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Perioperative Considerations of Patients with Pulmonary Hypertension

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<http://dx.doi.org/10.5772/56056>

1. Introduction

Pulmonary hypertension (PH) is a devastating and potentially life-threatening condition that results from a heterogeneous group of diseases. PH is characterized by a sustained increase of mean pulmonary artery pressure (PAP) of 25 mmHg or greater due to any etiology [1]. PH is the manifestation of abnormal pulmonary vascular bed anatomy, abnormal vasoconstrictive status, and pulmonary parenchymal abnormalities which result in obstruction to pulmonary blood flow, cardiac diseases which may impede venous return from the lungs, or a combination of the above. Although many different causes exist, hypertension in the pulmonary circulation is the result of increased vascular resistance, increased vascular bed flow, or a coexistence of both. Initially the signs and symptoms of PH are usually subtle and nonspecific, often ignored by the patients. If left untreated, however, these patients with PH will develop progressive symptoms of dyspnea, fatigue, poor exercise tolerance and right heart failure culminating in a markedly shortened survival [2]. The mechanism for the pathogenesis of pulmonary arterial hypertension (PAH) is not completely understood. There is a conceptual transition in recent decades from the traditional view of mechanical obstruction of blood flow leading to elevated pressure in the pulmonary circulation to cellular growth and vascular remodeling causing increased resistance in pulmonary vasculature resistance [3][4]. Though uncommon, there are patients with PH scheduled for various surgical procedures and requiring anesthetic care perioperatively. In recent years some emerging strategies in the management of PH are potentially applicable to anesthesia practice intraoperatively. From the

clinical anesthesia standpoint, although mild or transient PH won't considerably complicate anesthetic management, moderate or severe PH surely can dramatically deteriorate intraoperatively or postoperatively and potentially lead to acute right heart failure (RHF), cardiogenic shock and even death. The perioperative management of patients with PH varies depending upon the pathological features present, functional clinical classification, hemodynamic status, and success of current medical therapy. This chapter will review the epidemiology, etiologies, the mechanisms, especially cellular growth-related remodeling mechanisms, preoperative evaluation, intraoperative considerations and anesthetic management strategies, and postoperative management of patients with PH.

2. Definition and classifications of pulmonary hypertension

During the 4th World Symposium on Pulmonary Hypertension held in Dana Point, California in 2008, the thresholds for the diagnosis of PH were introduced: an mPAP ≥ 25 mm Hg was designated as manifest PH, while mPAP < 21 mm Hg was defined as normal, and mPAP from 21 to 25 mmHg was categorized as borderline. Correspondingly, echocardiographic systolic tricuspid regurgitation (TR) velocity thresholds < 2.5 m/s is defined as normal, 2.5 to 2.8 m/s as borderline, and > 2.8 m/s is highly indicative for manifest PH [1], as in Table-1.

	Invasive (mPAP)	Non-invasive (systolic TR velocity)
Normal	<21 mmHg	<2.5 m/s
Borderline	21-25 mmHg	2.5-2.8 m/s
Manifest PH	"/>25 mmHg	"/>2.8 m/s

mPAP: mean pulmonary artery pressure; TR: Tricuspid regurgitation; m/s: meter/second

Table 1. Definition of pulmonary hypertension [1]

The earliest PH Classification was introduced during a meeting sponsored by World Health Organization in 1973, basically this classification separated PH into two broad categories: primary or idiopathic (no identifiable causes can be found) and secondary (cause can be identified). Then in 1983 the Evian classification was proposed based on pathophysiological mechanism, clinical presentation and therapeutic options. PH Classification underwent two major modifications in Venice, Italy in 2003: the term idiopathic pulmonary arterial hypertension (IPAH) replaced the term primary pulmonary hypertension and, combined pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) from separate categories into a single subcategory of pulmonary arterial hypertension (PAH) [5] [6]. The latest classification (Dana Point classification) became available in 2008 during the 4th World Symposium on Pulmonary Hypertension, in which PH is categorized into five groups: Group I: Pulmonary arterial hypertension (PAH); Group II: PH owing to left heart diseases; Group III: PH owing to lung diseases and/or hypoxeia; Group IV: Chronic thromboembolic

pulmonary hypertension; Group V: Others (Tumor obstruction, fibrosing mediastinitis, chronic renal failure on dialysis). [5] [6], and is presented in Table-2.

	Subcategory of pulmonary hypertension	Hemodynamics
I	Pulmonary arterial hypertension (PAH): idiopathic or inheritable PAH A. Idiopathic B. Infectious C. Connective tissue disorders D. Congenital heart diseases	Pre-capillary mPAP ≥ 25 mmHg PCWP ≤ 15 mmHg CO normal or reduced ⁺
II	Pulmonary (venous) hypertension because of left-heart disease (PH with left-heart diseases)	Post-capillary, mPAP ≥ 25 mmHg PCWP ≥ 15 mmHg CO normal or reduced ⁺
III	Pulmonary hypertension associated with lung diseases and/or hypoxemia (PH with lung diseases)	Pre-capillary mPAP ≥ 25 mmHg PCWP ≤ 15 mmHg CO normal or reduced ⁺ Passive: TPG ≤ 12 mmHg Reactive: TPG ≥ 12 mmHg
IV	Pulmonary hypertension associated with chronic thrombotic and/or embolic disease (PH with thromboembolic diseases)	Pre- capillary mPAP ≥ 25 mmHg PCWP ≤ 15 mmHg CO normal or reduced ⁺
V	Pulmonary hypertension associated with unclear and/or multifactorial mechanisms. Functional versus pathophysiologic considerations are important issue in classification. A more detailed description of PH Classification is available in other chapters of the book	Pre-capillary mPAP ≥ 25 mmHg PCWP ≤ 15 mmHg CO normal or reduced ⁺

PAH: Pulmonary arterial hypertension; PH: Pulmonary hypertension; mPAP: mean pulmonary artery pressure; PCWP: pulmonary artery wedge pressure; TPG: transpulmonary pressure gradient ($P_{pa} - P_{pcw}$). #: all values measured at rest; +: high CO can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anemia, hyperthyroidism, etc.

Table 2. DANA POINT Classification of Pulmonary Hypertension [5] [6]

3. Epidemiology of pulmonary hypertension

A review of a large U.S. database by Memtsoudis *et al* was undertaken to identify mortality in patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA).[7] The authors studied 1359 THA and 2184 TKA patients who also carried the diagnosis of PH. In

comparison to a demographically-matched group of patients without PH, the THA patients demonstrated a 4-fold increased adjusted risk of in-hospital mortality and the TKA patients demonstrated a 4.5-fold increase ($p<.001$) [7]. Lai *et al* analyzed 62 patients with PH who underwent non-cardiac, non-local anesthetic surgery; they found that PH is an important predictor of adverse cardiopulmonary outcome in non-cardiac surgery as reflected by markedly increased postoperative complications, especially in patients with coexistent high-risk clinical and surgical characteristics [8]. Their results are listed in Table-3.

	Control (N=62)	PH (N=62)	P value
Morbidity %	2 (3.2)	15 (24.2)	0.002
Heart failure %	0(0)	6 (9.7)	0.028
Delayed extubation"/>24 hours %	2(3.2)	13(21)	0.004
Stroke %	0(0)	1(1.6)	NS
Myocardial ischemia/infarct %	0(0)	1(1.6)	NS
Major dysrhythmia %	0(0)	2(3.2)	NS
Mortality(in hospital death %)	0(0)	6(9.7)	0.028

PH= Pulmonary Hypertension

Table 3. Postoperative morbidity in patients with Pulmonary Hypertension [8]

Strange *et al* estimated community-based prevalence of PH in a district in Australia. They studied 10,314 individuals (6.2% of the surrounding Armadale community population) between 2003 and 2009 and they had 15,633 echocardiographic studies performed, 3,320 patients (32%) had insufficient tricuspid regurgitant (TR) or echocardiographic pulmonary artery systolic pressure (ePASP, echocardiographical calculation of PASP requires the measurement of regurgitant flow's Doppler velocity) and 936 individuals (9.1%) identified having PH regardless of etiology (defined as ePASP > 40 mmHg). Their minimum 'indicative' prevalence for all forms of PH is 326 cases/100,000 inhabitants of the local population, with left heart disease-associated PH being the most common cause (250 cases/100,000); these patients with PH secondary to left heart disease also had the worst prognosis. They identified 15 cases of pulmonary arterial hypertension/100,000 inhabitants and an additional 144 individuals (15% of all patients with PH) with no identifiable cause for their PH. The mean time to death for those with ePASP >40 mmHg (calculated from the first recorded ePASP) was 4.1 years. PH increased mortality regardless of the underlying causes, with those with idiopathic pulmonary arterial hypertension (IPAH) receiving disease-specific treatment having the best prognoses. Risk of death increased with PH severity: severe PH shortened the lifespan by an average of 1.1 years compared with mild PH [9]. Recent hemodynamic studies performed in large cohorts of adult patients with sickle cell disease have estimated the prevalence of PH in this disease group to be about 6 to 10% [10]. Over half of these patients have postcapillary PH. Precapillary arterial PH seems to be a relatively infrequent complication of sickle cell disease. It is characterized by a different hemodynamic profile from IPAH with lower levels of PAP and PVR. However, pulmonary vascular disease appears to have a significant impact on the functional status and vital prognosis of patients with

sickle cell disease. The predictive value of echocardiography to detect PH in this patient population is low (25-32%) when the threshold of tricuspid regurgitation velocity of 2.5m/s is used. At present, no specific treatment is currently approved for the treatment of PH associated with sickle cell disease due to lack of data in this specific population [10].

PH frequently accompanies childhood congenital heart disease (CHD) and may persist into adult life. The advent of specific therapies for PH prompted formation of a national Australia and New Zealand registry in 2010 to record the incidence, demographics, presentation and outcomes for these patients. They established a multicenter, prospective, web-based registry which enrolls patients with CHD-associated PH who are being followed at a tertiary medical center. The inclusion criteria stipulate patient age >16 years, a measured mPAP >25mmHg at rest or echocardiographic evidence of PH or a diagnosis of Eisenmenger's syndrome, and these patients have been followed since 1/1/2000. The investigators obtained the following results: of the first 50 patients enrolled, 30 (60%) are female, the mean age [Standard Deviation (SD)] at the time of PH diagnosis or confirmation in an adult center was 27.23 years (SD=10.07) and 32 patients (64%) are currently aged >30 years. Fourteen (28%) patients were in WHO functional Class (Table-4) II and 36 (72%) in Class III at the time of diagnosis. Forty-seven of 50 (94%) had congenital systemic-pulmonary shunts and 36 (72%) never underwent intervention. 13 (26%) had Down's syndrome. Confirmation of PH by recent cardiac catheterization was available in 30 (60%) subjects. During follow-up a total of 32 (64%) patients received a PH specific therapy. They concluded that CHD-associated PH in adult life has resulted in a new population with unique needs. This registry will allow documentation of clinical courses and long-term outcomes for these patients [11].

Class	Functional status of patients with pulmonary hypertension
I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. These patients are comfortable at rest, but less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
IV	Patients with pulmonary hypertension resulting in inability to perform any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

*--Modified from the New York Heart Association classification of patients with cardiac disease. Adapted with permission from Rich S., ed. Executive summary from the World symposium on Primary Pulmonary Hypertension 1998, Evian, France, September 6-10, 1998, cosponsored by the World health Organization. Retrieved April 14, 2000, from the World Wide Web: <http://www.who.int/ncd/cvd/pph.html>.

Table 4. WHO Functional Assessment of Patients with Pulmonary Hypertension*

PH can complicate interstitial lung disease (ILD). Anderson *et al* evaluated 212 ILD patients and found that PH occurred in 14% of a cohort of patients with ILD and was associated with lower lung function parameters. Mortality was markedly higher in ILD patients with PH, and the presence of PH reduced 6 Minutes Walk Test (MWT) independently of lung function. The present results emphasize the need for intensified treatment of patients with ILD and PH [12].

4. Etiologies of pulmonary hypertension

1. Causes of pulmonary arterial hypertension (PAH) [1]:
 - a. Idiopathic PAH (IPAH): No identifiable cause for the PH;
 - b. Familial PAH: A family history can be reported.
 - c. PAH associated with other diseases (APAH): Patient's PH can be associated with other co-existing diseases such as connective tissue diseases, infectious diseases as HIV infection,
 - d. Portal hypertension: like in many end-stage liver disease patient, they often have increased pressure in pulmonary artery;
 - e. Drugs & toxins: many decongestants containing ephedrine, pseudoephedrine, propylhexedrine, or oxymetazoline may lead to PAH. Other agents as NSAIDs, sodium and caffeine can also cause PAH [13]
 - f. Pulmonary veno-occlusive or capillary hemangiomatosis.
 - g. Regarding the pathogenesis of PAH, there is a conceptual transition in recent decades from the traditional view of mechanical obstruction of blood flow leading to elevated pressure in the pulmonary circulation to cellular growth and vascular remodeling causing increased pulmonary vasculature resistance [3][4].
2. PH with left-heart diseases: Congenital systemic-to-pulmonary shunts or left-sided atrial or ventricular diseases. Any congenital abnormality which leads blood circulating from high-pressure side to the low-pressure pulmonary circulation will have PAH;
3. PH with lung diseases and/or hypoxemia can be caused by following diseases:
 - a. Chronic obstructive pulmonary diseases
 - b. Interstitial pulmonary diseases
 - c. Sleep apnea or other sleep disorders with breathing problems;
 - d. Alveolar hypoventilation or other causes related hypoxemia
 - e. Developmental abnormalities.
4. PH caused by thrombotic and/or embolic diseases.

5. Miscellaneous: sarcoidosis, histiocytosis X, lymphangiomatosis, pulmonary vascular compression by various pathologies.

5. Pathophysiology of pulmonary hypertension

Though a small percentage of patients have idiopathic PH [14], most perioperative patients with PH acquired PH secondary to either cardiac or pulmonary disease processes or both. Left sided ventricular or atrial disease and left sided valvular heart disease are common causes of PH. Both of these conditions increase left atrial pressure and elevate pulmonary venous pressure (PVP) and lead subsequently to increased PAP. Multiple respiratory diseases can lead to the development of PH via hypoxia-induced pulmonary vasoconstriction (HPV) or elevated PVR due to pulmonary fibrosis [15]. Regardless of the cause, all pathways may lead to an altered vascular endothelium and smooth muscle function through cellular remodeling and growth [16] [17]. This results in increased vascular contractility or lack of vascular relaxation in response to various endogenous vasodilator substances. Morphological abnormalities of the vascular wall are present in all three layers of the pulmonary arteries of patients with PH, and medial hypertrophy due to overproliferation of smooth muscle cells is a constant feature of all forms of PH. The classical mechanical concepts of pressure, flow, shear stress, RV wall stress and impedance have been gradually complemented with the new concepts of cell injury, repair/remodeling and interactions of complex multi-cellular systems [17]. Integrating these recent concepts will become critically important in completely understanding the mechanisms of PH, as we develop new interventions in order to change the prognosis of the patients with this devastating condition. Since PH can develop in association with many different diseases and with multiple risk factors, it is believed that the multi-factorial interplay may very likely be responsible for the pathogenesis of PH. The right ventricle (RV) is a crescent shaped, thin walled and compliant muscle chamber intended for volume work, not pressure work. Chronic PH leads to right ventricular hypertrophy (RVH) as a compensatory mechanism. However, the ability of the RV to adapt is finite and may eventually lead to RV failure. Unlike the muscular left ventricular chamber, a hypertrophied RV may not tolerate the acute rises in PVR that are associated with pain, surgical stimulation and positive pressure ventilation. RV failure and dilatation can lead to left ventricular compression and diminished cardiac output. This in turn leads to decreased coronary blood flow and perfusion pressure and can become a viscous cycle that can be difficult for the patient to overcome. The mechanisms for the pathogenesis of PH can be simply outlined as one or more of the following aspects: vascular remodeling with narrowness of vascular lumen and increased resistance, abnormal vascular reactivity leading to persistent vasoconstriction and loss of relaxation, left-side cardiac diseases impeding pulmonary venous return and various lung diseases compromising the pulmonary vascular bed leading to increased PVR. Here we discuss the pathophysiological changes of PH:

5.1. Pulmonary vascular inflammation and immune responses

The presence of antinuclear and antiphospholipid antibodies in the serum of patients with PH has been documented for many years [18]. There is more evidence that lymphoid neogenesis

occurs in IPAH. Macrophages, mast cells, T- and B- lymphocytes, plasma cells and anti-endothelial cell antibodies are all present in and around the complex pulmonary vascular lesions in IPAH patients. Serum levels of IL-1 and IL-6 are high in IPAH patients, and serum IL-6 levels negatively predict patient survival. However, whether inflammation and aberrant immune responses in IPAH are cause or consequence remains unknown. Likely PH occurs when an inflammatory pulmonary arteriolar injury is not resolved by (normally) protective, innate anti-inflammatory mechanisms. Regulatory T-cells (Tregs) control not only other T-cells but also regulate monocytes, macrophages, dendritic cells, natural killer cells and B-cells, and recent evidence suggests that decreased Treg cell number or function may favor the development of PH. For example, conditions associated with PH, such as HIV, systemic sclerosis, systemic lupus erythematosus (SLE), Hashimoto's thyroiditis, Sjogren's Syndrome and the antiphospholipid syndrome are characterized by abnormal CD4+ T-cell number and function. Athymic rats lacking T-cells, develop pronounced PH after vascular injury with a vascular endothelial growth factor receptor blocker. The lungs in these animals are populated by infiltrating macrophages, mast cells and B cells, similar to human PH lesions. Most importantly, PH is prevented by immune reconstitution of Tregs prior to the induction of vascular injury. Putting these together all points to a possibility that aberrant Treg-cell function in the face of vascular injury can result in heightened innate and adaptive immune responses that could initiate and/or worsen the development of PH [19]. There is increasing evidence suggesting a role for immune deregulation in PH.

PH can potentially respond to immunosuppressive therapy (glucocorticoids or targeted B cell depletion) [20]. Sanchez *et al* reported on treatment of patients with mixed connective tissue disease or SLE- associated PH, where corticosteroid and cyclophosphamide has been used as first-line drugs, they found that PAH associated with SLE or mixed connective tissue disease may respond to a treatment combining glucocorticosteroids and cyclophosphamide and improve pulmonary hemodynamics. [21]. The effectiveness of B cell depletion is currently being examined in an NIH-trial studying the effectiveness of rituximab—a chimeric monoclonal antibody against the protein CD20, primarily expressed by B-cells – for systemic sclerosis-associated PAH. It is becoming clear that circulating factors can potentially amplify pulmonary vascular injury, attract immune cells and/or repair cells which respond to a variety of chemotactic stimulations, suggesting a systemic disease component contributing to the development or progression of PAH. In the “modern era” of PAH treatments, where standard vasodilation therapies have failed to reverse or stop the progression of PAH, novel targets such as discrete immune pathways hold promising alternatives [20][21]. Nevertheless, new drugs and clinical trials will all require assessing which patients may respond to anti-inflammatory or immune-modulating treatment strategies.

Several clinical studies indicated that obesity is a risk factor for the development of PH [22]. [23]; however, the mechanisms leading to this association are unknown. It is a well known fact that adipocytes secrete multiple bioactive mediators that can influence inflammation and tissue remodeling, suggesting that adipose tissue may per se directly influence the pathogenesis of PH. One of these mediators by adipocytes is adiponectin which is a protein with a wide range of metabolic, anti-inflammatory, and anti-proliferative activities. Adiponectin is present in high concentration in the serum of lean healthy individuals, but decreased level in obesity. There are

studies suggesting that relative adiponectin-deficiency may contribute to the development of inflammatory diseases in obesity, and recent animal studies implicate adiponectin in the pathogenesis of pulmonary hypertension. Experimental studies showed that adiponectin can reduce lung vascular remodeling in response to inflammation and hypoxia. Moreover, mice lacking adiponectin can develop a spontaneous lung vascular phenotype characterized by age-dependent increases in perivascular inflammatory cells and elevated PAP. Some emerging evidence indicates adiponectin's effects are mediated through anti-inflammatory and anti-proliferative actions on cells in the lung [22]. PH has been associated with autoimmune disorders [18] [24]. Cell-free hemoglobin (Hb) exposure alone can be a pathogenic mediator in the development of PH and when combined with chronic hypoxia, the potential for exacerbation of PH and vascular remodeling can be significantly more profound. Buehler *et al* found this Hb-exposure related PH is also largely mediated by inflammatory process [25].

5.2. Pulmonary vascular endothelial injury, cellular growth and remodeling

Endothelial injury is central to the development of PH, a proliferative vasculopathy of the pulmonary circulation. Pulmonary vascular remodeling plays an important role in the sustained development of PH. Platelet-derived growth factor (PDGF) signaling has been demonstrated to be a major mediator of vascular remodeling implicated in PH. Xing *et al* investigated cigarette smoking (CS)-induced PH in rats and the expression of PDGF and PDGF receptor (PDGFR) in pulmonary artery, they established the association of PDGF signaling with CS-induced PH. Forty male rats were randomly divided into control group and three experimental groups that were exposed to CS for 1, 2, and 3 months, respectively. CS significantly increased right ventricular systolic pressure (RVSP) and right ventricular hypertrophy index (RVHI). Histology staining demonstrated that CS significantly increased the thickness of pulmonary artery wall and collagen deposition. The expression of PDGFR isoform B (PDGFR-B) and PDGFR- β were significantly increased at both protein and mRNA levels in pulmonary artery of rats with CS exposure. Furthermore, Cigarette smoke extract significantly increased rat pulmonary artery smooth muscle cell (PASMC) proliferation, which was inhibited by PDGFR inhibitor Imatinib. Thus, their results indicated PDGF signaling is also implicated in CS-induced PH [26].

PH is a condition for which no disease-modifying therapies exist for the time being. PH is recognized as proliferative disease of the pulmonary artery (PA). In the experimental newborn calf model of hypoxia-induced PH, adventitial fibroblasts in the PA wall exhibit heightened replication index. Because elevated PDGFR- β signaling is associated with PH, Panzhinskiy *et al* tested the hypothesis that activation of PDGFR- β contributes to fibroblast proliferation and adventitial remodeling in PH. In their study, newborn calves were exposed to either ambient air (P(B) = 640 mm Hg) (Neo-C) or high altitude (P(B) = 445 mm Hg) (Neo-PH) for 2 weeks. PDGFR- β phosphorylation was markedly elevated in PA adventitia of Neo-PH calves as well as in cultured PA fibroblasts isolated from Neo-PH animals. PDGFR- β activation with PDGF-BB stimulated higher replication in Neo-PH cells compared to that of control fibroblasts. PDGF-BB-induced proliferation was dependent on reactive oxygen species (ROS) generation and extracellular signal regulated kinase1/2 (ERK1/2) activation in both cell populations, however only Neo-PH cell division via PDGFR- β activation displayed a unique

dependence on c-Jun N-terminal kinase1 (JNK1) stimulation as the blockade of JNK1 with SP600125, a pharmacological antagonist of JNK pathway, and JNK1-targeted siRNA blunted selectively Neo-PH cell proliferation. These data strongly suggest that hypoxia-induced modified cells engage PDGFR- β -JNK1 axis to confer distinctively heightened proliferation and adventitial remodeling in PH [27].

It is also known that 15-lipoxygenase (15-LO) plays an important role in chronic PH. Accumulating evidence for its down-stream participants in the vasoconstriction and remodeling processes of pulmonary arteries. Zhang *et al* investigated how hypoxia regulates 15-LO/15-hydroxyeicosatetraenoic acid (15-HETE) to mediate hypoxic PH, whether hypoxia advances the pulmonary vascular remodeling through the PDGF/15-LO/15-HETE pathway. What they found is pulmonary arterial medial thickening caused by hypoxia could be alleviated by treatment of the hypoxic rats with Imatinib, which was associated with down-regulations of 15-LO-2 expression and 15-HETE production. Moreover, the increases in cell proliferation and endogenous 15-HETE content by hypoxia were attenuated by the inhibitors of PDGFR- β in pulmonary artery smooth muscle cells (PASMCs). The effects of PDGF-BB on cell proliferation and survival were weakened after the administration of 15-LO inhibitors or 15-LO RNA interference. These results suggest that hypoxia promotes PASMCs proliferation and survival, contributing to pulmonary vascular medial hypertrophy, which is likely to be mediated via the PDGF-BB/15-LO-2/15-HETE pathway [28].

5.3. Pulmonary parenchymal diseases/fibrosis

The pathophysiology of PH in parenchymal lung diseases is partially related to hypoxic pulmonary vasoconstriction (HPV). This category is also called group III PH, namely PH attributable to lung diseases and/or hypoxia. Group III PH includes chronic obstructive pulmonary disease (COPD) and interstitial lung diseases (ILD); the most common parenchymal lung diseases associated with PH. Group III PH also includes sleep-disordered breathing and hypoventilation from any cause. Other parenchymal lung diseases associated with PH include sarcoidosis and systemic vasculitis (group V). There are controversies in terms of managing this group of patients [29].

5.4. Genetics and pharmacogenomics

Genetic factors may predispose some patients to the development or progression of severe PH. Mutations of the Bone Morphogenetic Type II Receptor (BMPR2) gene and a member of the transforming growth factor (TGF- β) superfamily were the first described in patients with familial/hereditary PH [30],[31][32]. Although BMPR2 mutations in PH have a high prevalence (70%), limited numbers of patients with PH have mutations, and only 20% of the carriers ever develop PH during their lifetime. BMPR2 mutation carriers at the time of PH diagnosis are younger and less likely to have a vasoreactive component [33][34]. A large number of mutations have been reported and the majority cause a loss of function or reduced BMPR2 expression. It has been reported that the disease appears to be more severe when patients carry a truncating BMPR2 mutation. However, this appears not to be the case in the French patients. Mechanistic studies indicate that BMPR2 mutations are permissive but not necessary for the

development of severe PH. BMPR2 may be one of the guardians of lung vessel homeostasis, as gene knockout and silencing experiments have clearly demonstrated that both apoptosis and cell proliferation of PASMCs and endothelial cells are controlled by BMPR2. Intact BMPR2 signaling may be necessary for the execution of a normal lung vascular wound-healing program, preventing apoptosis-induced compensatory cell proliferation. BMPR2 loss makes cells more susceptible to apoptosis, however, vascular cell-apoptosis alone, is insufficient for angioproliferation to occur. BMPR2 signaling appears to define the cellular identity during reparative responses. BMP signaling is regulated at many different levels and each level could potentially contribute to abnormal BMPR-2 function, without necessarily involving a mutation in the BMPR2 gene. For example, mutations in the type I TGF-receptor, ALK-1, have been observed in patients with severe PAH occurring in families with hereditary hemorrhagic telangiectasia. Moreover, although infrequent, mutations in the BMPR-2-downstream mediators, the smad proteins, have also been described in PH patients. Their data also indicated that BMP/TGF- β signaling plays an important role in the maintenance of the normal lung arteriolar structure [30][31]. Epigenetic mechanisms influence gene expression via modifications of the chromatin, histones and regulatory micro RNAs. At present, there is no firm evidence that PH has an epigenetic component. Downregulation of BMPR2 expression has been explained by activation of a 5 STAT3/miRNA-17-92 microRNA axis in normal human lung endothelial cells after interleukin-6 exposure. Interestingly, mice overexpressing IL-6 develop severe pulmonary hypertension and, unlike other PH mice models, also develop angioobliterative vascular remodelling and robust RV hypertrophy. Overexpression of miR-17 also increases proliferation of human PASMCs and inhibition with a specific miR-17 antagonist ameliorated PH in two experimental models [35] [36]. Another microRNA, miR204, has been found downregulated in pulmonary artery smooth muscle cells isolated from patients with PH. Upregulation of miR204 seems to induce an apoptosis-resistant phenotype in smooth muscle cells [37].

PAH is an uncommon disease in the general population, but a disease with significant morbidity and mortality. The prevalence of heritable PH remains unknown. The reason for incomplete penetrance of heritable PAH is not well understood. A patient's clinical response to disease-specific therapy is complicated with potential involvement of the disease severity, comorbidities, appropriateness of the prescribed therapy, and patient compliance. Dempsey *et al* studied the effects of gender on development of PH in mice with over-expressing Mts1 (Mts1+ mice) by measuring pulmonary arterial remodeling, systolic right ventricular pressure (sRVP) and RVH. Gender differences in pulmonary arterial Mts1 and the receptor for advanced glycosylation end products (RAGE) expression were assessed by qRT-PCR and immunohistochemistry. Western blotting and cell counts were applied to investigate interactions between 17 β -estradiol, Mts1 and RAGE on proliferation of human PASMCs. Statistical analysis methods used were one-way analysis of variance with Dunnetts post test or two-way analysis of variance with Bonferronis post test, as appropriate. Their results showed that female Mts1+ mice developed increased sRVP and pulmonary vascular remodeling, whereas male Mts1+ mice remained unaffected, and the development of plexiform-like lesions in Mts1+ mice was specific to females. These changes stained positive for both Mts1 and RAGE in the endothelial and adventitial layers. Expression of pulmonary arterial Mts1 was greater in female than male

Mts1⁺ mice, and was localized to the medial and adventitial layers in non plexiform-like pulmonary arteries. RAGE gene expression and immunoreactivity were similar between male and female Mts1⁺ mice and RAGE staining was localized to the endothelial layer in non plexiform-like pulmonary arteries adjacent to airways. In non-plexiform like pulmonary arteries not associated with airways RAGE staining was present in the medial and adventitial layers. Physiological concentrations of 17 β -estradiol increased Mts1 expression in PASMCs, while 17 β -estradiol-induced hPASMC proliferation was inhibited by soluble RAGE, which antagonizes the membrane bound form of RAGE. Authors believe Mts1 over-expression combined with female gender is permissive to the development of experimental PAH in mice. Up-regulation of Mts1 and subsequent activation of RAGE may contribute to 17 β -estradiol-induced proliferation of hPASMCs [38].

5.5. Chronic pulmonary thromboembolic events

Chronic thromboembolic events may lead to PH. Long-standing thromboembolic obstruction of pulmonary arterial vasculature by acute or recurrent thromboemboli with subsequent organization can cause progressive PH and RVF. Advances in diagnostic modalities and surgical pulmonary endarterectomy techniques have made this PH induced by these chronic thromboembolization treatable and even potentially preventable and/or curable. Although published guidelines are available, in the absence of randomized controlled trials regarding chronic thromboembolic PH, there is a lack of standardization, and treatment options have to be individualized [39].

5.6. Exercise-induced pulmonary hypertension

Though exercise-induced increase in pulmonary arterial pressure has been removed from current PH Classification, exercise stress tests of the pulmonary circulation can potentially help detect early or latent pulmonary vascular disease and may help understand the clinical evolution and effects of treatments in patients with established PH. Exercise stresses the pulmonary circulation through increases in cardiac output and left atrial pressure. Recent studies have shown that exercise-induced increase in PAP is associated with dyspnea-fatigue symptomatology, validating the notion of exercise-induced PH. Exercise in established PH has no diagnostic relevance, but may help in the understanding of changes in functional state and the effects of therapies [40] [41].

5.7. Chronic hypoxemia

Chronic hypoxic lung diseases can lead to PH which subsequently increases patients' morbidity and mortality. Since the identification of heterozygous morphogenetic protein (BMP) receptor mutations as the underlying factor in the rare heritable form of pulmonary arterial hypertension, the important role of altered BMP signaling in PH was then significantly more appreciated [42] [43]. Later studies demonstrated that BMP signaling was also reduced in other more common forms of PH. The mechanism of the BMP signaling reduction was recently elucidated by Cahill and associates. They found that expression of 2 BMP antagonists, Gremlin 1 and Gremlin 2 was significantly higher in the lung than in other organ systems. And Gremlin

1 was further increased in the walls of small intrapulmonary vessels of mice during the development of hypoxic PH. In vitro studies showed that hypoxia stimulated cultured human pulmonary microvascular endothelial cells to secrete Gremlin secretion which inhibited endothelial BMP signaling and BMP-stimulated endothelial repair. Haplodeficiency of Gremlin 1 augmented BMP signaling in the hypoxic mouse lung and reduced PVR by attenuating vascular remodeling. Furthermore, Gremlin was increased in the walls of small intrapulmonary vessels in IPAH and the rare heritable form of PAH in a distribution suggesting endothelial localization. Their findings demonstrated the central role for increased Gremlin in hypoxia-induced pulmonary vascular remodeling and the increased PVR in hypoxic PH. High levels of basal Gremlin expression in the lung may account for the unique vulnerability of the pulmonary circulation to heterozygous mutations of BMP type 2 receptor in PAH [42]. Interestingly, digoxin was found to inhibit the development of hypoxemia-induced PH in an animal model [43]. One of the mechanisms involved in the development of hypoxic PH is hypoxia-inducible factor 1 (HIF-1)-dependent transactivation of genes controlling pulmonary arterial smooth muscle cells (PASMC) intracellular calcium concentration ($[Ca^{2+}]_i$) and pH. Digoxin was shown to inhibit HIF-1 transcriptional activity, and potentially prevent and reverse the development of PH. And digoxin can attenuate the hypoxia-induced increases in RV pressure and PASMC pH and $[Ca^{2+}]_i$ [42].

The etiologies and mechanisms of PH are illustrated in Figure-1.

Figure 1. Etiologies and mechanisms of pulmonary hypertension (Illustrated by Henry Liu, MD)

Figure 2. Top: Apical four-chamber view (systole) showing enlarged right-side chambers with compressed and geometric distortion of an intrinsically normal LV secondary to marked RV pressure overload; severe TR. RA-right atrium; LA- left atrium. Bottom: Peak TR velocity of 4.68 m/s, with a peak gradient of 87.8 mm Hg indicating severe PH.

6. Perioperative management of pulmonary hypertension

6.1. Preoperative assessment

Patients with PH undergo surgical procedures with significantly higher risks for morbidity and mortality regardless of the etiologies of the PH, the types of surgery and the anesthetic technique [44] [45] [46] [47] [48] [49]. The clinical outcome is especially worse for those with Eisenmenger's syndrome. Kahn reported that patients with Eisenmenger's syndrome undergoing cesarean section had mortality as high as 70% [50]. Although there is not an overabundance of literature regarding the development of postoperative pulmonary complications following noncardiac surgery, the few available studies demonstrate the increased risk associated with these surgical procedures. Preoperative medical optimization is therefore necessary. During preoperative risk assessment, one should take into account the type of surgery, the patient's functional status, the severity of the PH, the function of the right ventricle

and any other co-morbidities. Generally superficial procedures and non-orthopedic procedures are associated with less hemodynamic and sympathetic nervous system perturbations than more invasive/traumatizing procedures. Orthopedic procedures with bony involvement can be quite stimulating for the patients and will increase the risk of elevating PVR and RV failure. Thoracic surgery is associated with significant changes in intrathoracic pressures, lung volumes and oxygenation, which may cause acute increases in PVR and decreased RV function [51]. Laparoscopic surgery requires pneumoperitoneum which may be poorly tolerated because it can decrease preload and increase afterload. Surgical procedures associated with rapid or massive blood loss will be poorly tolerated by patients with severe PH. WHO standardized the functional status definition as shown in Table-4.

History and Physical Exam: Preoperative evaluation should include a thorough history and physical examination with special attention to signs and symptoms of respiratory insufficiency and right ventricular dysfunction. Symptoms are typically nonspecific with the most frequent being progressive dyspnea. The signs depend on disease severity and include dyspnea at rest, low cardiac output with metabolic acidosis, hypoxemia, evidence of right heart failure (large V wave on jugular vein, peripheral edema, hepatomegaly), and syncope [52]. Laboratory studies and special tests should be determined by the surgical procedure that the patient is undergoing and the medication profile of the patient. Routine preoperative tests include electrocardiography (EKG), chest radiographs (CXR), complete blood counts (CBC), electrolytes, baseline arterial blood gas analysis (ABG), room air oxygen saturation. Although ECG changes alone cannot determine disease severity or prognosis of PH [53] [54], the ECG may show signs of right ventricular hypertrophy, such as tall right precordial R waves, right axis deviation and right ventricular strain [55]. The chest radiography may show evidence of right ventricular hypertrophy (decreased retrosternal space, cardiomegaly, enlarged cardiac silhouette) or prominent pulmonary vasculature. CBC will help decide the necessity of preoperatively optimizing the hematocrit of the patients or not. Plasma electrolytes assess baseline electrolytes and acid-base disturbances.

Delayed post-exercise heart rate recovery (HRR) has been associated with disability and poor prognosis in chronic cardiopulmonary diseases. Ramos *et al* investigated the usefulness of HRR to predict exercise impairment and mortality in patients with PH. They studied 72 PH patients with varied etiologies [New York Heart Association (NYHA) classes' I-IV] and 21 age- and gender-matched controls. Both groups underwent a maximal incremental cardiopulmonary exercise test (CPET) with heart rate being recorded up to the fifth minute of recovery. Their results revealed that HRR was consistently lower in the patients compared with the controls ($P < 0.05$). The best cutoff for HRR in 1 minute (HRR (1 min)) to discriminate the patients from the controls was 18 beats. Compared with patients with HRR (1 min) ≤ 18 ($n = 40$), those with HRR (1 min) > 18 ($n = 32$) had better NYHA scores, resting hemodynamics and 6-minute walking distance (6MWD). In fact, HRR (1 min) > 18 was associated with a range of maximal and submaximal CPET variables indicative of less severe exercise impairment ($P < 0.05$). The single independent predictor of HRR (1 min) ≤ 18 was the 6MWD (odds ratio 0.99, $P < 0.05$). On a multiple regression analysis that considered only CPET-independent variables, HRR (1 min) ≤ 18 was the single predictor of mortality (hazard ratio 1.19, $P < 0.05$). Thus they concluded preserved HRR (1

min) (>18 beats) is associated with less impaired responses to incremental exercise in patients with PH. To the contrary, a delayed HRR (1 min) response has negative prognostic implications, a finding likely to be clinically useful when more complicated (and costlier) analyses provided by a full CPET are not available [56]. Minai *et al* had a similar finding: they evaluate the association between HRR at 1 minute of rest (HRR1) after 6-min walk test (6MW test) and clinical worsening in patients with IPAH. HRR (1 min) was defined as the difference in heart rate at the end of 6MW test and at 1 minute after completion of the 6MW test. Seventy-five consecutive patients with IPAH underwent 6MW test and were included in the analysis. The results showed those patients with HRR1 less than 16 ($n = 30$) were more likely to have clinical worsening (odds ratio, 9.7, $P < 0.001$) and shorter time to first clinical worsening event (TCW) (6.7 mo vs. 13 mo; $P < 0.001$) during follow-up. With multivariable analysis, the best predictors of clinical worsening were HRR (1 min) less than 16 (hazard ratio, 5.2, $P = 0.002$) and mean PAP (hazard ratio, 1.04, $P = 0.02$). Compared with the distance walked during the 6MW test (6MWD), HRR (1 min) less than 16 was a better predictor of clinical worsening and TCW. The addition of HRR (1 min) increased the ability of 6MWD to predict clinical worsening events. HRR (1 min) after 6MW test is a strong predictor of clinical worsening and TCW in patients with IPAH. The addition of HRR (1 min) to 6MWD increases the capacity of 6MWD to predict clinical worsening and TCW in patients with IPAH [56].

Additional tests which can potentially benefit patients include echocardiography, right heart catheterization, pulmonary function testing, ventilation/perfusion (V/Q) scanning, pulmonary angiography, spiral computed tomography, serologic testing, liver function testing, and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Among these available tests, echocardiography is probably the best screening study. Echocardiography is used to assess right ventricular (RV) size, function and estimate pulmonary artery pressures [52]. Echocardiography is a useful tool for both assessment and monitoring of disease progression in PH. Although transthoracic echocardiography is the most widely used modality for this purpose, especially for the initial PH evaluation, transesophageal echocardiography (TEE) can be a more useful technology for patients with poor acoustic windows and for intraoperative monitoring. Compared to other monitoring modalities, TEE can be particularly useful in narrowing the differential diagnoses for intraoperative hemodynamic instability (hypovolemia, hypervolemia, right or left ventricular ischemia/failure) and in formulating a therapeutic plan. Multiple echocardiographic methods, M-mode, 2D and real-time 3D have been utilized to assess PH. The usual echocardiographic findings associated with PH include the following: 1) enlarged right atrial or right ventricular (RV) chambers; 2) mid-systolic closure or notching of the pulmonary valve; 3) diminished or absent atrial wave of the pulmonary valve; 4) intraventricular septal flattening; 5) paradoxical systolic motion of the intraventricular septum (IVS) toward the left ventricle; 6) a dilated inferior vena cava with reduced respiratory variability; 7) increased IVS/posterior left ventricular (LV) wall ratio (>1); 8) increased RV end-diastolic volume index; 9) increased RV endsystolic volume index, and 10) decreased RV ejection fraction [58] [59] [60]. 11). right ventricular enlargement with tricuspid regurgitation, small left ventricle with an asymmetric hypertrophic wall, with ventricular stiffness and diastolic incompetence [61]. Methods used to determine PAP by echocardiography include: measurement of the tricuspid annular plane systolic excursion (TAPSE), two-dimensional strain, tissue

Doppler echocardiography, the speckle tracking method, acceleration time across the pulmonic valve, the pulmonary artery regurgitant jet method and the tricuspid regurgitant jet method [62]. The tricuspid regurgitant jet method is most commonly used for determination of the pulmonary artery systolic pressure (PASP). The simplified Bernoulli equation, Pressure gradient ($P_1 - P_2 = 4V^2$, where V is the peak velocity, is used to approximate the PASP by continuous wave Doppler across the tricuspid valve regurgitant jet. In this case, $RVSP \approx PASP = 4V^2 + RAP$, where RVSP is the right ventricular systolic pressure and RAP is the right atrial pressure. The RVSP approximates PASP when no pulmonary valve stenosis or right ventricular outflow obstruction exists [62]. Although right heart catheterization (RHC) remains the gold standard for assessment of hemodynamic parameters in PH, advantages of echocardiography include wide availability, noninvasive modality, and lower costs. Intraoperatively, TEE allows dynamic interpretation and assessment of the therapeutic management of PH. Disadvantages include the need for specialized training for interpretation, modest diagnostic accuracy and the correlation to PH as compared to RHC [62] [63]. Janda *et al* revealed that the correlation coefficient of systolic pulmonary artery pressure (PASP) by echocardiography as compared with PASP by RHC to be 0.70 (95% CI 0.67 to 0.73) as well as a summary sensitivity and specificity of 83% (95% CI 73 to 90) and 72% (95% CI 53 to 85), respectively for diagnostic accuracy of echocardiography for pulmonary hypertension [62]. The variability of echocardiography to correlate to RHC is in part related to the underlying disease, lung conditions, time of the examination, and the skills of the echocardiographer [51] [64] [65]. Underestimation of PASP by echocardiography resulting in improper classification of PH (mild, moderate, severe) is more likely than overestimation, however inaccuracy in both under and overestimation occur with similar frequency [64]. Improvement in obtaining the tricuspid regurgitant jet peak velocity has been found with the use of an intravenous bolus of agitated saline [58] [59] [66]. Despite the technical challenges and inaccuracies associated with echocardiography, it remains a useful tool, especially for perioperative management of patients with PH. For the initial evaluation, monitoring, and management of PH. Takatsuki *et al* evaluated the usefulness of tissue Doppler imaging (TDI) in assessment of disease severity and prognostic value in children with IPAH. The authors studied TDI velocities (systolic myocardial velocity, early diastolic myocardial relaxation velocity [Em], late diastolic myocardial velocity associated with atrial contraction), brain natriuretic peptide, NYHA functional class, and hemodynamic parameters in 51 children (mean age; 11.6 years) with IPAH. Fifty-one healthy children with comparable demographics served as controls. They found that Tricuspid Em had significant inverse correlations with plasma brain natriuretic peptide levels ($r = -0.60$, $P < 0.001$), right ventricular end-diastolic pressure ($r = -0.79$, $P < 0.001$), and mean PAP ($r = -0.67$, $P < 0.001$). Em, Em/late diastolic myocardial velocity associated with atrial contraction ratio, and systolic myocardial velocity at mitral annulus, septum, and tricuspid annulus in IPAH were significantly reduced compared with controls. Statistically significant differences were observed in tricuspid Em between NYHA functional class II versus combined III and IV (mean and SD; 11.9 ± 4.2 cm/s versus 8.2 ± 3.6 cm/s, respectively, $P = 0.002$). Cumulative event-free survival rate was significantly lower when tricuspid Em was ≤ 8 cm/s (log-rank test, $P < 0.001$). So they believe Tricuspid Em velocity correlated with NYHA functional class as disease severity and may serve as a useful prognostic marker in children with IPAH. [67].

6.1.1. Right heart catheterization

Right heart catheterization is considered the gold standard for measuring PAP. Evidence of significant RV dysfunction should prompt reevaluation of the need for surgery [68]. All attempts to lower PAP should be done preoperatively. Treatment options include oxygen, bronchodilators, vasodilators and inotropes. In addition to the careful evaluation of the patient's current therapeutic regimen for pulmonary hypertension, all other medications should be reviewed for possible drug-drug interactions. Likewise, it is important to maintain the patient's current therapeutic regimen as discontinuation of medications can potentially lead to rebound or even worsened PH and RV dysfunction. Although medications such as inhaled prostacyclin (epoprostenol or Flolan) are associated with impaired platelet aggregation, they have not been implicated in clinically significant bleeding. Due to the short half-life of this medication, epoprostenol should not be stopped at any time in the perioperative period. The anesthesiologist must ensure preoperative maximization of the patient's therapeutic options being accomplished and coordinated, if needed, a perioperative strategy for continuance of chronic PH therapy [69].

6.1.2. Pulmonary function tests, ventilation/perfusion (V/Q) scanning and pulmonary angiography

Pulmonary function test (PFT) has been used for the assessment of the overall pulmonary function. PFT can help determine patient's tolerability to certain surgical procedures. He *et al* conducted V/Q scanning and computed tomography pulmonary angiography (CTPA) for a total of 114 consecutive patients (49 men and 65 women, average age 43.3 years) suspected of having CTEPH. Interpretation of V/Q images was based on the refined Pulmonary Embolism Diagnosis criteria. For threshold 1, high-probability and intermediate-probability V/Q scan findings were considered to be positive, and low-probability/normal V/Q scan findings were negative. For threshold 2, only a high-probability V/Q scan finding was considered to be positive. And intermediate-probability and low-probability/normal V/Q scan findings were considered to be negative. Their results indicated that 51 patients (44.7%) had a final diagnosis of CTEPH. V/Q scan showed high probability (52 patients), intermediate probability (2 patients), and low probability/normal scan (59 patients) respectively. CTPA revealed 50 patients with CTEPH and 64 patients without CTEPH. The sensitivity, specificity, and accuracy of the V/Q scan were 100, 93.7, and 96.5%, respectively, with threshold 1, and 96.1, 95.2, and 95.6%, respectively, with threshold 2; similarly, the sensitivity, specificity, and accuracy of CTPA were 92.2, 95.2, and 93.9%, respectively. They therefore concluded that both V/Q scanning and CTPA are accurate methods for the detection of CTEPH with excellent diagnostic efficacy [70].

6.1.3. Cardiac Magnetic Resonance Imaging (MRI)

Cardiac magnetic resonance imaging (MRI) has prognostic value in patients with IPAH before starting intravenous prostacyclin [71]. Swift *et al* studied the diagnostic accuracy of MRI derived RV measurements for the detection of pulmonary hypertension (PH) in the assessment of patients with suspected PH. They retrospectively reviewed 233 treatment-naïve patients with suspected PH including 39 patients with no PH who underwent MRI and right heart catheterization (RHC) within 48 hours. The diagnostic accuracy of multiple MRI measure-

ments for the detection of mPAP [greater than or equal to] 25 mmHg was assessed using Fisher's exact test and receiver operating characteristic (ROC) analysis. Ventricular mass index (VMI) was the MRI measurement with the strongest correlation with mPAP ($r=0.78$) and the highest diagnostic accuracy for the diagnosis of PH (area under the ROC curve of 0.91) compared to an ROC of 0.88 for mPAP measured by echocardiography. Using late gadolinium enhancement, VMI [greater than or equal to] 0.4, retrograde flow [greater than or equal to] 0.3 L/min/m² and PA relative area change [less than or equal to] 15% predicted the presence of PH with a high degree of diagnostic certainty with a positive predictive value of 98%, 97%, 95% and 94% respectively. No single MRI parameter could definitely exclude the presence of PH. Thus they concluded that MRI is a useful alternative to echocardiography in the evaluation of suspected PH. They support the routine measurement of ventricular mass index, late gadolinium enhancement and the use of phase contrast imaging in addition to right heart functional indices in patients undergoing diagnostic MRI evaluation for suspected pulmonary hypertension [72].

6.1.4. N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP)

Frantz *et al* used N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a biomarker of the disease severity in patients with PAH. They aimed to determine whether baseline NT-proBNP levels correlate with improvement in 6MWD in the pivotal randomized, placebo-controlled, double-blind study of the addition of inhaled treprostinil to oral therapy for PH. They found that baseline NT-proBNP levels demonstrated a strong correlation with treatment in predicting change from baseline for 6MWD ($p < 0.01$), indicating that in the upper quartile ($\geq 1,513.5$ pg/ml), patients on inhaled treprostinil had a better response (+64 versus +32 m), whereas patients on placebo fared worse (-13 versus +20 m) when compared with the lower 3 quartiles ($< 1,513.5$ pg/ml). Furthermore, least-squares mean difference in 6MWD between active and placebo groups was +67 and +16 m for the upper and lower 3 quartiles of NT-proBNP, respectively. The investigators concluded that greater improvement in 6MWD in actively treated patients with high levels of NT-proBNP predicts better clinical response to inhaled treprostinil in more advanced disease [73]. Diller *et al* followed up 181 patients (mean follow-up period is 3.3 years, 7 patients with Down syndrome) with 20 deaths. Their results showed that higher BNP concentrations were predictive of all cause mortality on univariate analysis in patients with or without Down syndrome. On multivariable Cox proportional hazard analysis, BNP predicted survival independently of renal function, Down syndrome, or 6MWD ($p=0.004$). Temporal increases in BNP concentration also predicted mortality in patients with concurrent Eisenmenger syndrome patients. Treatment with disease targeting therapies was associated with a significant reduction in BNP concentrations [74].

Perioperative Risks of PH: The patient with PH is at elevated risk for morbidity and mortality in the perioperative period [5], [76], [77], [78]. There is a relative paucity of literature studying outcomes in this patient population presenting for noncardiac surgery, however, the evidence that does exist points to significantly increased potential for complications in the perioperative period. Ramakrishna *et al* presented the results from an overview of 145 patients with PH presenting for noncardiac surgery. A 42% rate of early (<30 days) morbidity (congestive heart

failure, cardiac ischemic event, stroke, respiratory failure, hepatic or renal dysfunction, cardiac dysrhythmia) and a 9.7% rate of early mortality in this population have been reported [47]. Ramakrishna *et al* summarized the clinical characteristics associated with early morbidity and mortality in Table-5.

Clinical characteristics prone to early mortality	Clinical characteristics prone to early morbidity
1. Right axis deviation (RAD)	1. NYHA class 2 or higher
2. Right ventricular hypertrophy (RVH)	2. History of pulmonary embolism
3. RVSP/SBP ratio above 0.6	3. Obstructive sleep apnea
4. Intraoperative use of epinephrine or dopamine	4. High-risk surgery
	5. Anesthesia duration 3 hours or longer
	6. Intraoperative use of epinephrine or dopamine

NYHA=New York Heart Association, RVSP=right ventricular systolic pressure, SBP=systolic blood pressure.

Table 5. Clinical characteristics associated with increased morbidity and mortality in PA patients. Modified from reference [47].

Lai *et al.* performed a case-control study examining 67 patients with pulmonary systolic pressures greater than 70 mmHg compared to controls with normal pulmonary pressures [8]. As shown in Table-4, the pulmonary hypertension group developed postoperative heart failure more frequently (9.7 vs. 0%, $p = .028$), delayed tracheal extubation (21 vs. 0%, $p = .004$) and greater in hospital mortality (9.7 vs. 0%, $p = 0.004$). A review of a large U.S. database by Mementsoudis *et al.* estimated the mortality rate in patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) [7]. The authors identified 1359 THA and 2184 TKA patients with the diagnosis of PH. In comparison to a matched sample without PH, the THA patients had a 4-fold increased adjusted risk of in-hospital mortality and the TKA patients had a 4.5-fold increase ($p < 0.001$) [7]. Patients with PH are at considerably increased risk in the perioperative period morbidity and mortality. [8].

6.2. Intraoperative considerations

Dependent upon the nature of the scheduled surgical procedure, various anesthesia techniques including general anesthesia, neuraxial anesthesia, peripheral nerve blockade and monitored anesthesia care (MAC) have been reported to be success in the management of patients with PH [45] [79]. Except for few case reports, very little literature exists evaluating the differences of these management strategies for intraoperative and postoperative management of the patient with PH. Furthermore the choice of technique is less important as the ability to adhere to the goals of avoiding elevations in PVR and RHF.

For major procedures in patients with PH, routine ASA standard monitoring should be utilized. The following additional strategies are potentially critical for the appropriate perioperative management of patients with PH:

1. Arterial line for the continuous monitoring of arterial pressure. By using arterial pressure monitoring we can ensure adequate perfusion pressures for all vital organs including heart, lungs and brain. Arterial line can also be used for frequent blood gas analysis.
2. Pulmonary artery catheterization (PAC): PAC can be used for the monitoring of pulmonary artery pressure, for the measurement of CO and for the measurement of mixed venous oxygen saturation. By measuring PCWP, PAC can help determine left ventricular preload in pulmonary hypertensive patients whose cardiac output is limited by right ventricular function. PAP measurement is also critical in determining PH severity, and choice and dosing of therapeutic agents. However, intraoperative PAC placement is controversial in patients with PH because of the potential complications due to PAC placement. Hoepfer *et al* performed a multicenter 5-year retrospective and 6-month prospective evaluation of serious adverse events related to right heart catheter procedures in patients with pulmonary hypertension, as defined by a mean pulmonary artery pressure >25 mm Hg. Out of total 7218 PAC procedures, they found the overall number of serious adverse events was 76 (1.1%). The most frequent complications were related to venous access (e.g., hematoma, pneumothorax), followed by arrhythmias and hypotensive episodes related to vagal reactions or pulmonary vasoreactivity testing. The vast majority of these complications were mild to moderate in intensity and resolved either spontaneously or after appropriate intervention. Four fatal events were recorded in association with any of the catheter procedures, resulting in an overall procedure-related mortality of 0.055%. Thus they believe that in experienced centers, right heart catheter procedures in patients with pulmonary hypertension are still safe, only associated with low morbidity and mortality rates [80].
3. Central venous pressure (CVP) may be a more accurate guide for volume administration. Care should be taken in placing PAC and/or CVP catheters as these patients are reliant on sequential atrial-ventricular contraction for adequate preload and cardiac output. Arrhythmias associated with catheter insertion may not be well tolerated by these patients.
4. Non-invasive or minimally invasive CO measurement techniques may also be useful in PH patients undergoing surgical procedures and labor and delivery [81].
5. Bispectral index score (BIS) monitoring helps maintain appropriate depth of anesthesia.
6. Transesophageal echocardiography (TEE): Transesophageal echocardiography can be very useful in assessing the preload, contractility, anatomical irregularities and valvular abnormalities of both right-side and left-side of the heart. TEE can also help evaluate the result of cardiopulmonary surgical procedures [82] [83].

6.3. Strategies of controlling pulmonary arterial pressure

There are multiple methods available to control the increased PAP intraoperatively. These strategies can be categorized into pharmacological and non-pharmacological measures.

Pharmacological management of intraoperative hypertension includes the following:

1. **Inhaled nitric oxide:** Inhaled nitric oxide (INO) is one of the most potent medications commonly used perioperatively. The usual dose is 20–80 ppm (parts per million). The delivery system is shown in Figure-3. The INO delivery system includes a circuit and a control panel and related tank and tubing. INO can diffuse from the alveoli to the pulmonary capillaries and stimulates guanylate cyclase to increase cyclic guanosine monophosphate (cGMP) which leads to vasodilation. INO does not produce systemic vasodilatation because nitric oxide is inactivated when bound to hemoglobin. It also has the benefit of improving ventilation–perfusion matching by increasing perfusion to areas of the lung that are well ventilated. If the clinical picture is of pulmonary hypertension with systemic hypotension, IV vasodilators may cause worsening of systemic blood pressure, subsequent RV hypoperfusion, ischemia and failure. In this situation, the patient may benefit from therapy selective for the pulmonary vasculature such as inhaled nitric oxide (INO) or prostacyclin. INO has also been shown to improve PH in cardiopulmonary bypass settings [84] [85].

Figure 3. Inhaled nitric oxide delivery system Left: Inhaled nitric oxide delivery system control panel. Right: Inhaled nitric oxide delivery circuit, the arrow indicates the inspiratory limb. (Copyright owned by Henry Liu, MD)

2. **Milrinone:** Milrinone is a phosphodiesterase-3 inhibitor and prevents the breakdown of cyclic adenosine monophosphate (cAMP). It has shown to reduce both PVR and SVR in addition to causing increases in myocardial contractility [86]. The usual dose of milrinone is 50 mg/kg loading, then 0.5–0.75mg/kg/min for the maintenance.
3. **Thromboxane synthase inhibitor:** Dipyridamole (tradename: Persantine) can be used intraoperatively in managing PH; its usual dose is 0.2–0.6 mg/kg i.v. over 15 minutes, and it may be repeated after 12 hours. Lepore et al used intravenous dipyridamole combined with INO in 9 patients with congestive heart failure (CHF) and severe PH who were breathing 100% oxygen during right heart catheterization, we administered inhaled NO (80 ppm) alone and in combination with intravenous dipyridamole (0.2-mg/kg bolus, with an infusion of 0.0375 mg/kg/min), and found that Intravenous dipyrida-

mole augments and prolongs the pulmonary vasodilator effects of INO in CHF patients with severe PH [87].

4. **Inhaled prostacyclin:** Continuous intravenous administration of prostacyclin 50 ng/kg/min after reconstituting prostacyclin in sterile glycine diluent to 30,000 ng/ml (1.5mg of prostacyclin in 50 ml of diluent). For an 80 kg patient, 50 ng/kg/min is 8 ml of this solution per hour. It is nebulized into the inspiratory side of the ventilator circuit; an example of a prostacyclin nebulized delivery system that can be integrated into the anesthesia circuit is shown in Figure-4. Iloprost is a synthetic analogue of prostacyclin PGI₂. Iloprost dilates systemic and pulmonary arterial vascular beds. It also affects platelet aggregation but the relevance of this effect to the treatment of pulmonary hypertension is unknown. The two diastereoisomers of iloprost differ in their potency in dilating blood vessels, with the 4S isomer substantially more potent than the 4R isomer. Prostacyclin, available in inhaled and intravenous forms, stimulates adenylate cyclase and increases cAMP and release of endothelial NO leading to decreases in PAP, RAP, and increased cardiac output [88]. Combination therapy, with both INO and prostacyclin, has synergistic effects compared to monotherapy [89] [90]. Due to the extremely short half-life of these medications, one should ensure that the medication is delivered continuously without interruption to minimize the risk of rebound PH. Weaning from these medications should be performed gradually with frequent assessment of PAP and RV function. A disadvantage of INO compared to inhaled prostacyclin is its high cost. A recent analysis revealed that INO is approximately 20 times more expensive than prostacyclin (\$3000/day vs. \$150/day) [91]. Table-6 lists the medical management options, including common doses and common side effects, for intraoperative management of pulmonary hypertension. Lastly, in patients refractory to the above therapies, right ventricular assist device implantation should be considered.

Figure 4. Inhaled prostacyclin delivery system Figure-6: Inhaled prostacyclin delivery system. Reconstituted prostacyclin is delivered by a Lo-Flo Mini Heart nebulizer (a), which is driven by a separate oxygen source at 2 L/min (b). The nebulizer output is 8 mL/h, which allows for 1–3 h of continuous nebulization. The nebulizer should be supported by an IV pole or ventilator side arm to prevent spillage. An IV port (c) allows the chamber to be refilled without disconnecting from the anesthetic circuit. Prostacyclin is photosensitive and requires the nebulizing chamber to be covered from ambient light (d) [88].

5. Intravenous prostacyclin (if inhaled is not available) is 4–10 ng/kg/min. In the U.S., iloprost is inhaled specifically using the I-Neb AAD or Prodose AAD delivery systems. Ventavis is supplied in 1 mL single-use glass ampules containing either 10 mcg/mL or 20 mcg/mL. The 20 mcg/mL concentration is intended for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times which could result in incomplete dosing. Transitioning patients to the 20 mcg/mL concentration using the I-neb AAD System will decrease treatment times to help maintain patient compliance. The approved dosing regimen for iloprost is 6 to 9 times daily (no more than every 2 hours) during waking hours, according to individual need and tolerability.
6. Systemic hypotension should be treated according to the potential causes. Phenylephrine and norepinephrine have been used to treat persistent systemic hypotension. Norepinephrine has the advantage of being both a vasoconstrictor and positive inotropic agent. Vasopressin has also been advocated for treatment of hypotension [68] [92]
7. Sildenafil produced significant pulmonary vasodilatory effect relative to placebo in anesthetized cardiac surgical patients with pulmonary hypertension. With respect to the predominant selectivity of sildenafil to pulmonary vasculature shown in this study and other potentially beneficial effects such as myocardial protection, use of sildenafil in the intraoperative period in cardiac surgical patients with pulmonary hypertension should be considered [93]. Sildenafil citrate (INN sildenafil) is a selective phosphodiesterase type 5 inhibitor that is being increasingly recognized as a treatment modality for pulmonary hypertension.
8. Calcium channel blockers have been shown to inhibit the contraction of pulmonary artery smooth muscle cells, reduce right ventricular hypertrophy and improve long-term hemodynamics in PH in a small subset of patients who also show an acute hemodynamic response to calcium channel blockers. An interesting study demonstrated that survival was greatly improved in patients who showed a long-term response to calcium channel blockers; however, in patients that failed on long-term calcium channel blocker therapy, the 5-year survival rate was only 48% [94]. Calcium channel blockers are now only recommended for patients with a positive response during acute vasoreactivity testing and who show sustained hemodynamic improvement [94]. Calcium channel blockers are the only systemic antihypertensive drugs that have been shown to benefit patients with PH. By blocking calcium entry into cells of the pulmonary arterial vasculature, calcium channel blockers can induce vasodilation (or at least prevent vasoconstriction) of pulmonary arteries. In an initial trial in patients who demonstrated a response to calcium channel blockers during acute testing, use of calcium channel blockers led to a significant reduction in mPAP and PVR after 24 hours of treatment. Continued use over 1 year was associated with improvements in symptoms [94].

Non-pharmacological management of pulmonary hypertension is listed in Table-7.

Drug category	Drug name	Delivery pathway/dose	Common side effects
Prostaglandins	Epoprostenol (Tradename:Flolan)	Inhaled 31 mcg/kg/min	Occupational health concern
	Iloprost (Ventavis)	Inhaled, 6-9 times/day	Dizziness, headache, flushing, lightheadedness,
	Treprostinil (Tyvaso)	Inhaled, follow doctor's instruction	Cough, headache, throat irritation, pain, flushing
Nitric oxide	Inhaled nitric oxide	Inhaled, 20-50ppm	Methemoglobinemia, Lung toxicity,
Phosphodiesterase Type-5 inhibitors	Milrinone	Intravenous, 50mcg/kg loading, 0.25-0.75 mcg/kg/min maintenance	Ventricular dysrhythmia, tachycardia,
	Sildenafil	Oral, 50 mg preoperatively	hypotension
Endothelin receptor antagonist	Anbrisentan (Letairis in USA, Volibris in EU)	2.5-10mg/day, oral	Birth defects
	Bosentan(Tracleer)	62.5mg twice daily, oral for 4 weeks	Hepatotoxicity
			Birth defects Anemia
Nitrovasodilator	Nitroglycerin	Intravenous, 0.5 g/kg/min,	Hypotension, headache
Calcium channel blockers	Diltiazem	High oral dose:720mg/day	Constipation, dizziness, flushing, headache
	Nifedipine	Oral 240mg/day	Constipation, cough, flushing, giddiness

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Table 6. Pharmacological treatment for pulmonary hypertension [94] [95] [96] [97].

6.4. General anesthesia

Without any doubt, every effort should be made to have a smooth induction of anesthesia and endotracheal intubation which will minimize the hemodynamic instability in highly susceptible patients. Commonly used intravenous anesthetics such as propofol and thiopental are associated with hypotension and myocardial depression. Their use should be very judicious. Etomidate has much fewer effects on SVR, PVR and myocardial contractility and may be a more useful hypnotic for patient with severe PH. Use of volatile anesthetics is associated with decreased SVR, myocardial contractility and potential arrhythmias, all of which can impair right ventricular myocardial perfusion and also right ventricular cardiac output. A balanced technique utilizing high dose narcotics to blunt the sympathetically mediated cardiovascular response to surgical stimulation and minimal volatile anesthetics can limit these adverse effects. Additionally, the anesthesiologist should strive to use basic physiology to her/his advantage. These principles include utilization of 100% oxygen for its pulmonary vasodilator

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1. Ensure adequate oxygenation; avoid hypercarbia;
 2. Avoidance of acidosis;
 3. Avoidance of hypothermia;
 4. Whatever medication is used to control PH, wean the medication slowly to prevent rebound pulmonary hypertension;
 5. Neuraxial anesthesia, peripheral nerve blockade, and lumbar plexus block can all be used to provide surgical anesthesia for scheduled procedures. But the loading dose should be slow and adjusted according to patient's condition. Epidural anesthesia should be induced slowly. Mixtures of local anesthetics and opioids should be given to reduce the dose of local anesthetics and hypotension;
 6. Avoidance of elevating intrapleural pressure which will potentially be transmitted to increased pulmonary arterial pressure.
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Table 7. Non-Pharmacological management of pulmonary hypertension

effects, and aggressive treatment of hypercarbia, acidosis, and hypothermia as these may cause pulmonary vasoconstriction. Certain anesthetic agents such as nitrous oxide and ketamine have been associated with increases in PVR and should be used with caution [98] [99]. Uncompensated vasodilatation or myocardial depression induced by anesthetics and mechanical ventilation may be responsible for acute RV dysfunction associated with low systemic blood pressure. Cardiovascular collapse can develop after institution of one-lung ventilation and pulmonary artery clamping during thoracotomy. An acute increase in pulmonary pressure results in a decrease in RV ejection fraction and then acute RV failure. Interdependence of the right and left ventricles occurs such that RV function can alter LV function. Early detection of impending circulatory and/or respiratory deterioration is warranted to prevent an irreversible decline in cardiac output. Inhaled nitric oxide represents the first choice for treatment of PH and RV failure associated with systemic hypotension during lung transplantation. Intraoperative situations requiring CPB must be identified before development of systemic shock, which represents a late ominous sign of RV failure [61].

The anesthetic goals of intraoperative management include optimizing PAP, RV preload and avoiding RV ischemia and failure. Intraoperatively, often times there are significant alterations in all above parameters and appropriate vigilance and monitoring are paramount. Intraoperative management of the RV can be made on the presence of RV failure and the presence of systemic hyper- or hypotension. Initially, one should ensure that oxygenation, ventilation, and acid/base status are optimized. Treatment options for PH include both intravenous and inhaled agents. Intravenous vasodilators, such as nitroglycerin, sodium nitroprusside, beta blockers, calcium channel blockers, and certain prostaglandin preparations will cause dilation of both the pulmonary and systemic vascular beds and can be useful in the setting of PH with systemic hypertension. The advantages to intravenous preparations are the relative decreased cost, easier availability of medications, and longer duration of action and ease of administration in comparison to inhaled agents.

6.5. Regional anesthesia

Regional anesthetic techniques, including neuraxial blockade (epidural, spinal anesthesia, or combined epidural and spinal anesthesia) and peripheral nerve blockade (cervical plexus, axillary plexus, sciatic nerve, femoral, etc), have all been successfully used in surgical procedures in patients with severe pulmonary hypertension [100]. Among the benefits of regional anesthesia are potential minimization of the stimulation-related (direct laryngoscopy, endotracheal intubation, etc) sympathetic activation. Even with adequate intravenous anesthetic induction agents, opioids and neuromuscular blockade, it is difficult to avoid increases in sympathetic nervous system activity due to laryngoscopy and induction. These sympathetic responses include tachycardia, systemic hypertension and increased myocardial oxygen consumption, which could lead to increases in PVR and potential acute right heart failure. During surgery and general anesthesia, due to various surgery-related (incision, surgical dissection, blood loss etc) or other surgical environment-related stimulations (hypothermia, psychological stress etc), the anesthesiologist has to continually balance excessive sympathetic outflow, increased PVR and potential acute right heart failure on one hand and excessive depth of anesthesia, low cardiac output, low coronary perfusion and cardiovascular collapse on the other hand [101]. A healthier patient tolerates these variations well, but the patient with severe PH has limited reserve to compensate for acute increases in PVR or decreased coronary perfusion. A peripheral nerve block technique could potentially limit anesthesia to the specific location of the surgery and avoid the need for the stimulation of intubation and reduced likelihood of sympathectomy and low blood pressure as one would achieve with general anesthesia. An important distinction is that a sympathectomy is still possible when utilizing a regional anesthesia technique such as epidural or spinal anesthesia. This may lead to arterial and venous dilatation and reduced preload and cardiac output compromising coronary perfusion. When utilizing neuraxial or peripheral nerve block techniques, it is important to ensure adequate ventilation and oxygenation to prevent increases in PVR due to hypoxemia. For example, sedation provided to allow the patient to tolerate placement of a peripheral nerve block or to tolerate lying on the narrow, stiff operating table may lead to hypoxemia and hypercarbia secondary to hypoventilation. On the other hand, lack of adequate sedation can promote anxiety, pain and sympathetic stimulation. Achieving the delicate balance can be a daunting task for anesthesia providers.

For those patients with PH to undergo minor surgical procedures with only monitored anesthesia care (MAC), special attention should be paid to provide adequate sedation to minimize patients' anxiety, which can be harmful because it may lead to increased sympathetic outflow as we discussed previously. Over-sedation should be avoided to prevent respiratory suppression and subsequent hypoventilation and hypoxemia which may induce hypoxic vasoconstriction and elevated PAP.

6.6. Postoperative management

These patients with moderate to severe PH warrant intensive care monitoring in the postoperative period by experienced critical care personnel. As the analgesic and sympathetic nervous system effects of opioids, volatile anesthetics, and regional anesthetics disappear, the

patient can develop sudden worsening of PH and RV ischemia. Thus weaning from the ventilatory support and endotracheal extubation should be done gradually with close attention to adequate oxygenation, ventilation and analgesia. Even routine events such as bucking on the ventilator due to tracheal stimulation, while tolerated by the average patient, can lead to acute rises in PVR and RV failure in patient with severe PH [78]. Postoperative pain management of patients with PH warrants special attention, because in clinical practice, the most commonly used analgesic agents are opioids which are potent respiratory depressants also. Depression of respiratory drive will likely cause hypoventilation which leads to increased PAP. Thus using multimodal analgesic strategy is critical in minimizing the side effect of respiratory inhibition by opioids and avoiding hypoventilation-associated increase of PAP.

7. Special populations potentially with pulmonary hypertension

7.1. Pediatrics

Pediatric patients with PH have some unique clinical features comparing with adult PH patients. Genetic factors seem to play a more important role in the pathogenesis of PH. Chida *et al* studied fifty-four patients with IPAH or HPAH whose disease was diagnosed at <16 years of age. Functional characteristics, hemodynamic parameters, and clinical outcomes were compared in BMPR2 and ALK1 mutation carriers and noncarriers. Overall 5-year survival for all patients was 76%. Eighteen BMPR2 mutation carriers and 7 ALK1 mutation carriers were detected in the 54 patients with childhood IPAH or HPAH. Five-year survival was lower in BMPR2 mutation carriers than mutation noncarriers (55% vs 90%, hazard ratio 12.54, $p = 0.0003$). ALK1 mutation carriers also had a tendency to have worse outcome than mutation noncarriers (5-year survival rate 64%, hazard ratio 5.14, $p=0.1205$). These indicated that patients with childhood IPAH or HPAH with BMPR2 mutation have the poorest clinical outcomes. ALK1 mutation carriers tended to have worse outcomes than mutation non-carriers. It is important to consider aggressive treatment for BMPR2 or ALK1 mutation carriers [102]. Carmosino *et al* retrospectively studied 156 children with PH with median age 4.0 years who underwent anesthesia or sedation for noncardiac surgical procedures or cardiac catheterizations from 1999 to 2004. PH etiology was 56% idiopathic (primary), 21% AHD, 14% chronic lung disease, 4% chronic airway obstruction, and 4% chronic liver disease. Baseline PAP was subsystemic in 68% patients, systemic in 19%, and suprasystemic in 13%. The anesthetic techniques were 22% sedation, 58% general inhaled, 20% general IV. Minor complications occurred in eight patients (5.1% of patients, 3.1% of procedures). Major complications including cardiac arrest and pulmonary hypertensive crisis, occurred in seven patients during cardiac catheterization procedures (4.5% of patients, 5.0% of cardiac catheterization procedures, 2.7% of all procedures). There were two deaths associated with pulmonary hypertensive crisis (1.3% of patients, 0.8% of procedures). Based on their observation, they believe baseline suprasystemic PH was a significant predictor of major complications by multivariate logistic regression analysis (OR = 8.1, $P = 0.02$) and complications were not significantly associated with age, etiology of PH, type of anesthetic, or airway management. Children with suprasystemic PH have a significant risk of major perioperative complications, including cardiac arrest and

pulmonary hypertensive crisis [103]. Management of pediatric patients with PH poses unique challenges to pediatric anesthesiologists: PAC may not be available for many smaller pediatric patients due to the small sizes of their cardiac chamber and blood vessels. TEE may not be available to some pediatric patients due to lack of suitable size of TEE probe. So transthoracic or epicardial echocardiography will play a much more important role for those pediatric patients without TEE and PAC. Minimally invasive/non-invasive monitoring of MAP, CO/CI, SVV may play some role intraoperatively, however these current technologies may not work as well in children as in adults [104]. And information from randomized controlled clinical studies on the treatment of pediatric PH is currently very limited, unanimous opinions are to refer to the guidelines and treatment strategies for the treatment of adult PH. Therefore, the recommended treatment for children is only grade IIa with the level of evidence class C.

7.2. Obstetrics

Curry *et al* reported two maternal deaths out of 12 pregnancies in 9 patients. One of the two deaths was related to pre-eclampsia and the other related to cardiac arrhythmia. Maternal morbidity included postpartum hemorrhage (five cases), and one post-caesarean evacuation of a wound hematoma. There were no perinatal death, nine live births and three first-trimester miscarriages. Mean birthweight was 2197 grams, mean gestational age was 34 weeks (range 26-39), and mean birthweight percentile was 36 (range 5-60). Five babies required admission to the neonatal intensive care unit, but were all eventually discharged home. All women were delivered by caesarean section (seven elective and two emergency deliveries), under general anesthesia except for one emergency and one elective caesarean performed under regional block [105]. Maternal and fetal outcomes for women with PH has improved; however, the risk of maternal mortality remains significant, so that early and effective counseling about contraceptive options and pregnancy risks should continue to play a major role in the management of such women when they reach reproductive maturity.

8. Summary

We have gained better understanding of PH and have significantly more sophisticated management strategies now compared with two decades ago. PH can develop due to pulmonary vascular remodeling (cellular proliferation), abnormal vasoconstriction, mechanical obstruction (chronic thromboembolic events, interstitial lung diseases) or left-side heart diseases. Thorough preoperative evaluation is mandatory. A clear understanding of the etiology of pulmonary hypertension is extremely important to understand how to optimally manage these patients in the operating room. Echocardiography plays a key role in preliminary screening, monitoring the progress and evolution of PH, and intraoperative monitoring and treatment. Right heart catheterization remains the gold standard for the diagnosis of PH. Evaluation of the overall pulmonary functional status is also important in assessing patients' tolerability to the planned surgical procedure. Perioperatively these patients can present very challenging clinical scenarios due to the complexity of their PH and increased risks for significant complications with elevated morbidity and mortality. Several clinical characteris-

tics predict early mortality: right axis deviation, right ventricular hypertrophy, RVSP/SBP ratio above 0.6, and intraoperative use of epinephrine or dopamine. Intraoperative control of elevated pulmonary pressure can be achieved with inhaled nitric oxide or prostacyclin, PDE inhibitors (milrinone, sildenafil), calcium channel blockers, nitrodilators and adequate oxygenation. The ideal perioperative care of these patients requires a multidisciplinary approach with appropriate planning for pre-procedural optimization, comprehensive intraoperative monitoring and delicate management of PAP as well as intensive care unit monitoring in the postoperative period. This approach will test the expertise and resources of medical institutions. Anesthesiologists will require a thorough understanding of the current treatment options, pathophysiology of the disease, and the implications of various anesthetic agents and techniques to provide the highest level of patient safety and care to the patients with PH.

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