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# A Pathophysiological Approach to Understanding Pulmonary Hypertension in Cardiac Surgery

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## 1. Introduction

Pulmonary hypertension (PH) is associated with increased morbidity and mortality and is an important prognostic factor in cardiac surgery. As the average age and associated comorbidities of cardiac surgical patients increase, the prevalence of PH is likely to rise. In this chapter, we will define PH, classify it on the basis of pathophysiological etiology, and suggest treatment therapies according to this classification. The importance of PH in cardiac surgery, its relationship to right ventricular dysfunction and preventive therapies will also be discussed. When applicable, we will draw from our clinical experience with PH to suggest strategies for the prevention of possible complications.

## 2. Definition of pulmonary hypertension

### 2.1 Hemodynamic parameters used in clinical settings

There are several hemodynamic parameters used in defining PH (Table 1) (Gomez & Palazzo, 1998). These definitions have been used in various studies.

### 2.2 Diagnosis in awake and anesthetized patients

Pulmonary hypertension is usually diagnosed prior to cardiac surgery in awake patients. The diagnosis is obtained either directly by cardiac catheterization or indirectly by using Doppler signals from transesophageal echocardiography (TEE) and using Bernoulli's equation. In the presence of tricuspid regurgitation, the simplified Bernoulli's equation gives an estimation of the pressure gradient across the tricuspid valve (Fig. 1) (Denault et al., 2010a). This pressure gradient is equal to the difference in systolic pressure between the right ventricle (RV) and the right atrium. Therefore, with the measurement of right atrial pressure ( $P_{ra}$ ), the estimation of systolic right ventricular pressure ( $P_{rv}$ ) is possible. In the absence of right ventricular outflow tract obstruction (RVOTO) and pulmonic valve stenosis, systolic  $P_{rv}$  represents a reliable estimation of the systolic pulmonary artery pressure (SPAP).

Hemodynamic parameter	Normal value	Abnormal value
Systolic pulmonary artery pressure (SPAP)	15-30 mmHg	> 30 or $\geq$ 40 mmHg
Mean pulmonary artery pressure (MPAP)	9-16 mmHg	Moderate > 18 mmHg Significant > 25 mmHg Exercise-induced > 30 mmHg
Pulmonary vascular resistance (PVR) = (MPAP - PAOP) X 80/CO	60-120 dyn sec $\text{cm}^{-5}$	Mild > 125 dyn sec $\text{cm}^{-5}$ Moderate > 200-300 dyn sec $\text{cm}^{-5}$ Severe > 600 dyn sec $\text{cm}^{-5}$
Indexed pulmonary vascular resistance (PVRI) = (MPAP - PAOP) X 80/CI	250-340 dyn sec $\text{cm}^{-5} \cdot \text{m}^{-2}$	> 340 dyn sec $\text{cm}^{-5} \cdot \text{m}^{-2}$
Pulmonary to systemic vascular resistance index (PVRI/SVRI) X 100%	$\leq$ 10%	> 10%
Transpulmonary gradient (MPAP - PAOP)	$\leq$ 14 mmHg	> 14 mmHg
Mean pulmonary to systemic pressure ratio (MPAP/MAP) X 100%	< 25%	Moderate 33-50% Severe > 50%
Mean systemic to pulmonary pressure ratio (MAP/MPAP) X 100%	$\geq$ 4	< 4 (Robitaille et al., 2006)

CI: cardiac index; CO: cardiac output; MAP: mean arterial pressure; PAOP: pulmonary artery occlusion pressure; SVRI: indexed systemic vascular resistance. Adapted from Gomez (Gomez & Palazzo, 1998).

Table 1. Definitions of Pulmonary Hypertension Used in Clinical Settings

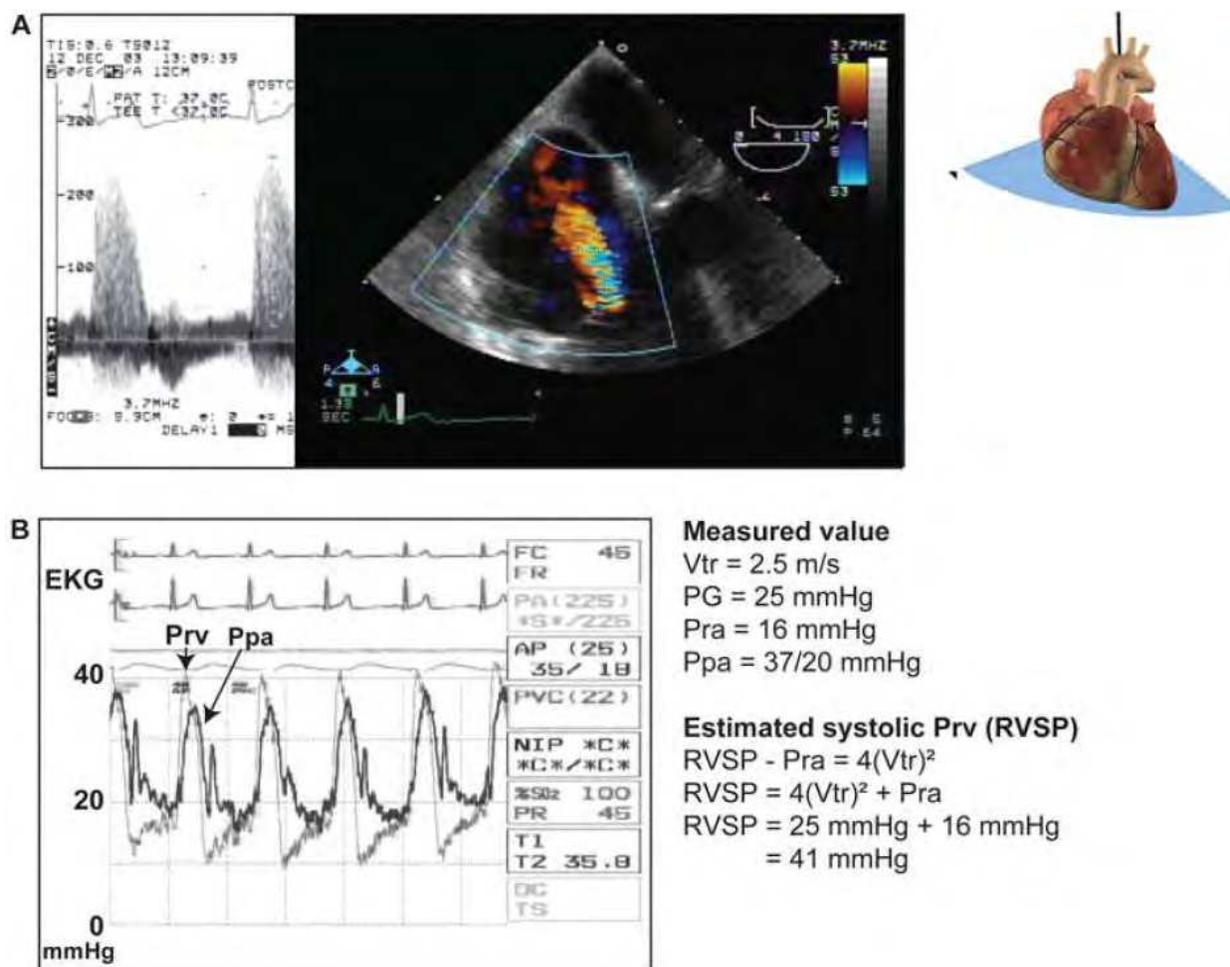


Fig. 1. (A) Estimation of right ventricular systolic pressure (systolic Prv or RVSP) using the pressure gradient (PG) obtained from tricuspid regurgitation (TR) and right atrial pressure (Pra). (B) Note that the RVSP is higher than the systolic pulmonary artery pressure (Ppa) due to a small gradient across the pulmonic valve. (EKG: electrocardiogram; V: velocity). With permission from Denault *et al.* (Denault *et al.*, 2010a).

### 2.3 Comparison of absolute and relative values in the assessment of pulmonary hypertension

Following the induction of general anesthesia, a reduction in both the systemic and the pulmonary artery pressures is observed. Consequently, using absolute values of SPAP in defining PH would underestimate its severity. To address this issue, Robitaille *et al.* studied 1557 patients undergoing cardiac surgery (Robitaille *et al.*, 2006). In the 32 patients with preoperative PH, induction of general anesthesia resulted in a significant reduction in mean arterial pressure (MAP) and mean pulmonary artery pressure (MPAP) but the ratio of MAP/MPAP remained stable (Fig. 2). The normal value for this ratio is > 4, and lower values can be used to quantify the severity of PH.

The relevance of the MAP/MPAP ratio was demonstrated after comparing its ability to estimate the probability of postoperative complications with the ability of other normally used hemodynamic parameters for this purpose (listed in Table 1). Values of the ratio obtained after induction of general anesthesia but before cardiopulmonary bypass (CPB) in 1439 patients undergoing cardiac surgery showed similar trend when compared to other

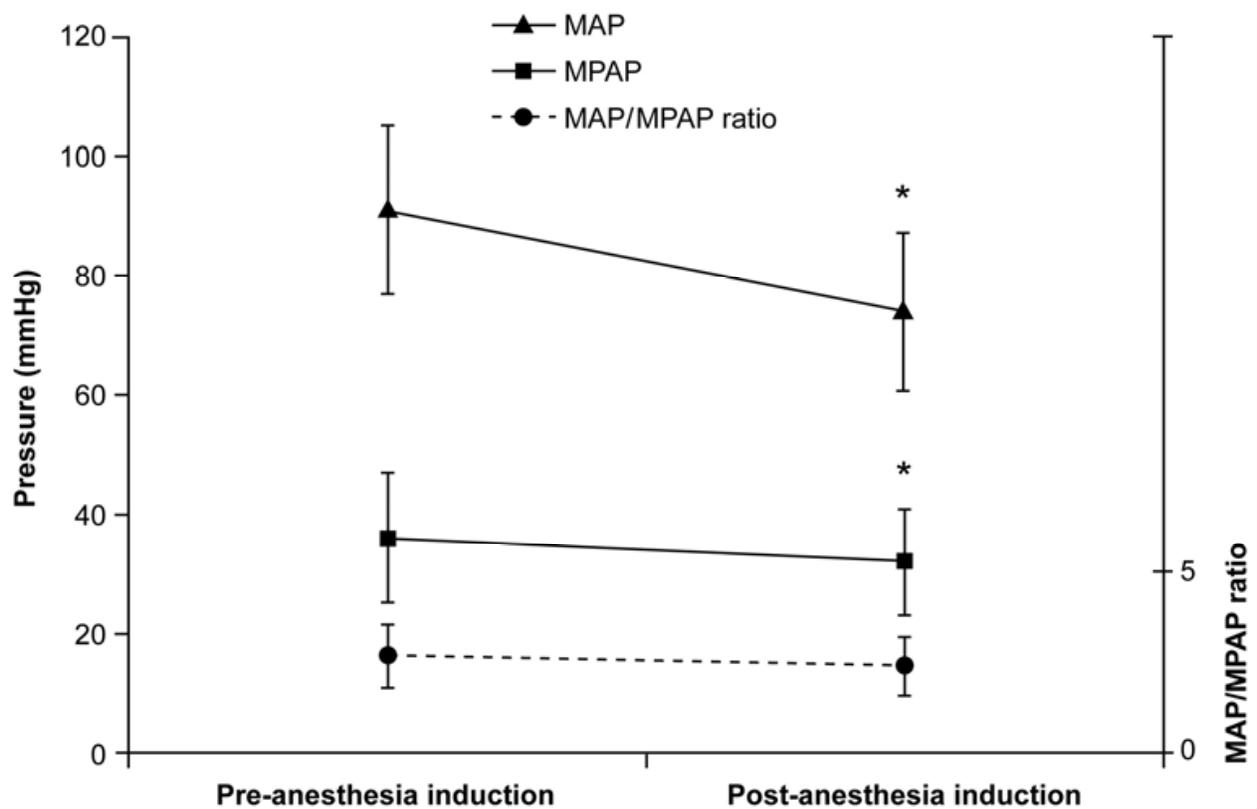


Fig. 2. Changes in mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), and the MAP/MPAP ratio after the induction of anesthesia in 32 patients with preoperative pulmonary hypertension. No significant change in the MAP/MPAP ratio was observed (\* $p < 0.05$ ). (Robitaille et al., 2006)

hemodynamic parameters (Fig. 3). Furthermore, the ratio turned out to be the best predictor of perioperative complications, defined as death, need for intra-aortic balloon pump, cardiac arrest, or use of vasoactive support for more than 24 hours.

An abnormal MAP/MPAP ratio was also recognized to be significantly correlated with abnormal systolic and/or diastolic cardiac function (Fig. 4) (Robitaille et al., 2006). The use of relative instead of absolute values to estimate PH is currently used in congenital cardiology (Therrien et al., 2001a; Therrien et al., 2001b).

In summary, the evaluation and diagnostic of PH in cardiac surgical patients must be done using specific criteria. In awake patients, the absolute values can be used since they correlate well with outcomes. However, in patients under general anesthesia, the ratio of MAP/MPAP allows to screen for PH when systolic blood pressures are lower due to the anesthetic agents.

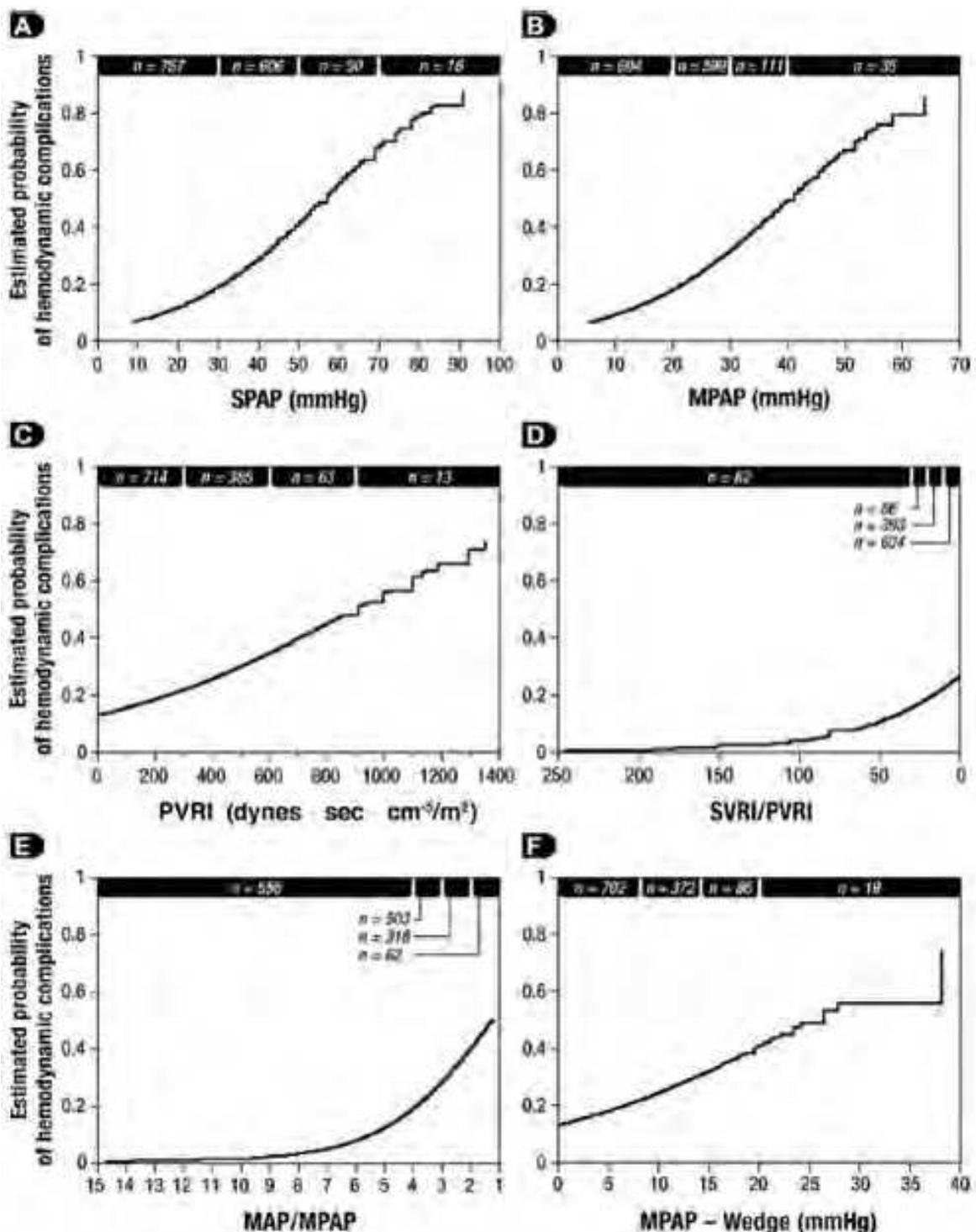


Fig. 3. Relationship between the estimated probability of hemodynamic complications and variables used in the evaluation of pulmonary hypertension: (A) systolic pulmonary artery pressure (SPAP), (B) mean pulmonary artery pressure (MPAP), (C) indexed pulmonary vascular resistance (PVRI), (D) systemic to pulmonary vascular resistance index ratio (SVRI/PVRI), (E) mean systemic to pulmonary pressure ratio (MAP/MPAP), and (F) transpulmonary gradient defined as MPAP - Wedge or pulmonary artery occlusion pressure (PAOP). For easier comparison, the scale of the x axis of the SVRI/PVRI and the MAP/MPAP are inverted. (n = number of patients). (Robitaille et al., 2006)

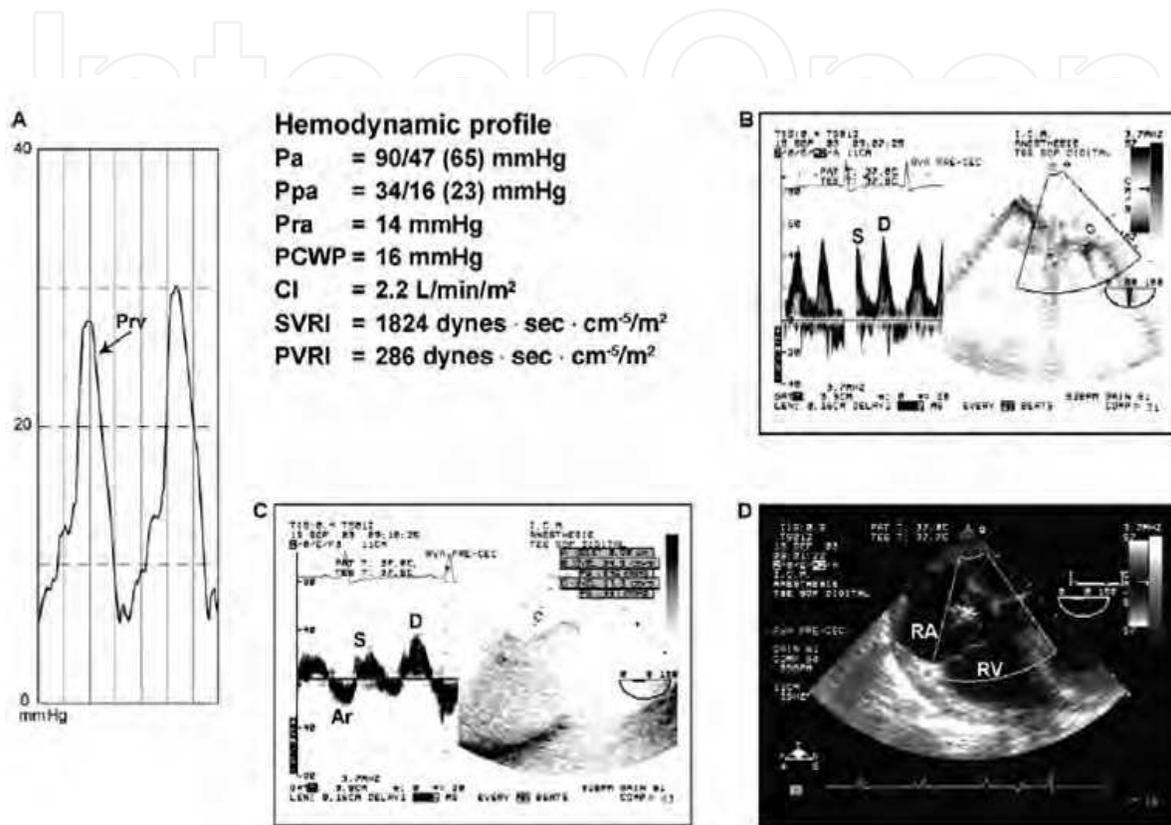


Fig. 4. Hemodynamic and transesophageal echocardiographic evaluation of a 46-year-old woman scheduled for aortic valve surgery. Despite a normal pulmonary artery pressure (Ppa) of 34/16 mmHg and pulmonary vascular resistance index (PVRI) at 286 dyn · s · cm<sup>-5</sup> · m<sup>-2</sup>, this patient had an abnormal right ventricular diastolic filling pressure waveform characterized by a rapid upstroke (A) and reduced systolic (S) to diastolic (D) pulmonary (B) and hepatic (C) venous flows consistent with left and right ventricular diastolic dysfunction. In addition, a dilated right atrium and ventricle were present without significant tricuspid regurgitation in a mid-esophageal right ventricular view (D). The mean systemic to pulmonary pressure ratio (MAP/MPAP) was 65/23 or 2.8. (CI: cardiac index; Pa: arterial pressure; PCWP: pulmonary capillary wedge pressure; Pra: right atrial pressure; Prv: right ventricular pressure; RA: right atrium; RV: right ventricle; SVRI: systemic vascular resistance index). (Robitaille et al., 2006)

### 3. Classification of pulmonary hypertension based on pathophysiology and etiology

The 2008 World Symposium on PH endorsed by The World Health Organization (WHO) proposed a classification system divided into 5 groups: 1) Pulmonary arterial hypertension, 2) PH owing to left heart disease, 3) PH owing to lung diseases and/or hypoxia, 4) Chronic thromboembolic PH, and 5) PH with unclear or multifactorial etiologies (Simonneau et al., 2009). In cardiac surgery, PH is more frequently classified as pre-capillary, capillary or post-capillary, depending on the site where the underlying cause of PH is found. In this context, PH during cardiac surgery is typically post-capillary since the cause is mainly of left ventricular (LV) origin, past the pulmonary capillary bed. To confirm this diagnosis, pulmonary artery catheterization can be used to demonstrate an equal value for diastolic pulmonary artery pressure (DPAP) and pulmonary artery occlusion pressure (PAOP). When the cause for PH is at the pre-capillary or capillary level, in absence of tachycardia, DPAP is significantly higher than PAOP (Gomez & Palazzo, 1998).

The causes underlying PH in cardiac surgery can be complex and may result from several mechanisms acting alone or in combination (Fig. 5). These mechanisms may exist before the operation or appear during or after the procedure. Exacerbation of PH may happen at any time during cardiac surgery, before, during or after CPB. Indeed, patients are at risk of LV failure at all times, especially after CPB when the reperfusion of the ischemic lungs can cause pulmonary reperfusion syndrome. Finally, PH can persist postoperatively secondary to a patient-prosthesis-mismatch (PPM) after mitral or aortic valve replacement. The treatment of PH is based on the identification of its etiology, whence the importance of distinguishing between the different pathophysiologicals.

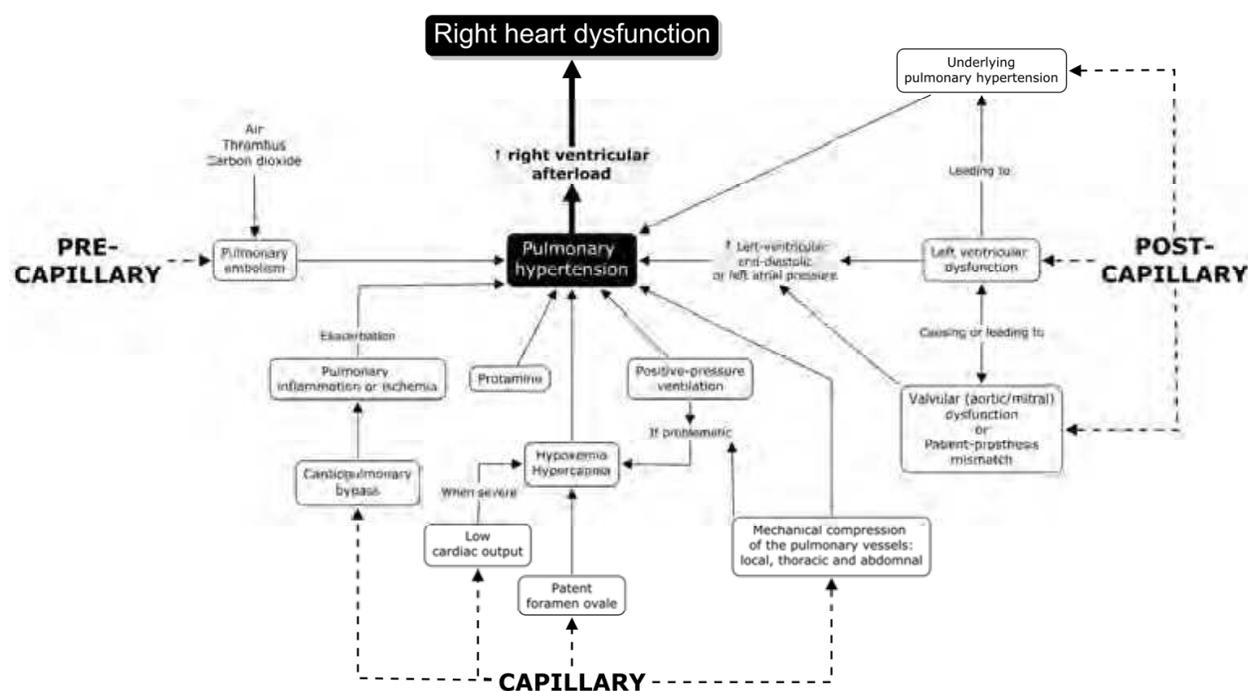


Fig. 5. Major mechanisms of pulmonary hypertension in cardiac surgery. Other mechanisms may be operating at several levels: for instance, hypoxia (capillary) may lead to pulmonary hypertension, right ventricular systolic failure and, through interventricular interaction, left ventricular diastolic function (post-capillary).

### 3.1 Review of the factors involved

The most important causes of PH in cardiac surgery, illustrated in Fig. 5, are classified according to their originating anatomical site: pre-capillary, capillary and post-capillary.

#### 3.1.1 Pre-capillary

##### Pulmonary embolism

Pulmonary embolism is an example of a pre-capillary PH. It may occur before, during or after CPB leading to the development or the exacerbation of PH. Thrombus, air and even carbon dioxide (Martineau et al., 2003) can cause pulmonary embolism. Pulmonary embolisms are rare in the immediate cardiac postoperative period. However, patients at risk include patients with predisposing factors to PH and patients with chronic thromboembolic pulmonary hypertension (CTEPH) (Fig. 6). The incidence of CTEPH is uncertain, but it represents a frequent cause of PH occurring in up to 4% of patients after an acute pulmonary embolism (Pengo et al., 2004; Tapson & Humbert, 2006).

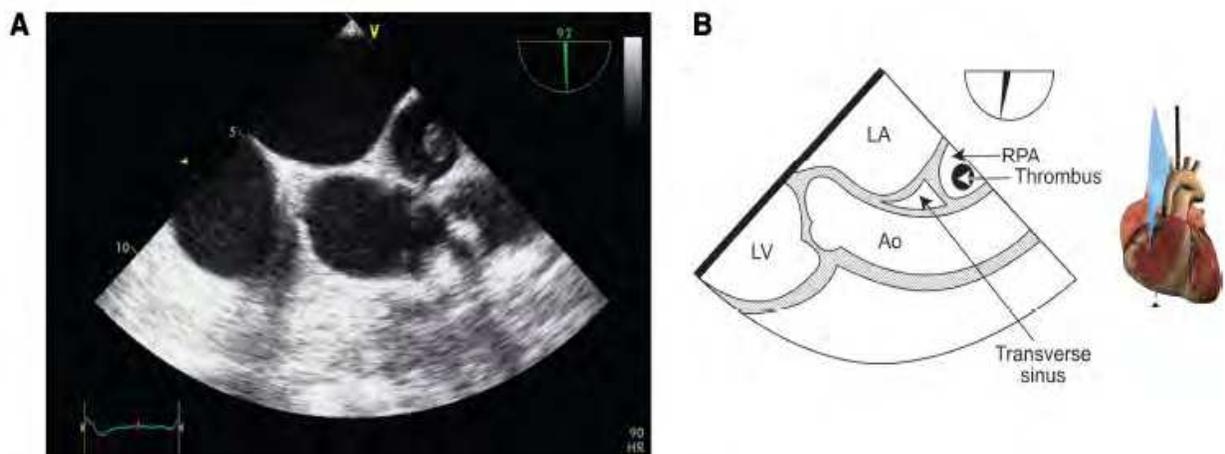


Fig. 6. Chronic pulmonary embolism. (A, B) Mid-esophageal ascending aorta (Ao) long-axis view in a 65-year-old woman with chronic pulmonary embolism shows the mobile clot adherent to the right pulmonary artery (RPA) wall. (LA: left atrium; LV: left ventricle). With permission from Denault *et al.* (Denault et al., 2010a).

#### 3.1.2 Capillary

##### Cardiopulmonary bypass

Pulmonary damage during cardiopulmonary bypass (CPB) is one of the important etiologies of PH in cardiac surgery. This is mainly due to the fact that the lungs are ischemic during CPB. The underlying mechanisms include 1) release of cytokines through endotoxin production (Downing & Edmunds, Jr., 1992), 2) complement activation and 3) ischemia reperfusion injury (Wan et al., 1997; Asimakopoulos et al., 1999) which leads to the production of free radicals, endothelin and prostacyclin derivatives with nitric oxide inhibition (Wan et al., 1997). The resulting systemic inflammatory response, pulmonary reperfusion syndrome as well as the transfusion of blood products may all exacerbate PH (Fig. 7) (Lesage et al., 1966; Kaul & Fields, 2000).

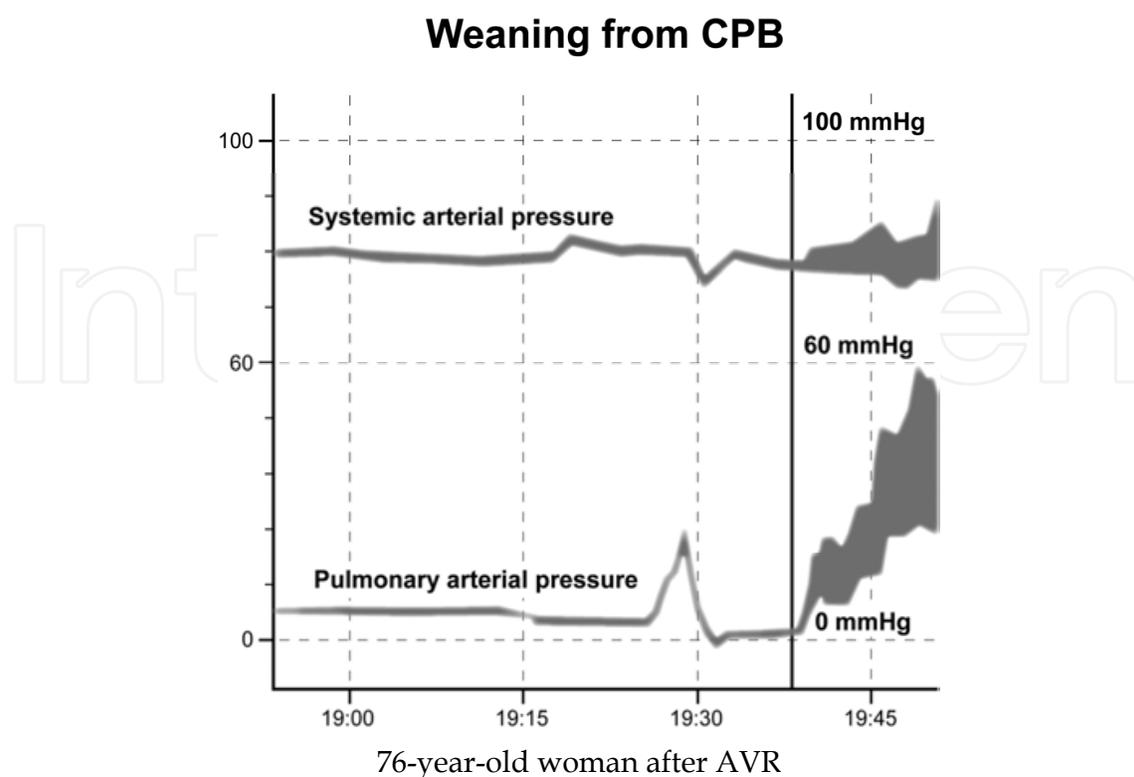


Fig. 7. Unexpected pulmonary hypertension upon weaning from cardiopulmonary bypass (CPB) in a 76-year-old woman after aortic valve replacement (AVR). The CPB duration was 71 minutes. A significant increase in pulmonary arterial pressure in relation to the systemic arterial pressure was observed as the patient was weaned from CPB. No mechanical causes were found.

During CPB, blood is exposed to an artificial surface for oxygenation before it is sent back into the systemic circulation. This is associated with an inflammatory reaction secondary to endothelial activation, activation of the complement cascade, neutrophils, thrombin and platelets. Since the heart and lungs do not receive blood during CPB, cardioplegia solutions are used to preserve heart function, however, no specific protection is undertaken for the pulmonary circulation. In some patients, this may result in pulmonary reperfusion syndrome associated with postoperative endothelial dysfunction and PH or in post-CPB respiratory distress syndrome. The latter phenomenon, similar to the respiratory distress syndrome in adults, is characterized by an increased capillary permeability leading to a reduction in oxygenation, increased alveolar-arterial gradient, decreased lung compliance, increased pulmonary vascular resistance (PVR), and exacerbation of preoperative PH. Activation of the endothelin system during CPB increases endothelin ET-1 concentrations and correlates with CPB duration, severity of PH and post-CPB myocardial dysfunction. For this reason, CPB duration plays a major role in the incidence of mortality in cardiac surgery. Post-CPB PH can lead to RV dysfunction which, when severe, is fraught with a 44 to 86% mortality rate.

#### Protamine

The administration of protamine can induce catastrophic pulmonary vasoconstriction in up to 1.8% of patients (Ocal et al., 2005). Protamine is administered in CPB to neutralize the

anti-clotting effects of heparin and has the capacity to activate the complement cascade. Thus, when given at the end of CPB, it can induce PH associated with adverse hemodynamic responses that range from minor perturbations to cardiovascular collapse, and may occur in three forms: systemic hypotension, anaphylactoid reaction and catastrophic PH (Viaro et al., 2002). The mechanism of protamine-induced PH is thought to be caused by an imbalance of vasoconstrictors and vasodilators leading to a reduction in nitric oxide release from the pulmonary vasculature (Viaro et al., 2002).

### Lung diseases and/or hypoxia

In this category, the predominant cause of PH is alveolar hypoxia as a result of impaired control of breathing or lung disease.

Lung volumes exert a differential effect on the resistance of intra- and extra-alveolar vessels, which accounts for the unique U-shaped relationship between lung volume and pulmonary vascular resistance (PVR) (Fig. 8). At functional residual capacity (FRC), PVR is minimal but increases at large or total lung capacity (TLC) and small lung volumes. Clinically, this may be observed when hyperinflation of the lungs greatly increases PVR (Fischer et al., 2003).

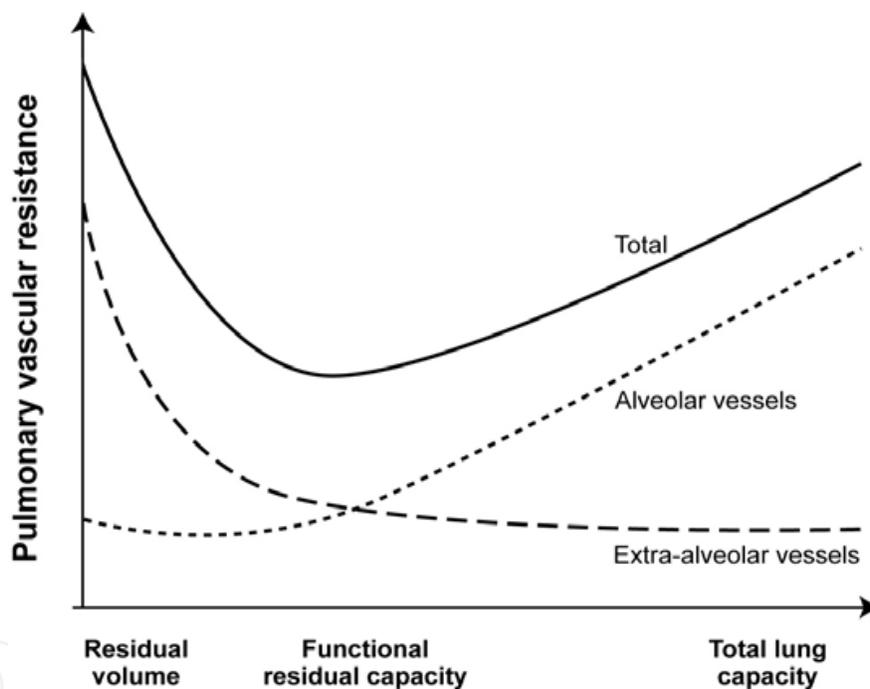


Fig. 8. Relationship between lung volume and pulmonary vascular resistance (PVR). At functional residual capacity (FRC) PVR is minimal and increases at large or total lung capacity (TLC) and residual volume decreases at small lung volumes. The differential effect on intra- and extra-alveolar vessels accounts for the U-shaped relationship of PVR and lung volume. Adapted from Fischer *et al.* (Fischer et al., 2003).

Changes in cardiac output (CO), airway pressure, and gravity may affect the pulmonary circulation. Therefore, patients with PH already have a restricted pulmonary circulation and increases in oxygen demand may further worsen PH and lead to right heart failure.

Application of high levels of positive end-expiratory pressure (PEEP) may narrow capillaries in well-ventilated lung areas (intra-alveolar) and divert blood flow to less well-ventilated or non-ventilated areas (extra-alveolar). Thus, intrapulmonary shunts may result in desaturation of mixed venous blood, potentially leading to hypoxia.

Hypoxia may also be caused by right-to-left intracardiac shunting through a patent foramen ovale (PFO) or a congenital heart defect. Pulmonary hypertension can lead to RV dysfunction causing increased pressure in the right atrium. In turn, the increase in  $P_{ra}$  may result in opening of a PFO, present in 20-30% of the general population (Sukernik et al., 2001), increasing the severity of hypoxia. In contrast to systemic arteries, pulmonary vessels constrict with hypoxia (Euler-Liljestrand reflex) and dilate in the presence of hyperoxia (Fischer et al., 2003), which explains the exacerbation of PH with hypoxia.

Hypercapnia can occur especially in the case of acute lung injury during or after the procedure. The increase in partial pressure of carbon dioxide ( $PCO_2$ ) will cause vasoconstriction and therefore worsen PH.

Increases in CO distend open vessels and recruit previously closed vessels so that when the cross-sectional area of pulmonary circulation increases, PVR decreases.

Mechanical compression of pulmonary vessels is transmitted to the surrounding cardiac pressure and contributes to increase PAP. Hemothorax or tension pneumothorax may be responsible for an elevation in intrathoracic pressure.

In addition, gravity influences blood flow in the pulmonary circulation. Both regional blood flow and ventilation are greater in the dependent areas of the lung (intra-alveolar). Hence, the relationship between alveolar and hydrostatic pressure bears important clinical consequences.

Multiple molecular pathways are involved in the regulation of PVR, namely nitric oxide, prostacyclin, endothelin-1 and serotonin pathways (Humbert et al., 2004). Nitric oxide and prostacyclin are endogenous vasodilators produced in the pulmonary vascular endothelium. Endothelin-1 is an endogenous vasoconstrictor peptide secreted by the vascular endothelium and plays a role in pulmonary vasoconstriction and vascular smooth muscle proliferation (McLaughlin & McGoon, 2006). The neurotransmitter serotonin and the serotonin receptor transporter are also involved in the regulation of pulmonary vascular tone. Therefore, an imbalance in these pathways may result in vasoconstriction and vascular remodelling, potentially leading to progressive pulmonary vascular disease.

### 3.1.3 Post-capillary

#### Left heart disease

Left ventricular disease represents the most frequent cause of PH in cardiac surgery (Oudiz, 2007). Left-sided dysfunction includes three distinct etiologies: systolic dysfunction, diastolic dysfunction, and valvular heart disease (mitral and/or aortic). Pre- or postoperative left-sided ventricular or valvular diseases may produce an increase in left atrial pressure, with passive backward transmission of the pressure leading to increased PAP. The elevation of PAP and PVR is due to either the increase of pulmonary artery vasomotor tone and/or pulmonary vascular remodeling (Delgado et al., 2005; Moraes et al., 2000).

#### Patient-prosthesis mismatch

Aortic patient-prothesis mismatch (PPM) through a reduction in coronary reserve would also contribute to postoperative PH (Bakhtiary et al., 2007) and persistent postoperative valvular gradients (Fig. 9). There is general agreement that the postoperative indexed effective orifice area (EOA) of the prosthesis being implanted should not be  $< 0.85$  to  $0.90$   $cm^2/m^2$ . Mitral PPM was recently described as another cause of residual postoperative PH. Magne *et al.*

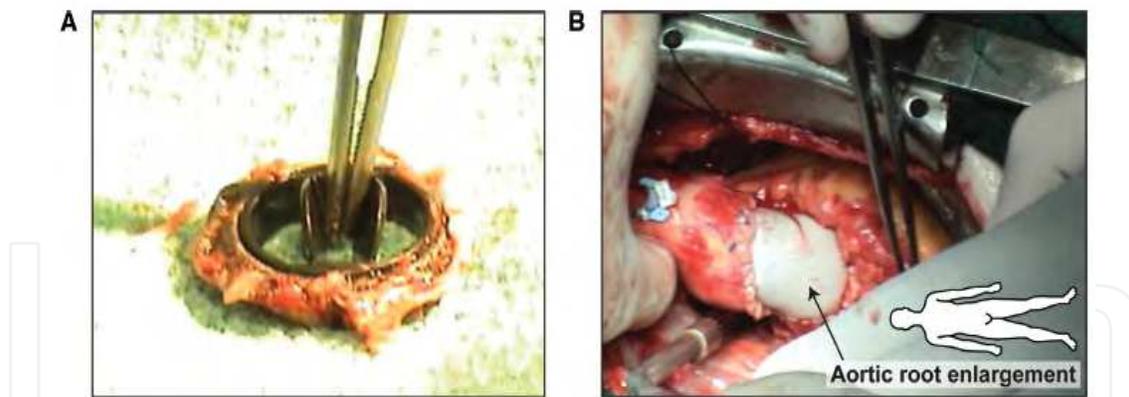


Fig. 9. Patient-prosthesis aortic valve mismatch. A 71-year-old man with a body surface area of 1.89 m<sup>2</sup> was re-operated for symptoms of severe aortic valve stenosis. He had an aortic valve replacement (AVR) 4 years before with a Carbomedics 19 mm mechanical bileaflet prosthesis (non-indexed effective orifice area = 1.06 cm<sup>2</sup>). (A) The preoperative mean gradient was 41 mmHg although the intraoperative inspection of the prosthetic valve was completely normal. (B) Intraoperative view of an aortic root enlargement procedure in a 69-year-old patient with a reduced aortic diameter requiring AVR. Courtesy of Dr. Michel Carrier. With permission from Denault *et al.* (Denault *et al.*, 2010a).

(Magne *et al.*, 2007) studied 929 patients who underwent mitral valve replacement (MVR), following them up to 15 years. Mitral valve PPM was defined according to the indexed valve EOA as not clinically significant (EOA > 1.2 cm<sup>2</sup>/m<sup>2</sup>), moderate (1.2 cm<sup>2</sup>/m<sup>2</sup> ≥ EOA > 0.9 cm<sup>2</sup>/m<sup>2</sup>), and severe (EOA ≤ 0.9 cm<sup>2</sup>/m<sup>2</sup>). Prevalence of moderate and severe PPM was 69% and 9%, respectively. In addition, severe PPM was found to be associated with residual PH and a 3-fold increase in postoperative mortality after adjustment for other risk factors. This relevant new finding is currently absent from the majority of studies involving predictors of survival in mitral valve surgery.

#### 4. Treatment of pulmonary hypertension in cardiac surgery based on pathophysiology and etiology

The approach to pharmacological and non-pharmacological treatment of PH will be directed towards the cause or the consequence of PH, as illustrated in Fig. 5. Most often, treatment of the underlying mechanism causing PH requires non-pharmacological approaches, while pharmacological approaches will usually be the solution for the treatment of persisting PH and its consequence, RV failure.

##### 4.1 Pharmacological and non-pharmacological approaches

Therapeutic management of PH has dramatically improved in the last years, offering both relief from symptoms and prolonged survival. However, there is still no cure for this disease. Moreover, in presence of PH, the choice of the appropriate therapy should rely on evidence-based medicine. By performing a Medline search using the keywords 'randomized controlled trial', 'humans', 'adults', 'pulmonary hypertension' and 'English', a total of 14 articles in cardiac surgery were retrieved. These publications were then classified according to their levels of evidence (Sackett, 1989; Moher *et al.*, 2001) and summarized in Table 2. Most of the studies reviewed were based on a small number of patients and had

Author	Country	Date	Agents used	Design	N	Inclusion criteria	Primary end-point	Efficacy	Level of evidence
Fernandes <i>et al.</i>	Brazil	2011	iNO vs oxygen	Single-center	29	MVR + PH after surgery	Hemodynamic	Yes	A1b
Kim <i>et al.</i>	Korea	2010	oral sildenafil + beraprost vs placebo	Single-center	50	PH before surgery	Hemodynamic	No	A1b
Khan <i>et al.</i>	USA	2009	iPGI <sub>2</sub> vs iNO	Crossover Single-center	25	PH, refractory hypoxemia, or RV dysfunction	Hemodynamic and oxynegation	Idem	A1b
Wang <i>et al.</i>	China	2009	Inhaled milrinone vs intravenous milrinone	Single-center	48	MVR + PH after surgery	Hemodynamic	Yes	A1b
Fattouch <i>et al.</i>	Italy	2006	iPGI <sub>2</sub> vs iNO vs intravenous vasodilators	Single-center	58	MVR + PH before the end of CPB	Hemodynamic	Yes	A1b
Ocal <i>et al.</i>	Turkey	2005	iPGI <sub>2</sub> vs NTG	Multicenter	68	CABG with protamine reaction after CPB	Hemodynamic	Yes	A1b
Stafford <i>et al.</i>	USA	2005	Heparinase vs protamine	Multicenter	167	CABG on + off pump after CPB	Bleeding	No	A1b
Fattouch <i>et al.</i>	Italy	2005	iPGI <sub>2</sub> vs iNO vs intravenous vasodilators	Single-center	58	MVR + PH in the intensive care unit	Hemodynamic	Yes	A1b
Hache <i>et al.</i>	Canada	2003	iPGI <sub>2</sub> vs placebo	Single-center	20	PH before CPB	Hemodynamic	Yes	A1b
Solina <i>et al.</i>	USA	2001	iNO vs milrinone	Single-center	62	PH after surgery	Hemodynamic	Yes	B
Feneck <i>et al.</i>	UK	2001	Milrinone vs dobutamine	Multicenter	120	CO < 2 L/min/m <sup>2</sup> et PAOP > 10 mmHg after cardiac surgery	Hemodynamic	Idem	A1b
Solina <i>et al.</i>	USA	2000	iNO vs milrinone	Single-center	45	PH after surgery	Hemodynamic	Yes	A1b
Schmid <i>et al.</i>	Switzerland	1999	iNO vs NTG vs PGE <sub>1</sub>	Crossover Single-center	14	PH after surgery	Hemodynamic	Idem	B
Hachenberg <i>et al.</i>	Germany	1997	Enoximone vs dobutamine+NTG	Single-center	20	PH in MVR before and after surgery	Hemodynamic	Idem	A1b

CABG: coronary artery bypass graft; CO: cardiac output; CPB: cardiopulmonary bypass; iNO: inhaled nitric oxide; iPGI<sub>2</sub>: inhaled prostacyclin; MVR: mitral valve replacement; NO: nitric oxide; NTG: nitroglycerin; PAOP: pulmonary artery occlusion pressure; PGE<sub>1</sub>: prostaglandin E<sub>1</sub>; PGI<sub>2</sub>: prostacyclin; PH: pulmonary hypertension; RCT: randomized controlled trial; UK: United Kingdom; USA: United States of America.

Table 2. Randomized Controlled Trial in the Treatment of Pulmonary Hypertension in Adult Cardiac Surgery

hemodynamic changes as their primary end-points. Various pharmacological agents were studied: inhaled prostacyclin I<sub>2</sub> (iPGI<sub>2</sub>), inhaled nitric oxide (iNO), heparinase, protamine and intravenous vasodilators including prostaglandin E<sub>1</sub> (PGE<sub>1</sub>), nitroglycerin (NTG), nitroprusside, milrinone, enoximone, dobutamine, oral sildenafil, beraprost and oxygen. Findings on pharmacological and non-pharmacological approaches for the treatment of PH in cardiac surgery will be discussed together in this section.

#### 4.1.1 Pre-capillary

##### Pulmonary embolism

Acute pulmonary embolism during cardiac surgery can lead to PH and, in some cases, evolve into CTEPH. Pulmonary thromboembolism, when surgically indicated, can help control PH and is currently the only curative treatment in patients with CTEPH (Jamieson & Nomura, 2000; Jamieson et al., 2003) (Fig. 6). In case of CTEPH, evaluation of the feasibility of surgery mainly depends on the location of the obstruction (central vs. more distal pulmonary arteries) (Dartevelle et al., 2004). Patients who are not candidates for surgery may also benefit from PH-specific medical therapy, however, the use of these medications in CTEPH requires further evaluation in randomized controlled trials (Jais et al., 2008; Rubin et al., 2006; Suntharalingam et al., 2008).

The rationale for systemic anticoagulant therapy for chronic lung embolism in patients with PH may be justified by well-recognized risk factors for venous thromboembolism, such as heart failure, a sedentary lifestyle, and a thrombophilic predisposition (Bjornsson & Edwards, 1985). However, no data actually support anticoagulant therapy specifically in patients with PH. Warfarin has been evaluated in only two nonrandomized studies, one retrospective and the other prospective, involving a small number of patients (Fuster et al., 1984; Rich et al., 1992).

#### 4.1.2 Capillary

##### Cardiopulmonary bypass

As discussed, CPB causes pulmonary damage during surgery through different mechanisms, potentially leading to PH but, more frequently, it contributes to the exacerbation of PH caused by other factors during the surgical procedure. In this context, patients can benefit from PH-specific medical therapy (Table 2) and prophylactic treatments for PH use in cardiac surgery, which will be discussed later in this chapter.

In 62 patients with preoperative PH (PVR > 125 dyn sec cm<sup>-5</sup> immediately before induction of anesthesia) Solina *et al.* (Solina et al., 2001) explored the dose-responsiveness of 10, 20, 30 and 40 ppm of iNO administered upon termination of CPB in comparison to an intravenous bolus of 50 mg/kg of milrinone given 15 minutes before separation from CPB followed by a 0.5 mg/kg/min regimen administered in the operating room thereafter. Treatment with iNO was associated with significant reductions in PVR at all doses but no improved benefit was observed for doses higher than 10 ppm. No significant difference was observed between iNO and milrinone in terms of reduction in PVR and inotropic requirement.

The same team compared 20 and 40 ppm of iNO to the same dose of intravenous milrinone in 45 patients after cardiac surgery (Solina et al., 2000). Study drugs were administered upon termination of CPB for a 24h-period in the intensive care unit (ICU). The group receiving 20 ppm iNO had a significantly higher MAP while the group receiving 40 ppm had higher

right ventricular ejection fraction (RVEF) on arrival in the ICU. The milrinone group required significantly more phenylephrine in the ICU with a trend towards higher heart rates.

In a crossover study, Schmid *et al.* (Schmid *et al.*, 1999) compared iNO, PGE<sub>1</sub> and NTG in 14 adult patients with severe PH (MPAP > 30 mmHg; PVR > 300 dyn·sec·cm<sup>-5</sup>) after cardiac surgery. The investigation was performed in the ICU within the first 24 h after the procedure. The generalization of results obtained from this study was limited, since it only included patients in stable postoperative circulatory conditions. However, in contrast to PGE<sub>1</sub> and NTG, iNO decreased PVR without exerting concomitant systemic vasodilatory effects. In addition, iNO did not affect the right coronary perfusion pressure and increased oxygen transport.

### **Protamine**

The administration of protamine can be associated with severe PH followed by RV failure. This condition requires immediate treatment. In coronary artery bypass graft (CABG) patients ( $n=3800$ ), Ocal *et al.* (Ocal *et al.*, 2005), two therapeutic approaches were compared for the treatment of the protamine reaction observed in 68 of them (1.8%). One group received iPGI<sub>2</sub> and the other intravenous NTG in addition to standard vasoactive agents. The iPGI<sub>2</sub> group showed improved hemodynamics and only 14 patients (39%) had to return to CPB compared with all 30 patients (100%) in the NTG group. A trend towards a shorter length of stay in the ICU and reduced mortality was observed in the iPGI<sub>2</sub> group, but the numbers were too small to achieve statistical significance.

In order to avoid protamine reaction, heparinase I, a heparin degrading enzyme, was compared to protamine in a multicenter randomized controlled trial (Stafford-Smith *et al.*, 2005). The prevention of protamine-induced PH was also explored as a secondary endpoint. Heparinase I was not associated with a reduction in bleeding or reduction in the need for intervention in the treatment of PH.

### **Lung diseases and/or hypoxia**

Low CO during cardiac surgery may affect the pulmonary circulation, potentially leading to hypoxia and worsen PH and RV failure. Thus, an acute perioperative low-output state should be reversed whenever possible before clinical manifestation of chronic hypoperfusion and organ dysfunction.

Khan *et al.* (Khan *et al.*, 2009) compared iNO to iPGI<sub>2</sub> in 25 heart and lung transplant recipients with PH, refractory hypoxia, or RV dysfunction. Patients were randomized to iNO (20 ppm) or iPGI<sub>2</sub> (20,000 ng/ml) as initial treatment in the operating room, followed by a crossover to the other agent after 6 hours. Both iNO and iPGI<sub>2</sub> reduced PAP and central venous pressure (CVP), and improved cardiac index (CI) and mixed venous oxygen saturation on initiation of therapy. At the 6-hour crossover trial, there were no significant differences between groups in the reduction of PAP and CVP, and the improvement of CI and mixed venous oxygen saturation on initiation of therapy. Neither iNO nor iPGI<sub>2</sub> affected the oxygenation index or systemic blood pressure.

In the case of chronic hypoxia, supplemental oxygen may be indicated to maintain arterial oxygen saturation at a level above 90 percent (Rubin & Rich, 1997).

In the presence of lung disease, improvement of symptoms of PH may be obtained using basic therapy for PH, for instance, therapy for chronic obstructive pulmonary disease COPD and corticosteroids for interstitial lung disease. Antibiotic therapy for pneumonia as well as

elimination of ventilation/perfusion mismatch from and atelectasis can also help control PH.

Chest drainage is required in patients with elevated intrathoracic pressure resulting from accumulated air or blood. However, chest closure may be associated with hemodynamic instability in patients requiring long procedures associated with prolonged CPB due to myocardial edema. The solution to this “thoracic compartment syndrome” consists in leaving the chest temporarily opened in order to reduce surrounding pressures until edema recedes.

#### 4.1.3 Post-capillary

##### Left heart disease

Left and right ventricular functions are interdependent. All LV function abnormalities induced by coronary artery disease, congestive heart failure, valvular heart disease, or systemic hypertension will influence RV function through ventricular interdependence mainly through an effect on the interventricular septum. Hence, a dilated LV and left atrium can shift the interatrial and interventricular septum and compress the right atrium and ventricle and reduce RV end-diastolic volume.

Fernandes *et al.* (Fernandes et al., 2011) compared iNO to oxygen in 29 patients with PH after MVR. Treatments were initiated for 48 hours immediately after surgery. After 24 and 48 hours, patients receiving iNO had a significantly greater increase in CI compared to patients receiving oxygen ( $p < 0.0001$ ). Pulmonary vascular resistance was also more significantly reduced in patients receiving iNO versus oxygen ( $p = 0.005$ ) at 48 hours. Patients in the iNO group required less systemic vasoactive drugs and had a shorter ICU stay ( $p = 0.02$ ).

Kim *et al.* (Kim et al., 2010) compared the pulmonary vasodilation effect of combined preoperative oral sildenafil (50 mg) and beraprost (40  $\mu$ g) (pulmonary vasodilators) to placebo in 50 patients scheduled for valvular heart surgery with PH (MPAP > 30 mmHg). Medication was initiated 15 min before the induction of anesthesia. The treatment group had a significantly lower systemic vascular resistance index (SVRI) at 60 min after medication. No other significant intergroup differences in hemodynamic variables were observed. In addition, significantly more patients in the treatment group required vasopressor therapy. In both groups, the PAP was significantly reduced by general anesthesia, and almost normalized after valvular heart surgery. The combination of preoperative oral sildenafil and beraprost treatment resulted in a loss of pulmonary selectivity, and did not provide any additional pulmonary vasodilation or benefits perioperatively.

Wang *et al.* (Wang et al., 2009) investigated the postoperative effects of inhaled milrinone in 48 patients with PH undergoing MVR. Patients were randomly assigned to receive inhaled milrinone (nebulized for 4 hours) or intravenous milrinone (control group bolus of 50 microg/kg i.v. milrinone and then received a continuous milrinone infusion, 0.5 microg/kg/min, for 4 hours) After milrinone administration, MPAP and PVR showed a comparable decrease in both groups. However, both mean MPAP and SVR in the inhaled group were significantly higher than in the control group. MPAP and PVR returned to baseline values 60 minutes after termination of milrinone inhalation. In addition, in the inhaled group, there was a reduction in intrapulmonary shunt fraction ( $Q_s/Q_t$ ), with an improvement in arterial oxygen tension/fraction of inspired oxygen ( $PaO_2/FiO_2$ ).

A study by Fattouch *et al.* (Fattouch *et al.*, 2005) evaluated the effects of inhaled prostacyclin  $iPGI_2$  and  $iNO$  and compared them with those of conventional intravenous vasodilators (i.e. NTG and nitroprusside) in 58 patients with PH (PVR > 250 dyn sec  $cm^{-5}$  and MPAP > 25 mmHg) suffering from severe mitral valve stenosis. Both drugs were administered by inhalation 5 min before weaning from CPB and continued in the ICU for up to 2 hours. Significant decreases in MPAP and PVR, as well as increases in CO and RVEF, were noted in both inhaled groups, which was not the case in the conventional group. Furthermore, patients in the inhaled groups showed easier separation from CPB, lower requirements for vasoactive drugs and shorter ICU and hospital lengths of stay.

The same investigators also compared the same three strategies in 58 patients with mitral valve stenosis and elevated PVR (>200 dyn sec  $cm^{-5}$  and/or a transpulmonary gradient (MPAP-PAOP)>10 mmHg) after MVR (Fattouch *et al.*, 2006). Intravenous nitroprusside (5–15 g/min),  $iPGI_2$  (10 g/min) or  $iNO$  (20 ppm) were started immediately after patient admission to the ICU. Reduction in MPAP, PVR, and transpulmonary gradient were observed in all groups. Only  $iPGI_2$  was associated with a significant increase in stroke volume and CO. Administration of nitroprusside was associated with a reduction in SVR and occurrence of systemic hypotension.

Feneck *et al.* (Feneck *et al.*, 2001) compared milrinone to dobutamine in 120 patients with PAOP > 10 mmHg and low output syndrome after CBP (CO < 2 L/min/m<sup>2</sup>). In a subset of patients with PH (PVR > 200 dyn sec  $cm^{-5}$ ; MPAP > 25 mmHg), milrinone and dobutamine had similar effects in reducing PVR and increasing CI. However, milrinone was more effective in reducing PAOP and systemic vascular resistance (SVR).

Finally, in 20 patients scheduled for mitral valve surgery with PH (MPAP > 25 mmHg), Hachenberg *et al.* (Hachenberg *et al.*, 1997) explored the role of enoximone compared to a combination of NTG and dobutamine, given after induction of anesthesia and then restarted before the end of CPB. Only enoximone was associated with a decrease in MPAP and PVR. In the presence of PH secondary to LV failure, intra-aortic balloon counterpulsation may facilitate LV recovery.

#### **Patient-prosthesis mismatch (PPM)**

In the presence of prosthetic valve dysfunction after CPB, returning under CPB to correct the problem is considered the treatment of choice (Fig. 9).

#### **4.2 Experience at the Montreal Heart Institute**

At the Montreal Heart Institute,  $iPGI_2$  (Hache *et al.*, 2001; Hache *et al.*, 2003) and inhaled milrinone (Lamarche *et al.*, 2005; Lamarche *et al.*, 2007) are commonly administered to patients when PH and RV dysfunction occur before or after cardiac surgery. Oral sildenafil and  $iNO$  are also used in refractory cases in the ICU. Administration by inhalation has the advantage of selectively reaching well-ventilated regions of the lung and thus avoiding undesired decreases of systemic pressures. Future strategies may include the combination of currently available drugs and improvement of methods of administration for current drugs.

### **5. Importance and impact of pulmonary hypertension in cardiac surgery**

Preoperative PH is associated with increased morbidity and mortality in cardiac surgery (Tuman *et al.*, 1992; Tremblay *et al.*, 1993; Reich *et al.*, 1999; Bernstein & Parsonnet, 2000; Malouf *et al.*, 2002). Therefore, awareness of PH is very important and its presence in any

form should be routinely reported to the surgeon and be evaluated in risk stratification models. Yet, this is not always the case, since only 4/19 risk stratification models in cardiac surgery include preoperative PH as a risk factor (Nilsson et al., 2006). Interestingly, PH is included in the EuroSCORE model which had the greatest discriminatory power over all other models. In a Swedish study including 4351 CABG patients, the receiver operating characteristics (ROC) of the EuroSCORE model was found to be 0.86 and 0.75 for the 30-day and one year mortality rates, respectively.

Analysis performed using the Montreal Heart Institute anesthesia database in 1999 on a total of 1439 patients revealed a mean preoperative SPAP of  $31 \pm 10$  mmHg. PH was defined as SPAP > 30 mmHg and was observed in 605 patients (42%). The type of procedures performed in this subpopulation were mainly MVR ( $n=80$ ,  $40 \pm 14$  mmHg), followed by combined CABG and valve procedures ( $n=126$ ,  $36 \pm 13$  mmHg), multiple valve procedures ( $n=60$ ,  $36 \pm 16$  mmHg) and heart transplantations ( $n=6$ ,  $36 \pm 14$  mmHg). Severe PH defined as MAP/MPAP ratio < 2 was observed in 16 patients, who all experienced difficult separation from CPB, half of them required postoperative vasoactive support for more than 24 hours while 3 of them died (18.7%).

Thus, PH present before, during or after the operation has an impact on survival mostly through its deleterious effect on right-sided heart function. The most dreaded consequence of PH is the increase in RV afterload and RV dysfunction which will be addressed herein.

## 5.1 Right ventricular dysfunction

Regardless of the underlying cause, uncontrolled PH leads to RV dysfunction. There is growing evidence showing that morbidity and mortality associated with PH depends on RV adaptation to the disease rather than on the absolute values of PAP (D'Alonzo et al., 1991; Yeo et al., 1998; Ramakrishna et al., 2005; Voelkel et al., 2006; Haddad et al., 2009). Furthermore, studies addressing hemodynamic variables and survival in idiopathic pulmonary arterial hypertension show that high mean Pra and low CO are consistently associated with poorer survival while PAP values are only moderately related to outcome (D'Alonzo et al., 1991; Chin et al., 2005).

Many studies, in a variety of clinical settings, have demonstrated the importance of RV function in cardiac surgery (Table 3) (Haddad et al., 2009). Typical pathologies and treatments in these studies included high risk coronary or valvular heart disease, congenital heart disease, heart transplantation, patients requiring mechanical assist devices, and unstable patients postoperatively. However, most of the evidence supporting the importance of RV function pertains to retrospective and small prospective studies. Moreover, parameters of RV function have not yet been included in large scale models of risk stratification and thus, their incremental value to the Parsonnet Score and the EuroSCORE has not been well established (Bernstein & Parsonnet, 2000; Nashef et al., 2002; Shroyer et al., 2003; Ambler et al., 2005). A panel in 2006 from the National Institute of Health (NIH) has emphasized the importance of conducting research to better understand RV failure (Voelkel et al., 2006).

### 5.1.1 Before the procedure

In patients with severe aortic stenosis, Boldt *et al.* (Boldt et al., 1992) demonstrated that preoperative RV dysfunction was associated with increased requirements for postoperative inotropic support.

Study	Population	Study Design	RV dysfunction	Results
Reichert <i>et al.</i>	Unstable post-operative patients	Prospective n=60	RVFAC < 35%	RV dysfunction associated with high mortality rates
Pinzani <i>et al.</i>	Mitral and combined mitro-aortic surgery	Retrospective n=382	Clinical definition	Postoperative RV failure is the strongest predictor of postoperative mortality
Cullen <i>et al.</i>	Tetralogy of Fallot	Prospective n=35	Restrictive RV physiology	Restrictive physiology predicts longer intensive care unit stay post repair and lower cardiac output
Gatzoulis <i>et al.</i>	Tetralogy of Fallot	Prospective n=41	Restrictive RV physiology	Restrictive physiology predicts smaller RV and better exercise tolerance
Kromos <i>et al.</i>	LVAD and RV failure	Retrospective n=31	Clinical mean RVEF = 11.8%	Preoperative clinical factors such as fever, pulmonary edema, and intraoperative blood transfusions were associated with RVAD need
Hosenpud <i>et al.</i>	Heart Transplantation	Retrospective (International Society for Heart & Lung transplantation) n=69,205	RV failure associated with circulatory failure	RV failure accounts for up to 20% of early deaths
Oehiai <i>et al.</i>	LVAD	Retrospective n=245	RV failure requiring RVAD	23 patients (9%) required RVAD. The need for circulatory support, female gender, and non-ischemic etiology were predictors of RVAD need
Maslow <i>et al.</i>	CAD undergoing coronary bypass surgery with LVEF < 25%	Retrospective n=41	RVFAC < 35%	RV dysfunction is associated with decreased long term survival
Therrien <i>et al.</i>	Tetralogy of Fallot	Prospective n=17	RV remodeling	Severe RV dilatation (RVEDV ≥ 170 ml/m <sup>2</sup> or RVESV > 85 ml/m <sup>2</sup> ) associated with incomplete RV remodeling
Webb <i>et al.</i>	Atrial septal defect	Retrospective series	RV remodeling	Older age at repair and abnormal RV myocardial relaxation were associated with incomplete RV remodeling
Denault <i>et al.</i>	Patients undergoing bypass surgery	Retrospective and prospective n=800	Dynamic RVOTO (Gradient > 25 mmHg)	Incidence: 4%, dynamic obstruction of RVOTO was associated with a higher incidence of difficult weaning from bypass
Haddad <i>et al.</i>	High risk valvular surgery	Prospective n=50	RVFAC < 32% or RVMPI > 0.50	Preoperative RV dysfunction was associated with a higher incidence of post-operative circulatory failure

CAD: coronary artery disease; LVEF: left ventricular ejection fraction; LVAD: left ventricular assist device; RV: right ventricular; RVAD: right ventricular assist device; RVESV: right ventricular end-systolic volume; RVEDV: right ventricular end-diastolic volume; RVEF: right ventricular ejection fraction; RVFAC: right ventricular fractional area change; RVMPI: right ventricular myocardial performance index; RVOTO: right ventricular outflow tract obstruction. (Haddad et al., 2009)

Table 3. Prognostic Value of Right Ventricular Function in Cardiac Surgery (selected studies)

In a retrospective study involving patients undergoing mitral and mitral-aortic valvular surgery, Pinzani *et al.* (Pinzani *et al.*, 1993) showed that preoperative RV failure was associated with increased perioperative mortality. Furthermore, in that study, postoperative RV failure was the most important independent predictor of late survival.

In a small prospective study of 14 patients with severe non-ischemic mitral regurgitation presenting high risk descriptors (LV ejection fraction (LVEF)  $\leq 45\%$  or RVEF  $\leq 20\%$ ), Wencker *et al.* (Wencker *et al.*, 2000) found that preoperative RVEF  $\leq 20\%$  predicted late postoperative death.

In a retrospective study of 41 patients undergoing non-emergent coronary artery bypass surgery, Maslow *et al.* (Maslow *et al.*, 2002) have shown that RV dysfunction (right ventricular fractional area change (RVFAC)  $< 35\%$ ) in presence of severe LV dysfunction (LVEF  $\leq 25\%$ ) was associated with an increased risk of postoperative morbidity and mortality. Furthermore, patients with RV dysfunction presented a higher prevalence of diabetes mellitus and renal disease, a higher incidence of postoperative support (inotropic or mechanical), longer ICU and hospital stays, as well as a decrease in short and long term survival.

### Experience at the Montreal Heart Institute

Haddad *et al.* (Haddad *et al.*, 2007) further assessed the value of RV function relative to other validated risk factors in open valvular heart surgery on 50 patients undergoing valvular surgery. Patients with RV myocardial performance index (RVMPI)  $< 50\%$  ( $n=20$ ) presented a significantly higher occurrence of circulatory failure (16/20 (80%) *vs* 6/30 (20%),  $p < 0.0001$ ) as well as a higher postoperative heart failure mortality (14/20 (74%) *vs* 3/30 (10%),  $p < 0.0001$ ). In addition, multivariate analysis revealed RVMPI as the only independent predictor of heart failure and mortality among all other demographic, hemodynamic and echocardiographic variables ( $p < 0.0001$ ).

#### 5.1.2 After the procedure

Right ventricular failure after CPB is associated with a mortality rate ranging from 44% to 86% (Davila-Roman *et al.*, 1995). The incidence of acute refractory RV failure ranges from 0.04 to 0.1% after cardiac surgery. Acute refractory RV failure has also been reported in 2-3% patients after heart transplantation and in 20-30% patients receiving support from a LV assist device with a reported initial salvage rate as low as 25-30% (Kaul & Fields, 2000).

### 5.2 Treatment of right ventricular failure

A proposed algorithm for the treatment of RV failure used at the Montreal Heart Institute is summarised in Fig. 10. Assessment of RV function is performed visually when the chest is opened, by analysing RV pressure waveforms and using transesophageal echocardiography. Once RVOTO is ruled out, the etiology of RV systolic dysfunction is divided in two categories, either ischemic or not and with or without LV failure. If ischemia is suspected of causing either RV failure or bi-ventricular failure, treatments (medical and surgical) will be oriented towards the promotion of RV perfusion by means of thrombolysis, percutaneous transluminal coronary angioplasty, or CABG. Finally, pulmonary artery balloon pump, RV assist device or cavopulmonary diversion have also been described as potential treatments for severe RV dysfunction (Kaul & Fields, 2000). Otherwise, if a non-ischemic etiology is more likely or if no LV failure is present, treatments will rather be oriented towards an increase in contractility (inotropes) and a reduction in RV afterload (iNO, iPGL<sub>2</sub>, inhaled milrinone, oral sildenafil).

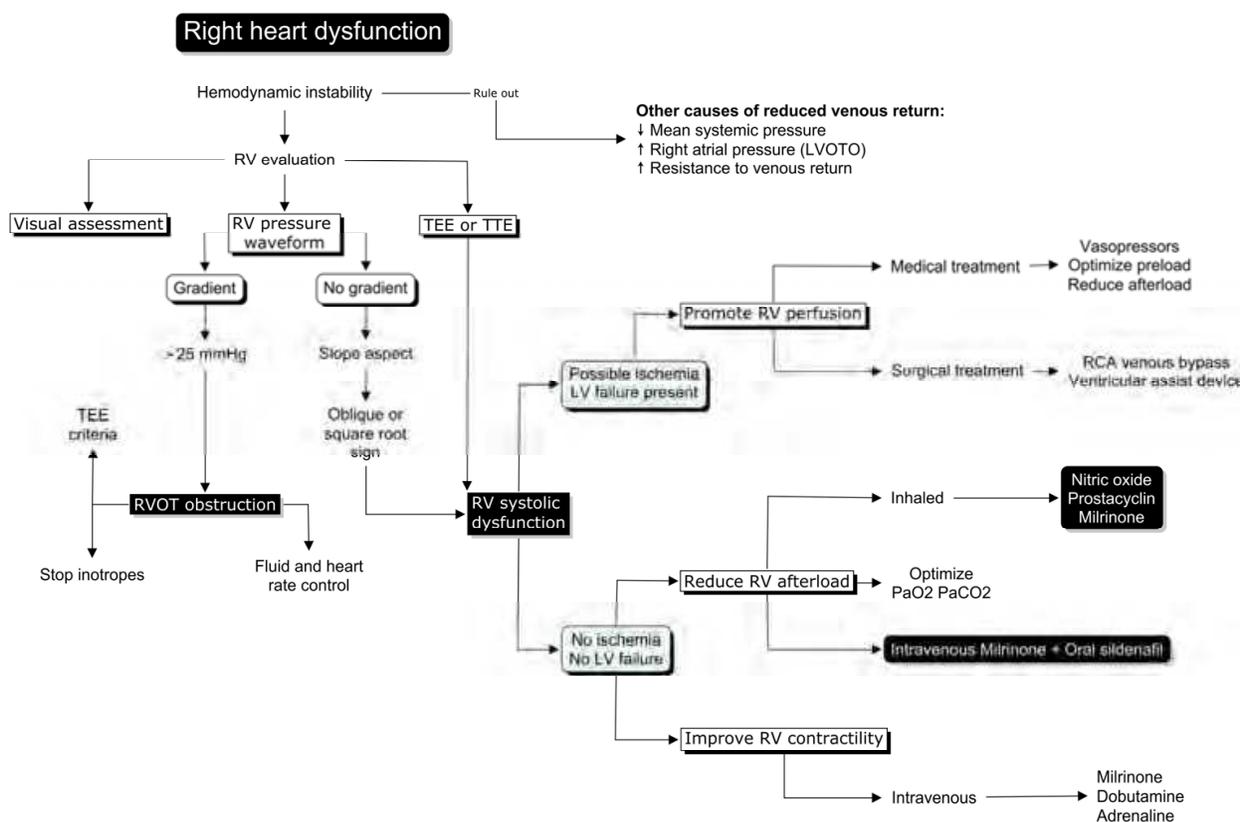


Fig. 10. Proposed approach in the treatment of right ventricular (RV) dysfunction. (LVOTO: left ventricular outflow tract obstruction; RCA: right coronary artery; RVOTO: right ventricular outflow tract obstruction; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography). Presented at the 2011 Canadian Anesthesiologist Society Annual Meeting in Toronto, ON, Canada.

Optimizing oxygenation and ventilation and ruling out other reversible causes of reduction in venous return such as reduction in MAP, increase in Pra and increase in resistance to venous return will also be important in managing these patients.

## 6. Prevention of pulmonary hypertension in cardiac surgery

### 6.1 Pharmacological

Prevention of PH represents a promising strategy to prevent RV failure, its most important consequence after cardiac surgery. To date, very few studies have addressed this issue and one of the potential avenues constitutes the prevention of the pulmonary reperfusion syndrome. In this regard, both iPGI<sub>2</sub> (Fortier et al., 2004) and inhaled milrinone (Lamarche et al., 2005) have been demonstrated to prevent CPB-induced endothelial dysfunction, in an animal model. A pilot randomized controlled trial (RCT) conducted by Hache *et al.* (Hache et al., 2003) in patients with preoperative PH concluded that iPGI<sub>2</sub> was superior to placebo in reducing PH and was also associated with lower requirements for vasoactive support.

A pilot RCT was conducted on the administration of inhaled milrinone before CPB in 21 patients, all undergoing valvular surgeries (Denault et al., 2010b). Procedures consisted of 14 complex surgeries and 5 reoperations. The study included a total of 8 males and 13 females with a mean age of 70±6.3 years old and a mean Parsonnet Score of 32±9. Inhaled milrinone (*n*=10) significantly reduced mean SPAP, which decreased from 66±20 mmHg (pre-CPB) to

46±20 mmHg (after CPB) ( $p<0.001$ ). In contrast, SPAP remained unchanged in the control group ( $n=11$ ) and no significant differences between groups were observed in decreased systemic arterial pressures.

A retrospective study reporting the preliminary experience on the use of inhaled milrinone at the Montreal Heart Institute was conducted in 70 high risk patients with a mean Parsonnet Score of 27±14 (Bernstein & Parsonnet, 2000; Lamarche et al., 2007). Results were compared to those of a control group with similar baseline characteristics. In conclusion, the administration of inhaled milrinone prior to CPB ( $n=30$ ) was associated with a lower chance of CPB re-initiation (9 vs 1;  $p=0.021$ ) and lower postoperative PAP. Further studies (# NCT00819377) are underway to determine the efficacy of this approach.

## 6.2 Non-pharmacological

In addition to therapeutic approaches to the prevention of PH, the choice of type and size of aortic prosthetic valve may be a very important factor. As previously discussed, it has been shown that, if the EOA of the aortic valve is too small relative to body size, the so-called PPM, the intraoperative and long-term mortality will increase (Milano et al., 2001; Rao et al., 2000; Pibarot & Dumesnil, 2000; Blais et al., 2003; Ruel et al., 2004; Pibarot & Dumesnil, 2006; Tasca et al., 2006; Kulik et al., 2006). Hence, prevention of PPM may contribute to reducing PH after cardiac surgery and facilitate separation from CPB. This includes strategies such as the implantation of a prosthesis with better performance (stentless bioprosthesis, new generation bileaflet mechanical valve, new generation supra-annular stented bioprosthetic valve) or enlargement of the aortic root (Fig. 9) in order to accommodate a larger prosthesis. On the other hand, some strategies used to prevent PPM are complex and may even increase the risk of difficult weaning from CPB extending the duration of the surgical procedure and consequently, CPB duration. Unfortunately, in some cases, the drawbacks of using alternative procedures may supercede the benefits of avoiding PPM. Therefore, the establishment of accurate criteria for a better assessment of the benefit-risk ratio with respect to the prevention of PPM is essential. In the case of mitral valve PPM, the best option would be to favor mitral valve repair rather than replacement. However, mitral valve repair may not be possible in a significant number of patients, which limits the options when compared to aortic valve replacement (Magne et al., 2007).

## 7. Conclusion

Pulmonary hypertension and its most dreaded consequence, RV dysfunction, are important mortality risk factors in cardiac surgery. Accordingly, all cardiac patients may benefit from early diagnosis and/or treatment prior to the surgical procedure. In patients with PH, further evaluation of potential alterations in the RV function would be relevant. Thus, future trials should prioritize in-depth exploration of preventive approaches in order to address the role of preemptive reduction of PH severity before cardiac surgery and to determine its impact on postoperative outcomes and survival improvement.

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## 9. Abbreviations

Ao	aorta
AVR	aortic valve replacement
CABG	coronary artery bypass graft
CAD	coronary artery disease
CI	cardiac index
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
CTEPH	chronic thromboembolic pulmonary hypertension
CVP	central venous pressure
D	diastolic
DPAP	diastolic pulmonary arterial pressure
EKG	electrocardiogram
EOA	effective orifice area
FRC	functional residual capacity
ICU	intensive care unit
iNO	inhaled nitric oxide
iPGI <sub>2</sub>	inhaled prostacyclin
LA	left atrium
LV	left ventricle or left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
LVOTO	left ventricular outflow tract obstruction
MAP	mean arterial pressure
MPAP	mean pulmonary artery pressure
MVR	mitral valve replacement
NIH	National Institutes of Health
NO	nitric oxide
NTG	nitroglycerin
PaO <sub>2</sub> /FiO <sub>2</sub>	arterial oxygen tension/fraction of inspired oxygen
PAOP	pulmonary artery occlusion pressure
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PEEP	positive end-expiratory pressure
PFO	patent foramen ovale
PG	pressure gradient
PGE <sub>1</sub>	prostaglandin E <sub>1</sub>
PGI <sub>2</sub>	prostacyclin
PH	pulmonary hypertension
Pa	arterial pressure
PCO <sub>2</sub>	partial pressure of carbon dioxide
Ppa	pulmonary artery pressure
PPM	patient-prosthesis mismatch
Pra	right atrial pressure
Prv	right ventricular pressure

PVR	pulmonary vascular resistance
PVRI	indexed pulmonary vascular resistance
Qs/Qt	intrapulmonary shunt fraction
RA	right atrium
RCA	right coronary artery
RCT	randomized controlled trial
ROC	receiver operating characteristics
RPA	right pulmonary artery
RV	right ventricle or right ventricular
RVAD	right ventricular assist device
RVEDV	right ventricular end-diastolic volume
RVEF	right ventricular ejection fraction
RVESV	right ventricular end-systolic volume
RVFAC	right ventricular fractional area change
RVMPI	right ventricular myocardial performance index
RVOTO	right ventricular outflow tract obstruction
RVSP	right ventricular systolic pressure
S	systolic
SAP	systemic arterial pressure
SPAP	systolic pulmonary artery pressure
SVR	systemic vascular resistance
SVRI	indexed systemic vascular resistance
TEE	transesophageal echocardiography
TLC	total lung capacity
Tr	tricuspid regurgitation
TTE	transthoracic echocardiography
UK	United Kingdom
USA	United States of America
V	velocity

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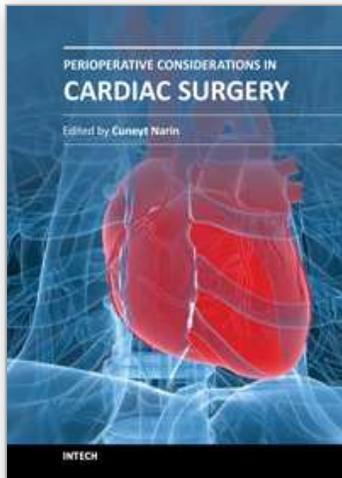
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## **Perioperative Considerations in Cardiac Surgery**

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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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