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# Perioperative Management of Pulmonary Hypertension

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## 1. Introduction

Pulmonary hypertension (PH) was first described over 100 years ago, but a thorough understanding of its pathogenesis and a successful approach to curing the disease still remain under investigation.

Advanced research in the field of PH has enhanced our understanding of this entity and has led to new therapies. PH is rare but can affect people of all ages and is associated with several seemingly unconnected diseases.

## 2. Definition

PH refers to increased pressure in the arterial site of the pulmonary circulation and is defined as persistent elevation of mean pulmonary arterial pressure (MPAP) above 25 mmHg.

The current hemodynamic definition of PH is described in **Table 1**. The first clinical classification of PH was proposed at the first international conference on primary pulmonary hypertension endorsed by the World Health Organization (Hatano & Strassert, 1975). The previous version of the European Society of Cardiology (ESC) PH guidelines adopted the Evian-Venice classification proposed at the second and third World meeting on PH in 1998 and 2003 respectively (Galiè et al., 2004). According to these classifications, clinical conditions associated with PH are divided in five groups according to pathological, pathophysiological and therapeutic characteristics. During the fourth World symposium on PH held in Dana Point, California, the consensus agreement of experts worldwide was to maintain the general philosophy and organization endorsed by the Evian-Venice classifications while at the same time amending some specific points so as to improve clarity and to take into account new information (Galiè et al., 2009). Accordingly, PH can be classified into six clinical groups with specific characteristics (**Table 2**).

Anesthesiologists encounter patients with PH in a variety of situations in the operating room (Tidswell & Higgins, 2007). The most common underlying pathology of cardiac surgery patients which leads to PH is due to left-sided valvular heart disease, left-sided ventricular heart disease and shear stress from increased pulmonary blood flow due to intracardiac shunts.

Definition	Characteristics	Clinical group(s)
PH	MPAP $\geq$ 25 mmHg	All
Pre-capillary PH	MPAP $\geq$ 25 mmHg PCWP $\leq$ 15 mmHg CO normal or reduced	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic pulmonary hypertension 5. PH with unclear and-or multifactorial mechanisms
Post-capillary PH	MPAP $\geq$ 25 mmHg PCWP $>$ 15 mmHg CO normal or reduced	2. PH due to left heart disease
Passive	TPG $\leq$ 12 mmHg	
Reactive (out of proportion)	TPG $>$ 12 mmHg	

Table 1. Hemodynamic definition of pulmonary arterial hypertension.  
*CO, cardiac output; MPAP, mean pulmonary arterial pressure; PH, pulmonary hypertension; PCWP, pulmonary capillary wedge pressure; TPG, transpulmonary pressure gradient (MPAP-PCWP)*

Data from the multinational database EuroSCORE have demonstrated that PH is an independent risk factor for increased morbidity and mortality in patients undergoing heart surgery (Roques et al., 1999).

3. Pathophysiology

Highlighting the pathophysiology of PH can help us properly manage acute PH in the specific context of cardiac surgery.

The cause of PH in the case of mitral or aortic valve disease, especially when PH is a complication of stenotic valve disease, is quite complex. Increased left arterial pressures result in chronic obstruction to venous drainage in the pulmonary vasculature, causing remodeling of the pulmonary vascular bed and ultimately PH.

The molecular pathophysiological mechanism of PH has been recently reviewed. The PH ‘phenotype’ is characterized by endothelial dysfunction, a decrease ratio of apoptosis / proliferation in the pulmonary artery muscle cells and a thickened disordered adventitia in which there is excessive activation of adventitial metalloproteases (McLaughlin et al., 2009).

The fundamental functions of the endothelium include: regulating the vascular tone, coordinating vascular cell growth, controlling inflammatory and immunological processes as well as maintaining the balance between thrombotic and fibrotic activities. Each of these functions is controlled by a finely tuned network of activating and inhibiting compounds.

In the case of PH, the endothelium is characterized by increased production of vasoconstrictor / mitogenic mediators, such as endothelin and thromboxane, and deficient

<b>1. Pulmonary arterial hypertension (PAH)</b> <ul style="list-style-type: none"><li>1.1 Idiopathic</li><li>1.2 Heritable<ul style="list-style-type: none"><li>1.2.1 BMPR2</li><li>1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)</li><li>1.2.3 Unknown</li></ul></li><li>1.3 Drugs and toxins induced</li><li>1.4 Associated with<ul style="list-style-type: none"><li>1.4.1 Connective tissue diseases</li><li>1.4.2 HIV infection</li><li>1.4.3 Portal hypertension</li><li>1.4.4 Congenital heart disease</li><li>1.4.5 Schistosomiasis</li><li>1.4.6 Chronic hemolytic anemia</li></ul></li><li>1.5 Persistent pulmonary hypertension of the newborn</li></ul>
<b>1a. Pulmonary venoocclusive disease and-or pulmonary capillary hemangiomatosis</b>
<b>2. Pulmonary hypertension due to left heart disease</b> <ul style="list-style-type: none"><li>2.1 Systolic dysfunction</li><li>2.2 Diastolic dysfunction</li><li>2.3 Valvular disease</li></ul>
<b>3. Pulmonary hypertension due to lung diseases and/or hypoxia</b> <ul style="list-style-type: none"><li>3.1 Chronic obstructive pulmonary disease</li><li>3.2 Interstitial lung disease</li><li>3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern</li><li>3.4 Sleep-disordered breathing</li><li>3.5 Alveolar hypoventilation disorders</li><li>3.6 Chronic exposure to high altitude</li><li>3.7 Developmental abnormalities</li></ul>
<b>4. Chronic thromboembolic pulmonary hypertension</b>
<b>5. Pulmonary hypertension with unclear and-or multifactorial mechanisms</b> <ul style="list-style-type: none"><li>5.1 Hematological disorders: myeloproliferative disorders, splenectomy</li><li>5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis</li><li>5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders</li><li>5.4 Others: Tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis</li></ul>

Table 2. Updated clinical classification of pulmonary hypertension (Dana Point, 2008).  
*ALK-1, activin receptor-like kinase 1 gene; BMPR2, bone morphogenetic protein receptor, type 2; HIV, human immunodeficiency virus*

production of vasodilators, such as prostacyclin (Christman et al., 1992; Giaid et al., 1993; Stewart et al., 1991). Elevated levels of fibrinopeptide A and plasminogen activator

inhibitor-1 and reduced levels of tissue plasminogen activator contribute to a procoagulant state. Endothelial injury may also expose the underlying smooth muscle cells to circulating mitogens and growth factors that stimulate cell proliferation.

The so-called endothelium-dependent mechanism is that receptors located on the surface of the endothelial cells react to various stimulators or mediators and subsequently change signals. Via a cascade of reactions, the presence of shearing forces or mediators such as bradykinine and acetylcholine leads to the formation of so-called second messenger substances such as cyclic adenosine monophosphate (cAMP) or guanosine monophosphate (cGMP). These substances exert vasodilator effects and are responsible for smooth muscle relaxation.

**Nitric oxide (NO)** is a vasodilator and inhibitor of platelet activation and vascular smooth muscle proliferation. The effects of NO are mediated by cGMP, which is rapidly inactivated by phosphodiesterase.

Vascular dilatation occurs via the NO-triggered proliferation of endothelial-dependent hyperpolarizing factors which, through the activation of tension dependent potassium channels leads to relaxation of the smooth muscle cell. NO leads to an increase in the production of prostacyclin. Other potassium channels (ATP-dependent,  $\text{Ca}^{++}$  - dependent) are also involved in the regulation of the myosin-actin-calcium interaction.

On the contrary, hypoxia or specific mediators (e.g. thrombin, metabolites of arachidonic acid, angiotensin II and endothelin) lead to vasoconstriction. They also function through signal transduction via various receptors on the endothelial cells themselves or on the smooth muscle cells.

**Prostacyclin and thromboxane  $\text{A}_2$**  are major arachidonic acid metabolites. Prostacyclin is a potent vasodilator, inhibits platelet activation and has antiproliferation properties, whereas thromboxane  $\text{A}_2$  promotes proliferation and platelet activation. In PH, the balance between the two molecules is shifted towards thromboxane  $\text{A}_2$ .

**Endothelin-1 (ET-1)** is a potent vasoconstrictor produced by endothelial cells, which exerts potent vasoactive properties by binding to specific receptors ( $\text{ET}_\text{A}$  and  $\text{ET}_\text{B}$ ) on vascular endothelial and smooth muscle cells. Following the bonding of ET-1 to the  $\text{ET}_\text{A}$  receptor, phospholipase C is activated which consecutively leads to the accumulation of inositol-triphosphates and intracellular calcium. Through this mechanism, vasoconstriction as well as cell proliferation take place in various tissues. Activation of the  $\text{ET}_\text{B}$  receptor upon the endothelial cells not only leads to the release of NO and prostacyclin and consequence vasodilatation, but also inhibits expression of the endothelin converting enzyme upon endothelial cell and apoptosis. Pulmonary clearance of circulating ET-1 as well as its reentrance into the endothelial cells is also regulated via these receptors.

**Serotonin (5-hydroxytryptamine, 5-HT)** (Jain et al., 2007) is a pulmonary vasoconstrictor and promotes pulmonary artery smooth muscle cells hypertrophy and hyperplasia. There is a transporter for 5-HT that controls serotonin uptake and clearance, which is located on the surface of platelets, neurons, and pulmonary endothelial cells. The presence of elevated levels of 5-HT in the blood of patients with PH suggests that this substance also plays a role in the pathogenesis of PH.

In summary, PH can simply be explained as a functional disturbance of the endothelium, caused by an imbalance between the dilative and contractive mechanisms within the vascular resistance of the pulmonary vascular bed. These functional changes occur together with morphological alterations within the pulmonary vasculature.

Thus, NO, endothelin and prostacyclin also have a direct influence upon the thrombocytes, the endothelial-leukocyte interaction as well as vascular cell proliferation. This imbalance leads to thrombotic tendency, vasoconstriction and proliferation.

### 3.1 Pathophysiology of post bypass exacerbation of PH

Post bypass pulmonary vasoconstriction has been demonstrated in a variety of experimental models as well as in the clinical setting and there is increased evidence that the severity of the vasoconstriction correlates with the extent of cardiopulmonary bypass (CPB)-induced endothelial injury (Riedel, 1999).

Endothelial injury and dysfunction is promoted by acidosis, hypoxia, shear stress from increased pulmonary blood flow (left-to-right intracardiac shunts), and fibrin from thromboembolism. Leukocyte activation, oxygen free radicals such as superoxide, hydroxyl radicals and peroxynitrate, tumor necrosis factor  $\alpha$ , interleukin-1, elastases and inflammatory mediators are involved in this process.

The most important mechanism underlying this endothelial dysfunction in the setting of cardiac surgery could be ischemia/reperfusion injury, with associated inflammatory cell and complement activation. Ischemia/reperfusion injury due to inadequate flow in the bronchial circulation plays a pivotal role in the exacerbation of post-CPB PH (Matuschak, 1999).

In summary, intraoperative pulmonary vasoconstriction is a result of complex interactions between various perioperative factors: *preoperative status* of the pulmonary vascular bed (valvular pathology, shear stress), *intraoperative vasospastic stimuli* (hypoxia, hypercarbia, acidosis, ischemia/reperfusion injury, inflammatory mediators, free radical formation, pulmonary leukosequestration, excess thromboxane or endothelin production and microemboli) and *postoperative factors* (atelectasis, adrenergic tone, hypoxic pulmonary vasoconstriction). Preexisting pulmonary hypertension, increased pulmonary blood flow states, in combination with intraoperative hypoxia, acidosis, hypothermia, and microembolism may exacerbate CPB-induced pulmonary hypertension.

The final result of this pathophysiology is the imbalance between vasoconstrictor and vasodilator factors at the pulmonary vascular bed, that is reduction in prostacyclin (PGI<sub>2</sub>) and NO levels and an increase in thromboxane A<sub>2</sub>, catecholamines, adhesion molecules and endothelin levels.

This can culminate to a life-threatening situation and disconnecting the patient from the extracorporeal circulation may prove particularly laborious, because of right ventricular failure.

Moreover, after discontinuation from bypass there is need for heparin reversal and this is accomplished by the administration of protamine. Protamine administration is commonly associated with hypotension due to systemic vasodilatation. This is suggested to be mediated by the release of NO (Raikar, 1996). A rare reaction brought about by protamine administration, which may be mediated by the release of complement pathway anaphylatoxins (C3a and C5b) and / or cyclooxygenase products (e.g. thromboxane A<sub>2</sub>), may lead to catastrophic pulmonary hypertension and subsequent right ventricular failure.

### 4. Clinical impact of post bypass exacerbation of PH

Independent of the exact cause, the exacerbation of preexisting PH can lead to a further increase in the right ventricular afterload and distension of an already dysfunctional right



ventricle, resulting in increased right ventricular free wall tension and myocardial oxygen consumption.

Normally, the pulmonary circulation is a low pressure, high flow vascular bed accommodating the entire cardiac output with each heartbeat. Elevated pulmonary vascular resistance (PVR) may significantly contribute to right ventricular dysfunction, which may compromise the preload of the left ventricle inducing systemic hypotension. In patients with pathologically increased PVR, the right ventricle and left ventricle are interdependent and have similar vitally important functions. Right ventricular dilatation causes shifting of the intraventricular septum towards the left ventricle, leading to a smaller underfilled left ventricular cavity. The normal thin walls and crescent shape of the right ventricle result in a highly compliant right ventricular chamber, which is able to accommodate large increases in volume. However, the right ventricular adaptive mechanisms are not well suited to acute, large increases in pressure, (Fischer et al., 2003), as this may happen after CPB.

Furthermore systemic hypotension decreases right ventricular coronary perfusion pressure and oxygen delivery. Therefore, a vicious circle starts that can lead to exacerbation of right ventricular dysfunction.

## 5. Diagnosis of PH

The existence of sophisticated monitoring in this particular group of patients is deemed necessary because early diagnosis and prompt institution of therapy for acute PH is required in order to prevent right ventricular failure.

Diagnosis is aided by awareness of existing preoperative risk factors, such as valvular pathology or intracardiac shunts that are associated with PH. The development of acute PH will result in clinical signs of relatively rapid onset relating to the development of tricuspid regurgitation: prominent central venous atrioventricular pulsatile pressure waveforms, right-sided heart failure and a holosystolic murmur at the lower border of the sternum that increases in intensity during inspiration.

Pulmonary artery pressure catheterization and transesophageal echocardiography (TOE) constitute a valid monitoring tool for early detection of acute PH.

Pulmonary artery pressure catheterization will demonstrate elevated right atrial pressure, right ventricular end-diastolic pressure and pulmonary artery pressure with normal or low pulmonary wedge pressures. In the case of right ventricular dysfunction without pulmonary vasoconstriction, the pulmonary artery pressure may also be normal. Hemodynamic parameters calculated and derived by thermodilution will reflect elevated PVR and a reduction in right ventricular stroke work index and right ventricular stroke work index / central venous pressure relationship and a reduction in cardiac output or right ventricular ejection fraction.

TOE is an invaluable tool in the diagnosis of PH and right ventricular dysfunction, demonstrating both right ventricular volume and pressure overload. The two- dimension mode provides a subjective view of the increased ratio of right ventricle-to- left ventricle chamber size, paradoxical septal bulging, and deterioration in right ventricular function as seen on five-chamber and 4-chamber long axis views (Figure 1).

Color flow mapping will often reveal pulmonary and tricuspid regurgitation. The use of continuous wave Doppler across the regurgitant tricuspid valve allows quantification of the



Fig. 1. Severe tricuspid regurgitation and enlargement of the right ventricle caused by severe pulmonary hypertension

pressure gradient across the valve and thereby an estimation of the pulmonary artery pressure.

Also TOE has been proved to be a useful tool in the continuous assessment of the results of the applied therapeutic strategy.

## 6. Treatment of PH

Therapeutic strategies should be aimed at the prevention of acute perioperative PH or at the prevention of further increases in the already existing PH. The cornerstone of treatment lies in prevention of right ventricular failure brought about by the abrupt increase of right ventricular afterload, since impaired RV function is associated with poor outcome in the surgical and non-surgical setting.

It is important to underline that the treatment of perioperative PH in cardiac surgery patients should start as promptly as possible. If clinicians do not react early, a vicious circle may start and the discontinuation from CPB may prove extremely difficult. Right ventricular failure and low cardiac output can occur several hours after weaning from CPB, so a high level of vigilance is required during the entire postoperative period.

The incidence of postoperative acute refractory right ventricular failure is only about 0.1% after cardiectomy, but this can rise to around 2-3% after heart transplantation and even to 20-30% when a left ventricular assist device has been implanted (Kaul & Fields, 2000).

The appropriate treatment in order to prevent right ventricular failure is based on the following principles (Winterhalter et al., 2010):

- Avoidance of factors that are well known to exacerbate PH, such as hypoxemia, hypercarbia, acidosis, hypervolemia, hypothermia, and light anesthesia.
- Optimization of right ventricular preload: If the right atrial pressure is low, volume infusion is indicated. If it is high, diuretics and nitroglycerin are preferable.
- Improvement of right ventricular contractility: The administration of inotropes, such as epinephrine, dobutamine or the phosphodiesterase-3-inhibitor milrinone may be useful to raise right ventricular contractility.
- Minimization of right ventricular afterload: This can be accomplished by different strategies. The use of intravenously or inhalable vasodilators such as milrinone, nitroprusside, NO or the stable prostacyclin analogue iloprost can be administered.



Readministration of heparin and postoperative reinstitution of CPB may be necessary in refractory cases.

### 6.1 Intravenous vasodilators

The main goal of pulmonary vasodilatation is to lower right ventricular impedance, so as to decrease afterload and thus improve ventricular performance.

Traditional methods of treatment for perioperative PH included nitrates, prostaglandins, phosphodiesterase -3 inhibitors and calcium channel blockers. The aforementioned therapeutic modalities represent three distinct pharmacological pathways.

**Nitrates** (sodium nitroprusside-SNP, nitroglycerin-NTG) are NO donors, releasing NO spontaneously, which is normally located in biological tissues. Both agents decrease PVR, but because of their nonselectivity, they often decrease systemic blood pressure to a degree that impairs right ventricular perfusion and can cause ischemia.

Normally, the right ventricle is perfused during the entire cardiac cycle. In the presence of PH, the hypertrophic right ventricle generates elevated intracavitary and intramural pressures, limiting the period of perfusion predominantly to diastole, thereby increasing the risk of right ventricular ischemia and failure in the presence of systemic hypotension. Therefore, nitrates can compromise right ventricular perfusion through their hypotensive action in the arterial part of the circulation. Furthermore, these drugs increase venous admixture by dilatation of pulmonary vessels supplying poorly ventilated alveoli and therefore abolishing the protective effect of hypoxic pulmonary vasoconstriction.

**Prostacyclins** (prostacyclin  $\text{PGI}_2$ , prostaglandin- $\text{E}_1$   $\text{PGE}_1$ ) have been reported to have beneficial effects on pulmonary artery pressure and right ventricular function perioperatively. They act by stimulating adenylate cyclase to generate cAMP, but they also act non-selectively when administered intravenously and systemic hypotension limits their clinical effectiveness.

**Phosphodiesterase-3 inhibitors** (whose milrinone is the major representative) cause vasodilatation via inhibition of enzyme phosphodiesterase-3, increasing cAMP, which causes vasodilatation.

**Calcium channel blockers** also induce systemic vasodilatation but without sparing the systemic circulation.

Due the lack of selectivity to the pulmonary circulation of the aforementioned agents and the risk of a massive drop in the systemic blood pressure and right ventricular perfusion pressure, their administration should be avoided (Kieler-Jensen et al., 1993).

On the other hand, the importance of inhalable vasodilators has risen continuously over recent years. The advantage of these inhalable substances is their pulmonary selectivity and the subsequent reduction of systemic side effects, such as systemic hypotension. Also, the probability of ventilation-perfusion mismatch is low, as by inhalation primarily blood vessels close to the ventilated alveoli are dilated. The risks of shunt development and severe hypoxia are thus eliminated (Walmrath et al., 1997).

### 6.2 Inhalable vasodilators

The administration of inhalable pulmonary vasodilators, such as inhaled nitric oxide (NO), prostaglandins, NO donors (SNP-NTG) and milrinone is preferable over intravenous agents because of their pulmonary selectivity which is exerted without a concurrent increase in shunt fraction.

**Inhaled NO:** NO stimulates soluble guanylate cyclase (sGC) and increases cGMP. The latter activates cGMP- dependent protein kinases that are abundant in the cerebellum, smooth and

cardiac myocytes, platelets, and leukocytes (Lucas et al., 2000). In turn, these kinases mediate a cGMP-induced decrease in intracellular calcium concentration in vascular smooth muscle and vasodilatation (Hanafy et al., 2001).

Inhaled NO is a selective pulmonary vasodilator without clinically significant effect on blood pressure and cardiac output. Its selective action results from the fixation of NO to the heme moiety of the hemoglobin molecule after passing through the pulmonary vessel wall. NO is then oxidized to nitrogen dioxide (NO<sub>2</sub>) and nitrogen trioxide (NO<sub>3</sub>). Hemoglobin is transformed to methemoglobin, which is secondarily reduced to hemoglobin by methemoglobin reductase. Although NO has no systemic hemodynamic effects, it does have extrapulmonary activity (Wang et al., 2003). That is, it interferes with platelet and leukocyte functions, fibrinolysis, and reperfusion injury by inhibiting expression of adhesion molecules at leukocyte surfaces and by activation of sCG, which lead to a rapid increase in platelet cGMP and inhibition of platelet aggregation. NO-induced favorable effect on cardiac function is based on reduction of right ventricular afterload. Even in patients with severe right ventricular dysfunction, NO improves cardiac output and right ventricular ejection fraction (Bhorade et al., 1999). Most of the studies used doses of 20 parts per million (ppm) (range 10-40 ppm). It is reasonable to start NO at the lowest possible dose and titrate upwards as required in patients with pulmonary hypertension.

Toxicity from NO results from the formation of methemoglobin, NO<sub>2</sub> and peroxynitrite. Life-threatening increases in PVR have been noted with acute withdrawal of NO. To prevent rebound pulmonary hypertension, NO should be tapered off progressively without any attempt to discontinue it completely if FiO<sub>2</sub> is higher than 50%. However, these disadvantages of NO therapy have called for research on inhaled alternatives to NO.

### Prostaglandins

- Inhaled **prostacyclin** (PGI<sub>2</sub>)

Prostacyclin is a member of the prostaglandin family derived from arachidonic acid.

Inhaled **prostacyclin** seems to be the more favorable agent because of its lack of toxicity, ease of application, and reduced cost. Similar to NO, it is produced by the vascular endothelium and is involved in the regulation of vascular tone and in localized thrombotic and inflammatory processes. PGI<sub>2</sub> stimulates the endothelial release of NO, while NO, in turn, increases the synthesis of endogenous PGI<sub>2</sub>. In vivo, PGI<sub>2</sub> is spontaneously hydrolyzed to its inactive metabolite 6-keto-prostaglandin-F<sub>1a</sub> with a half life of 3-6 min.

Inhaled PGI<sub>2</sub> produces comparable effects to NO. The two agents have been compared in both animal and clinical studies, which have showed that inhaled PGI<sub>2</sub> produces greater decreases in PVR while NO induces greater improvements in oxygenation (Lowson, 2002). Moreover, Fattouch et al (Fattouch et al., 2005) have shown similar effectiveness for NO and inhaled prostacyclin in the treatment of pulmonary hypertension after mitral valve replacement in a randomized, double-blinded clinical trial. PGI<sub>2</sub> and its metabolites are remarkably non-toxic compared with NO. A prominent side-effect of inhaled PGI<sub>2</sub> is inhibition of platelet aggregation. Impaired in vitro platelet aggregation was noted after 2h of inhaled PGI<sub>2</sub> in patients undergoing cardiac surgery, but was not associated with an increase in chest tubes drainage or transfusion requirements even when therapy was continued for 6 h (Lowson, 2002). Systemic hypotension is another potential side effect of inhaled PGI<sub>2</sub>, suggesting that there is a minimal absorption of inhaled PGI<sub>2</sub> from the lungs

into the systemic circulation. Moreover, abrupt withdrawal of inhaled  $\text{PGI}_2$  may cause rebound increases in PH. (Lowson, 2002)

Variable dose delivery, alteration of ventilation volumes, pressures,  $\text{FiO}_2$ , and solvent evaporation with drug-concentrating effect are other obvious disadvantages. Plasma half-life of prostacyclin is 3 to 6 minutes.

- **Iloprost**

Iloprost is a more stable carbacyclin derivative of prostacyclin and can be administered intermittently, as the hemodynamic effects of a single dose are sustained for approximately 60-120 min, although the plasma half-life time of intravenously administered iloprost is known to be between 20-30 min (Theodoraki et al., 2002). This form of treatment appears to be promising combining the advantages of NO and the lack of problems of intravenous administration. Iloprost causes a significant reduction in MPAP and PVR and a significant increase in cardiac output after its administration since there is a substantial reduction in right ventricular afterload. It cannot be ruled out that a decrease in systemic vascular resistance (SVR) may occur during its administration but not to a degree that can affect arterial blood pressure dramatically.

Aerosolized iloprost has been described as a more potent pulmonary vasodilator than NO in patients with PH (Winterhalter et al., 2008). Its longer half-life firstly confers effective protection against the rebound phenomenon and, secondly, may facilitate the pharmacological effective transfer of the inhaler material from the pulmonary into the systemic arterial circulation.

Iloprost remains stable at room temperature and does not undergo any molecular changes on exposure to light, in comparison to  $\text{PGI}_2$  (Fattouch et al., 2003). Also, inhaler iloprost can be rapidly and simply administered intraoperatively, irrespective of ventilator type. Unlike the situation with NO, inhaled iloprost treatment can also be continued with an ultrasonic nebulizer during weaning from the ventilator and after extubation.

Episodes of PH during heart transplantation procedures can be successfully treated with the administration of iloprost without unwanted side effects or significant systemic impact (Theodoraki et al., 2006).

Right heart failure after left ventricular assist device (LVAD) implantation is an acute life-threatening event. In patients with intraoperative severe acute right heart failure after implantation of a LVAD, successful weaning from CPB was possible after inhaled iloprost was added (Winterhalter et al., 2006).

In addition to its beneficial hemodynamic profile, aerosolized iloprost also exerted beneficial effects on arterial oxygenation, which probably reflected the more potent effects of iloprost on the pulmonary vascular bed and the more pronounced increase of mixed-venous oxygen saturation (Hoeper et al., 2000).

- **NO donors**

Inhaled NTG decreases PH without producing systemic vasodilatation (Yurtseven et al., 2003). Further studies are warranted to define their potential utility because nebulization of these drugs does not require an expensive apparatus like the one required for NO nebulization.

- **Phosphodiesterase - 3 inhibitors**

Milrinone inhibits the breakdown of cAMP, thereby promoting pulmonary vasodilatation. There are few recent studies which demonstrated the beneficial effects of inhaled milrinone on PH during weaning of patients from CPB.

Inhaled milrinone prevents pulmonary endothelial dysfunction after CPB, and its hemodynamic and oxygenation profiles are safer than those of intravenous milrinone (Lamarche et al., 2005).

## 6.2 Combination therapy

NO and PGI<sub>2</sub> / iloprost cause vasodilatation via two different intracellular signal pathways by relaxing smooth muscle cells. After diffusion into the smooth muscle cells, NO causes vascular smooth muscle cell relaxation by stimulating guanylate cyclase, leading to an increase in 3,5-cGMP and a reduction in intracellular calcium concentration. By contrast, PGI<sub>2</sub> / iloprost result in an increase in intracellular cyclic 3,5 cAMP concentrations, causing calcium-activated potassium channels to open through activation of adenylyl-cyclase. However these drugs can be administered as combination therapy.

## 6.3 Other drugs

Adenosine activates adenylyl cyclase and stimulates the generation of cAMP. Adenosine is rapidly inactivated with a plasma half-life of less than 10 seconds. In a study performed on ten patients who received an infusion of low-dose adenosine (50 mg/Kg/min) after weaning from CPB a significant reduction in MPAP and PVR and an increase in CO were demonstrated without adverse side effects without any adverse side effects (Fullenrton et al., 1996).

Phosphodiesterase-5-inhibitors such as zaniprast, dipyridamole, and sildenafil have been studied in the field of PH. There have been reports of variable beneficial effects of these agents on PH after cardiac surgery in combination with NO (Ichinose et al., 2001).

Bosentan is an endothelin antagonist which does not act acutely but has shown promising results as a sole agent and as combination chronic therapy for PH (Channick et al., 2004).

# 7. Special aspects of PH

## 7.1 PH in children

PH in children is associated with significant perioperative risk for major complications, including pulmonary hypertensive crisis and cardiac arrest (Friesen & Williams, 2008).

The goals of balanced and cautious anesthetic management are to provide adequate anesthesia and analgesia for the surgical procedure while minimizing increases in PVR and depression of myocardial function.

The development of the aforementioned specific pulmonary vasodilators has led to significant advances in the medical therapy of PH that can be incorporated in the anesthetic management of the pediatric population.

The incidence of complications in children with PH undergoing cardiac catheterization was found to be independent of the method of airway management. Tracheal intubation has been reported to precipitate pulmonary hypertensive crisis and death in critically ill pediatric patients with severe PH, so many anesthesiologists avoid intubation. Similarly, deep extubation can decrease exposure to noxious airway stimulation following selected procedures.

However, similarly to adult patients, PVR can be affected by many other aspects of anesthesia technique such as the inspired oxygen concentration, acid-base management, ventilation mode, drugs, blood products, CPB, pain management and stress response.



Given the multiple factors involved, it is not surprising that no single anesthetic agent has been shown to be ideal for that particular patient population and therefore, balanced anesthesia is preferred.

## 7.2 Anesthetic drugs

Numerous studies (Fischer et al., 2003; Blaise et al., 2003) investigate the effect of anesthetic drugs on pulmonary vascular tone. In general, it appears that the effect of anesthetic agents on the pulmonary circulation is different from their effect on the systemic circulation, often resulting in an increase in PVR.

*Propofol* decreases PAP, PVR as well as mean arterial pressure (MAP) after CPB. Propofol infusion to children undergoing cardiac catheterization decreased SVR significantly and cardiac contractility mildly. In addition, patients with cardiac shunts and fixed elevated PVR (Eisenmenger syndrome) may experience oxygen desaturation because the decrease in SVR will augment right-to-left shunt.

*Etomidate* is known for its lack of systemic hemodynamic effects on patients with heart disease, but its pulmonary vascular effects have not been investigated adequately.

*Thiopental* has been reported to increase PVR in adults, but in children a decrease of PVR by thiopental has been reported. However, thiopental is a less desirable choice for patient with PH, because it can cause significant myocardial depression and systemic hypotension.

An increase in PVR has been observed with *Ketamine* during spontaneous ventilation, but decreases in PVR have been reported during controlled ventilation. This effect makes ketamine the drug of choice for the anesthetic management of patients with PH, particularly of children with congenital heart diseases.

*Benzodiazepines* are associated with minimal hemodynamic effects and are considered useful for preanesthetic premedication.

*Fentanyl* and *sufentanil* have minimal pulmonary and systemic effects and attenuate pulmonary and vascular response to noxious stimuli in adults as well as in children.

*Volatile anesthetics* have variable effects on pulmonary vascular tone. Isoflurane and halothane potentiate the vasodilator response to  $\beta_1$  adrenoceptor activation. Isoflurane, halothane, enflurane and desflurane (but not sevoflurane) inhibit endothelium-dependent relaxation by inhibiting the activity of the adenosine triphosphate-sensitive potassium channels, which mediate the vasodilator effect of many endogenous mediators such as adenosine, PGI<sub>2</sub> and nitric oxide. In general, isoflurane and sevoflurane are associated with clinical pulmonary vasodilatation and are accepted components of a balanced anesthetic technique in patients with PH.

However, volatile anesthetic agents can lead to dose-dependent depression of cardiac contractility and reduction of SVR, which may be problematic. Moreover, volatile anesthetics, when administered in high minimal alveolar concentrations, attenuate hypoxic pulmonary vasoconstriction, thereby exacerbating ventilation-perfusion mismatching.

*Nitrous oxide* increases the pulmonary vascular tone in adult patients undergoing valve surgery preoperatively and postoperatively. In children, it has shown to have little effect on pulmonary hemodynamics.

## 8. Conclusion

In the present chapter, we described the pathogenesis and pathophysiology of PH as well as its perioperative management with specific emphasis in the period following cardiac



surgery. Aspects of perioperative manipulation aiming at optimizing right ventricular function and the application of novel therapeutic modalities were critically presented and evaluated.

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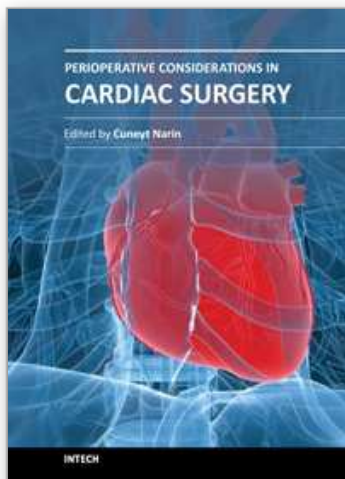
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Edited by Prof. Cuneyt Narin

ISBN 978-953-51-0147-5

Hard cover, 378 pages

**Publisher** InTech

**Published online** 29, February, 2012

**Published in print edition** February, 2012

This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

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Theofani Antoniou and Kassiani Theodoraki (2012). Perioperative Management of Pulmonary Hypertension, Perioperative Considerations in Cardiac Surgery, Prof. Cuneyt Narin (Ed.), ISBN: 978-953-51-0147-5, InTech, Available from: <http://www.intechopen.com/books/perioperative-considerations-in-cardiac-surgery/perioperative-management-of-pulmonary-hypertension-2>

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