valve replacement in severe pulmonary arterial hypertension. Asian Cardiovasc Thorac Ann 2008;16:37-42.

41. Cesnjevar RA, Feyrer R, Walther F, Mahmoud FO, Lindemann Y, von der Emde J. High-risk mitral valve replacement in severe pulmonary hypertension - 30 years experience. Eur J Cardiothorac Surg 1998;13:344-51.

42. Zuern CS, Eick C, Rizas K, Stoleriu C, Woernle B, Wildhirt S, et al. Prognostic value of mild-to-moderate pulmonary hypertension in patients with severe aortic valve stenosis undergoing aortic valve replacement. Clin Res Cardiol 2012;101:81-8.

43. Melby SJ, Moon MR, Lindman BR, Bailey MS, Hill LL, Damiano RJ Jr. Impact of pulmonary hypertension on outcomes after aortic valve replacement for aortic valve stenosis. J Thorac Cardiovasc Surg 2011;141:1424-30.

44. Ben-Dor I, Goldstein SA, Pichard AD, Satler LF, Maluenda G, Li Y, et al. Clinical profile, prognostic implication, and response to treatment of pulmonary hypertension in patients with severe aortic stenosis. Am J Cardiol 2011;107:1046-51.

45. Malouf JF, Enriquez-Sarano M, Pellikka PA, Oh JK, Bailey KR, Chandrasekaran K, et al. Severe pulmonary hypertension in patients with severe aortic valve stenosis: Clinical profile and prognostic implications. J Am Coll Cardiol 2002;40:789-95.

46. Pai RG, Varadarajan P, Kapoor N, Bansal RC. Aortic valve replacement improves survival in severe aortic stenosis associated with severe pulmonary hypertension. Ann Thorac Surg 2007;84:80-5.

47. Robitaille A, Denault AY, Couture P, Bélisle S, Fortier A, Guertin MC, et al. Importance of relative pulmonary hypertension in cardiac surgery: The mean systemic-to-pulmonary artery pressure ratio. J Cardiothorac Vasc Anesth 2006;20:331-9.

48. Balzer DT, Kort HW, Day RW, Corneli HM, Kovalchin JP, Cannon BC, et al. Inhaled nitric oxide as a preoperative test (INOP Test I): The INOP Test Study Group. Circulation 2002;106:I76-81.

49. Weiss BM, Zemp L, Seifert B, Hess OM. Outcome of pulmonary vascular disease in pregnancy: A systematic overview from 1978 through 1996. J Am Coll Cardiol 1998;31:1650-7.

50. Zwicke DL, Buggy PB. Pregnancy and pulmonary arterial hypertension: Successful management of 37 consecutive patients. Chest 2008;124:AS2331.

51. Yentis SM, Steer PJ, Plaat F. Eisenmenger's syndrome in pregnancy: Maternal and fetal mortality in the 1990s. Br J Obstet Gynaecol 1998;105:921-2.

52. Gleicher N, Midwall J, Hochberger D, Jaffin H. Eisenmenger's syndrome and pregnancy. Obstet Gynecol Surv 1979;34:721-41.

53. Kiely DG, Condliffe R, Webster V, Mills GH, Wrench I, Gandhi SV, et al. Improved survival in pregnancy and pulmonary hypertension using a multiprofessional approach. BJOG 2010;117:565-74.

54. Jaïs X, Olsson KM, Barbera JA, Blanco I, Torbicki A, Peacock A, et al. Pregnancy outcomes in pulmonary arterial hypertension in the modern management era. Eur Respir J 2012;40:881-5.

55. Smedstad KG, Cramb R, Morison DH. Pulmonary hypertension and pregnancy: A series of eight cases. Can J Anaesth 1994;41:502-12.

56. Budev MM, Arroliga AC, Emery S. Exacerbation of underlying pulmonary disease in pregnancy. Crit Care Med 2005;33 10 Suppl:S313-8.

57. Easterling TR, Ralph DD, Schmucker BC. Pulmonary hypertension in pregnancy: Treatment with pulmonary vasodilators. Obstet Gynecol 1999;93:494-8.

58. Madsen KM, Neerhof MG, Wessale JL, Thaete LG. Influence of ET(B) receptor antagonism on pregnancy outcome in rats. J Soc Gynecol Investig 2001;8:239-44.

59. Goland S, Tsai F, Habib M, Janmohamed M, Goodwin TM, Elkayam U. Favorable outcome of pregnancy with an elective use of epoprostenol and sildenafil in women with severe pulmonary hypertension. Cardiology 2010;115:205-8.

60. Robinson JN, Banerjee R, Landzberg MJ, Thiet MP. Inhaled nitric oxide therapy in pregnancy complicated by pulmonary hypertension. Am J Obstet Gynecol 1999;180:1045-6.

61. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107:216-23.

62. Ross AF, Ueda K. Pulmonary hypertension in thoracic surgical patients. Curr Opin Anaesthesiol 2010;23:25-33.

63. MacKnight B, Martinez EA, Simon BA. Anesthetic management of patients with pulmonary hypertension. Semin Cardiothorac Vasc Anesth 2008;12:91-6.

64. Roberts DH, Lepore JJ, Maroo A, Semigran MJ, Ginns LC. Oxygen therapy improves cardiac index and pulmonary vascular resistance in patients with pulmonary hypertension. Chest 2001;120:1547-55.

65. Rich S, Seidlitz M, Dodin E, Osimani D, Judd D, Genthner D, et al. The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. Chest 1998;114:787-92.

66. Teo YW, Greenhalgh DL. Update on anaesthetic approach to pulmonary hypertension. Eur J Anaesthesiol 2010;27:317-23.

67. Tonelli AR, Alnuaimat H, Mubarak K. Pulmonary vasodilator testing and use of calcium channel blockers in pulmonary arterial hypertension. Respir Med 2010;104:481-96.

68. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. J Am Coll Cardiol 2006;48:2546-52.

69. Spotoft H, Korshin JD, Sørensen MB, Skovsted P. The cardiovascular effects of ketamine used for induction of anaesthesia in patients with valvular heart disease. Can Anaesth Soc J 1979;26:463-7.

70. Williams GD, Maan H, Ramamoorthy C, Kamra K, Bratton SL, Bair E, et al. Perioperative complications in children with pulmonary hypertension undergoing general anesthesia with ketamine. Paediatr Anaesth 2010;20:28-37.

71. Shinohara H, Hirota K, Sato M, Kakuyama M, Fukuda K. Monitored anesthesia care with dexmedetomidine of a patient with severe pulmonary arterial hypertension for inguinal hernioplasty. J Anesth 2010;24:611-3.

72. But AK, Ozgul U, Erdil F, Gulhas N, Toprak HI, Durmus M, et al. The effects of pre-operative dexmedetomidine infusion on hemodynamics in patients with pulmonary hypertension undergoing mitral valve replacement surgery. Acta Anaesthesiol Scand 2006;50:1207-12.

73. Forrest P. Anaesthesia and right ventricular failure. Anaesth Intensive Care 2009;37:370-85.

74. Kerbaul F, Rondelet B, Motte S, Fesler P, Hubloue I, Ewalenko P, et al. Isoflurane and desflurane impair right ventricular-pulmonary arterial coupling in dogs. Anesthesiology 2004;101:1357-62.

75. Cheng DC, Edelist G. Isoflurane and primary pulmonary hypertension. Anaesthesia 1988;43:22-4.

76. Ciofolo MJ, Reiz S. Circulatory effects of volatile anesthetic agents. Minerva Anestesiol 1999;65:232-8.

77. Pagel PS, Fu JL, Damask MC, Davis RF, Samuelson PN, Howie MB, et al. Desflurane and isoflurane produce similar alterations in systemic and pulmonary hemodynamics and arterial oxygenation in patients undergoing one-lung ventilation during thoracotomy. Anesth Analg 1998;87:800-7.

78. Schulte-Sasse U, Hess W, Tarnow J. Pulmonary vascular responses to nitrous oxide in patients with normal and high pulmonary vascular resistance. Anesthesiology 1982;57:9-13.

79. Myles PS, Chan MT, Kaye DM, McIlroy DR, Lau CW, Symons JA, *et al.* Effect of nitrous oxide anesthesia on plasma homocysteine and endothelial function. Anesthesiology 2008;109:657-63.

80. Badner NH, Beattie WS, Freeman D, Spence JD. Nitrous oxide-induced increased homocysteine concentrations are associated with increased postoperative myocardial ischemia in patients undergoing carotid endarterectomy. Anesth Analg 2000;91: 1073-9.

81. Myles PS, Hall JL, Berry CB, Esmore DS. Primary pulmonary hypertension: Prolonged cardiac arrest and successful resuscitation following induction of anesthesia for heart-lung transplantation. J Cardiothorac Vasc Anesth 1994;8:678-81.

82. Jardin F, Vieillard-Baron A. Right ventricular function and positive pressure ventilation in clinical practice: From hemodynamic subsets to respirator settings. Intensive Care Med 2003;29:1426-34.

83. Repessé X, Charron C, Vieillard-Baron A. Right ventricular failure in acute lung injury and acute respiratory distress syndrome. Minerva Anestesiol 2012;78:941-8.

84. Kulkarni A, Singh TP, Sarnaik A, Walters HL, Delius R. Sildenafil for pulmonary hypertension after heart transplantation. J Heart Lung Transplant 2004;23:1441-4.

85. Peiravian F, Amirghofran AA, Borzouee M, Ajami GH, Sabri MR, Kolaee S. Oral sildenafil to control pulmonary hypertension after congenital heart surgery. Asian Cardiovasc Thorac Ann 2007;15:113-7.

86. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, *et al.* Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343-9.

87. Tonelli AR, Arelli V, Minai OA, Newman J, Bair N, Heresi GA, *et al.* Causes and circumstances of death in pulmonary arterial hypertension. Am J Respir Crit Care Med 2013;188:365-9.

88. Hoeper MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. Am J Respir Crit Care Med 2011;184:1114-24.

89. Ruiter G, Lankhorst S, Boonstra A, Postmus PE, Zweegman S, Westerhof N, *et al.* Iron deficiency is common in idiopathic pulmonary arterial hypertension. Eur Respir J 2011;37:1386-91.

90. Belenkie I, Dani R, Smith ER, Tyberg JV. Effects of volume loading during experimental acute pulmonary embolism. Circulation 1989;80:178-88.

91. Vlahakes GJ. Management of pulmonary hypertension and right ventricular failure: Another step forward. Ann Thorac Surg 1996;61:1051-2.

92. Vlahakes GJ, Turley K, Hoffman JI. The pathophysiology of failure in acute right ventricular hypertension: Hemodynamic and biochemical correlations. Circulation 1981;63:87-95.

93. Kwak YL, Lee CS, Park YH, Hong YW. The effect of phenylephrine and norepinephrine in patients with chronic pulmonary hypertension*. Anaesthesia 2002;57:9-14.

94. Smith AM, Elliot CM, Kiely DG, Channer KS. The role of vasopressin in cardiorespiratory arrest and pulmonary hypertension. QJM 2006;99:127-33.

95. Gold J, Cullinane S, Chen J, Seo S, Oz MC, Oliver JA, *et al.* Vasopressin in the treatment of milrinone-induced hypotension in severe heart failure. Am J Cardiol 2000;85:506-8, A11.

96. Price LC, Forrest P, Sodhi V, Adamson DL, Nelson-Piercy C, Lucey M, *et al.* Use of vasopressin after Caesarean section in idiopathic pulmonary arterial hypertension. Br J Anaesth 2007;99:552-5.

97. Tayama E, Ueda T, Shojima T, Akasu K, Oda T, Fukunaga S, *et al.* Arginine vasopressin is an ideal drug after cardiac surgery for the management of low systemic vascular resistant hypotension concomitant with pulmonary hypertension. Interact Cardiovasc Thorac Surg 2007;6:715-9.

98. Russ RD, Walker BR. Role of nitric oxide in vasopressinergic pulmonary vasodilatation. Am J Physiol 1992;262:H743-7.

99. Lobato EB, Gravenstein N, Martin TD. Milrinone, not epinephrine, improves left ventricular compliance after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2000;14:374-7.

100. Vizza CD, Rocca GD, Roma AD, Iacoboni C, Pierconti F, Venuta F, *et al.* Acute hemodynamic effects of inhaled nitric oxide, dobutamine and a combination of the two in patients with mild to moderate secondary pulmonary hypertension. Crit Care 2001;5:355-61.

101. Chen EP, Bittner HB, Davis RD Jr, Van Trigt P 3rd. Milrinone improves pulmonary hemodynamics and right ventricular function in chronic pulmonary hypertension. Ann Thorac Surg 1997;63:814-21.

102. Jenkins IR, Dolman J, O'Connor JP, Ansley DM. Amrinone versus dobutamine in cardiac surgical patients with severe pulmonary hypertension after cardiopulmonary bypass: A prospective, randomized double-blinded trial. Anaesth Intensive Care 1997;25:245-9.

103. Solina A, Papp D, Ginsberg S, Krause T, Grubb W, Scholz P, *et al.* A comparison of inhaled nitric oxide and milrinone for the treatment of pulmonary hypertension in adult cardiac surgery patients. J Cardiothorac Vasc Anesth 2000;14:12-7.

104. Bhorade S, Christenson J, O'connor M, Lavoie A, Pohlman A, Hall JB. Response to inhaled nitric oxide in patients with acute right heart syndrome. Am J Respir Crit Care Med 1999; 159:571-9.

105. Fattouch K, Sbraga F, Bianco G, Speziale G, Gucciardo M, Sampognaro R, *et al.* Inhaled prostacyclin, nitric oxide, and nitroprusside in pulmonary hypertension after mitral valve replacement. J Card Surg 2005;20:171-6.

106. Rajek A, Pernerstorfer T, Kastner J, Mares P, Grabenwöger M, Sessler DI, *et al.* Inhaled nitric oxide reduces pulmonary vascular resistance more than prostaglandin E(1) during heart transplantation. Anesth Analg 2000;90:523-30.

107. Schmid ER, Bürki C, Engel MH, Schmidlin D, Tornic M, Seifert B. Inhaled nitric oxide versus intravenous vasodilators in severe pulmonary hypertension after cardiac surgery. Anesth Analg 1999;89:1108-15.

108. De Santo LS, Mastroianni C, Romano G, Amarelli C, Marra C, Maiello C, *et al.* Role of sildenafil in acute posttransplant right ventricular dysfunction: Successful experience in 13 consecutive patients. Transplant Proc 2008;40:2015-8.

109. Lee JE, Hillier SC, Knoderer CA. Use of sildenafil to facilitate weaning from inhaled nitric oxide in children with pulmonary hypertension following surgery for congenital heart disease. J Intensive Care Med 2008;23:329-34.

110. Schroeder RA, Wood GL, Plotkin JS, Kuo PC. Intraoperative use of inhaled PGI(2) for acute pulmonary hypertension and right ventricular failure. Anesth Analg 2000;91:291-5.

111. Haché M, Denault AY, Bélisle S, Couture P, Babin D, Tétrault F, *et al.* Inhaled prostacyclin (PGI2) is an effective addition to the treatment of pulmonary hypertension and hypoxia in the operating room and intensive care unit. Can J Anaesth 2001;48:924-9.

112. De Wet CJ, Affleck DG, Jacobsohn E, Avidan MS, Tymkew H, Hill LL, *et al.* Inhaled prostacyclin is safe, effective, and affordable in patients with pulmonary hypertension, right heart dysfunction, and refractory hypoxemia after cardiothoracic surgery. J Thorac Cardiovasc Surg 2004;127:1058-67.

113. Haraldsson A, Kieler-Jensen N, Nathorst-Westfelt U, Bergh CH, Ricksten SE. Comparison of inhaled nitric oxide and inhaled aerosolized prostacyclin in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. Chest 1998;114:780-6.

114. Mikhail G, Gibbs J, Richardson M, Wright G, Khaghani A, Banner N, *et al.* An evaluation of nebulized prostacyclin in patients with primary and secondary pulmonary hypertension. Eur Heart J 1997;18:1499-504.

115. Rocca GD, Coccia C, Pompei L, Ruberto F, Venuta F, De Giacomo T, et al. Hemodynamic and oxygenation changes of combined therapy with inhaled nitric oxide and inhaled aerosolized prostacyclin. J Cardiothorac Vasc Anesth 2001;15:224-7.

116. Winterhalter M, Simon A, Fischer S, Rahe-Meyer N, Chamtzidou N, Hecker H, et al. Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: A prospective randomized trial. J Cardiothorac Vasc Anesth 2008;22:406-13.

117. Rex S, Schaelte G, Metzelder S, Flier S, de Waal EE, Autschbach R, et al. Inhaled iloprost to control pulmonary artery hypertension in patients undergoing mitral valve surgery: A prospective, randomized-controlled trial. Acta Anaesthesiol Scand 2008;52: 65-72.

118. Theodoraki K, Rellia P, Thanopoulos A, Tsourelis L, Zarkalis D, Sfyrakis P, et al. Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass. Can J Anaesth 2002;49:963-7.

119. Fontana M, Olschewski H, Olschewski A, Schlüter KD. Treprostinil potentiates the positive inotropic effect of catecholamines in adult rat ventricular cardiomyocytes. Br J Pharmacol 2007;151:779-86.

120. Sitbon O, Badesch DB, Channick RN, Frost A, Robbins IM, Simonneau G, et al. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary arterial hypertension: A 1-year follow-up study. Chest 2003;124:247-54.

121. Williamson DJ, Wallman LL, Jones R, Keogh AM, Scroope F, Penny R, et al. Hemodynamic effects of Bosentan, an endothelin receptor antagonist, in patients with pulmonary hypertension. Circulation 2000;102:411-8.

122. Wang H, Gong M, Zhou B, Dai A. Comparison of inhaled and intravenous milrinone in patients with pulmonary hypertension undergoing mitral valve surgery. Adv Ther 2009;26:462-8.

123. Lamarche Y, Perrault LP, Maltais S, Tétreault K, Lambert J, Denault AY. Preliminary experience with inhaled milrinone in cardiac surgery. Eur J Cardiothorac Surg 2007;31:1081-7.

124. Buckley MS, Feldman JP. Nebulized milrinone use in a pulmonary hypertensive crisis. Pharmacotherapy 2007;27:1763-6.

125. Mandal B, Kapoor PM, Chowdhury U, Kiran U, Choudhury M. Acute hemodynamic effects of inhaled nitroglycerine, intravenous nitroglycerine, and their combination with intravenous dobutamine in patients with secondary pulmonary hypertension. Ann Card Anaesth 2010;13:138-44.

126. Goyal P, Kiran U, Chauhan S, Juneja R, Choudhary M. Efficacy of nitroglycerin inhalation in reducing pulmonary arterial hypertension in children with congenital heart disease. Br J Anaesth 2006;97:208-14.

127. Ewert R, Opitz CF, Wensel R, Winkler J, Halank M, Felix SB. Continuous intravenous iloprost to revert treatment failure of first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension. Clin Res Cardiol 2007;96:211-7.

128. Ichinose F, Erana-Garcia J, Hromi J, Raveh Y, Jones R, Krim L, et al. Nebulized sildenafil is a selective pulmonary vasodilator in lambs with acute pulmonary hypertension. Crit Care Med 2001;29:1000-5.

129. Kleber FX, Bollmann T, Borst MM, Costard-Jäckle A, Ewert R, Kivikko M, et al. Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: Results of a pilot study. J Clin Pharmacol 2009;49:109-15.

130. Kerbaul F, Rondelet B, Demester JP, Fesler P, Huez S, Naeije R, et al. Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure. Crit Care Med 2006; 34:2814-9.

131. Keogh AM, Mayer E, Benza RL, Corris P, Dartevelle PG, Frost AE, et al. Interventional and surgical modalities of treatment in pulmonary hypertension. J Am Coll Cardiol 2009;54 1 Suppl:S67-77.

132. Berman M, Tsui S, Vuylsteke A, Klein A, Jenkins DP. Life-threatening right ventricular failure in pulmonary hypertension: RVAD or ECMO? J Heart Lung Transplant 2008;27:1188-9.

133. Reichenberger F, Pepke-Zaba J, McNeil K, Parameshwar J, Shapiro LM. Atrial septostomy in the treatment of severe pulmonary arterial hypertension. Thorax 2003;58:797-800.

134. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC), European Respiratory Society (ERS), International Society of Heart and Lung Transplantation (ISHLT), Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219-63.