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# Saudi guidelines on diagnosis and treatment of pulmonary arterial hypertension

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## Introduction

Pulmonary arterial hypertension (PAH) represents a heterogeneous group of disorders sharing similar histological abnormalities and pathophysiology. PAH is defined as a disease characterized by a progressive increase of pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP), with a normal pulmonary artery wedge pressure (PAWP). These progressive abnormalities can lead to right ventricular failure secondary to increased right ventricular afterload and subsequent decline in right ventricular cardiac output.<sup>[1]</sup> The median survival from the time of diagnosis in patients with idiopathic pulmonary arterial hypertension (IPAH) before the availability of modern (target) therapy was 2.8 years.<sup>[2]</sup>

Normal mean PAP (mPAP) is approximately 14 mmHg at rest. In PAH patients, the mPAP is greater than 25 mmHg at rest and/ or 30 mmHg during exercise. Such high pressure is associated with changes in the small blood vessels in the lung, leading to complex pathological sequences that finally result in detrimental outcome.

In the last few years, there have been major improvements in our understanding of the mechanism of the disease and its pathophysiology, which subsequently led to significant advances in the diagnostic processes and treatment options, which will be discussed in great details in this guideline.

## Epidemiology and Natural History

The true incidence of IPAH is unknown. The first reported case occurred in 1891, which described

a patient who at autopsy showed thickening of the pulmonary artery but no heart or lung disease that might have caused the condition. In 1951, 39 subsequent cases were further reported, and the illness received its name - 'primary pulmonary hypertension.'

The current estimated incidence of IPAH is 1-2 cases per 1 million persons in the general population. However, this is probably an underestimation of the disease, mainly because of under-diagnosing. In the United States, it has been estimated that 300 new cases of IPAH are diagnosed each year; most cases are reported in women between the ages of 21 and 40 years. Indeed, at one time the disease was thought to occur among young women almost exclusively, but recently it has been recognized, however, that men and women in all age ranges can develop IPAH. Apparently, the disease also affects people of all racial and ethnic origins equally.

The natural history of IPAH has been well described. The National Institute of Health (NIH) Registry<sup>[2]</sup> followed up 194 patients with IPAH enrolled at 32 clinical centers from 1981 to 1985. The estimated median survival was 2.8 years, with 1-, 3- and 5-year survival rates of 68, 48 and 34% respectively. Other series have studied the natural history of IPAH with similar results. Among a cohort of 61 IPAH patients followed up in Mexico, the mean survival was 25.9 months<sup>[3]</sup>; and it was 33 months among a cohort of 223 patients followed up in Japan.<sup>[4]</sup> In a single-center, uncontrolled case series<sup>[5]</sup> from India, the median survival was 22 months, with 2-, 5- and 10-year survival rates of 48, 32 and 12% respectively.

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Unfortunately, no data about the incidence or the prevalence of PAH is available in the Kingdom of Saudi Arabia or other Arab Gulf countries. However, the Saudi Thoracic Society (STS)/ The Saudi Advisory Group for Pulmonary Hypertension (SAPH) will soon implement a national registry in order to collect statistical information in this regard.

### Causes and Risk Factors

It is believed that in most people who develop IPAH, the blood vessels are exposed to certain internal or external stimulus (injury) that can lead to vasoconstriction. Diet suppressants, cocaine and HIV are some of the factors that are thought to initiate the injury process and trigger constriction or narrowing in the pulmonary artery. In about 6-10% of cases, IPAH disease is considered familial. Table 1 shows some recognized risk factors for the development of IPAH.

The recent identification of mutations in the bone morphogenetic protein receptor 2 (BMPR2) in the majority of cases of familial PAH (FPAH) has been a major advance in the explanation of the pathogenic sequence in PAH.<sup>16,71</sup> BMPR2 is a component

of the transforming growth factor beta (TGF- $\beta$ ) family, which plays a key role in cell growth. Analysis of genes within a region (PPH1 locus) on chromosome 2q33, led to the identification of a series of mutations in the BMPR2 gene. Gene mutation has been found in up to 60% of patients with family history of clinical disease of PAH and up to 25% in sporadic cases. Experiments with pulmonary vascular smooth muscle cells in culture indicate that bone morphogenetic protein receptor inhibits growth. The mutations identified in BMPR2 are believed to disrupt binding and/or receptors signaling, impair BMPR2 function and remove a mechanism for keeping vascular remodeling under control. Other hypothesis suggests that loss-of-function mutations in BMPR2 could lead to increased pulmonary endothelial cells apoptosis, representing a possible initiating mechanism in the pathogenesis of pulmonary arterial hypertension.<sup>181</sup>

It is clear, however, that loss of one BMPR2 allele is not in itself sufficient to cause the disease phenotype. Not only does the disease rarely manifest itself until the third or fourth decade, but also people with BMPR2 mutation have been identified who have no evidence of PH. It is likely that a second insult is necessary before the phenotype is expressed.

**Table 1: Risk factors and associated conditions**

1. Diseases
Definite causal relationship:
• Human immunodeficiency virus infection
• Schistosoma
• Systemic sclerosis (scleroderma)
• Thromboembolic diseases
Causal relationship:
• Portal hypertension and/or liver disease
• Other collagen vascular diseases
• Congenital systemic-to-pulmonary cardiac shunts
• Sickle cell disease
Possible causal relationship:
• Thyroid disorders
• Other hematological conditions
• Chronic myeloproliferative disorders
• Thalassemia
• Asplenia secondary to surgical splenectomy
2. Demographic factors and medical conditions:
Definite causal relationship:
• Gender
Possible causal relationship:
• Pregnancy
• Systemic hypertension
Unlikely causal relationship:
• Obesity
3. Drugs and toxins:
Definite causal relationship:
• Aminorex
• Fenfluramine
• Dexfenfluramine
• Toxic rapeseed oil
Likely causal relationship:
• Amphetamines
• L-Tryptophan
• Meta-amphetamines
• Cocaine
• Chemotherapeutic agents
Unlikely causal relationship:
• Antidepressants
• Oral contraceptives
• Estrogen therapy
• Cigarette smoking

### Clinical Classification of Pulmonary Hypertension

The initial clinical-based classification of pulmonary hypertension (PH) was proposed<sup>191</sup> in 1998 in Evian, France. The aim of Evian classification was to classify the disease according to the similarities in pathophysiological mechanisms, clinical presentation and therapeutic options. Later on, the 2003 Third World Symposium on PAH held in Venice, Italy, provided the opportunity to further assess the Evian classification and to propose some modifications [Table 2]. It represents the present understanding of pathophysiology, as well as of clinical-based differences or similarities within PH. The important modification that has been proposed in the Venice symposium is to update risk factors and associated conditions for PAH.

However, despite the fact that Venice classification has grouped certain diseases that share similar pathophysiological mechanisms under one category, it is quite obvious that some of the diseases within the same class (e.g., class 1 PAH group) have a very different presentation, response to treatment and long-term prognosis. For example, PAH associated with both connective tissue disease and portal hypertension seems to have a worse prognosis compared to IPAH, while PAH associated with congenital heart disease seems to have a far better prognosis.

Venice classification may change following the 2008 February 4<sup>th</sup> World Symposium on pulmonary hypertension in United States of America that may address some of the limitations in Venice classification.

### Histopathology and Pathophysiology of Pulmonary Arterial Hypertension

The exact stimulus or injuries that initiate the histopathophysiological process seen in PAH are still unknown and are probably multi-factorial. Irrespective of the nature of the primary stimulus, it stimulates a cascade of events

**Table 2: Clinical classification of pulmonary hypertension - Venice 2003**

Class 1: Pulmonary arterial hypertension (PAH):	<ul style="list-style-type: none"> <li>• Idiopathic (IPAH)</li> <li>• Familial (FPAH)</li> <li>• Conditions associated with: <ul style="list-style-type: none"> <li>• Connective tissue disease</li> <li>• Congenital systemic-to-pulmonary shunts</li> <li>• Portal hypertension</li> <li>• HIV infection</li> <li>• Drugs and toxins</li> <li>• Other, which include thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy</li> </ul> </li> <li>• Conditions associated with significant venous or capillary involvement: <ul style="list-style-type: none"> <li>• Pulmonary veno-occlusive disease (PVOD)</li> <li>• Pulmonary capillary hemangiomatosis (PCH)</li> <li>• Persistent pulmonary hypertension of the newborn (PPHN)</li> </ul> </li> </ul>
Class 2: Pulmonary hypertension associated with left-heart diseases:	<ul style="list-style-type: none"> <li>• Left-sided atrial or ventricular heart disease, including left ventricular diastolic dysfunction</li> <li>• Left-sided valvular heart disease</li> </ul>
Class 3: Pulmonary hypertension associated with respiratory diseases and/or hypoxia:	<ul style="list-style-type: none"> <li>• Chronic obstructive pulmonary disease</li> <li>• Interstitial lung disease</li> <li>• Sleep-disordered breathing</li> <li>• Alveolar hypoventilation disorders</li> <li>• Chronic exposure to high altitude</li> <li>• Developmental abnormalities</li> </ul>
Class 4: Pulmonary hypertension due to chronic thrombotic and/or embolic disease	<ul style="list-style-type: none"> <li>• Thromboembolic obstruction of proximal pulmonary arteries</li> <li>• Thromboembolic obstruction of distal pulmonary arteries</li> <li>• Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)</li> </ul>
Class 5: Miscellaneous	<ul style="list-style-type: none"> <li>• Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)</li> </ul>

that involve various biochemical pathways and cell types. Different mechanisms that include vasoconstriction, shear stress abnormality, pulmonary vascular wall remodeling, inflammation and thrombosis are the results of the initial injury and can lead to increased pulmonary vascular resistance and right ventricular afterload.

Various forms of PAH share the same histopathological changes<sup>[10]</sup> but have quantitative differences in the distribution of these pathological changes in the different components of the pulmonary vascular bed (arterioles, capillaries or veins). Three distinct subsets have been clearly observed in the disease.

Plexogenic arteriopathy is the most common subset. In this form, the pre-capillary vessels display varying degree of abnormality involving both the intima and media. It is characterized by concentric intimal fibrosis, plexiform lesions and necrotizing arthritis.

The second subset is the pulmonary veno-occlusive disease, in which the small veins and venules are the primary site of injury. In this entity, a downstream obstruction takes place due to fibrosis of the endovascular walls of the small- and medium-sized veins.

The third subset is the pulmonary capillary hemangiomatosis, which is the least common form and is characterized by proliferation of the capillary network.

Pathophysiologically, many abnormalities and dysfunctions in different signaling pathways have been identified in PAH. The following short discussion will highlight a few important pathways that are believed to play major roles in the pathophysiology of the disease.

- Mutations in the BMPR2 are the major genetic cause of FPAH (see above). Although smooth muscle cell proliferation contributes to the vascular remodeling observed in PAH, the role of bone morphogenetic proteins (BMPs) in this process and the impact of BMPR2 mutation remains unclear. Many studies that involved normal human pulmonary artery smooth muscle cells (PASMCs) suggest site-specific responses to BMPs. For example, BMP-4 inhibited proliferation of PASMCs isolated from proximal pulmonary arteries but stimulated proliferation of PASMCs from peripheral arteries and conferred protection from apoptosis. These differences are not caused by differential activation of BMP-signaling pathways, as in experimental models, exogenous BMP-4 led to phosphorylation of Smad1, p38<sup>MAPK</sup> and ERK signaling in both proximal and distal cell types. However, the pro-proliferative effect of BMP-4 on peripheral PASMCs was found to be p38<sup>MAPK</sup>/ERK-dependent. Conversely, over-expression of dominant-negative Smad1 converts the response to BMP-4 in proximal PASMCs from inhibitory to proliferative. Furthermore, it has been shown that proximal PASMCs harboring kinase domain mutations in BMPR2 are deficient in Smad signaling and are unresponsive to the growth-suppressive effect of BMP-4. Moreover, the pulmonary vasculatures of patients with familial and idiopathic PAH are found to be deficient in the activated form of Smad1. In one study, it was shown that defective Smad signaling and unopposed p38<sup>MAPK</sup>/ERK signaling, as a consequence of mutation in BMPR2, underlie the abnormal vascular cell proliferation observed in FPAH.<sup>[11]</sup>
- Serotonin pathway has gained significant popularity lately as an important pathway in the pathophysiology of PH. In one study,<sup>[12]</sup> it was found that PASMCs from patients with PH grow faster than PASMCs from controls when stimulated by serotonin. These effects were found to be due to increased expression of the serotonin transporter (5-HTT). This study also documented that in the presence of 5-HTT inhibitors, the growth-stimulatory effects of serotonin were markedly reduced and the difference between growth of PASMCs from patients and controls was no longer observed. As compared with controls, the expression of 5-HTT was increased in cultured PASMCs, as well as in platelets and lungs from patients with PH, where it predominated in the media of thickened pulmonary arteries and in onion-bulb lesions. The L-allelic variant of the 5-HTT gene promoter, which is associated with 5-HTT

over-expression and increased PASMC growth, was present in homozygous form in 65% of patients but in only 27% of controls.<sup>[12]</sup> Another study<sup>[13]</sup> evaluated the pulmonary circulation of mice deficient in *BMPR2* (*BMPR2*<sup>-</sup> mice) and showed that pulmonary hemodynamics and vascular morphometry of *BMPR2*<sup>-</sup> mice were similar to wild-type littermate controls under normoxic or chronic hypoxic (2-3 weeks) conditions. However, chronic infusion of serotonin caused increased pulmonary artery systolic pressure, right ventricular hypertrophy and pulmonary artery remodeling in *BMPR2*<sup>-</sup> mice compared with wild-type littermates, an effect that was exaggerated under hypoxic conditions. In addition, pulmonary, but not systemic from *BMPR2* mice exhibited increased contractile responses to serotonin mediated by both 5-HT<sub>2</sub> and 5-HT<sub>1</sub> receptors. A further link between serotonin pathway and PH was evaluated in a recent case-control study<sup>[14]</sup> by looking at the association between PH and the exposure to the selective serotonin-reuptake inhibitor (SSRI) during late pregnancy. There was a significant increased risk for developing PH in infants who were exposed to SSRI after the completion of 20<sup>th</sup> week of gestation (adjusted odds ratio, 6.1) as compared with control infants.

- The role of the inward potassium (K<sup>+</sup>) channel and the cyclic AMP (cAMP)-dependent pathway in mediating vasorelaxation and the potential role of these in the pathophysiology of PH has been recently found. Hypoxic pulmonary vasoconstriction is initiated by the inhibition of voltage-gated K<sup>+</sup> channels (K<sub>v</sub>). Several channels (K<sub>v1.2</sub>, K<sub>v1.5</sub>, K<sub>v2.1</sub> and K<sub>v3.1b</sub>) have been proposed, based on similarities between their characteristics in expression systems and the properties of O<sub>2</sub>-sensitive K<sup>+</sup> current in PASMCs. A selective down-regulation of the K<sub>v</sub> channel K<sub>v1.5</sub> has been described in human and animal PAH. The resultant increase in intracellular free Ca<sup>2+</sup> ([Ca<sup>2+</sup>]<sub>i</sub>) and K<sup>+</sup> ([K<sup>+</sup>]<sub>i</sub>) concentrations may explain the PASMC contraction, proliferation and resistance to apoptosis. A recent study on PASMC and lungs from 6 PAH patients and 4 controls and blood from 23 PAH patients and 10 healthy volunteers supported this theory.<sup>[15]</sup> Compared with normal, PAH PASMC had decreased K<sub>v</sub> current and K<sub>v1.5</sub> expression and increased [Ca<sup>2+</sup>]<sub>i</sub>, [K<sup>+</sup>]<sub>i</sub>, mitochondrial potential and bcl-2 levels. PAH, but not normal, PASMC and lungs showed activation of nuclear factor of activated T cells (NFATc<sub>2</sub>), suggesting an inflammatory pathway. Inhibition of this factor was found to restore K<sub>v1.5</sub> expression and current, decrease [Ca<sup>2+</sup>]<sub>i</sub>, [K<sup>+</sup>]<sub>i</sub>, leading to decreased proliferation and increased apoptosis *in vitro*. In this study, NFATc<sub>2</sub> levels were increased in circulating leukocytes in PAH versus healthy volunteers, and CD<sub>3</sub>-positive lymphocytes with activated NFATc<sub>2</sub> were seen in the arterial wall in PAH but not normal lungs.
- Furthermore, prothrombotic abnormalities have been demonstrated in PAH patients,<sup>[16]</sup> and thrombi are present in both microcirculation and elastic pulmonary arteries.<sup>[17]</sup> In fact, fibrin peptide-A levels that reflect thrombin activity<sup>[18]</sup> and thromboxane A<sub>2</sub> (Tx-A<sub>2</sub>) levels are elevated in patients with IPAH.

Irrespective of the initiating injury and the subsequent complex pathophysiological mechanism, the outcome tends to end in two distinct phases: vasoconstriction and remodeling.

## I. Vasoconstriction phase

As a result of the pathological process that is triggered by the initial injury, the smooth muscle contracts, leading to 'abnormal' vasoconstriction, which is believed to be an early process in the pulmonary hypertension.<sup>[19]</sup>

Normally, vascular tone and caliber are regulated by endothelial shear stress (which is regulated by endothelial cell deformity) and endothelial mediators' release. Such shear stress is directly related to flow rate and blood viscosity. This normal physiology is disturbed in patients with PAH because of endothelial dysfunction. Such mechanism of endothelial dysfunction can lead to chronically impaired production of vasodilators such as nitric oxide (NO) and prostacyclin (PGI-2), along with over-expression of vasoconstrictors such as Tx-A<sub>2</sub> and endothelin-1 (ET-1).<sup>[20]</sup> Many of these abnormalities both elevate vascular tone and promote vascular remodeling. The characteristics of these mediators are shown in the Table 3.

ET-1 activity is mediated normally by ET<sub>A</sub> and ET<sub>B</sub> receptors.

- ET<sub>A</sub> receptors are located in vascular and airway smooth muscle.
- ET<sub>B</sub> receptors are located primarily in endothelial cells and to a lesser extent on smooth muscle.
- These two receptors work in delicate harmony and tune, balancing the counter-receptor function. Selective stimulation of ET<sub>A</sub> receptors leads to vasoconstriction, which results in reduction of pulmonary blood flow. However, binding and stimulation of ET-1 to endothelial cell ET<sub>B</sub> receptor induces NO and PGI-2, which promotes vasodilatation. Elevated ET-1 level is found to positively correlate with disease severity and to negatively correlate with prognosis.

Available clinical data in subjects (patients and health volunteers) show that:

- selective ET<sub>A</sub> receptor blockade results in a vasodilatory response and increased blood flow;
- selective ET<sub>B</sub> receptor blockade results in a vasoconstrictive response and reduced blood flow;
- concomitant ET<sub>A</sub>/ET<sub>B</sub> blockade may attenuate the vasodilatory response relative to selective ET<sub>A</sub> receptor blockade;<sup>[21,22]</sup>
- ET<sub>B</sub> receptors are up-regulated in PAH-disease state as opposed to normal healthy volunteers, which may suggest that selective ET<sub>A</sub> antagonism may be a better treatment option than nonselective ET<sub>A</sub>/ET<sub>B</sub> antagonism; however, to date, there is no convincing data to substantiate one over the other.

NO is normally released by the endothelium secondary to many factors that stimulate NO synthetase enzyme, which in turn helps the conversion of L-Arginine to NO, which diffuses

**Table 3: Endothelium-derived factors**

Endothelin-1 (ET-1)	- Potent vasoconstrictor - Proliferative activity
Nitric oxide (NO)	- Potent vasodilator - Antiproliferative activity
Prostacyclin (PGI-2)	- Potent vasodilator - Antiproliferative activity

to smooth muscle and leads to accumulation of cGMP. PGI-2, on the other hand, is released by the endothelium via Cox-1 pathway. After its release, PGI-2 diffuses to smooth muscle, where it leads to accumulation of cAMP. Both cGMP and cAMP lead to calcium influx and smooth muscle relaxation.

Many stimuli, such as decreased blood flow, hypoxia and shear stress, may initially induce an increase in ET-1 by stimulating ET<sub>A</sub> receptors and a decrease in NO and PGI-2 production by the endothelial cell; thus resulting in an ongoing imbalance between ET-1 and NO/PGI-2 levels and leading to pulmonary vasoconstriction.

## II. Vascular remodeling phase

If the above process is allowed to continue, it eventually results in the development of extra deposition of fibrous tissue in the walls of the pulmonary arteries. Muscle hypertrophy takes place in some arteries and new muscles appear in the walls of arteries that normally have no muscle. With time, scarring or fibrosis of the arteries takes place. Some vessels may become completely blocked. The process of pulmonary vascular remodeling involves all layers of the vessel wall and is characterized by both proliferative and obstructive changes that involve several cell types, including endothelial, smooth muscle and fibroblasts.<sup>[17,23]</sup> Inflammatory cells and platelets may also play a significant role in remodeling process in PAH patients. Alterations in the metabolic pathways of serotonin, a pulmonary vasoconstrictor substance stored in platelets, have also been detected in PAH patients<sup>[24]</sup> (see above).

Vascular remodeling is stimulated by many factors, such as ET-1, pressure, tension, shear stress and hypoxia. Unfortunately, clinical data is currently insufficient to evaluate the effect of medication on the remodeling process itself, but *in vivo* studies (in preclinical disease models) show that:

- there are beneficial effects on vascular remodeling with selective ET<sub>A</sub> blockade, PGI-2 and nonselective ET<sub>A</sub>/ET<sub>B</sub> blockade;<sup>[25]</sup>
- in contrast, selective ET<sub>B</sub> receptor blockade has been shown to worsen vascular remodeling by reducing NO/PGI-2 production<sup>[26]</sup>;
- medial thickening of pulmonary arteries from hypoxic rats was not only attenuated but actually was reversed toward values seen in normoxic animals when rats were treated with either selective ET-A or nonselective ET<sub>A</sub>/ET<sub>B</sub> antagonists<sup>[27]</sup>;
- further rise in PAP was prevented or reversed by these agents.<sup>[27]</sup>

## III. Right ventricular failure

PAH is a disease of pulmonary circulation leading to steady rise in PVR, which increases right ventricular afterload. The disease manifests as a problem of flow or compromised cardiac output due to RV dysfunction. Initially, there is an inability to meet the increased demands at exercise, but eventually symptoms even manifest at rest. RV performance is the single most important factor in explaining symptoms, pathophysiology and survival in PAH. In the NIH Registry,<sup>[21]</sup> about 50% of deaths were attributed to RV failure.

Physiologically, the lung's circulation bed exhibits tremendous cross-sectional area. This complex system provides little

resistance and maintains low pressure despite accommodating the entire cardiac output. Furthermore, the vascular bed has the remarkable ability to dilate functional vessels and to recruit underutilized ones during time of increasing blood flow, such as exercise or pregnancy. Because of this unique feature, the RV normally works against low resistance and persists as a thin-walled compliant chamber. Because of this, a normal RV can handle sudden increase in volume but does not tolerate sudden increase in afterload, such as after massive pulmonary embolism.

In PAH the increased afterload develops slowly. The RV initially adapts with myocardial hypertrophy that minimizes wall stress. However, this hypertrophic response of the RV is limited and the chamber ultimately dilates, leading to greater wall stress. Contributing to the deterioration, RV ischemia eventually ensues from declining coronary perfusion in the setting of rising RV oxygen demands, creating classic supply-demand mismatch. Further on, displacement of the interventricular septum to the left secondary to high RV pressure leads to reduction in left ventricular compliance, and LV filling is postponed to late diastole. Ultimately, LV end-diastolic volume diminishes and stroke volume is further compromised, even though LV systolic function is preserved.

Despite the fact that interventricular septum shift might be the main mechanism behind LV-filling limitation and secondary reduction in LV cardiac output, other mechanisms were found to have concurrent significant contribution to LV output reduction:

- The role of intact pericardium that contains both ventricles may have significant negative effect on LV systolic performance in patients with dilated RV, secondary to the geometric change of both ventricles. In an animal study,<sup>[28]</sup> integrated conductance catheters and micromanometers were placed in both the LV and RV to allow simultaneous recordings of pressure and volume and derivation of indices of contractile function with both intact pericardium and with the pericardium wide open. RV ischemia was induced by balloon occlusion of the proximal right coronary artery (RCA). With an intact pericardium, RCA occlusion led to acute RV dilatation that produced a decrease in LV end-diastolic volume associated with a marked decline in the contractile function. On the other hand, with the pericardium open, the same ischemic insult resulted in both LV and RV dilatation, which produced a significantly smaller negative effect on LV cardiac output, LV systolic pressure and LV end-systolic pressure-volume relations.<sup>[28]</sup>
- Direct interaction between RV and LV that share the same myocardial fibers does also take place and may negatively affect LV function in patients with PAH and dilated RV. As a matter of fact, LV systole is known to contribute to generation of right ventricular pressure and stroke volume. This interaction was tested in 46 patients with PAH and 18 control subjects.<sup>[29]</sup> Stroke volume, right and left ventricular volumes, left ventricular filling rate and interventricular septum curvature were measured by magnetic resonance imaging, while left atrial filling was measured by trans-esophageal echocardiography. Among PAH patients, left ventricular stroke volume did

not correlate directly to the right ventricular end-diastolic volume or mean pulmonary arterial pressure but did correlate to left ventricular end-diastolic volume.<sup>[29]</sup> Another study examined the importance of ventricular systolic and ventricular interdependence on right ventricular function and confirmed that left ventricular contraction is very important for right ventricular developed pressure and volume outflow.<sup>[30]</sup>

It is clear from this pathophysiological data that a strong correlation is present between right and left ventricles that

are contained in a single pericardium and share the same myofibers. This interaction explains the detrimental effect of right ventricular dilatation and failure on left ventricular performance and function in PAH patients.

### Management Approach for Pulmonary Arterial Hypertension

During the following discussion, the strength of recommendation will be applied to each diagnostic strategy whenever applicable [Table 4].

**Table 4: Strength of recommendation**

A	Strong recommendation
B	Moderate recommendation
C	Weak recommendation
D	Negative recommendation
I	No recommendation possible (inconclusive)
E/A	Strong recommendation based on expert opinion only
E/B	Moderate recommendation based on expert opinion only
E/C	Weak recommendation based on expert opinion only
E/D	Negative recommendation based on expert opinion only

PAH is rarely picked up in a routine medical examination. Even in its later stages, the signs of the disease are nonspecific and can be easily confused with other cardiac or pulmonary conditions. Thus, PH is usually not diagnosed until late in the disease process.

From our perspective, we will discuss the issue of management approach from three main aspects: (1) the diagnostic approach, (2) disease evaluation (evaluation of Venice class) and

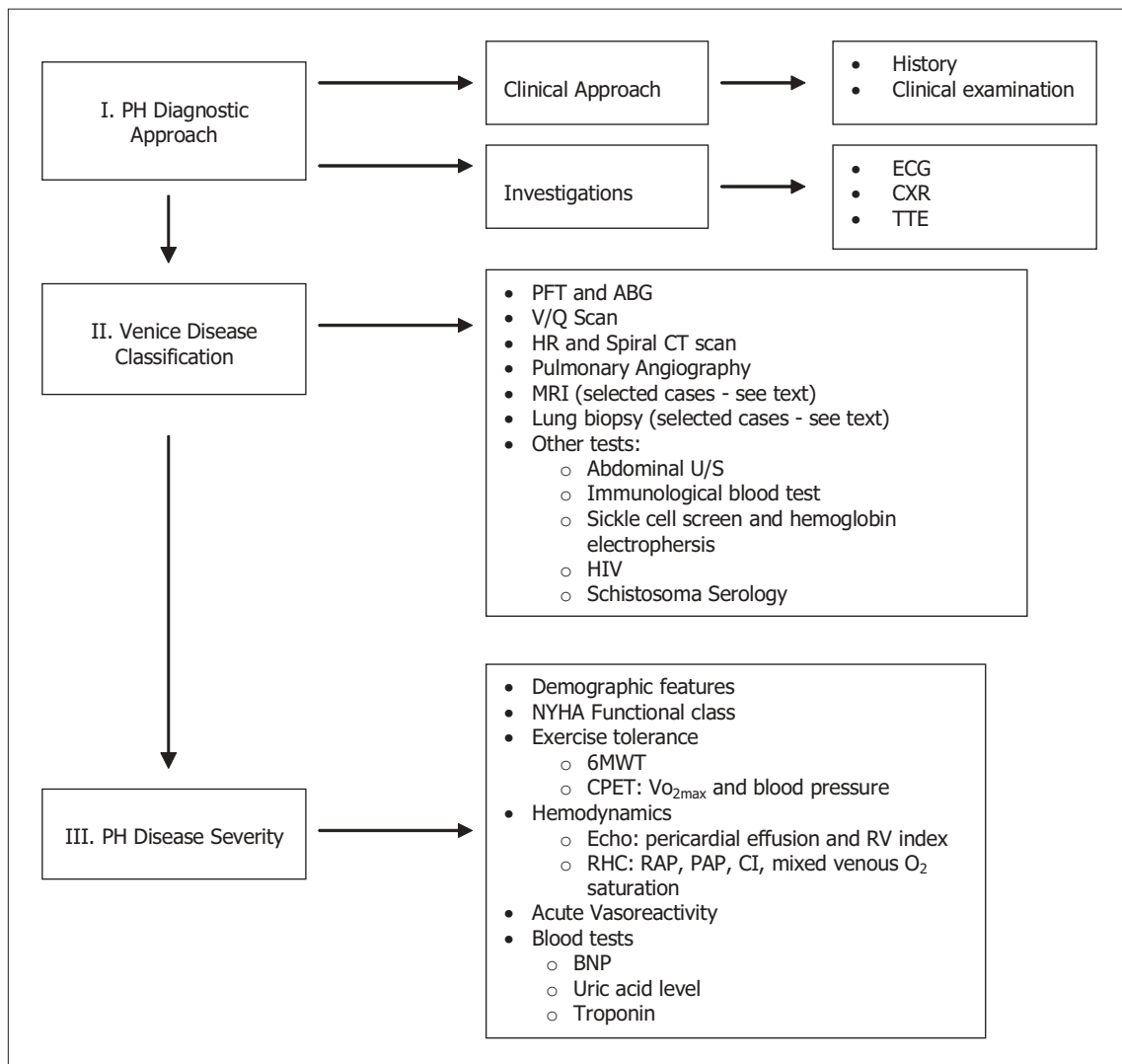


Figure 1: Pulmonary hypertension management approach

(3) assessment of disease severity [Figure 1]:

## I. The diagnostic approach

### a. Clinical approach of pulmonary hypertension

Patients with PAH generally present with a spectrum of symptoms attributable to impaired oxygen transport and reduced cardiac output. The symptoms of PH<sup>[31]</sup> are however nonspecific and can include fatigue, weakness, chest pain and syncope. Symptoms at rest are reported only in very advanced cases. The clinical suspicion of PH usually arises in case of unexplained dyspnea or when the level of dyspnea is unexplained by the level of severity of the underlying lung or heart disease.

The physical signs of PH<sup>[31]</sup> are usually those of right heart failure/strain. They include left parasternal heave, accentuated pulmonary component of S<sub>2</sub>, pansystolic murmur of tricuspid regurgitation and right ventricular S<sub>3</sub> gallop. These signs require special experience to be picked up. Furthermore, the signs of fluid overload and generalized anasarca, which include jugular vein distension, hepatomegaly, peripheral edema, ascites and cool extremities, characterize patients in a more advanced state of compromised right ventricular output at rest. In very advanced situations and because of the development of right-to-left shunt, central and peripheral cyanosis may also be present.

The threshold of clinical suspicion is usually lower when these symptoms and signs are present in subjects with conditions that predispose to PAH, such as connective tissue diseases (CTDs), portal hypertension, HIV infection and chronic thromboembolic diseases. In the presence of these predisposing abnormalities, a rationale for periodic screening assessments to identify asymptomatic patients in the early stage of PH maybe justified.<sup>[32]</sup>

### b. Investigation tools for the diagnosis of pulmonary hypertension

This phase includes certain tests that can suspect/confirm the diagnosis of PH. These tests include ECG, chest radiograph (CXR) and transthoracic echocardiography (TTE).

#### ECG

##### **ECG: Strength of recommendation: C<sup>[33]</sup>**

ECG is nonspecific in early disease. Some of the ECG findings are suggestive of PAH and may include:

- right-axis deviation;
- a tall R wave and small S wave in lead V1;
- rSR' pattern in lead V1 and a large S wave and small R wave in lead V5 or V6;
- ST-T segment depression and/or inversion are often present in the right precordial leads;
- right atrial enlargement is manifested as a tall P wave ( $\geq 2.5$  mm) in leads II, III and aVF.

Right ventricular hypertrophy on ECG is present in 87% of the cases and right axis deviation in 79%.<sup>[31]</sup> However, the ECG is found to have low sensitivity (55%) and specificity (70%) to be used as a screening tool for detecting significant PAH.<sup>[34]</sup> A normal ECG does not exclude the presence of severe PH.

Finally, prognostic values of ECG parameters have been

identified. P-wave amplitude in lead II of  $\geq 0.25$  mV is found to be associated with a 2.8-fold increase in mortality over a 6-year follow-up period. Each additional 1 mm of P-wave amplitude in lead III corresponds with a 4.5-fold increased risk of death.<sup>[35]</sup>

#### Chest radiograph

##### **CXR: Strength of recommendation: C<sup>[33]</sup>**

Chest radiograph is abnormal at the time of diagnosis in majority of the cases.<sup>[31]</sup> Radiographic signs that can be suggestive of PH are as follows:

- Enlarged main and hilar pulmonary arterial shadows, with concomitant attenuation of peripheral pulmonary vascular markings ('pruning'). Despite the fact that pruning was present in most IPAH patients in the NIH Registry, its absence should not be interpreted as excluding PAH.
- Right ventricular enlargement is usually detected by the lateral CXR by filling the retro-sternal space.

The CXR may also be useful in identifying certain diseases that could be related to PH, such as pulmonary edema secondary to congestive heart failure, hyperinflation secondary to chronic obstructive airway disease or kyphosis or interstitial lung diseases causing restrictive ventilatory defect. Other radiological abnormalities that can be suggestive of chronic thromboembolic pulmonary hypertension (CTEPH) are cardiomegaly with right ventricular enlargement, mosaic oligemia, right descending pulmonary arterial enlargement and atelectasis or pleural effusion.<sup>[36]</sup> Other studies<sup>[37]</sup> have reported high prevalence of pulmonary trunk and central pulmonary arterial dilation in patients with confirmed CTEPH.

However, it is important to emphasize that a normal chest radiograph does not exclude the diagnosis of PAH.

#### Transthoracic Doppler-echocardiography (TTE)

##### **TE: Strength of recommendation: see below**

Transthoracic Doppler-echocardiography (TTE) is the most popular screening test for PH.

Tricuspid regurgitation (TR) jets are used to estimate the right ventricular systolic pressure (RVSP) that should be equal to systolic pulmonary artery pressure (sPAP) in the absence of pulmonary outflow obstruction. However, the accuracy of TTE in diagnosing PH was always of concern. A number of studies addressed the issue of reliability of Doppler-echocardiography in detecting and quantifying PAH. TR jets are analyzable in 39-86% of patients.<sup>[38-40]</sup> The variability points out that technical and operator factors can affect the usefulness of this test. Another source of error in estimating the pulmonary pressure arises for the estimation of the RAP used in the modified Bernoulli equation. Some laboratories assign an arbitrary value of 10 mmHg and not on the basis of inferior vena cava size and collapsibility.

In a cohort study of 374 lung transplant candidates,<sup>[41]</sup> the accuracy of echocardiography compared with right heart catheterization in the determination of systolic pulmonary artery pressure and diagnosis of PH was investigated. The prevalence of PH was 25% in the study population. Estimation of sPAP by echocardiography was achieved in 166 patients (44%). The correlation between sPAP estimated by echocardiography and measured by cardiac catheterization

was good ( $r = 0.69$ ,  $P < 0.0001$ ). However, 52% of pressure estimations were found to be inaccurate (more than 10 mmHg difference compared with measured pressure), and 48% of patients were misclassified as having pulmonary hypertension by echocardiography. Sensitivity, specificity and positive and negative predictive values of sPAP estimation for diagnosis of PH were 85, 55, 52 and 87% respectively.

Many studies have reported good correlation between right ventricular systolic pressure estimated from TR jets and hemodynamic right-heart catheterization values. One study<sup>[42]</sup> of 51 patients found a relatively poor correlation between these two measurements ( $r = 0.31$ ). Other studies,<sup>[43-48]</sup> however, reported statistically significant correlations, with the correlation coefficient ranging between 0.76 and 0.93.

Other parameters have been used to assess the severity of PH. These include pre-ejection period, acceleration and deceleration, relaxation and contraction times.<sup>[49-51]</sup> These parameters may be especially useful when TR and pulmonic valve regurgitation jets are not present or measurable.

Recently, systolic right ventricular ejection fraction and function assessment by pulsed wave tissue Doppler imaging of the tricuspid annulus has emerged as a useful test. In one study of 258 individuals,<sup>[52]</sup> a good correlation was found between right ventricular ejection fraction as determined by biplane two-dimensional echocardiography and respective value as assessed by MRI ( $P < 0.0001$ ).

The assessment of RV regional contractility by two-dimensional strain echocardiography is a new method that proves to be helpful. In a recent study,<sup>[53]</sup> 37 patients with PAH and 38 normal subjects underwent two-dimensional echocardiography and tissue Doppler echocardiographic evaluation of right ventricular global function and regional contractility. Moderate or severe RV dysfunction was detected in all patients with PAH compared with normal subjects ( $P < 0.001$ ).

Besides estimation of sPAP and RV dysfunction, TTE can also provide additional information about the cause and consequences of PH. This includes left ventricular dimensions and function; tricuspid, pulmonary, aortic and mitral valve abnormalities; left ventricular filling characteristics; right atrial size; inferior vena cava dimensions; and pericardial effusion size.<sup>[39,54]</sup>

The venous injection of agitated saline (the shunt study) as contrast medium can help the identification of patent foramen ovale or small atrial septal defects (ASDs) in patients with shunt that can be overlooked on the standard TTE examination. Shunt studies are also helpful for diagnosing sinus venosus ASDs, which can be difficult to visualize in TTE. Despite the fact that trans-esophageal echocardiography (TEE) is extremely useful to diagnose sinus venosus ASDs, some experts recommend avoiding it, if at all possible, due to the potential for precipitating a vaso-vagal episode that can be poorly tolerated by PAH patients.

The yield of Doppler echocardiography in screening asymptomatic individuals depends not only on the sensitivity and the specificity of the test but also on the prevalence of the disease in the study population because the pretest probability

affects the post-test probability of the disease (Bayesian theory). The cut off value of the sPAP used to diagnose PH further affects the sensitivity and the specificity of TTE in this patient population.

Despite all limitations, TTE is still the most widely used screening test for PH. TEE is rarely required and is usually limited to confirm the presence, and assess the exact size, of small atrial septal defects.

The following recommendations can be made based on the current available data:

- In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed as the first noninvasive screening test that can detect PH (*Strength of recommendation: A*).<sup>[33]</sup>
- In patients with a clinical suspicion of PAH, Doppler echocardiography should be performed to estimate the level of RV systolic pressure and to assess the presence of associated anatomic abnormalities such as right atrial enlargement, right ventricular enlargement and pericardial effusion (*Strength of recommendation: E/B*).<sup>[33]</sup>
- In asymptomatic patients at high risk, such as patients with connective tissue diseases, screening Doppler echocardiography should be performed to detect elevated pulmonary arterial pressure (*Strength of recommendation: E/B*).<sup>[33]</sup>
- In patients with suspected or documented PAH, Doppler echocardiography with agitated saline (shunt study) should be obtained to look for evidence of intracardiac shunting (*Strength of recommendation: B*).<sup>[33]</sup>

## II. PAH class evaluation (according to Venice classification)

The next step after confirming the diagnosis of PH is to identify the clinical class according to the clinical classification of Venice [Table 1].<sup>[1]</sup> However, it should be again emphasized that the classification may change following the 4<sup>th</sup> World Symposium on Pulmonary Hypertension that will be held in February 2008. The role of different diagnostic tests will be discussed in details below.

### a. Pulmonary function tests (PFTs) and arterial blood gases (ABGs)

*Strength of recommendation: B*

PFT is an important initial investigation for all patients with PH, mainly to assess the basic pulmonary (either airway or parenchymal) disease and its contribution to the abnormal pulmonary hemodynamics. Generally, 20% of PAH patients will have a restrictive defect, defined as a reduction in total lung capacity (TLC) or forced vital capacity (FVC) to <80% of predicted.<sup>[55]</sup> In one study,<sup>[56]</sup> 50% of the IPAH patients involved in that particular study had FVC values <80%. In chronic thromboembolic pulmonary hypertension, the restrictive defect noticed in this condition is thought to be due to parenchymal scarring from prior pulmonary infarcts.<sup>[57-58]</sup> The diffusion capacity for carbon monoxide (DLco) is mildly reduced, to approximately 40-80% of predicted, secondary to diminished pulmonary lung volume and subsequent V/Q mismatch.<sup>[59]</sup> On the other hand, the degree of reduction in DLco showed a strong correlation with peak oxygen uptake, peak work rate and NYHA class but not with the degree of severity of PH itself.<sup>[33,56]</sup>

Measurement of oxygen saturation during rest and exercise may show a degree of desaturation that may be managed by supplemental oxygen therapy. Nocturnal oximeter may disclose sleep-disordered breathing with repeated episodes of desaturation (see below under specific conditions). Nocturnal hypoxemia occurs in >75% of patients with IPAH, independent of the severity of ventilatory disturbances.<sup>[60]</sup>

Patients with PAH usually have the following PFTs and ABGs abnormalities:

- Decreased DLco (typically in the range of 40-80% of predicted) indicates abnormality in gas exchange, V/Q mismatching and venous admixture. Coexisting mild-to-moderate reduction of lung volumes may be also present.
- The arterial oxygen tension (PaO<sub>2</sub>) is normal or only slightly reduced with widening alveolar-arterial O<sub>2</sub> gradient. Arterial carbon dioxide tension (PaCO<sub>2</sub>) is decreased as a result of alveolar hyperventilation.
- Chronic obstructive pulmonary disease as a cause of hypoxic PH is diagnosed on the evidence of irreversible airflow obstruction,<sup>[61]</sup> usually by measuring the forced expired volume in one second (FEV<sub>1</sub>). These patients often have a normal or increased PaCO<sub>2</sub> together with airflow limitation and increased residual volumes and reduced DLco. Emphysema is now diagnosed using high-resolution CT scan (HRCT) (see below).
- A decrease in lung volume together with a decrease in DLco may indicate a diagnosis of interstitial lung disease (ILD). Again the HRCT is a helpful method for assessing the severity of ILD.<sup>[62]</sup>
- If clinically suspected, screening overnight oximeter and polysomnography will exclude significant obstructive sleep apnea/hypopnea and nocturnal desaturation.

### **b. Ventilation and perfusion (V/Q) lung scan**

#### **Strength of recommendation to exclude CTEPH: B**

Because CTEPH is a potentially curable disease, it should be considered in all patients with unexplained PH. Ventilation-perfusion (V/Q) lung scans of patients with CTEPH are quite helpful and generally show one or more segment-sized or larger mismatched perfusion defects.<sup>[63]</sup> A normal V/Q scan almost always excludes the diagnosis of CTEPH as the cause of PAH. However, false-positive scan results may still occur with pulmonary artery sarcoma, large-vessel pulmonary vasculitis, extrinsic vascular compression, pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis.<sup>[64]</sup> Such conditions require careful further investigation (see section on HRCT). In patients with parenchymal lung disease, the perfusion defects are generally matched by ventilation defects.

Furthermore, V/Q scanning is quite helpful in differentiating IPAH from CTEPH. Its sensitivity in this regard ranges from 90 to 100% with specificity of 94 to 100%.<sup>[65,66]</sup> Patchy, nonsegmental diffuse defects are less specific but may still be associated with thromboembolic disease.<sup>[67]</sup> Because of this, no further studies will be required to rule out CTEPH in case of normal V/Q scan. However, intermediate or high-probability scan should be followed by further diagnostic studies (see below).

Perfusion scans tend to correlate poorly with the severity of

obstruction. It also underestimates the degree of severity of large-vessel obstruction in CTEPH.<sup>[68]</sup>

### **c. CT scan of the lung**

#### **Strength of recommendation to exclude CTEPH: D**

Chest CT scan is an extremely important test in the evaluation process of the type of PAH. HRCT provides detailed images of the lung parenchyma, which can be very helpful in confirming or ruling out the presence of certain diseases that could be responsible for the development of PAH; interstitial lung diseases and emphysema are the most commonly recognized diseases. Furthermore, certain radiological signs such as lymphadenopathy, apical scarring, pleural shadows and effusions<sup>[69]</sup> are findings that may suggest granulomatous disease, sarcoidosis or pneumoconiosis.

The role of contrast-enhanced spiral CT is rapidly increasing in the evaluation of CTEPH and to some extent replacing that of the V/Q scanning. Generally speaking, spiral CT is indicated in PH patients when the V/Q lung scanning is undetermined. However, some experts recommend selective bilateral pulmonary angiography in this case, as spiral CT scan has a 7% false-negative result for operable CTEPH. Different abnormalities on CT scan have been described in patients with CTEPH that include right ventricular enlargement, dilated central pulmonary arteries, complete occlusion of pulmonary arteries, eccentric filling defects consistent with thrombi and parenchymal consolidation/atelectasis consistent with prior infarcts.<sup>[70,71]</sup> The mosaic attenuation is characteristic for vascular injuries that are characteristic for CTEPH. However, such abnormality is not very specific and can also be present in airways disease causing gas trapping.

Other pulmonary vascular diseases can also be diagnosed by CT scan. Pulmonary capillary hemangiomatosis can be identified by the presence of diffuse bilateral thickening of the interlobular septae and the presence of small centrilobular, poorly circumscribed, nodular opacities. The presence of interstitial markings similar to those seen with advanced left ventricular failure, diffuse central ground-glass opacification and thickening of interlobular septa suggest pulmonary veno-occlusive disease.

Unilateral perfusion defects seen on contrast-enhanced spiral CT scan may suggest alternative diagnoses, such as sarcoma, vasculitis, malignancy and mediastinal fibrosis.<sup>[72]</sup> Finally, CT may also be useful in determining the extent of small-vessel involvement and the likelihood of improvement after thromboendarterectomy.<sup>[73]</sup>

It is always crucial that the scan is reviewed by radiologists with significant experience in diagnosing CTEPH, or operable patients can be missed and carried with the diagnosis of IPAH.

### **d. Pulmonary angiography**

#### **Strength of recommendation: E/A**

Despite the growing advantages of contrast-enhanced spiral CT, pulmonary angiography is still required in the workup of CTEPH, especially in those patients that are considered for surgical intervention for pulmonary artery endarterectomy.<sup>[74]</sup> In usual situation, pulmonary angiography is superior to spiral CT scan in the identification of distal obstructions or in cases

of inconclusive contrast-enhanced spiral CT in patients with clinical and V/Q lung scanning suspicion of CTEPH. Despite the usual concern about using this diagnostic tool in critically ill patients, pulmonary angiography has been shown to be safe when performed by experienced staff.

#### **e. Magnetic resonance imaging (MRI)**

*Strength of recommendation: E/A*

MRI is a very promising tool for the evaluation of pathological changes of both heart and pulmonary circulation in PAH patients.<sup>[70]</sup> MRI has an advantage over CT by providing functional data, especially when lung parenchyma is involved. MRI is able to noninvasively visualize right ventricular chamber size and volume (assess both end-diastolic and end-systolic volumes) and also assess myocardial mass and thickness.<sup>[75]</sup> Abnormalities in these parameters may provide noninvasive clues to the presence of PH. A linear correlation has been found between mPAP measured by right heart catheterization and MRI-measured right ventricular wall thickness, inferior vena cava diameter and main pulmonary artery diameter.<sup>[76]</sup> MRI also can yield an mPAP estimate based on regression analysis of the measured dimensions of the main pulmonary artery and mid-descending thoracic aorta. Finally, MRI-measured stroke volume (by velocity-encoded cine) has demonstrated a high correlation ( $r=0.90$ ) with that obtained by thermodilution techniques during right heart catheterization. However, additional experience is needed before introducing this tool in the routine assessment of patients with PAH.

#### **f. Lung biopsy**

*Strength of recommendation: E/C*

Open or thoracoscopic lung biopsy carries substantial risks of morbidity and mortality in PAH patients.<sup>[77]</sup> Additionally, the histopathological findings in the small pulmonary arteries are nonspecific and may not differentiate between CTEPH, PAH due to a variety of causes and IPAH. Furthermore and because of the parenchymal heterogeneity in this disease, a biopsy sample may miss a treatable diagnosis or inadequately diagnose a condition that is not clinically significant. Because of the low likelihood of altering the diagnosis and treatment, routine biopsy is usually not recommended except under circumstances in which a specific question can only be answered by tissue examination.

#### **g. Other investigations**

*Testing for connective tissue diseases, hemoglobinopathy and HIV*

*Strength of recommendation: E/A*

At the initial investigation, blood biochemistry, hemoglobin and hematocrit, sickle cell screen, thyroid function tests, Schistosoma titer and HIV serology are essential. Thrombophilia screen should be performed in selected cases and especially if CTEPH is suspected; it includes anti-phospholipid antibodies (lupus anticoagulant and anti-cardiolipin antibodies), protein C and protein S level, Factor V laden and anti-thrombin III. Autoimmune screen that consists of antinuclear antibodies (ANA), rheumatoid factors, anti-centromere antibody, anti-SCL70 and RNP is also important. About one-third of patients with IPAH have positive ANA titer, but it is usually low (1:80 dilutions).<sup>[78]</sup> Finally, abdominal ultrasound scan is of great significance if the patient is also suffering from chronic liver disease and portal hypertension cannot be excluded, because of the coexistence of portopulmonary hypertension (see below

#### **Table 5: Levels of evidence for efficacy**

Level of evidence A:	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B:	Data derived from a single randomized clinical trial or multiple trials with heterogeneous results
Level of evidence C:	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

#### **Table 6: Classes of recommendation**

Class I	Strong recommendation
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment:
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy;
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful

under specific conditions). The color-Doppler examination is also needed to differentiate passive portal hypertension, due to right heart failure, from portal hypertension caused by an increase in the trans-hepatic venous gradient associated with liver cirrhosis.

### **III. Assessment of disease severity and prognostic markers**

When the diagnosis of PAH is confirmed and the Venice class has been determined, additional investigations may be required for clear assessment of disease severity, exercise capacity and hemodynamics. Several variables have been shown to predict prognosis in IPAH when assessed at baseline or after specific treatments.<sup>[79]</sup> However, the significance of these prognostic variables is less clear when applied to other conditions such as PAH associated with CTD, congenital heart disease, HIV infection or portal hypertension. Some of the difficulties in these diseases are additional factors that are related to the primary disease itself more than PH but may contribute to the overall outcome. Table 7 shows the different variables that carry prognostic value in PAH.

#### **a. Demographics**

Reports of prognostic significance of demographic variables such as age, gender and time from onset of symptoms to diagnosis are inconsistent. In the NIH Registry, which was the first large-scale registry in IPAH, age, time from onset of symptoms to diagnosis and gender were not predictive of survival.<sup>[2]</sup> A national survey of IPAH was conducted in Israel<sup>[80]</sup> for the period between 1988 and 1997. Forty-four patients were identified. The mean age was  $43 \pm 13$  years, and the age variable did not carry prognostic significance. However, longer time of onset from symptoms to diagnosis was associated with a worse prognosis. In a retrospective Indian study,<sup>[5]</sup> younger age at the time of diagnosis was associated with a worse prognosis when compared to older patients. On the contrary, in another study<sup>[81]</sup> that included patients with many etiologies of PAH who were treated with epoprostenol, older age at diagnosis indicated a worse prognosis. Such finding, however, may be affected by including patients with the scleroderma spectrum of disease, who tend to be older and also had a worse prognosis (see below).

#### **b. Functional status**

Baseline NYHA functional classification has a definite prognostic

**Table 7: Prognostic parameters in patients with idiopathic pulmonary arterial hypertension**

Clinical parameters:
<ul style="list-style-type: none"> <li>• NYHA functional classification</li> <li>• NYHA functional class on chronic epoprostenol treatment</li> <li>• History of right-heart failure</li> </ul>
Exercise capacity:
<ul style="list-style-type: none"> <li>• 6 MWT distance</li> <li>• 6 MWT distance on chronic epoprostenol treatment</li> <li>• Peak systolic BP and peak VO<sub>2max</sub></li> </ul>
Echocardiographic parameters:
<ul style="list-style-type: none"> <li>• Pericardial effusion</li> <li>• Right atrial size</li> <li>• Left ventricular eccentricity index</li> <li>• Doppler right ventricular (Tei) index</li> </ul>
Hemodynamics:
<ul style="list-style-type: none"> <li>• Right atrial pressure</li> <li>• Mean PAP</li> <li>• Cardiac output</li> <li>• Mixed venous O<sub>2</sub> saturation</li> <li>• Positive acute response to vasoreactivity tests</li> <li>• Fall in pulmonary vascular resistance &lt;30% after 3 months of epoprostenol</li> </ul>
Blood tests:
<ul style="list-style-type: none"> <li>• Hyperuricemia</li> <li>• Baseline brain natriuretic peptide</li> <li>• Brain natriuretic peptide after 3 months' therapy</li> <li>• Troponin - detectable, especially persistent leakage</li> <li>• Plasma norepinephrine</li> <li>• Plasma endothelin-1</li> </ul>

predictive value in patients with IPAH.<sup>[2]</sup> This predictive value is consistent even when NYHA classification is assessed either before or 3 months after the initiation of epoprostenol treatment.<sup>[82,83]</sup> Such functional classification should be always considered in managing patients with PHT. The classification below is the World Health Organization (WHO) modification of the heart failure NYHA classification for PH.

**Class I:** Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain or pre-syncope.

**Class II:** Patients with pulmonary hypertension who have mild limitation of usual physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain or pre-syncope.

**Class III:** Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less-than-ordinary activity causes increased dyspnea, fatigue, chest pain or pre-syncope.

**Class IV:** Patients with pulmonary hypertension who are unable to perform any physical activity and who may have signs of right ventricular failure at rest. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity.

NYHA functional class was found to be a significant predictor of mortality in many studies.<sup>[2,80,84]</sup> Among the 194 IPAH patients that were identified in the NIH study,<sup>[2]</sup> the risk of death was higher among patients in NYHA class III or IV than among

those in NYHA class I or II. The median survival time was much shorter in advanced NYHA classes: nearly 6 years for NYHA class I and II, 2.5 years for patients in NYHA class III and 6 months for patients in NYHA class IV. In a retrospective study<sup>[35]</sup> of 51 patients with IPAH (37 of whom received epoprostenol), patients in NYHA class III or IV had double mortality rate [hazard ratio (HR) = 2.4] than patients in NYHA class II. In another cohort study<sup>[80]</sup> of 44 patients with IPAH, only 6 of them were receiving epoprostenol therapy; patients who were in NYHA class IV at the time of diagnosis had a significantly higher risk of death than patients in NYHA classes I, II or III. Finally, 162 patients with IPAH receiving epoprostenol were evaluated retrospectively.<sup>[82]</sup> NYHA class III patients at baseline had a 3-year and 5-year survival rate of 81 and 79% respectively, while NYHA class IV patients had a 3-year and 5-year survival rate of 47 and 27% ( $P = 0.0001$ ) respectively. After a mean of 17 months of therapy, those in NYHA class I or II had subsequent 3-year and 5-year survival rate of 89 and 73%, vs. 62 and 35% for patients in NYHA class III; while NYHA class IV patients had a 2-year survival rate of 42%.

History of right heart failure before the initiation of epoprostenol treatment has a negative predictive value.<sup>[83]</sup>

### c. Exercise tolerance

Objective assessment of exercise tolerance in patients with PAH is an extremely important tool for evaluating disease severity,<sup>[85,86]</sup> disease outcome and treatment effectiveness.<sup>[79,87]</sup> Six-minute walk test (6MWT) and cardiopulmonary exercise test (CPET) are the most common used tests for this purpose.

Although the 6MWT is technically very simple,<sup>[88]</sup> it still has a learning curve for both patients and technicians and thus needs to be validated in any site using it for clinical care and/or clinical trials. As the name implies, it measures the walking distance covered in 6 minutes' walk. It is usually combined with the Borg dyspnea score for the subjective assessment of the level of dyspnea with the exercise. It is predictive of survival in IPAH<sup>[85]</sup> and is the most commonly used primary end point in clinical trials.<sup>[87]</sup> It proved to be reproducible and correlated with other measures of functional status, including NYHA functional classes. Six-MWT distance also correlates with hemodynamic findings in patients with IPAH. It correlates inversely with PVR and directly with baseline cardiac output, peak exercise oxygen consumption, peak oxygen pulse and the minute ventilation/carbon dioxide output slope.<sup>[85]</sup> Furthermore, reduction of arterial oxygen saturation of more than 10% during 6MWT increases mortality risk by 2.9 times over a median follow-up of 26 months.<sup>[89]</sup>

Many studies have shown that the 6MWT carries the most important prognostic value in PAH. In one study,<sup>[85]</sup> 43 patients with IPAH were evaluated. All patients underwent right heart catheterization (RHC), had 6MWT, blood sampling for catecholamines and echocardiographic assessment. The patients were followed over a mean follow-up period of 21 ± 16 months. Thirteen patients were treated with IV epoprostenol, 25 patients with the oral prostacyclin analogue beraprost and 5 patients were intolerant to prostacyclin therapy; no patient received lung or heart-lung transplantation during the study. Among the noninvasive variables that were studied, only 6MWT distance

was independently associated with survival. Furthermore, it has been calculated that there is an 18% reduction in the risk of death per additional 50 m walked in patients with IPAH.<sup>[89]</sup> Patients in NYHA functional class III or IV, walking <250 m before the initiation of epoprostenol or <380 m after 3 months of epoprostenol treatment had a worse prognosis as compared to patients walking for a longer distance.<sup>[83]</sup>

CPET is a more complicated test compared to 6MWT. It gives detailed measurements of ventilation and pulmonary gas exchange parameters during exercise testing combined with cardiac parameters. PAH patients characteristically show reduced cardiac reserve: reduced peak oxygen consumption ( $VO_{2max}$ ), reduced peak work rate, reduced anaerobic threshold and reduced peak oxygen pulse indirectly reflecting low cardiac stroke volume.<sup>[397]</sup> Decreased ventilatory parameters as manifested by increased minute ventilation (VE) and  $VCO_2$  slope can also be present<sup>[86]</sup> and reflect the hyperventilation process practiced by PAH patients to overcome hypoxia and to improve their oxygen-carrying capacity and oxygen transfer. As a matter of fact,  $VO_{2max}$  determined by CPET was found to be an independent predictor of survival in one study in patients with IPAH.<sup>[86]</sup> In this study, 70 patients (out of 86 consecutive patients) with IPAH were studied by CPET. Baseline treatments included calcium channel blockers oral anticoagulants, nasal oxygen supplementation and inhaled iloprost (2 patients). Subsequent treatment included IV iloprost in 13 patients; inhaled iloprost in 55 patients, followed by IV iloprost in 25 of these patients; and oral beraprost in 5 patients. After multivariate analysis,  $VO_{2max}$ , peak systolic BP (SBP) during exercise and peak diastolic BP (DBP) were independent predictors of survival. Patients with peak  $VO_{2max}$  of >10.4 ml/kg/min have a better survival than those with lower  $VO_{2max}$ .<sup>[86]</sup> (91% vs. 50%;  $P < 0.0001$ ). Anaerobic threshold of <11 ml/kg/min and ventilatory efficiency (slope of VE versus  $VCO_2$ ) >34, combined, have been shown to better identify patients at high risk for early death from CHF than did peak  $VO_{2max}$ .<sup>[90]</sup> Finally, patients with a peak SBP >120 mmHg during CPET were also shown to have a better 1-year survival than those patients who did not achieve this systolic pressure.

- Prognostic variables: Patients in NYHA functional class III or IV walking <250 m before the initiation of epoprostenol or <380 m after 3 months of epoprostenol treatment, >10% desaturation with 6MWT: Strength of recommendation: A.
- Prognostic variables: Low  $VO_{2max}$ , low peak exercise SBP and DBP, low anaerobic threshold and high ventilatory efficiency as determined by CPET: **Strength of recommendation: B.**

#### **d. Echocardiographic and hemodynamics prognostic variables**

Pericardial effusion has been found to be a common finding in echocardiography in patients with IPAH. Fifty-four percent of patients, who were evaluated in the randomized trial<sup>[91]</sup> of IV epoprostenol, were found to have pericardial effusion. A correlation has been found between the size of the pericardial effusion and exercise limitation, as patients with larger effusions had more severely impaired exercise performance. Larger pericardial effusion size was also found to correlate with more right atrium (RA) dilatation, greater displacement of the intraventricular septum during diastole and more TR than patients with no or small effusion. Pericardial effusion size was correlated with death at 1 year. Echocardiographic

indices that were predictive of survival in many studies were the presence of a pericardial effusion [hazard ratio (HR), 3.89] and RA area index (HR, 1.54). Recently, RV index (the RV index is obtained by dividing the sum of both isovolumetric contraction and relaxation intervals by ejection time) was also found to be a predictive variable. In a small study<sup>[89]</sup> of 26 consecutive patients with IPAH, all 6 patients who died during the follow-up period had a Doppler echocardiography RV index above the median. A larger series of 53 patients with IPAH confirmed the predictive value of the Doppler echocardiography RV index.<sup>[92]</sup>

Although Doppler echocardiography is a reasonable screening method for PAH and has some prognostic value, confirmation of diagnosis by right heart catheterization remains to be the golden standard diagnostic procedure of choice and is required in most situations and especially in cases of symptomatic patients (NYHA class II and III) with mild PH as assessed by Doppler echocardiography. RHC, however, is also important in patients with definite moderate-to-severe PAH in order to get hemodynamic measurements that may have prognostic relevance<sup>[2]</sup> in this patient population.

Many hemodynamic parameters, which have both diagnostic and prognostic significance, can be obtained by RHC. These parameters include heart rate, right atrial pressure (RAP), PAP, PAWP, cardiac output by thermodilution (or by the Fick method in cases of systemic-to-pulmonary shunts, severe TR or very low cardiac output status), blood pressure, pulmonary and systemic vascular resistance, arterial and mixed venous oxygen saturation (and superior and inferior vena cava oxygen saturation in cases of systemic-to-pulmonary shunts). When Fick method is used to determine cardiac output, measured  $VO_2$  should be used rather than the equation-based estimated value because the discrepancy between the two values can be substantial in patients with PAH and therefore might lead to inaccurate estimation of the cardiac output and cardiac index.

The assessment of PAWP is specifically important in distinction between arterial and venous PH in patients with concomitant left-sided heart diseases.

In the NIH Registry,<sup>[2]</sup> three measured hemodynamic variables were associated with an increased risk of death: increased mPAP [odds ratio (OR), 1.16], increased mRAP (OR, 1.99) and decreased cardiac index (CI) (OR, 0.62). In another series, decreased mixed venous oxygen saturation was also an indicator of poor outcome and decreased survival (HR, 4.28). In the previously mentioned national survey that was conducted in Israel,<sup>[80]</sup> the most predictive values for survival were time until the diagnosis and mRAP. However, more recently, mPAP has been shown to be a dichotomous variable due the fact that PAP decreases with disease progression and secondary to worsening right heart cardiac output; and thus the reliance on estimated or measured PAP can be very misleading.

Baseline hemodynamic variables, although important, appear to have less prognostic value compared to post-treatment measurement in IPAH patients who are treated with epoprostenol. In a series of 178 patients with IPAH treated with epoprostenol,<sup>[83]</sup> lower mPAP and higher mRAP were found to have negative prognostic implications by univariate

analysis, while only mRAP was prognostic by multivariate analysis. In another study of 81 patients with IPAH treated with epoprostenol,<sup>[93]</sup> baseline hemodynamic variables appeared to have less prognostic value in patients with IPAH who were treated with epoprostenol. In this study, mRAP, mixed venous O<sub>2</sub> saturation (MVO<sub>2</sub>) and heart rate were found to be significant predictors of survival. Furthermore, an absolute value of RAP >12 mmHg and an absolute value of mPAP <65 mmHg in IPAH patients subsequently treated with epoprostenol for 3 months were found to have a poor prognosis.<sup>[83]</sup> Similarly, inadequate fall in PVR (<30%) relative to baseline after 3 months' treatment with epoprostenol was associated with poor prognosis.<sup>[83]</sup> From the other aspect, in patients who received only conventional therapy, higher baseline mRAP and low cardiac index were both of significant prognostic value.

Unfortunately, at the present time, there is an inadequate data to assess these prognostic variables of hemodynamics in patients with IPAH treated with agents other than epoprostenol and in patients with PAH with a diagnosis other than IPAH.

RHC is also especially helpful in ruling out left ventricular diastolic dysfunction (LVDD), which is quite common secondary to the increasing prevalence of obesity, systemic hypertension, obstructive sleep apnea syndrome, diabetes and older age at presentation. Many patients with LVDD may be misdiagnosed as PAH and treated as such. This is of special concern, as PAH treatment may be harmful in patients with LVDD and left ventricular failure.

It should be acknowledged, however, that RHC also has its own limitations: measurements are generally obtained only under resting conditions in the supine position, which may not be representative of hemodynamic responses to upright posture, activity or sleep. Even under these static circumstances, measurements may vary. Prolonged measurement of pulmonary hemodynamics in a group of 12 patients with PAH found wide intra-individual spontaneous variability in pulmonary arterial pressure, by >20 mmHg in some patients.<sup>[94]</sup> Nevertheless, RHC remains the 'gold standard' for pulmonary hemodynamic measurement and is a necessary component of the evaluation of PAH.

The risks associated with RHC procedures in patients with PH were recently evaluated in a multi-center 5-year retrospective and 6-month prospective study.<sup>[95]</sup> A total of 7,218 RHC procedures were performed. 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%.

The following is the summary of prognostic hemodynamic markers and the strength of recommendation according to current available data:

- Presence of a pericardial effusion: *Strength of recommendation: A*
- Elevated Doppler echocardiography RV index: *Strength of recommendation: C*
- Elevated mRAP: *Strength of recommendation: A*
- Reduced CI: *Strength of recommendation: A*
- Elevated mPAP: *Strength of recommendation: I*
- Inadequate fall in PVR (<30%) relative to baseline after 3 months' treatment with epoprostenol: *Strength of recommendation: B*

#### e. Acute vasodilator testing

Acute vasodilator testing should be done using short-acting pulmonary vasodilators.<sup>[96]</sup> Half-lives, dose ranges, increments and duration of administration for used agents are provided in Table 8.

The rationale for acute vasodilator testing is based on the concept of the presence of reversible vasoconstrictive component in the increase of PVR in patients with PAH, probably indicating earlier stages of the disease. Most of the histopathological components present in pulmonary vasculature are unfortunately irreversible (see above under pathology section). The presence of 'simple' vasoconstriction, which is the target of treatment with vasodilators such as calcium channel blockers (CCBs), is highly variable and probably present as the main mechanism in minority of the patients. The importance of vasoconstriction, which should be considered as one among several factors responsible for the increased PVR, is likely related to different pathogenetic mechanisms, the precocity of diagnosis and other individual factors that characterize the heterogeneous group of patients with IPAH. Acute vasoreactive test is the only method by which the identification of patients with reversible vasoconstrictive component, which should correspond to a subgroup with better chance to respond to long-term vasodilator treatment, is possible (see below).

A positive acute vasoreactive response (positive acute responders) is defined as a reduction of mean PAP by >10 mmHg to reach an absolute value of mPAP <40 mmHg with an increase or unchanged cardiac output (revised criterion).<sup>[97-99]</sup> Alternative criteria for vasoreactivity are 1) a 20% decrease in indexed pulmonary vascular resistance (PVRi), 2) a 20% decrease in mean pulmonary artery pressure (mPAP) and 3) an increased or unchanged cardiac output (classic

**Table 8: Route of administration, half-lives, dose ranges, increments and duration of administration of the most used substances in pulmonary vasoreactivity tests**

Drugs	Route	Half-life	Dose Range <sup>(*)</sup>	Initial dose	Increments <sup>(*)</sup>	Duration <sup>(*)</sup>
Epoprostenol	IV	3 min	2-16 ng/kg/min	2 ng/kg/min	2 ng/kg/min	10 min
Adenosine	IV	5-10 s	0.001-0.05 mg/kg/min	0.001 mg/kg/min	0.01-0.02 mg/kg/min	2 min
Nitric oxide	Inhaled	15-30 s	10-80 ppm	10 ppm	20 ppm	5 min

\*Initial dose and maximum dose suggested. <sup>†</sup>Increments of dose by each step. <sup>‡</sup>Duration of administration on each step

criterion). However, the revised criterion seems to reflect the degree of vascular remodeling more accurately and identify patients with better preserved cardiac function in the earlier phase of the disease.

While it has been suggested that the incidence of positive acute response is approximately 20%, more recent data suggests that the true incidence of patients with IPAH who may be long-term responders to CCBs is much less than this,<sup>[98,100]</sup> probably around 7%.<sup>[101]</sup>

Positive acute responders are most likely to show a sustained response to long-term treatment with high doses of calcium channel blockers (CCB) and are the only patients that can safely be treated with this type of therapy. It needs to be clearly emphasized that PAH patients should not be treated empirically with CCBs before confirming their vasoreactivity status (see below under treatment). Also, CCBs should not be considered in the management of patients with right-sided heart failure, regardless of their acute vasoreactive response.

The acute vasodilator response to IV epoprostenol was evaluated in 91 consecutive patients with IPAH.<sup>[102]</sup> The patients were classified into three groups based on their acute response to epoprostenol: highly responsive with a reduction in PVRi of >50%, moderately responsive with a fall in PVRi of between 20 and 50% and nonresponsive with a fall in PVRi of <20%. Patients who were either highly or moderately responsive were treated with prolonged oral vasodilator therapy, while all patients received anticoagulation. The survival rate was significantly higher among the highly responsive patients compared to the nonresponsive and moderately responsive patients (62% vs. 38 and 47% respectively). Interestingly, the survival was not significantly greater among the moderate responders compared to the nonresponders in this series. Another group of 60 patients with IPAH was followed after acute vasodilator testing.<sup>[3]</sup> A 'complete response' was defined as a >20% reduction in both mPAP and PVRi and a 'partial response' as a >20% reduction in only PVRi. Both complete and partial responders were treated with oral vasodilators, while nonresponders (and those who did not undergo vasodilator testing) were not. The median survival for those not given vasodilator treatment was 2.1 years, while the mean survival for those receiving vasodilator treatment was 5 years.

#### **f. Blood tests**

Brain natriuretic peptide (BNP) is elevated in RV pressure overload and correlates with severity of right ventricular dysfunction and mortality in PAH. In one study,<sup>[103]</sup> 63 consecutive patients with IPAH were evaluated. The authors also studied 15 age-matched healthy control subjects. Patients with IPAH had their blood tested at the time of baseline catheterization. Patients were followed up for a mean follow-up period of 24 months. Plasma BNP level was low in control subjects and was increased and correlated with functional class in patients with IPAH. BNP level was also correlated with mRAP, mPAP, cardiac output (CO) and PVR and was found to be an independent predictor of survival. Furthermore, a marked increase in survival was demonstrated in IPAH patients with a follow-up BNP level below the median value of 180 pg/ml.

Neurohormonal plasma levels of norepinephrine<sup>[103]</sup> and ET-1<sup>[104]</sup> were also found to correlate with survival. However, these findings were not found to be consistent in other studies. Recently, troponin<sup>[105]</sup> levels, both at baseline and after targeted treatments, have also been found to have prognostic value in PAH patients.

Increased uric acid (UA) levels reflect impaired oxidative metabolism, since tissue hypoxia depletes adenosine triphosphate with degradation of adenosine nucleotides to many compounds including UA.<sup>[106,107]</sup> In a study of 102 consecutive patients with IPAH,<sup>[108]</sup> 94% of these patients were in NYHA class III or IV. Unfortunately, treatments were not specified for the majority of patients. Thirty age-matched healthy volunteers served as control subjects. UA levels were significantly elevated in patients with IPAH as compared to those in control subjects. Furthermore, serum UA levels were found to increase in proportion to the severity of the functional class and correlated with CO, PVR and MVO<sub>2</sub>. Among the noninvasive variables that were studied, serum UA levels were independently related to mortality.

## **Treatment**

*Level of evidence and class of recommendation:* Treatment of pulmonary hypertension is challenging and should ideally be done in specialized centers with full capability for hemodynamic measurements and adequate experience in handling critically ill patients.

The following discussion is intended to review each class of therapy and evaluate it by evidence-based classification as suggested by the European Society of Cardiology<sup>[109]</sup> and the American College of Chest Physicians. We will also provide, when applicable, the strength of the recommendation [Table 4], which results from the interaction of two components: the level of evidence [Table 5] and the class of recommendation [Table 6]. We will propose a treatment algorithm that is evidence based and intended to provide a guide to the selective use of each form of therapy.

The level of evidence is based on the number and the methodologies of positive trials performed with a given treatment strategy.<sup>[109]</sup> The class of recommendation, however, is related to the level of clinical efficacy, which depends on the net pharmacodynamic effects of the drug.<sup>[110]</sup>

Table 9 provides the level of evidence, the class of recommendation and the strength of recommendation, when applicable, for each treatment profile.

### **I. General measures**

*(Class of recommendation = IIa; Level of evidence = C)*

#### **a. Physical activity**

Balanced physical activities to maintain muscular rehabilitation and strength but not aggravating the symptoms are probably helpful and should be encouraged whenever possible. It is obvious that activities leading to hazardous symptoms, such as severe dyspnea, syncope and chest pain, should be clearly avoided. Appropriate adjustments of daily activities may improve quality of life, self-wellbeing; and reduce the

**Table 9: Class of recommendations and level of evidence for treatment efficacy in idiopathic pulmonary arterial hypertension**

Treatment	Disease Type	Class of recommendation			Level of evidence	NYHA Class	Strength of Recommendation
		I	Ila	Ilb			
General measures	All	-	X	-	C	All	-
Oxygen a	All	X	-	-	C	All <sup>a</sup>	E/A
Oral anticoagulation	IPAH	-	X	-	C	All	B
	Other PAH	-	-	X	C	All	E/C
Diuretics <sup>b</sup>	All	X	-	-	C	All <sup>b</sup>	E/B
Digoxin c	All	-	-	X	C	All <sup>c</sup>	E/C
Calcium channel blockers <sup>d</sup>	IPAH	X	-	-	B	II & III	B
	Other PAH	-	-	X	C	II & III	E/C
Parenteral Epoprostenol	All	X	-	-	A	III & IV	A
Inhaled Iloprost	All	X	-	-	A	III	A
	All	-	-	-	-	IV	E/B
Treprostinil (Subcutaneous)	All	-	-	X	B	II & III	B
	All	-	-	-	-	IV	C
Treprostinil (Intravenous)	All	-	-	-	-	III & IV	C
Beraprost	All	-	-	X	B	II & III	B
Bosentan	All	X	-	-	A	III	A
	All	-	-	-	-	IV	B
Sitaxsentan	All	X	-	-	A	II & III	A
	All	-	-	-	-	IV	C
Ambrisentan	All	X	-	-	A	II & III	A
	All	-	-	-	-	IV	C
Sildenafil	All	X	-	-	A	II & III	A
	All	-	-	-	-	IV	C
L-Arginine	All	-	-	X	C	II & III	I
Combination therapy	All	X	-	-	B	III & IV	-
Atrial septostomy	All	-	X	-	B	III & IV	-
Lung transplantation	All	X	-	-	C	III & IV	-

a. If arterial oxygen saturation is <90%; b. Patients with congestive heart failure or fluid overload; c. Patients with congestive heart failure or supraventricular arrhythmia; d. Only in patients who responded to acute reactivity test

frequency of symptoms.

### **b. Travel/ altitude**

High-altitude hypoxia (including air travel) and the resultant pulmonary vasoconstriction in PAH patients are hazardous and should be avoided. Oxygen supplementation in PAH patients should always be considered if the patient is hypoxic on room air, aiming to maintain oxygen saturation to above 90%.

### **c. Prevention of infections**

Any condition that can cause increased work of breathing, hypoxia and reduction in oxygen-carrying capacity of the blood will be poorly tolerated by PAH patients and needs to be promptly recognized and treated. Vaccination against influenza and pneumococcal pneumonia is recommended. Persistent fever in patients with IV catheter for continuous administration of epoprostenol should always raise the suspicion of catheter-related infection and should be dealt with promptly.

### **d. Pregnancy, birth control and postmenopausal hormonal therapy<sup>[111]</sup>**

The potential risk for pregnancy is probably related to pregnancy-induced increased cardiac output and hyperdynamic circulation that will be poorly tolerated by the already stressed RV in patients with PH and is associated with an increased rate of morbidity and mortality that might be as high as 50% in severe cases.<sup>[112-114]</sup> Despite the fact that successful pregnancies have been reported in IPAH patients,<sup>[115]</sup> an appropriate method of birth control is highly recommended in women

with childbearing potential. There is an agreement between all experts in the field of pulmonary vascular diseases and clinical guidelines that pregnancy is to be avoided or terminated in women with PH. However, there is no agreement on the most appropriate birth control method in these subjects. Hormonal contraception carries some risk for its potential hypercoagulable effects. However, the concomitant oral anticoagulant treatment (and the current availability of low-estrogen dose products) may limit the risk of these agents. In addition, recent studies of large numbers of patients failed to prove any direct relationship between intake of hormonal contraceptive agents and PAH.<sup>[116]</sup> However, estrogen-free products, surgical sterilization or barrier contraceptives are usually recommended in this situation. The use of an intrauterine coil impregnated with progesterone (e.g., Mirena coil) offers acceptable efficacy and can be considered. Finally, the teratogenic effects of some of the drugs used to treat PAH may further complicate the issue (see below).

### **e. Hemoglobin levels**

Oxygen delivery depends mainly upon hemoglobin level, oxygen saturation and cardiac output. Patients with PAH are highly sensitive to reductions in hemoglobin levels that will lead to reduction of blood's oxygen-carrying capacity, which can not be compensated secondary to fixed cardiac output and limited ventilation in this group of patients. This will eventually lead to drop in oxygen delivery and worsening of the symptoms. Because of this, mild anemia should be aggressively treated and probably prevented in patients with high risk, such as young menstruating females with poor oral intake. From the other

perspective, there is increasing evidence that transfusion of red blood cells, platelets and fresh frozen plasma is associated with a significant incidence of acute PH crisis, which can be fatal. Thus if transfusions are needed, consideration of pre-treating patients with stress steroids, paracetamol and antihistamines is recommended. As a general recommendation, blood products transfusion should be avoided unless absolutely needed.

On the other hand, polycythemia secondary to longstanding hypoxia will increase blood viscosity, which interferes with proper oxygen delivery and might create new symptoms. However, it should be clearly emphasized that phlebotomies are indicated only if hematocrit is above 65% in symptomatic patients (headache, poor concentration), in order to reduce adverse effects of hyperviscosity.<sup>[117]</sup> However, overuse of phlebotomy can be hazardous; but unfortunately, it continues to be practiced by many treating physicians.

#### **f. Psychological assistance**

Patients with PAH are usually young and exercise limitation may interfere considerably with their previous life style. Depression is quite common in this group of patients and should be carefully evaluated and treated. However, some antidepressant agents can have a complex drug interaction with medication used in treating pulmonary hypertension patients, and special care should be taken with respect to this aspect. The role of the PAH expert is important in facilitating adequate communication with different specialties and in supporting patients with adequate information.<sup>[118]</sup>

#### **g. Elective surgery**

Despite the absence of clear scientific evidence, elective surgeries have probably an increased risk in patients with PAH. This risk is increased with the severity of NYHA functional class and, like in other pulmonary conditions, in cases of thoracic and upper abdominal interventions. The type of anesthesia is left to the experience of the anesthetist, as no clear evidence is available to prefer one method of anesthesia over the others. Generally speaking, epidural method is believed to be better tolerated than general anesthesia. Pulmonary artery floating catheter (swan ganz) should be probably inserted for invasive monitoring of hemodynamics during the surgery in order to detect any abnormality early enough to provide supportive therapy. Patients on IV epoprostenol treatment should continue with their treatment and are expected to have fewer problems than subjects on oral or inhaled treatments. In case a prolonged period of withdrawal is expected (more than 12-24 h), it is advisable to shift those patients who are on inhalation or oral therapy to IV treatments and revert to the original therapy subsequently. Alternatively, consideration should be given to using inhaled nitric oxide and/ or inhaled iloprost intra- or postoperatively on elective basis to prevent or minimize the risk of acute PH crisis. As the usual care, anticoagulant treatment should be interrupted for the shortest possible time and deep venous thrombosis prophylaxis should be strongly considered.

## **II. Pharmacological treatment**

### **a. Oxygen**

*Strength of recommendation = E/A (Class of recommendation = I; and level of evidence = C)*

The pathophysiological mechanism of hypoxia is usually multifactorial in PAH and is mainly related to a low mixed venous oxygen saturation caused by low cardiac output, increased oxygen extraction and, to a less extent, an altered ventilation perfusion matching. In patients with PAH associated with congenital cardiac defects or Eisenmenger syndrome, hypoxemia is related to reversal of left-to-right shunting and is refractory to increased inspired oxygen. However, most patients with PAH present with mild degree of arterial hypoxemia at rest.

Despite the absence of clear data about the effects of long-term oxygen treatment in PAH, extrapolation of such data from COPD literatures suggests that it is generally important to maintain oxygen saturation at a higher level than 90% at all times to avoid hypoxia-induced pulmonary vasoconstriction, which can contribute to the development and/or progression of PAH. In a retrospective analysis of the Mayo clinic experience, systemic arterial oxygen saturation was the single factor most predictive of survival of patients with IPAH.<sup>[119]</sup> Another review reported that the low values of systemic arterial oxygen saturation in patients with IPAH were associated with a high incidence of sudden death.<sup>[120]</sup>

The use of high-flow oxygen treatment in patients with PAH associated with cardiac shunts is more controversial. Indeed, the risk of oxygen toxicity should be weighed against any small benefit that can be accomplished by this therapy in this particular situation. In a controlled study on Eisenmenger syndrome patients, nocturnal oxygen therapy was found to have no significant effect on hematological variables, quality of life or survival.<sup>[121]</sup>

### **b. Oral anticoagulant treatment**

*For IPAH: Strength of recommendation = B (Class of recommendation = IIa; and level of evidence = C)*

*For other PAH conditions: Strength of recommendation = E/C (Class of recommendation = IIb; and level of evidence = C)*

The rationale for the anticoagulant treatment in patients with PAH is based on two main reasons: first, the presence of traditional risk factors for venous thromboembolism, such as heart failure and sedentary life style; and second, the demonstration of *in-situ* thrombophilic predisposition<sup>[16,18]</sup> and of thrombotic changes in the pulmonary microcirculation.<sup>[10,17]</sup> Such thrombotic process may further compromise the cross-sectional area of the pulmonary vasculature, leading to progressive increase in PVR and contributing to the deteriorating course observed in a significant number of PAH patients.

Favorable effects and improved survival have been reported with oral anticoagulation in patients with IPAH.<sup>[92,119,122]</sup> Caution, however, is indicated in patients who manifest syncope or hemoptysis.

The target international normalized ratio (INR) in patients with IPAH is 1.5-2.5 in most centers of North America (and is our preference in the SAPH group) and 2.0-3.0 in European centers.

Anticoagulation in diseases other than IPAH, such as

scleroderma, is controversial. Extrapolation of data supporting anticoagulation in IPAH to other conditions should be considered with caution as these patients may have a higher risk of complications and bleeding<sup>[123]</sup> compared to IPAH patients. In these situations, the risk versus the benefit should be carefully considered. The role of anticoagulation is more difficult in patients with Eisenmenger syndrome; and because of inadequacy of clinical data, no recommendation is to be given at the present time; and again, the risk-versus-the-benefit issues should be considered carefully by the treating physician for individual cases.

Overall, oral anticoagulation treatment has been offered to the majority of PAH patients included in clinical trials. The highest prevalence of anticoagulation was seen in the trials involving mainly IPAH patients in NYHA class III and IV, while the lowest prevalence was observed in the trial that included only patients with scleroderma.<sup>[124]</sup>

### c. Diuretics

*Strength of recommendation = E/B (Class of recommendation = I; and level of evidence = C)*

Diuretics clearly have a role in treating the symptomatic manifestations of right-sided cardiac failure, particularly systemic venous congestion, hepatic engorgement and peripheral edema. They also appear to provide symptomatic relief in dyspnea and orthopnea by reducing pulmonary capillary congestion and extravascular lung water in patients with right ventricular failure. In these patients, left ventricular function might be compromised by right ventricular hypertrophy and dilatation and by alternations in the geometry and function of interventricular septum.

Maintaining near-normal intravascular volume with diuretics and careful dietary salt and fluid restriction, is generally recommended for the long-term management of PAH patients. However, rapid and excessive diuresis may lead to systemic hypotension, renal insufficiency and syncope. Serum electrolytes and indices of renal function should be followed closely in patients receiving diuretic therapy.

In the recent RCTs on new targeted treatments, 49-70% of patients were treated with diuretics.

### d. Digitalis and dobutamine

*Strength of recommendation = E/C (Class of recommendation = IIb; and level of evidence = C)*

Inotropic agents have been considered for the treatment of pulmonary hypertension with decreased right ventricular cardiac output. Short-term IV administration of digoxin in IPAH has shown to produce a modest increase in cardiac output and a significant reduction in circulating norepinephrine levels.<sup>[125]</sup> However, digitalis was also found to directly increase PVR, an effect that increases the right ventricular afterload and can adversely affect exercise capacity in patients with PAH.<sup>[126]</sup>

With the current state of knowledge and because of a lack of strong evidence, the use of digitalis in PAH patients with refractory right heart failure is based primarily on the judgment of the physician rather than on scientific evidence of efficacy.

Digoxin was administered in 18-53% of patients enrolled in clinical trial in PAH patients. As the currently recommended dose of digoxin for heart failure is only 0.125 mg, routine measurement of drug level is not routinely recommended unless the patient has renal dysfunction; or a higher dose of the drug is used to treat certain arrhythmia, such as atrial flutter/fibrillation, which is poorly tolerated by PH patients.

In patients with end-stage PAH, treatment with IV dobutamine is considered by some experts<sup>[118]</sup> despite the lack of well-designed studies. Similar to the effect in advanced left ventricular failure, this treatment often results in short-term clinical improvement and is considered as a form of 'palliative' treatment.

### e. Calcium-channel blockers (CCBs)

*Strength of recommendation (for IPAH and vasoactive responders) = B (Class of recommendation = I; and level of evidence = B)*

*Strength of recommendation (for other PH and vasoactive responders) = E/C (Class of recommendation = IIb; and level of evidence = C)*

In the late 1980s, CCBs gained attention as a simple, yet promising, treatment for IPAH. The basis for 'vasodilator' therapy was based on the evidence of the presence of medial hypertrophy in the smooth muscle and muscular contraction with the resultant elevation in the PVR.

Favorable outcome, including survival advantages, of high-dose CCBs (in vasoreactive patients) in IPAH has been shown in many nonrandomized, noncontrolled studies.<sup>[98,102,127,128]</sup> The 1-, 3- and 5-year survival rates were 94, 94 and 94% in patients treated with CCBs compared to 68, 47 and 38% respectively in those who were classified as nonresponders. In these studies, the control group, however, consisted of nonvasoreactive patients who may have a poorer prognosis as compared to vasoreactive individuals.<sup>[102]</sup>

Generally, only about 10-15% of IPAH will meet the criteria for a positive acute vasoreactive response, and only a subset of them will demonstrate clinical and hemodynamic long-term response to CCB treatment. Recently, characteristics of patients with IPAH who benefit from long-term CCB treatment were studied in 557 IPAH patients.<sup>[129]</sup> Acute pulmonary vasodilator testing with epoprostenol or nitric oxide was performed in all patients. Acute responders received long-term oral CCB. Patients who benefit from long-term CCB were defined as those being in NYHA functional class I or II after at least 1 year on CCB monotherapy. Among the 70 (12.6%) patients who displayed acute pulmonary vasoreactivity and received CCB therapy, only 38 (6.8%) showed long-term improvement (95% CI, 4.7-8.9%). Long-term CCB responders were found to have less severe disease at baseline than patients who failed this treatment. During acute vasodilator testing, long-term CCB responders displayed a more pronounced fall in mean PAP ( $-39 \pm 11\%$  vs.  $-26 \pm 7\%$ ;  $P < 0.0001$ ), reaching an absolute value of mean PAP lower than that measured in patients who failed the treatment ( $33 \pm 8$  vs.  $46 \pm 10$  mmHg;  $P < 0.0001$ ). After 7.0 ( $\pm 4.1$ ) years, all but 1 long-term CCB responders were alive in NYHA class I or II, with a sustained hemodynamic improvement. In the group of patients who failed on CCB, the 5-year survival rate was 48%. Of

those who respond to CCBs, prognosis is generally very good, with 5-year survival of 95%. Favorable results of long-term administration of high doses of calcium-channel antagonists have also been shown in children with IPAH.<sup>[130]</sup>

The long-term outcome of CCBs treatment in IPAH pediatric children was evaluated recently,<sup>[131]</sup> in which an identified cohort of 77 children diagnosed between 1982 and 1995 with IPAH was followed up through 2002. Survival rates for all children treated with CCBs (acute responders,  $n = 31$ ) at 1, 5 and 10 years were 97, 97 and 81% respectively. Treatment success rates were reported to be 84, 68 and 47% respectively. Treatment success on CCB decreased significantly when acute responders became nonresponders. This study emphasizes that despite a good 5-year survival in acute responders, CCBs-treated patients' survival falls off when looking at a longer follow-up period, confirming the need for long-term monitoring.

Unfortunately, there is no RCT of oral CCBs for other forms of PAH. Based on the available data, it would be reasonable to treat patients who demonstrate a significant response to the acute administration of a short-acting vasodilator (see above) cautiously with oral CCBs.

Patients should be followed up closely for both safety and efficacy, with an initial reassessment after 3 months of therapy. If a patient does not improve to functional class I or II, additional or alternative PAH therapy should be instituted.

CCBs with a significant negative inotropic effect, such as verapamil, should be avoided. Nifedipine, diltiazem or amlodipine are used most frequently, with the choice often based on the heart rate at baseline (relative bradycardia favoring nifedipine and relative tachycardia favoring diltiazem). The doses of these drugs that have shown efficacy in IPAH are relatively high (i.e., up to 120-240 mg/day for nifedipine and 240-720 mg/day for diltiazem).<sup>[127]</sup> While early recommendations seemed to favor starting with relatively high doses of CCBs, it is probably more advisable to start with low doses to be increased cautiously and progressively in the subsequent weeks to the maximal tolerated regimen.

Side effects and limiting factors for dose increase are usually related to systemic hypotension. Lower limb edema is another bothering side effect, but not a limiting one. Addition of digoxin and/or diuretics may decrease the CCB side effects.<sup>[132]</sup>

## **f. Prostacyclin**

### **Introduction and rationale**

Prostacyclin (PGI<sub>2</sub>) is mainly synthesized by vascular endothelium. It is a potent vasodilator of all vascular beds. Furthermore, it is the most potent endogenous inhibitor of platelet aggregation and has significant antiproliferative activities.<sup>[133]</sup> An imbalance of the prostacyclin metabolic pathways has been shown in patients with PAH as assessed by a reduction of prostacyclin synthase expression in the pulmonary arteries and of prostacyclin urinary metabolites.<sup>[134]</sup> Such imbalance, whether it is a cause or consequence of PH, represents a convincing basis for the therapeutic use of prostacyclin in PAH patients. From the other aspect, although PGI<sub>2</sub> is considered as a 'vasodilator,' it was found to have a beneficial effect on the balance between endothelin-1 clearance and release in many

patients with PH<sup>[135]</sup> and may provide one explanation for the salutary effect of epoprostenol in this disease.

Initially, PGI<sub>2</sub> was basically used as a vasodilator agent that has a short half-life and some pulmonary selectivity. However, the effectiveness of the drug in those patients who failed to show a positive vasoreactive component during acute vasoreactive test<sup>[136]</sup> and the fact that long-term IV administration of epoprostenol lowers PVR beyond the level achieved in the acute vasoreactivity tests<sup>[137]</sup> suggest another mode of action. Currently, the long-term effect of the drug is thought to be related to its anti-remodeling effects that are mainly related to the inhibitory effects of prostacyclin on vascular growth, muscular hypertrophy and thrombotic obliteration. In a recent study,<sup>[138]</sup> the antiproliferative effect of several PGI<sub>2</sub> analogues on human pulmonary arterial smooth muscle cells was tested. Serum-induced proliferation was significantly inhibited by different analogues that showed different potency. Intracellular cAMP was elevated by all tested analogues, suggesting that PGI<sub>2</sub> analogues potentially inhibit proliferation of human pulmonary artery, probably via a cAMP-dependent pathway.

However, the precise mechanism of PGI<sub>2</sub> action in PAH is not yet fully understood and is likely to be multifactorial.

### *Epoprostenol*

*Strength of recommendation for NYHA class III and IV = A (Class of recommendation = I; and level of evidence = A)*

### *FDA approval: 1995*

Epoprostenol is a synthetic prostacyclin. It has a short half-life in circulation (3-5 min). It is rapidly converted to stable breakdown products or metabolites and is stable at room temperature for only 8 h. Because of these features, the drug is usually administered by continuous IV route by means of infusion pumps and permanent intravascular (Hickman) catheters.

The efficacy of continuous IV administration of epoprostenol has been tested in controlled clinical trials in IPAH<sup>[136,139]</sup> and in PAH associated with scleroderma.<sup>[124]</sup> In a 12-week prospective multi-center randomized controlled open-label trial,<sup>[136]</sup> epoprostenol given by continuous IV infusion plus conventional therapy (including oral CCBs, anticoagulation, diuretic, digoxin and oxygen) was compared to conventional therapy alone in 81 patients with severe IPAH (75%, NYHA class III; and 25%, class IV). Exercise capacity improved in the 41 patients treated with epoprostenol (6MWT distance, 362 m at 12 weeks, versus 315 m at baseline) and decreased in the 40 patients treated with conventional therapy alone (204 m at 12 weeks versus 270 m at baseline;  $P < 0.002$  for comparison of the treatment groups). There were also improvements in indexes of the quality of life, hemodynamics and survival. In the second trial,<sup>[139]</sup> 23 IPAH patients (9% were class II; 65%, class III; and 26%, class IV) received intravenous infusion of epoprostenol for 2 months. There was a 45-meter gain in 6MWT distance and improved hemodynamics in the treatment group at the end of the study.

Survival advantage for epoprostenol was shown in many studies. The first study<sup>[83]</sup> tested a group of 178 IPAH patients treated with long-term epoprostenol therapy, who were

compared to a historic control group of 135 patients (from the same center) treated with conventional therapy. Estimated 1-, 2-, 3- and 5-year survival rates in the epoprostenol group were 85, 70, 63 and 55% respectively and were significantly better than those of the control group: 58, 43, 33 and 28% respectively. The survival was related to the severity at baseline, as well as to the 3-month response to therapy. Another study reported long-term experience with epoprostenol in 162 consecutive IPAH patients.<sup>[82]</sup> In distinction to the previous study, the treated group's observed survival was compared with its predicted survival based on the NIH equation. One- 2- and 3-year survival estimates were significantly better with epoprostenol (88, 76 and 63% respectively) than their predicted survival.

Factors associated with long-term survival in patients with IPAH treated with continuous epoprostenol infusion are many. On univariate analysis, the baseline variables associated with a poor outcome were a history of right-sided heart failure, NYHA functional class IV, 6MWT distance of less than 250 m, RAP  $\geq$  12 mmHg and mPAP  $<$ 65 mmHg. On multivariate analysis, including both baseline variables and those measured after 3 months on epoprostenol, a history of right-sided heart failure; persistence of NYHA functional class III or IV at 3 months; and the absence of a fall in total pulmonary resistance of  $>$ 30%, relative to baseline, were associated with poor survival.<sup>[83]</sup>

Epoprostenol has also been studied in the 'PAH associated with scleroderma' (PSS) patient population. A randomized controlled investigation of 111 patients noted impressive improvement in the 6MWT distance, hemodynamics and NYHA functional classification, which were similar to improvements appreciated in the IPAH trial.<sup>[119]</sup> However, 7% of the epoprostenol group died during the 12-week study in PSS, which was not different from the control group.<sup>[119]</sup> Another multicenter randomized controlled open-label study<sup>[124]</sup> of long-term IV epoprostenol treatment in patients with PAH occurring in association with PSS spectrum of the disease was conducted. Exercise capacity improved with epoprostenol (median 6MWT distance, 316 m at 12 weeks, compared with 270 m at baseline) but decreased with conventional therapy (192 m at 12 weeks, compared with 240 m at baseline). The difference between treatment groups in the median distance walked at week 12 was 108 m ( $P < 0.001$ ). Hemodynamic parameters also improved significantly. Again, a survival advantage was not demonstrated in this group of PAH patients.

The dissociation between symptomatic and hemodynamic improvements with respect to survival benefit in PSS-associated PAH is not clearly explainable. However, PSS patients are typically older and have a systemic and chronic disease that has often been present for years.

Favorable results have also been shown in uncontrolled studies in other subsets, such as PAH associated with systemic lupus erythematosus<sup>[140]</sup> and other CTDs,<sup>[141]</sup> PAH in portopulmonary hypertension<sup>[141,142]</sup> and HIV infection.<sup>[143]</sup> Epoprostenol has also shown favorable results in PAH associated with congenital heart defects (with or without systemic-to-pulmonary shunts).<sup>[141,144]</sup> In one study,<sup>[144]</sup> 20 patients who had negative acute response and failed conventional treatment were treated with chronic PGI<sub>2</sub>. While on treatment, mPAP decreased by 21%, cardiac index and PVR also improved significantly [3.5  $\pm$

2.0 to 5.9  $\pm$  2.7 L $\cdot$ min<sup>-1</sup> m<sup>-2</sup> ( $P < 0.01$ ,  $n = 16$ ); and 25  $\pm$  13 to 12  $\pm$  7 U  $\cdot$  m<sup>2</sup> ( $P < 0.01$ ,  $n = 16$ )] respectively. NYHA functional class improved by at least 1 class in 19 patients, and exercise capacity increased from 408  $\pm$  149 to 460  $\pm$  99 m ( $P = 0.13$ ).

Epoprostenol was tested in pediatric patients with PAH and showed encouraging results.<sup>[130]</sup> In a recent study<sup>[131]</sup> in which an identified cohort of 77 children diagnosed between 1982 and 1995 with IPAH was followed up through 2002, survival rates for all children treated with epoprostenol ( $n = 35$ ) at 1, 5 and 10 years were 94, 81 and 61% respectively. Treatment success rates were reported to be 83, 57 and 37% respectively. Because of the inconsistent availability of epoprostenol before 1995, the authors defined a 'recent medical era' subset by excluding children from the total 77-patient cohort for whom epoprostenol was recommended but was unavailable. Survival rates in the recent medical era subset ( $n = 44$ ) at 1, 5 and 10 years were 97, 97 and 78%, and treatment success rates were 93, 86 and 60% respectively.

Finally, there is no consensus on the effectiveness of epoprostenol treatment in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) even if some positive effects have been shown<sup>[84,145]</sup> (see below under specific conditions). Despite the fact that intravenous epoprostenol seems to have some efficacy in preoperative stabilization of patients with CTEPH, more studies are definitely needed before clear recommendations can be given in this particular indication.

Long-term treatment with epoprostenol is usually started at a low dose, ranging from 2 to 4 ng/kg/min and increased at a rate limited by side effects. Optimal dose varies between individual patients, ranging in the majority between 20 and 40 ng/kg/min.

Adverse effects of epoprostenol are usually mild and depend upon the dose (mainly initial dosing) and duration of therapy. Flushing, jaw pain, diarrhea, headache, backache, foot and leg pain, abdominal cramping, nausea and rarely hypotension are among the most commonly observed side effects. Ascites has also been reported, which may be related to an increased permeability of the peritoneal membrane induced by epoprostenol. Dose reduction is required only if the intensity of the side effect is moderate to severe. Recurrence of side effects is less likely to occur if the dose is increased slowly, and it is usually mild and self-limiting over time without dose changes.

Epoprostenol use in pregnancy was reported in case reports in women with PAH. In a case report,<sup>[146]</sup> a woman with an Eisenmenger atrial septal defect was diagnosed during the last trimester of pregnancy. On presentation, she was critically ill and there was evidence of fetal distress. She was emergently treated with IV epoprostenol, and subsequently her status improved. She underwent cesarean section and delivered a male infant with Apgar scores of 8 and 9. Her dyspnea improved and she was characterized as WHO functional class II on a subsequent clinical visit. However, despite this anecdote, it should be clear that the current recommendation is to advise against pregnancy, giving appropriate contraceptive recommendations and, if necessary, termination of pregnancy

(see above under general measure).

Complications of the delivery system, such as pump malfunction, local cellulitis, catheter obstruction and sepsis, are usually serious and require prompt identification and management. In the two large series mentioned above,<sup>[82,83]</sup> 0.14 and 0.19 episodes of sepsis per patients-year were reported; and 8 deaths (2.8%) out of a total of 340 subjects were directly related to catheter infections. Localized infections can also occur, such as exit site reactions, tunnel infections and cellulitis. In case of sepsis, our recommendation is to start empiric antimicrobial treatment for both gram-positive and gram-negative coverage, until the organism is identified.

Abrupt interruption of the epoprostenol infusion should be avoided by all means, as a rebound worsening of PH with symptomatic deterioration and even death can happen in a short period of time (20-30 min). However, fatalities have been reported with treatment interruption for as short as 5 min.

#### *Inhaled iloprost*

*Strength of recommendation for IPAH NYHA class III = A (Class of recommendation = I; and level of evidence = A)*

*Strength of recommendation for NYHA class IV = E/B*

*FDA approval: 2004*

Iloprost is a chemically stable prostacyclin analogue available for IV and aerosol administration. Inhaled therapy for PAH is an attractive concept for drug delivery in pulmonary vascular diseases because of the theoretical advantage that the deposition of the drug in a well-ventilated alveoli will lead to selective vasodilatation of its capillary supply and hence improve the V/Q matching and subsequently improve oxygenation and pulmonary hemodynamics with minimum effect of systemic parameters. It is critical that aerosolized particles be small enough (diameter 3-5 micron) to ensure alveolar deposition.

After a single inhalative dose of iloprost, 10-20% of mean PAP was observed, and it lasted up to 1 h.<sup>[147]</sup> The short duration of action requires frequent inhalations (from 6 to 12 times daily) to obtain a persistent effect with long-term administration. With jet nebulizers, the duration of each inhalation takes about 15 min; the inhalation time, however, can be shortened to about 5 min with ultrasound nebulizers.

A 3-month randomized double-blind placebo-controlled European multicenter trial with inhaled iloprost was performed.<sup>[148]</sup> A total of 203 NYHA functional class III and IV patients with IPAH and PAH occurring in association with collagen vascular disease or inoperable chronic thromboembolic PAH, were enrolled. The daily dose of iloprost was 2.5-5 µg 6 to 9 times a day (maximum dose: 45 µg/day; median dose: 30 µg/day). The primary combined end point of a 10% improvement in the 6MWT distance and NYHA functional class improvement in the absence of clinical deterioration or death was achieved in 17% of treated patients, compared to 5% in patients receiving placebo ( $P = 0.007$ ). The treatment effect on the 6MWT distance was a mean increase of 36 m in the overall population in favor of iloprost ( $P = 0.004$ ) and 59 m

in the subgroup of IPAH patients. There was also a statistically significant beneficial effect of iloprost on NYHA functional class ( $P < 0.05$ ), quality of life ( $P < 0.05$ ) and the Mahler dyspnea index ( $P < 0.05$ ). As compared with baseline values, hemodynamic variables were significantly improved at 3 months when measured after iloprost inhalation. One patient in the iloprost group died during the study period versus 4 patients in the placebo group (not significant). Overall, inhaled iloprost was well tolerated; cough, flushing and headache occurred more frequently in the iloprost group. These adverse events were mild and mostly transient. Syncope occurred with similar frequency in the two groups, but was more frequently considered to be serious in the iloprost group; although this adverse effect was not associated with clinical deterioration.

A long-term uncontrolled study of 25 patients with IPAH treated for at least 1 year with inhaled iloprost has been also reported.<sup>[149]</sup> The results showed a mean increase of 85 m in the 6MWT, a reduction of 7 mmHg in mean PAP and an increase in cardiac index of 0.6 L/min/m<sup>2</sup>.

More recently, a group of 76 NYHA functional class II or III IPAH patients treated with inhaled iloprost was evaluated.<sup>[150]</sup> During the follow-up period of 535 ± 61 days, 11 patients (14%) died, 6 patients (9%) underwent transplantation, 25 patients (33%) were switched to IV prostanoids, 16 patients (23%) received additional/oral PAH therapies and 12 patients (17%) discontinued inhaled iloprost for other reasons. Event-free survival rates at 1 year and 2 years were 53 and 29% respectively.

Based on the above data, inhaled iloprost is considered to be a safe, effective and well-tolerated treatment for severe PAH. The most important drawback of inhaled iloprost is related to the relatively short duration of action, requiring the use of 6 to 9 inhalations a day, which is not convenient for most patients.

Finally, some experience is available with regard to the use of inhaled iloprost in pregnant women with PH. In a case study of three pregnant women who suffered from PH (the first had IPAH, the second had familial PH and the third had ostium secundum atrial septal defect) and decided to continue their pregnancies against physician's advice,<sup>[151]</sup> Nebulized iloprost was commenced as early as 8 weeks of gestation, and patients were admitted to hospital between 24 and 36 weeks of gestation. All pregnancies were completed and all deliveries were by caesarian sections. All delivered children were free from congenital abnormalities and there was no postpartum maternal or infant mortality.

#### *Treprostinil*

*Strength of recommendation for NYHA class II and III = B (subcutaneous)*

*Strength of recommendation for NYHA class IV = C (subcutaneous)*

*Strength of recommendation for NYHA class III and IV = C (intravenous, in patients not tolerating subcutaneous route)*

*FDA approval: 2002 (subcutaneous) and 2004 (intravenous)*

Treprostinil is an analogue of epoprostenol, with sufficient

chemical stability to be administered at ambient temperature in a physiological solution. These characteristics allow the administration of the compound by IV and subcutaneous route. The subcutaneous administration of treprostinil is delivered by micro-infusion pumps and small subcutaneous catheters, and so the complications and side effects of this delivery system are much less than those of the IV system used for IV epoprostenol treatment.

The effects of continuous subcutaneous administration of treprostinil in PAH were studied. A placebo-controlled study of subcutaneously infused treprostinil in patients with functional class II, III or IV PAH (IPAH or PAH associated with connective tissue disease or congenital systemic-to-pulmonary shunts) demonstrated improved exercise capacity as measured by the 6MWT distance [median between treatment group difference 16 m ( $P = 0.006$ )].<sup>[152]</sup> The greatest exercise improvement was observed in patients who were more compromised at baseline and in subjects who could tolerate upper quartile dose (dose  $>13.8$  ng/kg/min). This effect did appear to be dose related, and subcutaneous dosing was limited by infusion site pain and reaction. In a more recent study,<sup>[153]</sup> the efficacy of long-term subcutaneous treprostinil therapy in the treatment of PAH (IPAH and CTEPH) was tested in a long-term multicenter retrospective study. In this study, 99 patients with PAH and 23 patients with CTEPH in NYHA classes II-IV were followed up for a mean of  $26.2 \pm 17.2$  months. Long-term efficacy was assessed by 6MWT, Borg dyspnea score and NYHA class. Clinical events were also monitored to assess survival and event-free survival. At 3 years, significant improvements from baseline were observed in mean 6MWT distance ( $305 \pm 11$  to  $445 \pm 12$  m,  $P = 0.0001$ ), Borg dyspnea score ( $5.7 \pm 0.2$  to  $4.5 \pm 1$ ,  $P = 0.0006$ ) and NYHA class ( $3.20 \pm 0.04$  to  $2.1 \pm 0.1$ ,  $P = 0.0001$ ). Subcutaneously infused treprostinil was well tolerated, and local pain at the subcutaneous site accounted for treatment interruption in only 5% of the cases. Survival was 88.6 and 70.6% at 1 year and 3 years respectively; at the same time points, the event-free survival rates, defined as survival without hospitalization for clinical worsening, transition to IV epoprostenol and need for combination therapy or atrial septostomy were 83.2 and 69% respectively.

Given potential advantages over IV epoprostenol, including a longer half-life, IV treprostinil has been studied. In an open-label study, 16 PAH patients (functional class III or IV PAH) were treated with IV treprostinil.<sup>[154]</sup> After 12 weeks of therapy, 6MWT distance improved by a mean of 82 m ( $P = 0.001$ ). There were also improvements in hemodynamics, including mean PAP ( $P = 0.03$ ), cardiac index ( $P = 0.002$ ) and PVR index ( $P = 0.001$ ) at week 12 compared to baseline. One death, which was thought not to be related to the study drug, occurred during the 12-week study - a patient who received IV treprostinil for 3 days died 2 weeks later.

Infusion site pain was the most common side effect of treprostinil, leading to discontinuation of the treatment in up to 8% of cases on active drug.

Treprostinil is not currently available for clinical administration in Saudi Arabia.

### *Sodium beraprost*

*Strength of recommendation = B (in IPAH NYHA II and III)*

Beraprost is an orally active prostacyclin analogue. It has rapid absorption in fasting conditions, and peak concentration is reached after 30 min.

Beraprost has been evaluated in PAH patients in two RCTs.<sup>[155,156]</sup> In the first study,<sup>[155]</sup> 130 patients with PAH NYHA class II and III were randomized to the maximal tolerated dose of beraprost (median dose 80 µg four times a day) or to placebo for 12 weeks. The primary end point was the change in exercise capacity assessed by the 6MWT. Secondary end points included changes in Borg dyspnea index, cardiopulmonary hemodynamics and NYHA functional class. Patients who were treated with beraprost showed improved exercise capacity and symptoms (6MWT difference at week 12 was 25 m,  $P = 0.036$ ; while the difference in the mean change of Borg dyspnea index was  $-0.94$ ,  $P = 0.009$ ). Cardiopulmonary hemodynamics and NYHA functional class had no statistically significant changes. Drug-related adverse events were common in the titration phase and decreased in the maintenance period. The second randomized trial was a 12-month study.<sup>[156]</sup> In this study, a total of 116 patients with NYHA functional class II or III IPAH or PAH related to either collagen vascular diseases or congenital systemic-to-pulmonary shunts were enrolled. Patients were randomized to receive the maximal tolerated dose of sodium beraprost (median dose 120 µg four times a day) or placebo for 12 months. The primary end point was disease progression, which includes death, transplantation, epoprostenol rescue or  $>25\%$  decrease in  $VO_{2max}$ . Secondary end points included exercise capacity assessed by 6MWT and  $VO_{2max}$ , Borg dyspnea score, hemodynamics, symptoms of PAH and quality of life. Patients treated with beraprost exhibited less evidence of disease progression at 6 months ( $P = 0.002$ ), but this effect was not evident at either shorter or longer follow-up intervals. Similarly, beraprost-treated patients had improved 6MWT distance at 3 months - by 22 m from baseline; and at 6 months - by 31 m ( $P = 0.010$  and  $0.016$  respectively) compared with placebo, but not at either 9 or 12 months. Drug-related adverse events were common and were related to the disease and/or expected prostacyclin adverse events.

Whether beraprost will prove efficacious as a concomitant medical therapy in combination/multimodal treatment regimens for PAH requires further study.

Beraprost is not currently available for clinical use in Saudi Arabia.

### *g. Endothelin-1 receptor antagonists (ERAs)*

#### *Introduction and rationale*

The activation of the ET-1 system has been clearly demonstrated in both plasma<sup>[157]</sup> and lung tissues of PAH patients.<sup>[158]</sup> Although it is not clear if the increases in ET-1 plasma level are a cause or a consequence of PH,<sup>[157]</sup> many studies on tissue ET system expression support a prominent role of ET-1 in the pathogenesis of PAH.<sup>[159]</sup>

ET-1 is a potent vasoconstrictor and a smooth-muscle mitogen that might contribute to the increase in vascular tone and the

pulmonary vascular hypertrophy associated with PAH (see the section of pathogenesis above). In a small cohort of patients with IPAH, plasma concentrations of ET correlated with PAP and PVR, as well as with exercise capacity.<sup>[104]</sup> Two distinct endothelin-receptor types have been identified, ET<sub>A</sub> and ET<sub>B</sub>.<sup>[160]</sup> Activation of ET<sub>A</sub> receptors facilitates vasoconstriction and proliferation of vascular smooth-muscle cells.<sup>[160]</sup> In contrast, ET<sub>B</sub> receptors are thought to be principally involved in the clearance of endothelin, particularly in the vascular beds of the lung and kidney.<sup>[160]</sup> Activation of ET<sub>B</sub> receptors may also cause vasodilation and NO release. It is not clear whether it makes any clinical difference - to block both the ET<sub>A</sub> and ET<sub>B</sub> receptors or to target the ET<sub>A</sub> receptor alone.

Based on the above data, which clearly document the activation of the ET system in PAH, the use of ET-1 antagonists in managing PAH patients became an attractive treatment strategy.

### **Bosentan**

**Strength of Recommendation: A for NYHA class III (Class of recommendation= I, Level of evidence= A) & B for NYHA class IV**

#### **FDA approval: 2001**

Bosentan is a nonspecific oral dual ET<sub>A</sub> and ET<sub>B</sub> receptor antagonist.<sup>[161]</sup> The efficacy of bosentan was evaluated in many RCTs, which have shown improvement in exercise capacity, functional class, hemodynamics, echocardiographic and Doppler variables and time to clinical worsening.<sup>[54,162,163]</sup> The first randomized double-blind placebo-controlled multi-center study<sup>[164]</sup> of bosentan demonstrated an improvement in the 6MWT distance of 70 m at 12 weeks, whereas no improvement was seen with placebo ( $P < 0.05$ ). Treatment with bosentan also improved cardiopulmonary hemodynamics and functional class. Asymptomatic increases in hepatic aminotransferases were observed in two bosentan-treated patients. In a second double-blind placebo-controlled study (the Bosentan Randomized Trial of Endothelin Antagonist Therapy for Pulmonary Hypertension-1 Study, BREATHE-1),<sup>[163]</sup> bosentan (125 or 250 mg b.i.d.) was evaluated in 213 patients with functional class III and IV PAH (either IPAH or associated with connective tissue disease), for a minimum of 16 weeks (started dose of 62.5 mg b.i.d. for 4 weeks; then target dose, 125 mg or 250 mg). Bosentan improved the 6MWT distance by 36 m, whereas deterioration (-8 m) was seen with placebo. The difference between treatment groups in the mean change in 6MWT distance was 44 m in favor of bosentan ( $P = 0.0002$ ). The risk of clinical worsening was also reduced by bosentan compared to placebo ( $P = 0.0015$ ). Although both bosentan dosages induced a significant treatment effect, the placebo-corrected improvement tended to be more pronounced for the 250-mg b.i.d. than for the 125-mg b.i.d. dosage (+54 m and +35 m of 6MWT treatment effect respectively). However, no formal dose response for efficacy could be identified. In subgroups analysis, although a similar treatment effect was achieved in patients with IPAH and in those with PAH associated with PSS, bosentan improved the walking distance from baseline in IPAH patients (+46 m in the bosentan group vs. -5 m in the placebo group); whereas it prevented the walking distance deterioration in the PSS patients (+3 m in the bosentan group vs. -40 m in the placebo group). Abnormal hepatic function

test findings, syncope and flushing occurred more frequently in the bosentan group.

Two important studies have further described the long-term outcomes with bosentan therapy in patients with PAH. In the first one,<sup>[165]</sup> bosentan was used as the first-line therapy, with the subsequent addition of, or shifting to, other therapy as necessary. This treatment resulted in survival estimates of 96% at 1 year and 89% at 2 years. In contrast, predicted survival rates from the NIH Registry<sup>[2]</sup> were 69 and 57% respectively. In addition, at the end of first and second years, 85 and 70% of patients respectively remained alive and continued receiving bosentan monotherapy. NYHA functional class IV and 6MWT distance below the median (358 m) at baseline predicted a poorer outcome. In the second study,<sup>[166]</sup> the survival outcome was compared in 139 IPAH patients with NYHA functional class III treated with bosentan with historical data from similar patients ( $n = 346$ ) treated with epoprostenol. However, the baseline characteristics showed that the epoprostenol group was suffering from more severe disease. Kaplan-Meier survival estimates after 1 year and 2 years were 97 and 91% respectively in the bosentan cohort and 91 and 84% in the epoprostenol cohort. In the bosentan cohort, 87 and 75% of patients followed up for 1 year and 2 years respectively remained on monotherapy. No evidence was found to suggest that initial treatment with oral bosentan followed by, or with the addition of, other treatment if needed adversely affected the long-term outcome compared with initial IV epoprostenol in patients with class III IPAH.

The effect of first-line bosentan therapy on survival was evaluated in 169 bosentan-treated patients with IPAH in two placebo-controlled trials and their extensions.<sup>[167]</sup> Data on survival and alternative treatments were collected from September 1999 (start of the first placebo-controlled study) to December 31, 2002. Observed survival up to 36 months was reported as Kaplan-Meier estimates and compared with predicted survival as determined for each patient by the National Institutes of Health Registry formula. Kaplan-Meier survival estimates were 96% at 12 months and 89% at 24 months. In contrast, predicted survival was 69 and 57% respectively. In addition, at the end of 12 and 24 months, 85 and 70% of patients respectively remained alive and on bosentan monotherapy. Similar to previous studies, factors that predicted a worse outcome included WHO functional class IV and 6-min walk distance below the median (358 m) at baseline.

The role of bosentan in PAH associated with congenital heart defect was also evaluated. In a pilot open-label study,<sup>[168]</sup> the safety and tolerability of bosentan were evaluated in 10 patients with Eisenmenger physiology. Baseline and 3-month assessment included WHO functional class, resting oxygen saturations, 6-min walk test, transthoracic echocardiography and respiratory mass spectrometry. Patient clinical status and liver enzymes were closely monitored throughout. No major adverse events or significant liver enzyme elevations were observed in any patient. All but one patient felt better; none felt worse. Four patients experienced transient leg edema. Resting oxygen saturations and 6MWT distance increased relative to baseline ( $83 \pm 5$  vs.  $80 \pm 5\%$ ,  $P = 0.011$ ; and  $348 \pm 112$  vs.  $249 \pm 117$  m,  $P = 0.004$  respectively). Changes in echocardiographic parameters suggested improved pulmonary hemodynamics and improved right ventricular systolic function by study end.

More recently, a multi-center 16-week double-blind randomized and placebo-controlled study of bosentan therapy in patients with functional class III Eisenmenger syndrome (BREATH-5)<sup>[169]</sup> was reported. The effect of bosentan was specifically tested on systemic pulse oximeter (primary safety end point) and pulmonary vascular resistance (primary efficacy end point) in this group of patients. Hemodynamic measurements were assessed by right- and left-heart catheterization. Secondary end points included exercise capacity assessed by 6MWT, additional hemodynamic parameters, functional capacity and safety. Fifty-four patients were randomized 2:1 to bosentan ( $n = 37$ ) or placebo ( $n = 17$ ). The placebo-corrected effect on systemic pulse oximeter was 1.0%, demonstrating that bosentan did not worsen oxygen saturation. Compared with placebo, bosentan reduced PVR index ( $P = 0.0383$ ). Mean PAP decreased ( $P = 0.0363$ ) and exercise capacity increased by a mean of 53 m ( $P = 0.0079$ ). Treatment was discontinued in 4 patients as a result of adverse events: 2 patients (5%) in the bosentan group and 2 patients (12%) in the placebo group.

The use of Bosentan in children 4-17 years of age with PAH was evaluated in an open-label uncontrolled single and multiple-dose study (BREATHE-3) to assess pharmacokinetics, tolerability and safety of oral bosentan.<sup>[170]</sup> In this study, a significant improvement in hemodynamics was observed after 12 weeks of treatment in the 18 enrolled children either with bosentan alone or in combination with epoprostenol. In a retrospective study,<sup>[171]</sup> 86 children with IPAH, PAH associated with congenital heart disease or connective tissue disease were treated with bosentan (with or without concomitant IV epoprostenol or subcutaneous treprostinil therapy). At the cut off date, 68 patients (79%) were still treated with bosentan, 13 patients (15%) had treatment discontinued and 5 patients (6%) had died. Median exposure to bosentan was 14 months. In 90% of the patients ( $n = 78$ ), functional class improved (46%) or was unchanged (44%) with bosentan treatment. Mean PAP and PVR decreased significantly. Survival estimates at 1 year and 2 years were 98 and 91% respectively. More recently, the long-term outcome of children with PAH treated with bosentan therapy, with or without concomitant prostanoid therapy, was reported in a retrospective study of 86 patients with PAH (idiopathic, associated with congenital heart or connective tissue disease).<sup>[172]</sup> At the cut off date, 68 patients (79%) continued treatment with bosentan, 13 (15%) were discontinued and 5 (6%) had died. Median exposure to bosentan was 14 months. WHO functional class improved in 46% of the treated patients; and in 44%, it stayed unchanged. Mean PAP and PVR decreased ( $64 \pm 3$  mmHg to  $57 \pm 3$  mmHg,  $P = 0.005$ ; and  $20 \pm 2$  U·m<sup>2</sup> to  $15 \pm 2$  U·m<sup>2</sup>,  $P = 0.01$  respectively;  $n = 49$ ). Kaplan-Meier survival estimates at 1 and 2 years were 98 and 91% respectively.

Hepatic toxicity is the most serious side effect of bosentan. The most likely mechanism for the liver enzyme changes with bosentan treatment is a dose-dependent competition by bosentan and its metabolites with the biliary excretion of bile salts, resulting in retention of bile salts that can be cytotoxic to hepatocytes.<sup>[173]</sup> Due to this potential side effect, the FDA requires that liver function tests be performed at least monthly in patients receiving bosentan. Also, the hemoglobin/hematocrit should be checked on regular basis because bosentan use may also be associated with the development

of anemia, which is usually mild. Hemoglobin decreases on an average by 0.8 g/dl for all ERAs, and the decrease usually occurs within the first 12-16 weeks. Fluid retention and lower limb edema have been also reported in patients treated with bosentan. Women of childbearing age should have clear instructions about the potential teratogenic effect of the drug, and proper contraceptive methods should be considered. Drug-drug interaction with contraceptive medication has been noticed with bosentan; and for this reason, oral contraceptive pills should not be used as a sole mechanism for contraception. Rather, it is suggested that some other form of contraception be included, such as the use of double-barrier techniques (condom and diaphragm) with a spermicide. Regular pregnancy testing is recommended in women of childbearing age. Finally, there is a concern that the endothelin antagonists as a class may cause testicular atrophy and male infertility. Younger females who may consider conceiving should be counseled regarding this potential side effect before taking these drugs.

#### *Sitaxsentan*

*Strength of recommendation = A for NYHA class II and III (Class of recommendation = I; level of evidence = A)*

*Strength of recommendation = C for NYHA class IV*

#### *EMEA approval: 2007*

Sitaxsentan is a selective orally active ET<sub>A</sub>-receptor antagonist. The drug was tested in a RCT (STRIDE-1) on 178 patients with PAH who were in NYHA class II, III and IV.<sup>[174]</sup> Etiology included IPAH and PAH associated with CTD or congenital heart diseases. Patients were randomized to placebo, sitaxsentan 100 mg or sitaxsentan 300 mg given orally once daily for 12 weeks. The primary end point was change in peak VO<sub>2</sub> at week 12. Secondary end points included 6MWT, NYHA class, VO<sub>2</sub> at anaerobic threshold, VE per carbon dioxide production at anaerobic threshold, hemodynamics, quality of life and time to clinical worsening. Although the 300-mg group demonstrated increased peak VO<sub>2</sub> compared with placebo (+3.1%,  $P < 0.01$ ), none of the other end points derived from cardiopulmonary exercise testing were met. However, the treatment effects in the sitaxsentan groups were 35 m ( $P < 0.01$ ) for the 100-mg dose and 33 m ( $P < 0.01$ ) for the 300-mg dose. NYHA functional class and cardiopulmonary hemodynamics also improved. Incidence of abnormal liver function tests, which reversed in all cases, was 0% for 100 mg and 9.5% for 300 mg. It should be noted that in an earlier pilot study,<sup>[175]</sup> sitaxsentan was associated with fatal hepatitis when used at higher doses.

STRIDE-2 trial was a double-blind placebo-controlled study<sup>[176]</sup> in which 247 patients with PAH (IPAH, PAH related to CTD or congenital heart disease) were randomized to receive sitaxsentan (50 mg or 100 mg), placebo, or open-labeled bosentan (62.5 mg twice daily for 4 weeks followed by 125 mg twice daily for 14 weeks). The enrolled patients had NYHA class II to IV. The primary end point was 6 MWT distance. After adjusting for placebo effect, the 100-mg dose of sitaxsentan resulted in an average gain of 31 m in walking distance ( $P = 0.03$ ) and improvement in NYHA functional class ( $P = 0.04$ ). For those receiving the 50-mg dose, the average gain in 6MWT distance was 24 m ( $P = NS$ ); and 29 m for those receiving bosentan.

The liver function abnormality occurred in 6.5% in placebo group, 3.2% in 100-mg sitaxsentan, 4.9% in 50-mg sitaxsentan and 11.5% in bosentan group. Discontinuation of therapy occurred in 11 patients receiving placebo, 4 patients receiving 100-mg dose of sitaxsentan, 8 patients receiving 50-mg dose of sitaxsentan and 9 patients receiving bosentan.

The safety and efficacy of sitaxsentan in patients discontinuing bosentan have been recently evaluated. In a study<sup>[177]</sup> of 48 patients with IPAH or PAH associated with connective tissue disease or congenital heart disease, the patients were randomized in a double-blinded fashion to a single daily dose of either 50 mg or 100 mg sitaxsentan. Thirty-five of the 48 patients discontinued bosentan because of inadequate efficacy, as judged by the investigator; and 13 discontinued bosentan for safety concerns. Study end points included change in 6MWT distance, change in WHO functional class, time to clinical worsening and change in Borg dyspnea score from baseline to week 12. With 100 mg sitaxsentan, 5 of 15 patients (33%) who discontinued bosentan because of inadequate efficacy improved, demonstrating a >15% increase in 6MWT distance, versus 2 of 20 patients (10%) treated with 50 mg sitaxsentan. Fifteen percent and 20% of these patients had a >15% decrease in 6MWT distance in the 50- and 100-mg groups respectively. Similar results were seen for the Borg dyspnea score and WHO functional class. Of the 12 patients discontinuing bosentan because of hepatotoxicity, 1 developed elevated liver enzymes at 13 weeks of sitaxsentan therapy. Overall, sitaxsentan was well tolerated.

The most frequently reported clinical adverse events with sitaxsentan treatment were headache, peripheral edema, nausea, nasal congestion and dizziness; these reactions were previously noted with other endothelin receptor antagonists. Sitaxsentan may also increase the INR or prothrombin time (PT), due to the inhibition of CYP2C9 P450 enzyme, the principal hepatic enzyme involved in the metabolism of warfarin. This interaction can be managed by reducing the warfarin dose to achieve the desired INR.

#### **Ambrisentan**

*Strength of recommendation = A for NYHA class II and III (Class of recommendation = I; level of evidence = A)*

*Strength of recommendation = C for NYHA class IV*

*FDA approval: 2007*

Ambrisentan is a selective orally active ET<sub>A</sub>-receptor antagonist. An initial phase II study examined the efficacy and safety of four doses of ambrisentan in patients with PAH.<sup>[178]</sup> In this double-blind dose-ranging study, 64 patients with functional class II and III IPAH or PAH associated with connective tissue disease, anorexigen use or HIV infection were randomized to receive 1, 2.5, 5 or 10 mg of ambrisentan once daily for 12 weeks followed by 12 weeks of open-label ambrisentan. The primary end point was an improvement from baseline in 6MWT distance; secondary end points included Borg dyspnea index, WHO functional class, a subject global assessment and cardiopulmonary hemodynamics. At 12 weeks, 6MWT distance was increased by an average of 36 m ( $P < 0.0001$ ), with similar and statistically significant increases for each dose

group. Improvements were also observed in Borg dyspnea index, functional class, subjective global assessment, mean PAP ( $P < 0.0001$ ) and cardiac index ( $P < 0.0008$ ). Adverse events were mild and were dose unrelated. Elevation in serum aminotransferase more than three times the normal occurred in 3.1%.

Two phase III clinical trials (ARIES-1 and ARIES-2) were initiated in January 2004 so as to further evaluate the safety and efficacy of this drug in the treatment of PH. The studies' design anticipates enrolling 186 patients in each trial. ARIES-1 trial evaluated ambrisentan doses of 5 mg and 10 mg administered daily for 12 weeks versus placebo, while ARIES-2 evaluated 2.5-5 mg administered daily for 12 weeks. (Ultimately, ARIES-1 enrolled 202 patients primarily from USA, while ARIES-2 enrolled 192 patients primarily from Europe). The primary end point in both studies is exercise capacity (6MWT) compared to placebo. Secondary end points are Borg dyspnea index, WHO functional class and time to clinical worsening. In ARIES-1,<sup>[179]</sup> a total of 202 patients were randomized to one of the three treatment groups (5 mg, 10 mg or placebo) for the 12-week study duration. Significant improvements in the placebo-corrected 6MWT distance change from the baseline to week 12 versus placebo were seen in both groups (+31 m for 5 mg,  $P = 0.008$ ; and +51 m for 10 mg,  $P < 0.001$ ). Improvements in WHO functional class and Borg dyspnea index were also observed. Results of ARIES-2,<sup>[180]</sup> in which 192 patients with PAH were randomized to receive ambrisentan 2.5 mg, 5 mg or placebo, demonstrated that the once-daily dosing of ambrisentan (5 mg) improved the placebo-corrected mean 6MWT distance by 59 m ( $P = 0.001$ ); and 2.5 mg of ambrisentan improved the placebo-corrected mean 6MWT distance by 32 m ( $P = 0.022$ ). For the placebo group, the mean 6MWT distance at week 12 decreased by 10 m from baseline. Improvements in time to clinical worsening compared to placebo were observed for both 5-mg dose group ( $P = 0.008$ ) and the 2.5-mg dose group ( $P = 0.005$ ). Ambrisentan was generally well tolerated. The most frequent side effect was headache, which occurred in 12.7% of patients in the 5-mg group and 7.8% in the 2.5-mg group, compared to 6.2% in the placebo group. Other side effects were leg swelling, nasal congestion, sinusitis and skin flushing. No patients treated with ambrisentan developed serum aminotransferase concentration greater than three times the upper limit of the normal range. Furthermore, ambrisentan has no apparent effect on the activity or dosage of sildenafil<sup>[181]</sup> or warfarin.<sup>[182]</sup>

The top-line results of ambrisentan data may suggest:

- Improvement in exercise capacity
- Significant improvement in time to clinical worsening
- Suggestive survival benefit when compared with predictive survival based on the NIH data
- Effectiveness with once-daily dosing
- Low incidence of hepatic toxicity (however, the drug should be avoided in patients suffering from moderate-to-severe hepatic damage)
- No apparent drug-drug interaction with sildenafil or warfarin
- The drug is contraindicated in pregnancy

#### **h. Type 5 phosphodiesterase inhibitors**

##### *Introduction and rationale*

Modulation of cGMP content in vascular smooth muscle plays a major role in the regulation of vascular tone and structure. The vasodilator effects of NO are indeed dependent on its ability to sustain cGMP content in vascular smooth muscle. The half-life of intracellular cGMP is short because of its rapid degradation by phosphodiesterases enzymes;<sup>[183,184]</sup> the most important is phosphodiesterase type 5 (PDE-5). PDE-5 gene expression and activity are found to be increased in chronic PH,<sup>[185,186]</sup> and PDE-5 is strongly expressed in the lung. Drugs that selectively inhibit cGMP-specific PDE-5 were found to augment the pulmonary vascular response to endogenous or inhaled NO in PH.<sup>[187-190]</sup> A recent *in vitro* study demonstrated that inhibition of PDE-5 produced an antiproliferative effect in human pulmonary artery smooth muscle cells that was mediated by an interaction between the cGMP-protein kinase G (cGMP-PKG)-activated pathways and the cAMP-protein kinase A (cAMP-PKA)-activated pathways.<sup>[191]</sup> Whereas inhibition of cAMP-specific phosphodiesterases (type 3) has played a role in the treatment of asthma (e.g., theophylline) and myocardial dysfunction (e.g., milronone and amrinone), these drugs were believed to have relatively weak effects on the pulmonary circulation. More recently, however, inhibition of other phosphodiesterases (e.g., type 3 and 4) has gained great interest as a potential important pathway in the management of pulmonary hypertension.

Several phosphodiesterase type 5 inhibitors cause potent pulmonary vasodilation in animal models of acute and chronic PH.<sup>[187-190,192,193]</sup> Sildenafil is the only phosphodiesterase type-5 inhibitor that has been approved for the treatment of PH.

#### *Sildenafil*

*Strength of recommendation = A for NYHA class II and III (Class of recommendation = I; level of evidence = A)*

*Strength of recommendation = C for NYHA class IV*

*FDA approval: 2005*

Sildenafil is a highly specific PDE-5 inhibitor. However, this drug has a very interesting case history that has been recently published.<sup>[194]</sup> A number of uncontrolled studies have reported favorable effects of sildenafil in many forms of PAH,<sup>[195-197]</sup> including IPAH, CTEPH<sup>[198]</sup> and PH associated with lung fibrosis.<sup>[199]</sup> In a pilot study,<sup>[197]</sup> 3 months of sildenafil (50 mg orally every 8 h) added to standard treatment was studied in 5 consecutive patients (4 with idiopathic pulmonary arterial hypertension, 1 with Eisenmenger syndrome; WHO functional class II to III). The functional class improved by more than one class in all patients after adding sildenafil to standard treatment. Post-treatment values with sildenafil compared to pre-treatment values showed significant improvement in 6MWT distance (504 ± 27 m vs. 376 ± 30 m); mean PA pressure (52 ± 3 vs. 70 ± 3 mmHg); and pulmonary vascular resistance index (996 ± 92 vs. 1702 ± 151 dyne·s·cm<sup>-5</sup>·m<sup>-2</sup>).<sup>[197]</sup> In an RCT with a cross-over design,<sup>[200]</sup> sildenafil 25-100 mg (weight-adjusted dose) administered three times daily in 22 PAH patients (WHO functional class II and III) improved symptoms after 6 weeks, the exercise capacity as assessed by the Naughton protocol on the treadmill (from 475 ± 168 s of exercise time at the end of placebo phase to 686 ± 224 s at the end of sildenafil phase) and the hemodynamics.<sup>[200]</sup> A pivotal RCT (The Sildenafil Use in PAH, SUPER-1) evaluated the efficacy and safety of

oral sildenafil 20 mg, 40 mg and 80 mg three times daily and placebo, for 12 weeks, in the treatment of 278 WHO functional class II and III PAH patients (≥18 years of age and have either idiopathic or 'associated with connective tissue' disease or with repaired congenital systemic-to-pulmonary shunts).<sup>[201]</sup> The primary efficacy end point was exercise capacity as measured by 6MWT distance at week 12. The mean placebo-corrected treatment effects on 6MWT distance were around 45 m for 20, 40 and 80 mg sildenafil three times daily with no apparent dose response ( $P < 0.001$  for all doses). All sildenafil doses reduced mPAP at week 12 by about 3-5 mmHg and improved NYHA functional class. Sildenafil was associated with side effects such as headache, flushing, epistaxis, dyspepsia and diarrhea. In contrast to results obtained in studies of different therapies, no significant difference was observed in clinical worsening in this study (defined by death, hospitalization, lung transplantation or initiation of prostacyclin or bosentan therapy). This may be attributed to differences in patient populations (39% of subjects in this study were functional class II, who would not be expected to have as many worsening events); and also, the trial duration of only 12 weeks may have been insufficient to allow clinical-worsening events to occur.<sup>[201]</sup> Very recent study tested the effect of sildenafil on ventilatory efficiency and exercise tolerance in PH patients.<sup>[202]</sup> In this study, 28 PAH patients with ( $n = 14$ ) and without ( $n = 14$ ) sildenafil treatment were evaluated by CPT.  $\dot{V}O_{2max}$ , peak  $O_2$  pulse, VE/ $CO_2$  and PETCO<sub>2</sub> improved significantly after adding sildenafil ( $P = 0.012, 0.008, 0.008$  and  $0.0002$  treated vs. controls respectively), whereas control patients worsened.

From another perspective, another study of 13 consecutive PAH patients (referred for consideration of heart-lung transplantation or as a guide to medical therapy) compared the acute hemodynamic effects of a single dose of sildenafil to inhaled nitric oxide (iNO).<sup>[203]</sup> All but one were functional class III or IV. Nine patients had IPAH, 1 had PAH secondary to ASD, 1 had PAH secondary to liver cirrhosis and 2 had PH secondary to left ventricular failure. Hemodynamic readings were measured at baseline and at peak effects of iNO (80 ppm), sildenafil (75 mg) and their combination. The decrease in pulmonary vascular resistance was similar with iNO (-19 ± 5%) and sildenafil (-27 ± 3%), whereas sildenafil plus iNO was more effective than iNO alone (-32 ± 5%). Sildenafil and 'sildenafil plus iNO' increased cardiac index (17 ± 5% and 17 ± 4% respectively), whereas iNO did not (-0.2 ± 2.0). Systemic arterial pressure was similar among groups and did not decrease with treatment.

Sildenafil was compared to bosentan in a randomized double-blinded study<sup>[204]</sup> of 26 patients with PH (WHO class III with IPAH or PAH associated with connective tissue disease). The patients were randomized to receive sildenafil 50 mg twice daily for 4 weeks and then 50 mg three times daily or bosentan 62.5 mg twice daily for 4 weeks and then 125 mg twice daily for 16 weeks. The study measured RV mass changes (using cardiovascular magnetic resonance), 6MWT distance, cardiac function, quality of life (QOL), plasma B-type natriuretic protein (BNP) and Borg dyspnea index. Baseline characteristics did not differ significantly between the treatment groups. Six-MWT distance and QOL score improved more significantly in sildenafil group compared to bosentan group. (Both groups were significantly better than baseline values.) Even though

no significant difference between treatment groups regarding RV mass and BNP occurred, patients on sildenafil experienced a significant reduction from baseline with both RV mass and BNP.<sup>[204]</sup>

More recently, sildenafil has been shown to inhibit altitude-induced hypoxia and pulmonary hypertension. In a randomized double-blind placebo-controlled study, the effects of oral sildenafil on altitude-induced pulmonary hypertension and gas exchange in normal subjects were examined.<sup>[205]</sup> Twelve subjects (sildenafil  $n = 6$ ; placebo  $n = 6$ ) were exposed for 6 days at 4,350 m. Treatment (40 mg  $\times$  3/day) was started 6-8 h after arrival from sea level to high altitude and maintained for 6 days. Systolic pulmonary artery pressure assessed by echocardiography increased at high altitude before treatment (+29% versus sea level,  $P < 0.01$ ). These values were normalized in subjects who received sildenafil (-6% versus sea level, NS) and remained elevated in placebo group (+21% versus sea level,  $P < 0.05$ ). PaO<sub>2</sub> was higher, and alveolar-arterial difference in O<sub>2</sub> was lower in sildenafil than in placebo groups at rest and exercise ( $P < 0.05$ ).<sup>[205]</sup>

In general, the studies report relatively few minor side effects of sildenafil treatment. Headache, nasal congestion and visual disturbances are the most widely reported side effects. Information on the risk of visual toxicity is drawn from materials that include scientific articles suggesting that sildenafil may be associated with the development of non-arteritic anterior ischemic optic neuropathy (NAION).<sup>[206]</sup> To date, the literature contains 14 case reports, including a single report of positive re-challenge (recurrence of NAION when drug therapy was restarted). The spontaneous reporting systems of the National Registry of drug-induced ocular side effects, FDA and the WHO record 86 cases of blindness associated with sildenafil therapy. In 2 cases, the patients' visual acuity did not recover. The author has encountered one case of transient complete visual loss in the left eye in a 14-year-old patient, which was completely reversed after discontinuation of sildenafil treatment (unreported data). Recently, the FDA has generated a warning about visual loss related to sildenafil treatment, which created great concern among both clinicians and patients. However, until further data is available, there is no conclusive evidence that there is a direct causal relationship between sildenafil and visual loss.

### ***i. L-Arginine***

***Strength of recommendation: I (Class of recommendation = IIb; level of evidence = C)***

Nitric oxide (NO) contributes to the maintenance of normal vascular function and structure. NO is generated by three isoforms of NO synthase (NOS), which are present in multiple and diverse cell types. Amino acid L-arginine is the sole substrate for NOS and thus is essential for NO production. Arginine deficiency has been shown to be associated with persistent PH of the newborn (PPHN),<sup>[207]</sup> and acute L-arginine infusion (500 mg/kg over 30 min) in infants with PPHN resulted in a rise in PaO<sub>2</sub> over the 5-hour period following infusion.<sup>[208]</sup> Whether long-term arginine supplementation can lead to long-term improvement and reduce ongoing vascular injury in the lung circulation in patients with PAH is still unknown. However, certain findings support such possibility,

as a chronic administration of L-arginine improved chronic PH and vascular remodeling induced in rats by either chronic hypoxia or monocrotaline injection.<sup>[209]</sup>

However, the improved hemodynamic parameters after L-arginine treatment are, unfortunately, inconsistent, and different studies gave mixed results. Short-term administration of L-arginine (500 mg/kg infused over 30 min) in 10 subjects with PAH led to significant reduction in mPAP - by  $15.8 \pm 3.6\%$  ( $P < 0.005$ ); and PVR - by  $27 \pm 5.8\%$  ( $P < 0.005$ ). This was very similar to effects obtained by prostacyclin titrated to maximally tolerated dose [mPAP decreases of  $13.0 \pm 5.5\%$  ( $P < 0.005$ ) and PVR of  $46.6 \pm 6.2\%$  ( $P < 0.005$ )].<sup>[210]</sup> Another study of 19 patients with PAH used CPET to measure peak VO<sub>2</sub> and the ventilatory response to carbon dioxide production as the end points before and 1 week after treatment with L-arginine (1.5 g/10 kg body weight per day) or placebo. A 1-week supplementation of L-arginine resulted in a slight increase in peak oxygen uptake ( $831 \pm 88$  to  $896 \pm 92$  ml/min,  $P < 0.05$ ) and a significant decrease in the ventilatory response to carbon dioxide production ( $43 \pm 4$  to  $37 \pm 3$ ,  $P < 0.05$ ) without significant systemic hypotension. Hemodynamics and exercise capacity remained unchanged during placebo administration.<sup>[211]</sup> In contrast, a small study<sup>[212]</sup> of acute L-arginine infusion in 4 patients with IPAH demonstrated little favorable effect on pulmonary hemodynamics and significant decreases in systemic resistance in 2 patients. In another short-term study<sup>[213]</sup> of L-arginine infusion (500 mg/kg over 30 min), 5 patients with PAH associated with PSS and 5 normotensive volunteers demonstrated no significant effect on hemodynamics or cGMP level in both groups.

Based on this conflicting data, it is thus not clear at this time whether short-term effects of L-arginine supplementation will translate into long-term benefits. Further clinical studies are needed.

### **III. Combination therapy**

***Class of recommendation = I; level of evidence = B***

With the development of therapeutic agents with different mechanisms of action, combination therapy is becoming an attractive option to cover the multiple pathophysiological mechanisms that are present in PAH. This is similar to the strategies utilized in the treatment of systemic hypertension, some forms of cancer, asthma and other chronic diseases.

***Epoprostenol and bosentan:*** The efficacy and safety of the concurrent initiation of bosentan and epoprostenol were investigated in 33 NYHA class III and IV PAH patients randomized to receive either epoprostenol and placebo or epoprostenol and bosentan (BREATHE-2).<sup>[214]</sup> Improved hemodynamics, exercise capacity and functional class were observed in both groups. There was a trend for greater improvement in all hemodynamic parameters in the 'epoprostenol + bosentan' group, but that did not reach statistical significance.<sup>[214]</sup> Adverse events were more common in the combination group as compared to epoprostenol alone. However, it has been concluded that this study was underpowered to allow definite conclusions.<sup>[215]</sup>

An open-label study has addressed the combination of

nonparenteral prostanoids and bosentan in 20 patients with IPAH.<sup>[216]</sup> All patients had been treated with either aerosolized iloprost ( $n = 9$ ) or with beraprost ( $n = 11$ ) for a mean period of 16 months. Bosentan was used as an add-on medication because of insufficient response to prostanoid treatment. The primary end point was exercise tolerance as measured by 6MWT and CPET. Three months after starting bosentan, there was a significant increase in the 6MWT distance - by  $58 \pm 43$  m. Also, there was a significant improvement in other variables, such as  $VO_{2\max}$ , oxygen pulse, anaerobic threshold and peak systolic blood pressure as measured by CPET.<sup>[86]</sup> Combination therapy was well tolerated by all patients, and there were no episodes of serious adverse events. Similarly, another study of 16 PAH patients also found an increase in the 6MWT distance when bosentan was added to the aerosolized or IV iloprost. In addition, the RV Tei-index also improved with combination therapy.<sup>[217]</sup>

Recent studies adopted the opposite approach by adding prostacyclin treatment to bosentan. In one study,<sup>[218]</sup> the addition of a long-acting prostacyclin analogue (inhaled treprostinil) was evaluated in 12 patients with symptomatic PAH despite bosentan treatment. Patients received either 30  $\mu$ g of inhaled treprostinil four times daily ( $n = 6$ ) or 45  $\mu$ g four times daily ( $n = 6$ ), via an ultrasonic nebulizer. Six-MWT distance, functional class and hemodynamics were assessed at baseline and 12 weeks. Inhaled treprostinil was associated with an increase in 6MWT distance at 12 weeks (67 m, 1 h post-inhalation,  $P = 0.01$ ; and 49 m during the trough period, just before inhalation of treprostinil,  $P = 0.009$ ). Significant decreases were also noted in mPAP (-10%) and in PVR (-26%). Functional class improved from III to II in majority of the patients.

Finally, Iloprost Inhalation Solution Safety and Pilot Efficacy Trial in Combination with Bosentan for Evaluation in Pulmonary Arterial Hypertension (STEP-1) adopted the opposite approach by adding aerosolized iloprost to bosentan. This study was designed as a randomized double-blind study and included 67 PAH patients (55% IPAH, 45% PAH associated with other diseases). The results of this study have not been fully published but were presented at the American College of Chest Physicians Annual Meeting (CHEST) 2005 and will be published soon in the *American Journal of Respiratory and Critical Care Medicine*.<sup>[219]</sup> Consistent with the typical demographics of PAH, the mean age of study participants was 50 years, and 79% were women. At study entry, 94% of patients had WHO functional class III disease, and the baseline 6MWT distance was 335 m. Although this was primarily a safety study, efficacy data were also available for analysis. At week 12, the 6MWT distance had increased to 367 m, which was a significant gain of 30 m over the placebo group ( $P < 0.001$ ). WHO class improved by one functional class in 34% of iloprost-treated patients compared with 6% for placebo ( $P = 0.0023$ ). No clinical deterioration was reported in iloprost-treated patients compared with 15% of the 33 placebo-treated patients ( $P = 0.022$ ). Dyspnea also improved with iloprost, as demonstrated by a reduction in Borg dyspnea index score from baseline ( $P = 0.03$ ). Mean PAP decreased by 8 mmHg compared with placebo ( $P < 0.0001$ ). The most common adverse events in the iloprost group were cough, headache, jaw pain and flushing. Syncope was reported in 1 iloprost-treated patient versus 2 patients in the placebo group. The study investigators concluded that inhaled iloprost

is safe and well tolerated in combination with bosentan. As well, combination therapy should be considered in patients with NYHA functional class III or IV and suboptimal exercise endurance while on bosentan monotherapy.

**Epoprostenol and sildenafil:** The impact of adjunct sildenafil on exercise capacity and hemodynamic parameters in patients with PAH who had deterioration despite ongoing treatment with inhaled iloprost was tested in 73 PAH patients receiving long-term inhaled iloprost treatment.<sup>[220]</sup> Out of those, 14 fulfilled criteria of deterioration unresponsive to conventional treatment. These patients received adjunct oral sildenafil over a period of 9-12 months, leaving the inhalative iloprost regimen unchanged. Before iloprost therapy, the baseline 6MWT distance was  $217 \pm 31$  m (mean  $\pm$  SEM), with an improvement to  $305 \pm 28$  m within the first 3 months of iloprost treatment and a subsequent decline to  $256 \pm 30$  m after  $18 \pm 4$  months. Adjunct therapy with sildenafil reversed the deterioration and increased the 6MWT distance to  $346 \pm 26$  m ( $P = 0.002$ ) at 3 months of combined therapy, with a sustained efficacy up to 12 months ( $349 \pm 32$  m,  $P = 0.002$ ). All hemodynamic variables changed favorably: pulmonary vascular resistance decreased from  $2,494 \pm 256$  before sildenafil to  $1,950 \pm 128$  dynes $\cdot$ s $\cdot$ cm<sup>-5</sup> $\cdot$ m<sup>2</sup> after 3 months of adjunct sildenafil ( $P = 0.036$ ). Two patients died of severe pneumonia during the period of combined therapy, and no further serious adverse events occurred.<sup>[220]</sup>

A multinational multi-centre randomized double-blind placebo-controlled parallel-group efficacy study (PACES-1) of a subject-optimized, tolerance-based dose of sildenafil (20 mg, 40 mg or 80 mg) used in combination with IV prostacyclin to treat PAH is currently underway. The preliminary data suggest that sildenafil/epoprostenol combination therapy significantly increased 6MWT distance by 30 m at 16 weeks ( $P = 0.0009$ ). Other hemodynamic variables that also improved included mPAP (0.00003), mRAP ( $P = 0.0012$ ) and cardiac output ( $P < 0.0001$ ). Time to clinical worsening was significantly delayed in sildenafil group compared to placebo ( $P = 0.0046$ ). Another study looked at the short-term effect of the combination of aerosolized iloprost and sildenafil in 5 patients with 'primary' pulmonary hypertension.<sup>[221]</sup> The combination of 'sildenafil plus iloprost' lowered mean PAP significantly more than iloprost alone ( $13.8 \pm 1.4$  vs.  $9.4 \pm 1.3$  mmHg;  $P = 0.009$ ). No significant changes in heart rate or systemic arterial pressure were observed during any treatment. The treatments were well tolerated, without major adverse effects.<sup>[221]</sup> Finally, 30 patients with severe PAH ( $n = 16$ ), CTEPH ( $n = 13$ ) or PH due to aplasia of the left pulmonary artery ( $n = 1$ ) (all classified as NYHA class III or IV) were evaluated in a randomized controlled open-label trial.<sup>[222]</sup> All patients received inhaled nitric oxide and aerosolized iloprost (inhaled dose, 2.8  $\mu$ g). They were then randomly assigned to receive 12.5 mg of oral sildenafil, 50 mg of sildenafil, 12.5 mg of sildenafil plus inhaled iloprost or 50 mg of sildenafil plus inhaled iloprost. Sildenafil 50 mg plus iloprost was the most effective 'vasodilator regimen' (maximum reduction of pulmonary vascular resistance and increase in cardiac index), followed by 12.5 mg of sildenafil plus iloprost. Iloprost alone and 50 mg of sildenafil were almost equally effective but were less potent than the combination regimens, and the least potent treatments were 12.5 mg of sildenafil and nitric oxide. In patients who received 50 mg of

sildenafil plus iloprost, the maximum change in pulmonary vasodilatory potency was -44.2% (95% CI, -49.5% to -38.8%), compared with -14.1% (95% CI, -19.1% to -9.2%) in response to nitric oxide. With administration of 50 mg of sildenafil plus iloprost, the vasodilatory effect lasted longer than 3 h, and systemic arterial pressure and arterial oxygenation were maintained. No serious adverse events occurred.

**Bosentan and sildenafil:** The combination of bosentan and sildenafil has been tested in clinical trials. In one study that included 9 patients with severe IPAH, the patients were started on bosentan; and sildenafil was added when clinical deterioration occurred, which was after a mean interval of 11 months of bosentan therapy. Three months after the addition of sildenafil, the 6MWT distance had increased by 115 m and was accompanied by a significant improvement in  $VO_{2max}$  as measured by CPET. The improvement in exercise capacity was maintained throughout the observation period, which lasted between 6 and 12 months. Combination therapy with bosentan and sildenafil was tolerated without adverse events.<sup>[223]</sup> More recently, the benefit of adding sildenafil in patients with PAH who failed monotherapy with bosentan was tested.<sup>[224]</sup> Within a 4-year period, 82 patients with either IPAH or PAH associated with PSS were treated with bosentan. Among those, 13 IPAH patients and 12 PSS patients showed signs of clinical worsening such that sildenafil was added to bosentan. The clinical response to combination therapy was mixed: in IPAH patients, the 6MWT distance improved by 47 m; whereas in PSS patients, the 6MWT distance deteriorated by 7 m. During follow-up, only 1 IPAH patient needed additional therapy (intravenous treprostinil); whereas 5 PSS patients required further escalation of treatment by addition of either inhaled or intravenous prostanoids. Death occurred in 1 IPAH patient (from gastrointestinal bleeding unrelated to PAH) and in 4 patients with PSS. The author concluded that addition of sildenafil to bosentan was more effective in patients with IPAH than in patients with PSS.<sup>[224]</sup>

It is important to mention that in contrast to the other combination regimens, co-administration of bosentan and sildenafil may be associated with relevant pharmacokinetic interactions.<sup>[225]</sup> Sildenafil has inhibitory effects on cytochrome P450 3A4 (CYP3A4) activity, which may lead to increased plasma concentrations of bosentan. Bosentan, like other ERAs, may exert hepatotoxic effects; and there is always concern about a higher risk of liver damage with combined administration of bosentan and sildenafil. None of the patients in the studies previously described experienced elevations in hepatic aminotransferases when sildenafil was added to bosentan, but the small number of patients precludes any meaningful safety analysis. On the other hand, induction of CYP3A4 activity by bosentan may accelerate the metabolism of sildenafil, which may decrease the plasma concentrations of sildenafil by as much as 60%.<sup>[225]</sup>

#### IV. Future treatment

New drugs directed towards the classical targets (PDE-5, ET-receptors, NO agonist and prostacyclin analogues with longer half-life) are under clinical trials. A study<sup>[226]</sup> comparing the short-term impact of three different PDE-5 inhibitors on pulmonary and systemic hemodynamics and gas exchange parameters in patients with PAH was recently published. In

this study, 60 consecutive PAH patients (NYHA class II to IV) were assigned to oral intake of 50 mg sildenafil ( $n = 19$ ); 10 mg ( $n = 7$ ) or 20 mg ( $n = 9$ ) vardenafil; or 20 mg ( $n = 9$ ), 40 mg ( $n = 8$ ) or 60 mg ( $n = 8$ ) tadalafil. Hemodynamics and changes in oxygenation were assessed over a 120-min observation period. The outcome showed that all three PDE-5 inhibitors caused significant pulmonary vasorelaxation, with maximum effects being obtained after 40-45 min (vardenafil), 60 min (sildenafil) and 75-90 min (tadalafil). Sildenafil and tadalafil, but not vardenafil, also caused a significant reduction in the pulmonary-to-systemic vascular resistance ratio. Significant improvement in arterial oxygenation (equal to NO inhalation effect) was only noted with sildenafil. Such data shows that in patients with PAH, PDE-5 inhibitors may differ markedly in their kinetics of pulmonary vasorelaxation (most rapid effect by vardenafil), their selectivity for the pulmonary circulation (sildenafil and tadalafil, but not vardenafil) and their impact on arterial oxygenation (improvement with sildenafil only). So, careful evaluation of each new PDE-5 inhibitor, when being considered for PAH treatment, has to be undertaken, despite common classification as PDE-5 inhibitors.

Furthermore, new lines of management targeting different goals of pathophysiological pathways are under extensive research and will be subjected to clinical trial soon. Some of these lines are as follows:

- The recent finding that PSMCs from PAH patients grow faster than control subjects once stimulated by serotonin<sup>[12]</sup> brings new interest to serotonin pathway and its potential therapeutic role (see above under pathophysiology). Such stimulatory effect of serotonin on PSMCs was found to be due to increased expression of the serotonin transporter (5-HTT), which mediates internalization of indoleamine. 5-HTT was also found to increase RV pressure, even before the development of RV hypertrophy or PA remodeling. 5-HTT inhibitors were found to inhibit the growth acceleration of PSMCs and may prove to be therapeutically efficacious in the management of PAH.
- Thromboxane  $A_2$ , which is a powerful vasoconstrictor, platelet aggregant and smooth muscle mitogen, was found to contribute to the progression of vascular narrowing in IPAH. In one study,<sup>[227]</sup> the effect of a potent orally active thromboxane synthetase inhibitor and thromboxane receptor antagonist, terbogrel, given for 12 weeks was evaluated in patients with PAH (NYHA functional classification II and III). The study had a multi-center randomized placebo-controlled design. The primary end point was a change in the 6MWT distance. Unfortunately, this study was halted after only 71 patients had been randomized - because of the unforeseen side effect of leg pain, which occurred almost exclusively in patients with terbogrel treatment. Only 52 patients completed the 12-week study, and only 22 patients (31%) were fully compliant with the study medication. The leg pain confounded the primary end point of walking distance. However, terbogrel was effective from a pharmacologic standpoint, reducing thromboxane metabolites by as much as 98% ( $P < 0.0001$ ), with a modest but statistically insignificant (39%) rise in prostacyclin metabolites. Despite the inconclusive results of this study because of side effects, targeting thromboxane pathway may prove to be useful in future in treating PAH patients.

- The role of soluble guanylate cyclase (sGC) stimulator and activator as a treatment option for PAH has recently gained interest. In one study,<sup>[228]</sup> activation of sGC has been shown to reverse the hemodynamic and structural changes associated with monocrotaline-induced and chronic hypoxia-induced experimental PAH. The mechanism of action is complicated but was partially dependent on endogenous nitric oxide generated by nitric oxide synthase enzyme.
- A cancer theory has been attributed to PAH, indicating that the disease has potential neoplastic features, including antiapoptosis, proliferation, but not metastasis. Inflammation has also found to play a major pathological role in the disease process. A selective down-regulation of the potassium channels has been described in human and animal PAH that results in increase in intracellular free  $\text{Ca}^{2+}$  and  $\text{K}^{+}$  concentrations, which play an important role in PASM contraction, proliferation and resistance to apoptosis.<sup>[15]</sup> This down-regulation mechanism has been attributed to inflammatory process and to the activation of nuclear factor of activated T cells (NFATc2). Furthermore, NFATc2 levels were increased in circulating leukocytes in PAH versus healthy volunteers, and CD3-positive lymphocytes with activated NFATc2 were seen in the arterial wall in PAH but not normal lungs. Inhibition of NFATc2 by VIVIT or cyclosporine<sup>[15]</sup> has been shown to restore the potassium channel (Kv1.5) expression and current, decrease intracellular free  $\text{Ca}^{2+}$  and  $\text{K}^{+}$ , leading to decreased proliferation and increased apoptosis *in vitro*. *In vivo*, cyclosporine has been shown to decrease established monocrotaline-induced PAH in rats. The generalized activation of NFAT in human and experimental PAH might regulate the ionic, mitochondrial and inflammatory remodeling and be a therapeutic target and biomarker in the future.

## V. Interventional/surgical procedures

### a. Atrial septostomy

*Grade of recommendation = IIa; level of evidence = B*

Atrial septostomy (AS) is done by three different methods: blade balloon atrial septostomy (BBAS); balloon atrial septostomy (BAS); and more recently, cutting balloon atrial septostomy (CBAS). However, additional techniques are being explored to minimize risks and to reduce the incidence of spontaneous closure. Many studies<sup>[229,230]</sup> have suggested that an inter-atrial defect might be beneficial in the management of severe PH. The presence of an atrial septal defect would allow right-to-left shunting and subsequently 'decompress' the RV, leading to improvement in right ventricular function and so the left heart filling leading to increased left ventricular 'systemic' output that, in spite of the fall in systemic arterial oxygen saturation, will subsequently lead to an increase in systemic oxygen delivery (oxygen delivery = cardiac output  $\times$  oxygen-carrying capacity). Furthermore, the impact of a decline in arterial oxygenation and its effect on oxygen-carrying capacity of blood would be further balanced by compensatory polycythemia.

The efficacy of AS in the treatment of PAH patients has been reported in small series.<sup>[231,232]</sup> In addition to symptomatic and hemodynamic relief, an increase in survival as compared with historical control groups has been reported.<sup>[79]</sup> At present, only patients with 'severe PAH' who fail medical treatment should

be considered for the procedure. The definitions of 'severe PAH' vary and may include the following: NYHA class III or IV, a history of recurrent syncope or 'refractory' right-heart failure.

Improvements in cardiac index, which range from 15 to 58% in different studies,<sup>[79,233,234]</sup> and arterial deoxygenation take place immediately following the procedure; while mPAP shows little changes in the immediate postoperative period.

Longer-term hemodynamic parameters have been reported in several studies. In one study,<sup>[234]</sup> 3 NYHA class IV patients underwent repeat catheterization at 18 months, 21 months and 27 months after BAS. In all 3 patients, a sustained decrement in mean RAP and an increase in cardiac index were found. In another study,<sup>[79]</sup> 4 of 15 patients who survived initial septostomy developed closure of their septal defect and subsequently underwent repeat AS, with 2 patients requiring more than one repeat procedure. A third study that addressed the long-term changes in RAP<sup>[235]</sup> after AS showed that this hemodynamic parameter had remained unchanged immediately after septostomy but fell significantly at follow-up catheterization 7-27 months after the procedure. In another study looking at the outcome of 12 PAH patients waiting lung transplantation,<sup>[236]</sup> 9 patients had primary and 3 patients had secondary pulmonary hypertension. Five patients deteriorated despite long-term intravenous prostacyclin infusions. An atrial septal defect was successfully created in each patient and dilated until systemic oxygen saturation decreased by 5-10%. The mRAP decreased from 23 to 18 mmHg, and the mean systemic oxygen saturation decreased from 93% to 85%. The mean cardiac index increased from 1.7 to 2.1 L/min/m<sup>2</sup>, and the mean systemic oxygen transport increased from 268 to 317 ml/min/m<sup>2</sup>. Complications occurred in 3 patients and included transient hypotension during trans-esophageal echocardiography, a femoral pseudoaneurysm and a femoral arteriovenous fistula. After septostomy, 6 patients had clinical improvement (resolution of ascites, edema and no further episodes of syncope); 5 of these 6 patients underwent lung transplantation a mean of 6.1 months after septostomy. Six patients did not have clinical improvement after septostomy. Finally, a recent study<sup>[237]</sup> evaluated 46 atrial septostomies that were performed on 43 patients (29 had IPAH, 10 had PH associated with repaired congenital heart defects and 4 had other secondary causes of PH). Mean baseline PVR was  $35 \pm 17$  Wood units and mPAP was  $74 \pm 19$  mmHg. Patients surviving  $\geq 30$  days had immediate improvement in cardiac index ( $P < 0.0001$ ), mRAP ( $P < 0.05$ ) and oxygen delivery ( $P < 0.01$ ), with a decrease in systemic oxygen saturation (from 93 to 86%,  $P < 0.001$ ). PAP was unchanged ( $P = 0.3$ ). NYHA class and symptoms of syncope improved significantly after the procedure ( $P < 0.01$ ). Event-free survival rates at 1, 2 and 3 years were 84, 77 and 69% respectively. Using the NIH Registry model, predicted survival probability significantly improved ( $P < 0.001$ ) after AS. Ten patients (22%) died within 30 days of catheterization. Increased mortality was associated with preceding decompensations in the intensive care unit ( $P < 0.001$ ) and a higher RAP at the baseline (21.4 vs. 9.8 mmHg,  $P < 0.001$ ).

Procedural mortality ranges from 5 to 50%. Appropriate selection of patients for AS procedure is clearly critical. However, despite the lack of clear criteria for patients' selection,

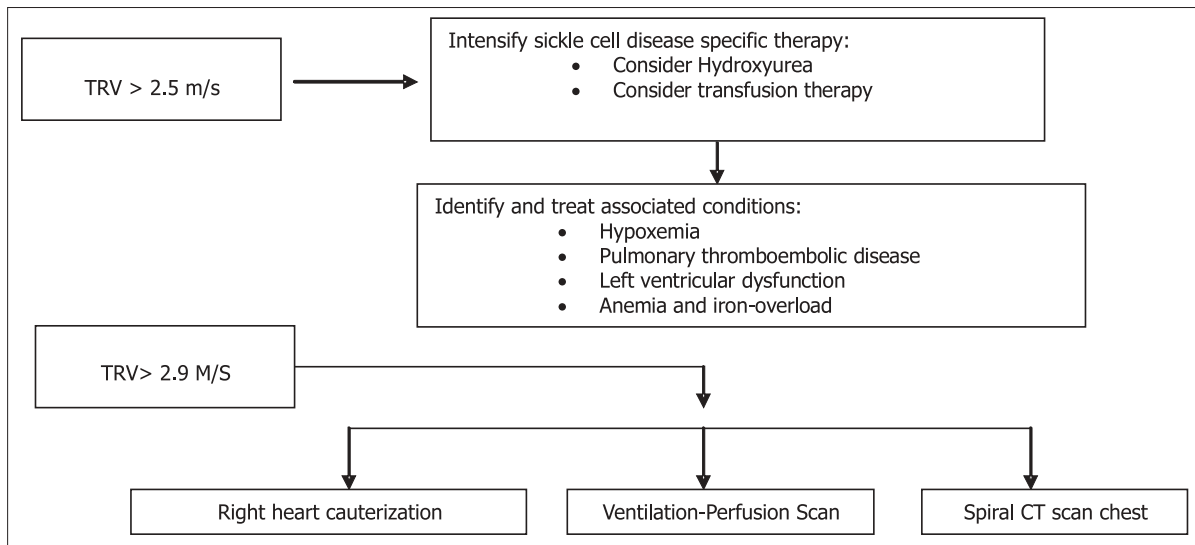


Figure 2: Approach of SCD patients with PAH

it seems that patients with markedly elevated PVR, arterial oxygen saturations <80% at rest and severe right-heart failure (manifested by low cardiac output and high RAP) appear more likely to have a higher morbidity and mortality following the procedure. In this particular group, massive right-to-left shunting may result in inadequate pulmonary flow and severe hypoxemia. RAP >20 mmHg was the most significant variable associated with death.<sup>[238]</sup>

AS should only be performed in specialized centers with an extensive experience in the medical and surgical treatment of PAH.

### **b. Heart-lung and lung transplantation**

*Grade of recommendation = I; level of evidence = C*

Because formal RCTs are considered unethical in the absence of alternative treatment options, lung transplantation (LT) and heart-lung transplantation (HLT) in PAH have been assessed only in uncontrolled studies.<sup>[232]</sup> LT has been a mainstay of treatment for PH since 1980s, and it is the only available 'curative' method of treatment.

Lung (and heart-lung) transplantation are indicated in PAH patients with advanced NYHA class III and IV symptoms that are refractory to available medical treatments. The 3- and 5-year survival after lung (and heart-lung) transplantation is approximately 55 and 45% respectively.<sup>[239]</sup>

The timing of transplantation depends on many factors, which include primary diagnosis, stage of disease (NYHA functional class and exercise endurance), response to conventional therapies, the availability of target treatments. Prior to the availability of target therapy, the diagnosis of PAH mandated immediate listing and transplantation. Currently and with the availability of effective treatment, LT in any form should not be considered until failure of medical therapy is documented. Because the death on the waiting list has been found to be a particular problem in patients with poor NYHA functional status, those patients who have NYHA class III or IV symptoms on presentation should be referred for LT evaluation while their

response to therapy is being evaluated in order to avoid delays in evaluation and listing and minimize their waiting time.

Both single and bilateral lung transplantation have been performed for IPAH. Each procedure has its own advantages and disadvantages. Single-lung transplant (SLT) is generally an easier procedure to perform than bilateral lung transplant (BLT) or HLT. However, SLT has the potential for V/Q mismatch and a higher likelihood of reperfusion injury. BLT, despite being a more difficult procedure, results in better hemodynamics, lesser V/Q mismatch, as well as fewer complications in the perioperative period. BLT may also offer a better long-term post-transplant survival than SLT. A survival advantage of BLT compared with SLT in IPAH has been reported,<sup>[240,241]</sup> but in one study,<sup>[241]</sup> this was only true in patients with high preoperative PAP (>40 mmHg). The optimal transplant procedure for patients with PAH will depend on individual patient characteristics and on organs availability. Decisions about which procedure is the most appropriate for each individual patient should be left to the transplant center's local experience. Finally, in patients with Eisenmenger syndrome and in those with end-stage heart failure, the option of heart-lung transplantation should be considered. For some complex defects and in cases of ventricular septal defects, a survival advantage of heart-lung transplantation has been shown.

Studies have shown that postoperative survivors have a mean PAP of 20-25 mmHg. Other immediate hemodynamic improvements in cardiac index and PVR have also been documented. More than 80% of survivors of LT or HLT reported no limitation in activity at 1 year, 3 years and 5 years following transplantation, and 40-50% were working either full-time or part-time.<sup>[242]</sup>

As in the other forms of LT, bronchiolitis obliterans (chronic rejection) is the major limitation to long-term survival in LT in PAH patients. While any injury to the lung allograft (infection, rejection, ischemia, reperfusion injury) is likely to contribute to the development of bronchiolitis obliterans, the relationship of bronchiolitis obliterans to a primary diagnosis of PH and the type of transplant procedure performed

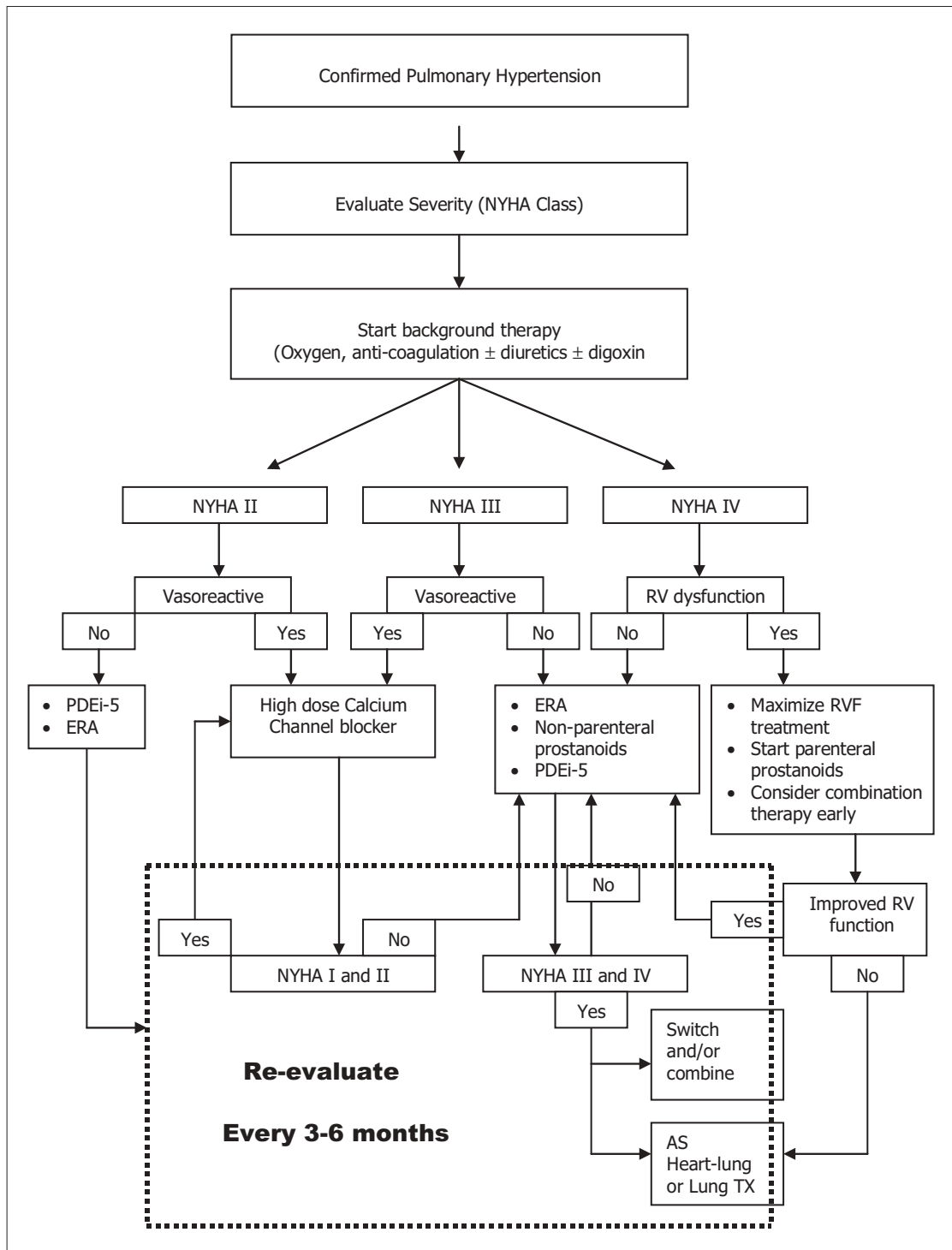


Figure 3: Evidence-based treatment algorithm

remains unknown.<sup>[243,244]</sup>

### Treatment Algorithm

Evidence-based treatment algorithm is shown in Figure 3.

The treatment algorithm is mainly applicable to patients in NYHA functional class III or IV because they represent the

predominant population included in RCTs. For NYHA class II patients, scarce data are available and the most appropriate strategy has still to be determined and possibly validated by specific studies.

#### I. NYHA class II patients

All NYHA class II patients should be treated with general measures and initiation of background therapy that includes

oral anticoagulant drugs (if no contraindications exist), diuretics in case of fluid retention, supplemental oxygen in case of hypoxemia and digoxin in case of refractory right-sided heart failure and/or supraventricular arrhythmias.

- If NYHA class II patients are *vasoreactive*, treatment with optimally tolerated dose of calcium-channel blockers (CCBs) is a reasonable option and should be tried. Maintenance of response (which is defined as NYHA functional class I or II with near-normal hemodynamics) should be confirmed after 3 to 6 months of treatment; as well as long term, as some patients may convert from vasoreactive to nonvasoreactive over time. However, it should be re-emphasized that CCBs are contraindicated in patients with right-sided heart failure, even if they are vasoreactive (see text above).
- NYHA class II patients who are *nonvasoreactive* should continue with the background therapy and should be kept under close clinical follow-up. In this group of patients, CCBs are contraindicated. Currently, the only target therapies approved for functional class II patients are sildenafil and subcutaneous and IV treprostinil. Clinical trials with sitaxsentan and ambrisentan have included functional class II patients in their patient population. Furthermore, bosentan may also be approved for class II patients, based on a recently completed study. Due to the ease of administration and relative efficacy, sildenafil is our first recommendation for most functional class II patients. Enrollment into clinical trials is also encouraged.
- It needs to be clear that cost-effectiveness of target therapy for NYHA class II patients has not been fully established and so the recommendation towards starting target therapy in *nonvasoreactive* group of patients should be left to the agreement between the patient and the treating physician and only after careful evaluation and consideration of the 'risk versus the benefit' issues.

## II. NYHA class III patients

All NYHA class III patients should be treated with background therapy (see above).

- NYHA class III patients who are *vasoreactive* should be treated with optimally tolerated doses of CCBs; maintenance of the response (defined as NYHA functional class I or II with near-normal hemodynamics) should be confirmed after 3-6 months of treatment.
- NYHA class III patients who are *nonvasoreactive* (or *vasoreactive* patients who remain in NYHA functional class III despite treatment with background therapy and CCBs) should be considered candidates for treatment with target therapy. We recommend the following approach:
  - i. Start sildenafil 25 mg b.i.d. and increase the dose, if tolerated, to 80 mg t.i.d.; or
  - ii. start bosentan 62.5 mg orally b.i.d. for the first 4 weeks and then up-titrate to the target dose of 125 mg b.i.d. (do serial liver function tests for liver toxicity and optimize contraception in young females - see text above) [sitaxsentan and ambrisentan are not yet available in the Kingdom of Saudi Arabia but can also be considered here once available]; or
  - iii. start inhaled iloprost 1 ampoule (2.5-5 µg) Q4 hourly (the dose might be increased up to Q2H, see text above).

The choice of the drug is dependent on a variety of factors, including the cost, availability status, route of administration, side effect profile, patient's preferences and physician's experience.

Response to treatment should be evaluated in 3 months' time:

- a. If the patient shows favorable response (defined as NYHA functional class I or II with near-normal hemodynamics), then treatment should continue with monotherapy by using one of the above-mentioned agents and be monitored periodically in 3-6 months' period.
- b. If the patient failed to show a favorable response, consider changing the treatment to alternative group of therapy or consider combination therapy. The following combinations have been tested in RCTs (see text above under combination therapy):
  - Sildenafil plus inhaled iloprost
  - Inhaled iloprost plus bosentan
  - Sildenafil plus bosentan
  - IV epoprostenol plus sildenafil
 If the patient shows favorable response (defined as NYHA functional class I or II with near-normal hemodynamics), then treatment should continue with the combination therapy and be monitored periodically in 3-6 months' period.
- c. If the patient failed to show a favorable response on combination therapy, one or all of the following should be considered:
  - Start IV epoprostenol infusion. A starting dose of 2 ng/kg/min is recommended. The dose should be increased by 2 ng/kg/min Q 15 min until the optimal dose is achieved or limiting side effects prevent further dose increase. Most patients will tolerate an average dose of 20-40 ng/kg/min. However, optimal dose can vary significantly from one patient to another; in particular, children require a much higher dose of epoprostenol for optimal response (i.e., 80-200 ng/kg/min).
  - Consider atrial septostomy.
  - Refer the patient for lung transplantation program.

## III. NYHA class IV patients

All NYHA class IV patients should be treated with background therapy (see above). NYHA class IV patients do not need vasoactive testing, as the management of these patients is guided in general by right ventricular status and not vasoreactivity.

- NYHA class IV patients with compensated right ventricular function should be treated exactly as NYHA class III *nonvasoreactive* patients.
- NYHA class IV patients with decompensated RV should be treated by continuous IV epoprostenol infusion as first-line therapy.
- Despite lack of good evidence and despite the high cost, combination therapy with the drugs mentioned above should probably be considered early in the course of management.
- Atrial septostomy and/or lung transplantation are indicated for refractory patients and especially those with recurrent syncope and/or right-sided heart failure. These procedures should be performed only in experienced centers (see above).

## Specific Conditions

### I. Pulmonary arterial hypertension associated with systemic-to-pulmonary shunt and congenital heart disease (Eisenmenger syndrome)

**Incidence:** Eisenmenger syndrome (ES) is defined as a congenital heart defect that initially causes large left-to-right shunt that induces severe pulmonary vascular disease and PAH, with resultant reversal of the direction of shunting.<sup>[245]</sup> ES can be caused by simple or complex congenital heart defects (CHDs).<sup>[123]</sup> Among simple defects, ventricular septal defects (VSDs) appear to be the most frequent, followed by atrial septal defects (ASDs) and patent ductus arteriosus.<sup>[123]</sup> The estimated prevalence of PAH in patients who have never received the indicated surgeries is 30% versus 15% in patients who have CHDs and have received such surgeries.<sup>[246]</sup> It has been assumed that 10% of patients with VSDs of any size that are older than 2 years can develop ES as compared to 4-13% of subjects with ASDs.<sup>[247,248]</sup> In patients with ASDs, those with sinus venosus defects have a higher incidence of PAH (26%) as compared to ostium secundum defects (9%) and a higher incidence of increased PVR of 16% versus 4%, respectively.<sup>[249]</sup>

The development of PAH with pulmonary vascular disease appears to be related to the size of the defect. With small-to-moderate-sized VSD, only 3% of patients develop PH.<sup>[246,250]</sup> In contrast, with larger defects (>1.5 cm in diameter), 50% will be affected.

**Pathogenesis:** At the earlier phases, the exposure of the pulmonary vasculature to persistent increased blood flow may result in pulmonary vascular obstructive disease and rise in PVR, leading to gradual elevation in pulmonary pressure. As the PVR approaches or exceeds systemic resistance, the shunt is reversed. Pathophysiologically, mediators similar to those in IPAH have been implicated to play a role in the pathogenesis of ES, e.g., endothelin. Furthermore, it has been shown in one study that 6% of these patients carry a mutation in the BMPR2.<sup>[251]</sup>

**Clinical picture:** Most patients will have impaired exercise tolerance and exertion-induced dyspnea; these symptoms may be well compensated for years. However, even in less symptomatic patients, ventilatory response to exercise - expressed as ventilation per unit of carbon dioxide production ( $VE/VCO_2$  slope) - is abnormal across the spectrum of CHD.<sup>[252]</sup> Cyanosis is a powerful stimulus for such exaggerated ventilatory patterns irrespective of the presence of PAH.<sup>[252]</sup> On the other hand, hemoptysis is an alarming sign that may occur as a result of rupture of dilated bronchial arteries. Because of hypoxia and abnormal hemostasis, there is a risk for both bleeding and thrombosis. Cerebrovascular accidents may occur as a result of paradoxical embolization, venous thrombosis of cerebral vessels or intracranial bleeding. In addition, patients with this condition are at risk for brain abscess. In one study,<sup>[253]</sup> 162 patients with cyanotic CHD were retrospectively evaluated for any well-documented cerebrovascular events. Twenty-two patients (13.6%) had 29 cerebrovascular events. There was no significant difference between those with and without a cerebrovascular event in terms of age, smoking history, degree of erythrocytosis, ejection fraction or use of aspirin or warfarin. Patients with ES may have syncope owing to

inadequate cardiac output or arrhythmia. Symptoms of heart failure, which are uncommon until the disease is far advanced, carry a poor prognosis. Patients who had a cerebrovascular event had a significantly increased tendency to develop hypertension and atrial fibrillation. Cerebral vascular events occur far more frequently in patients who have had serial phlebotomies ( $P < 0.05$ ) as opposed to patients who remain polycythemic and in iron-replete status without phlebotomies (except in the rare instance of significant hyperviscosity signs and symptoms). Patients with ES have higher incidence of intrapulmonary thrombosis (in up to a third of the patients).<sup>[254-256]</sup> In a recent study, 20% of patients with ES were found to have intrapulmonary thrombosis.<sup>[257]</sup>

Survival of patients with ES is far better than that of patients with IPAH with comparable functional class. In a series of 100 patients listed for transplantation, survival rates of patients that did not receive transplants were 97% at 1 year, 89% at 2 years and 77% at 3 years for patients with ES; and 77, 69 and 35% respectively for patients with IPAH.<sup>[258]</sup> In a single-centre study,<sup>[259]</sup> 171 Eisenmenger patients were followed up for median 67 months. During this period, 20 patients died. When compared with healthy individuals, median survival was reduced by approximately 20 years in Eisenmenger patients and was worst in those with complex lesions. Predictors of mortality included NYHA functional class, signs of heart failure, history of clinical arrhythmia and low serum albumin and potassium levels. The acute responsiveness to inhaled NO was also found to predict survival in adult patients with ES.<sup>[260]</sup> Overall, the estimated 5-year survival for ES patients is 80%, and the 25-year survival is 40%.

**Treatment:** The recommendations given for the general treatment of ES patients are mainly based on experts' opinion and not on specific RCTs.<sup>[117,261]</sup>

Phlebotomy with isovolumic replacement<sup>[117]</sup> should be performed *only* in patients with moderate or severe symptoms of hyperviscosity (headache and poor concentration) that usually are present when hematocrit is >65%; however, phlebotomy should not be done in asymptomatic patients. Generally speaking, phlebotomies should be performed no more than 2-3 times per year to avoid depletion of the iron stores and the production of iron-deplete red cells that, in turn, increase blood viscosity. Diuretics can be used cautiously in case of signs of right heart failure. Furthermore, iron deficiency anemia should be aggressively treated, because it limits exercise tolerance and increases the risk of stroke.

Maintenance of fluid balance is equally important, and dehydration should be avoided. This is very important, especially in our geographic area secondary to high temperature and dry weather. Furthermore, during fasting season, Ramadan, this might be of greater importance.

The use of supplemental oxygen therapy is controversial<sup>[121]</sup> and should be resorted to only in certain cases, in which it produces a consistent increase in arterial oxygen saturation and/ or improved clinical wellbeing. Anticoagulation is controversial in this patient population. In the absence of contraindications, some centers elect to anticoagulate their patients with ES similar to other subjects with PAH. Other authors suggest avoiding this

treatment, which can exacerbate the bleeding risk.<sup>[262]</sup>

Unfortunately, few RCTs evaluating the effects of the new medical regimens in PAH have included patients with ES.<sup>[152,155,263]</sup> Although the natural history of IPAH and PAH associated with congenital heart disease is very different, the similarity in their histopathology suggests that a common approach to treatment may be appropriate.

The use of intravenous epoprostenol has been shown to exert favorable effects on hemodynamics and exercise capacity in this group of patients. In one study,<sup>[144]</sup> 20 patients with PAH associated with CHD (9 atrial septal defect, 7 ventricular septal defect, 4 transposition of the great vessels, 3 patient ductus arteriosus, 3 partial anomalous pulmonary venous drainage and 1 aorto-pulmonary window), who had negative acute response and failed conventional treatment, were treated with chronic PGI<sub>2</sub>. While on treatment, mPAP decreased by 21%; cardiac index and PVR also improved significantly ( $P < 0.01$ ,  $n = 16$ ) and ( $P < 0.01$ ,  $n = 16$ ) respectively]. NYHA functional class improved by at least one class in 19 patients, and exercise capacity increased from  $408 \pm 149$  to  $460 \pm 99$  m ( $P = 0.13$ ). The effects of subcutaneous treprostinil in Eisenmenger patients were not different from those in IPAH patients.<sup>[264]</sup>

The role of bosentan in patients with CHD was evaluated in a pilot open-label study.<sup>[168]</sup> Ten patients were evaluated. Resting oxygen saturations ( $83 \pm 5$  vs.  $80 \pm 5\%$ ;  $P = 0.011$ ) and 6MWT distance ( $348 \pm 112$  vs.  $249 \pm 117$  m;  $P = 0.004$ ) improved relative to baseline. Changes in echocardiographic parameters suggested improved pulmonary hemodynamics with bosentan treatment.

More recently, the effect of bosentan was specifically tested on systemic pulse oximeter (primary safety end point) and PVR (primary efficacy end point) in a multi-center 16-week double-blind randomized and placebo-controlled study in 54 patients with functional class III Eisenmenger syndrome (BREATH-5).<sup>[169]</sup> Secondary end points included exercise capacity assessed by 6MWT, additional hemodynamic parameters, functional capacity and safety. Compared with placebo, bosentan reduced PVR index ( $P = 0.0383$ ) and mean PAP ( $P = 0.0363$ ) and improved exercise capacity by a mean of 53 m ( $P = 0.0079$ ). Bosentan did not worsen oxygen saturation.

Lung transplantation with repair of the cardiac defect or combined heart-lung transplantation is an option for patients with Eisenmenger syndrome that have markers of a poor prognosis, such as syncope, refractory right-sided heart failure, NYHA functional class III or IV or severe hypoxemia. Because of the 'reasonable' prognosis for patients with Eisenmenger syndrome and the limited success of transplantation, careful selection of patients for transplantation is imperative.

## II. Portopulmonary hypertension

Incidence: PAH is a well-recognized complication of chronic liver disease.<sup>[265-267]</sup> Portal hypertension, rather than the hepatic disorder itself, seems to be the main determining risk factor for developing PH, leading to the concept of portopulmonary hypertension (PPHTN).<sup>[266]</sup> The current evidence suggests that simultaneous existence of both portal hypertension and PAH is noncoincidental.<sup>[266,268]</sup> Indeed, the incidence of PAH in patients

with portal hypertension is much higher than the estimated incidence of IPAH in the general population. Many studies since the early 1980s confirmed this higher incidence.<sup>[268-270]</sup> Recently, studies have estimated that 2-5% of patients with portal hypertension have PPHTN.<sup>[271]</sup> In fact, studies in patients that were being evaluated for liver transplantation suggest even a higher prevalence - between 3 and 12%.<sup>[270,272-275]</sup> However, it should be noted that some of these studies reporting a higher prevalence rate may have overestimated PPHTN due to less stringent diagnostic criteria. A more comprehensive assessment suggested a prevalence rate of 6%.<sup>[275]</sup>

The presence of chronic parenchymal liver disease and its severity is not associated with the risk of PAH since this complication may occur in patients with noncirrhotic portal hypertension.<sup>[276]</sup> Similarly, the degree of portal hypertension estimated by the hepatic venous pressure gradient and systemic hemodynamic changes are not associated with the development of PAH.<sup>[265]</sup> While the duration of portal hypertension could increase the risk of developing PAH,<sup>[268]</sup> this as yet remains unconfirmed.<sup>[275]</sup>

Definition: PPHTN can be defined as a PAH associated with portal hypertension, with or without hepatic disease.<sup>[277]</sup> Diagnosis of PPHTN is based on pulmonary hemodynamic criteria obtained via RHC.<sup>[80]</sup> A moderate increase in mean PAP (25-35 mmHg) is seen in up to 20% of patients with cirrhosis and portal hypertension.<sup>[21]</sup> This increase in pulmonary artery pressure is most commonly caused by increases in cardiac output (despite reduced PVR) and/or in blood volume (increased mean PAWP),<sup>[21]</sup> without pulmonary vascular remodeling. Less commonly, moderate-to-severe PAH with extensive pulmonary vascular remodeling, i.e., increased PVR, develops.<sup>[272,278,279]</sup>

In order to distinguish between these two forms of PAH, criteria have evolved for the diagnosis of PPHTN [Table 10].<sup>[271,273,280,281]</sup> Unlike hepatopulmonary syndrome, arterial deoxygenation is not a major functional feature of PPHTN. The presence of portal hypertension, however, is an essential feature and may be inferred by a combination of clinical (splenomegaly, ascites), endoscopic (varices), radiological (portal vein anomalies, ascites, splenomegaly and varices) criteria; or may be confirmed by hemodynamic studies.

Staging of severity: A classification of severity of PPHTN is proposed based on mean pulmonary artery pressure [Table 11]. Such severity staging correlates with the increased mortality following liver transplantation in moderate-to-severe PPHTN.

### Table 10: Diagnostic criteria for portopulmonary hypertension

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Liver disease (causing clinical portal hypertension)  
 Mean pulmonary artery pressure >25 mmHg  
 Mean PAWP <15 mmHg  
 PVR >240 dyn.s.cm<sup>-5</sup>

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### Table 11: Staging of severity of portopulmonary hypertension

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Mild (early): mean pulmonary artery pressure >25 – <35 mmHg  
 Moderate: mean pulmonary artery pressure ≥35 – <45 mmHg  
 Severe: mean pulmonary artery pressure ≥45 mmHg

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**Pathogenesis:** The exact mechanism whereby portal hypertension facilitates the development of PAH remains unknown.<sup>[266]</sup> The presence of porto-systemic shunt might allow vasoconstrictive and vasoproliferative substances, normally cleared by the liver, to reach the pulmonary circulation. Serotonin produced by the enterochromaffin cells of the gut may be one of these substances. Histopathological findings of PPHTN are indistinguishable from those commonly observed in IPAH.<sup>[279]</sup> A decrease in prostacyclin expression in the pulmonary arteries of PPHTN patients has been noted.<sup>[282]</sup> Portal hypertension induces systemic inflammatory changes and increased vascular wall shear stress, which may trigger a cascade of intracellular signals. Activation or suppression of various genes in the endothelial and/or smooth muscle cells may follow, and this could lead to pulmonary vascular remodeling and/ or vasculogenesis in genetically susceptible patients.<sup>[6,283]</sup> Abnormal plasma levels of vasoconstrictors (i.e., noradrenalin, rennin-angiotensin-aldosterone and arginine vasopressin) and vasodilators (i.e., NO, glucagon, vasoactive peptide and substance P) have been measured in the setting of portal hypertension.<sup>[284-286]</sup> Plasma levels of endothelin (ET-1), a potent pulmonary vasoconstrictor and smooth muscle mitogen, have been found increased in patients who have PAH and in patients with portal hypertension, suggesting a potential link between the two syndromes. A recent study has shown ET-1 levels to be higher in patients with PPHTN than in patients with cirrhosis and portal hypertension alone.<sup>[287]</sup>

**Clinical picture and investigations:** The clinical picture of patients with PPHTN may be indistinguishable from that of IPAH or may include a combination of symptoms and signs of the underlying liver disease.<sup>[266]</sup>

**Echocardiographic screening for detection of PAH in patients with liver diseases** is appropriate in symptomatic patients and/ or in candidates for liver transplantation. Left-sided valvular abnormalities or left ventricular dysfunction makes PPHTN much less likely. Since cirrhosis and portal hypertension are associated with several hemodynamic states that can increase right-sided cardiac pressures, a diagnosis of PPHTN cannot be made by TTE. An RHC should be performed in all cases with increased systolic PAP in order to clarify the underlying hemodynamic changes and define prognostic and therapeutic implications.

Hemodynamically, compared with patients with IPAH, patients with PPHTN have a significantly higher cardiac output and significantly lower systemic vascular resistance and PVR.<sup>[288]</sup> Because of these unique pathophysiological features compared to those of other forms of PAH, the diagnosis of portal hypertension with RHC requires the determination of a gradient between free and occluded (wedge) hepatic vein pressure or hepatic venous pressure gradient, of more than 10 mmHg (normal is <5 mmHg).<sup>[281]</sup>

During vasoreactive testing, it is possible that patients with PPHTN could be less reactive to NO because liver cirrhosis is a condition of persistent endogenous NO overproduction.<sup>[289]</sup> Indeed, significant acute pulmonary vasodilatation has been shown in PPHTN when using higher concentrations of NO (40 ppm).<sup>[290,291]</sup> Accordingly, changes in selected hemodynamic parameters, such as PVR, should take into account the vasodilating agent that has been employed. Most investigators agree that acute decreases in both mPAP and PVR (>20% from baseline), with no change or increase in cardiac output, can be considered a significant vasodilatory response.<sup>[292,293]</sup> As in other forms of PAH, the goal of such vasodilator testing is to determine staging severity and therapeutic expectations. The acute vasodilatory effect of IV epoprostenol in PPHTN seems to be greater than that of NO. A significant decrease in pulmonary arterial pressure (>20%) in almost half of a small subset of patients with severe PPHTN during acute infusion of IV epoprostenol was reported.<sup>[294,295]</sup> In patients with PPHTN tested with both agents, the proportion of hemodynamic responders was greater when using IV epoprostenol than with inhaled NO.

Unlike IPAH, most patients with advanced liver disease experience a hyperdynamic circulatory state, namely, increased cardiac output and decreased systemic vascular resistance. In addition, some patients may have increased pulmonary venous volume due to increased systemic volume or left ventricular abnormalities. It is clinically useful, therefore, to characterize the pulmonary hemodynamics that complicate liver disease into three subsets (hyperdynamic circulatory state, volume overload or PPHTN) on the basis of measured hemodynamic outcomes, such as mPAP, cardiac output and mPAWP, and calculated PVR, via RHC in the stable resting state [Table 12]. Prognostic implications for liver transplant using staging of severity and pulmonary hemodynamic subsets have been suggested. The combination of an mPAP of <35 mmHg and a PVR of <250 dyn.s.cm<sup>-5</sup> has been associated with an excellent post-transplant outcome.<sup>[271]</sup> By contrast, an mPAP of >35 mmHg has been associated with increased mortality.<sup>[271,296]</sup> In a retrospective study,<sup>[266]</sup> patients with PPHTN had a better rate of survival than patients with IPAH, although this issue is still controversial.<sup>[297]</sup>

**Treatment:** The treatment of PPHTN can be challenging and has not been thoroughly studied. The lack of data regarding effective therapy for PPHTN stems from the routine exclusion of such patients from virtually every randomized clinical trial that has been performed in PAH.

Supplemental oxygen should be used as needed to maintain arterial oxygen saturations >90%. Diuretic therapy should be utilized to control volume overload, edema and ascites. Anticoagulant therapy has not been carefully studied in this population and should probably be avoided in patients with

**Table 12: Pulmonary hemodynamic subsets most frequently associated with advanced chronic liver disease**

	mPAP	PVR	Cardiac output	mPAWP
Hyperdynamic circulatory state	Moderate ↑	Mild ↓	Severe ↑	Mild ↓
Excess volume	Moderate ↑	No change	Moderate ↑	Severe ↓
Vascular obstruction with by Vasoproliferation	Severe ↑	Severe ↑	Severe ↑ followed by severe ↓	Mild ↓

an increased risk of bleeding from gastro-esophageal varices. In the absence of a markedly increased cardiac output and relatively low PVR, patients with mild-to-moderate PAH should have acute vasoreactivity assessed in the catheterization laboratory. If such patients demonstrate a favorable acute response to vasodilator, consideration should be given to the cautious introduction of a CCB. Beta-blockers, which are normally used to treat portal hypertension and reduce the risk of variceal bleeding, may be poorly tolerated in cases of associated PAH due to the negative inotropic effect on the right ventricular myocardium and should be cautiously used, if at all.<sup>[298]</sup>

There have been a number of case reports and small case series describing the use of IV epoprostenol for treatment of PPHTN.<sup>[142,294,295,299]</sup> It appears as though patients with PPHTN respond to chronic IV epoprostenol in a manner somewhat similar to that of patients with IPAH. However, an increased incidence of ascites and splenomegaly with this treatment has been reported.<sup>[300]</sup>

It may be reasonable to try to reduce mPAP and PVR, making a borderline candidate for liver transplantation an acceptable one, through aggressive treatment by the use of epoprostenol.<sup>[297]</sup> A recent retrospective study evaluated the impact of continuous intravenous epoprostenol in 19 patients with moderately severe PPHTN compared to 17 patients not on epoprostenol (10 patients on other vasoactive medications).<sup>[301]</sup> There was significant improvement in the mPAP, PVR and cardiac output in the epoprostenol group after a mean follow-up of 15.4 months. While survival was no different between the groups, a minority of patients improved sufficiently to undergo liver transplantation. In cases thought to have such severe disease as to require multi-organ transplantation such as combined liver and (heart-) lung transplantation, the risks are considered to be very high.<sup>[302]</sup>

Recently, the use of sildenafil has been tested in this patient population. In an uncontrolled study of 12 unstable patients with PPHTN, the result of giving sildenafil ( $\leq 50$  mg three times daily) as either initial monotherapy ( $n = 6$ ) or as an addition to existing prostacyclin therapy ( $n = 6$ ) was recently reported.<sup>[303]</sup> These patients had moderate-to-severe PPHTN as defined by mPAP and PVR. Sildenafil appeared to provide therapeutic benefit (decreasing mPAP and PVR) when evaluated at 3 months; but the hemodynamic benefit was not sustained at 12 months in 7 patients, as measured by PVR, mPAP and cardiac index. Curiously, the 6MWT distance did continue to improve at both 3 months and 12 months. Compared with baseline, the small group who received combination therapy seemed to have the best benefit in terms of PVR at 12 months.<sup>[303]</sup>

Due to its potential for hepatotoxicity, some experts would probably recommend avoiding an oral endothelin antagonist, e.g., bosentan, in this population. The risk/benefit ratio of endothelin receptor antagonists in patients with liver disease needs to be carefully evaluated on a long-term basis. However, one report evaluated the use of bosentan in patients with nondecompensated cirrhosis and severe PPHTN.<sup>[304]</sup> In this report, 11 consecutive patients with cirrhosis and severe PPHTN in NYHA functional classes III and IV were treated for  $>1$  year with bosentan. After 1 year of treatment, all patients showed

improved symptoms and exercise capacity. The 6MWT distance increased from  $310 \pm 102$  m at baseline to  $388 \pm 81$  m at 1 year. Cardiopulmonary exercise testing disclosed a significant increase in peak oxygen uptake, from  $12.6 \pm 3.5$  to  $16.6 \pm 2.8$  ml.  $\text{min}^{-1} \cdot \text{kg}^{-1}$ . Pulmonary vascular resistance fell from  $944 \pm 519$  to  $635 \pm 321$  dynes.s.L<sup>-1</sup>. Bosentan was well tolerated by all patients, and there was no evidence of added risk of drug-related liver injury in this small group of patients.<sup>[304]</sup> A more recent trial compared bosentan with prostacyclin analogue, iloprost, in 31 patients with severe PPHTN treated for 3 years. The effects of bosentan were significantly superior in terms of exercise capacity, hemodynamics and event-free survival rates.<sup>[305]</sup>

No data is currently available regarding the use of other oral endothelin antagonists (e.g., sitaxsentan or ambrisentan, which are supposedly less hepatotoxic compared to bosentan) in this group of patients.

Trans-jugular intrahepatic porto-systemic shunts (TIPS), used for the management of refractory ascites and variceal bleeding, are contraindicated in the presence of severe PPHTN. However, the role of these shunts in the presence of moderate PPHTN is as yet unclear.<sup>[306]</sup>

The safety of liver transplantation in patients who have PPHTN is controversial since there are no well-designed prospective studies to guide decision-making. Retrospective studies and case reports suggest that moderate-to-severe PPHTN is a clear contraindication to liver transplantation due to excessive perioperative mortality.<sup>[307]</sup> Some patients seem to demonstrate improvement in their PAH following liver transplantation.<sup>[308]</sup> This may be particularly true for those with a relatively high cardiac output pre-transplantation, which decreases following successful transplantation. However, other patients may develop worsening of their PAH well after liver transplantation. For those patients with moderately severe PPHTN, the goal of vasodilator treatment pre-transplantation should be to reduce mPAP to  $<35$  mmHg and PVR to  $<400$  dyn.s.cm<sup>-5</sup> before proceeding to liver transplantation.<sup>[309]</sup> Occasionally, it may be possible to wean a patient off IV epoprostenol following liver transplantation. This should probably be done in a specialized center and under close observation.

### III. Pulmonary arterial hypertension associated with HIV infection

**Incidence:** PAH is a rare but well-documented complication of HIV infection; more than 200 cases have been reported in the literature.<sup>[310-312]</sup> Currently noninfectious cardiovascular manifestations of HIV infection such as dilated cardiomyopathy, pericardial effusion, nonbacterial thrombotic endocarditis, accelerated atherosclerosis and PAH are more commonly detected as a result of longer survival and better prophylaxis against opportunistic infections.<sup>[313]</sup> In a large case-control study, over a period of 5.5 years, 3,349 HIV-infected patients demonstrated a cumulative incidence of PH of 0.57%, resulting in an annual incidence of 0.1%.<sup>[314]</sup>

**Pathogenesis:** The mechanism of the development of PAH in HIV patients is unknown. An indirect action of HIV through second messengers such as cytokines,<sup>[315]</sup> platelet growth factors<sup>[315]</sup> or ET-1<sup>[316]</sup> is strongly suspected because of the absence of viral DNA in pulmonary endothelial cell.<sup>[315-317]</sup>

This hypothesis is reinforced by the presence of peri-vascular inflammatory cells in HIV-associated PAH.<sup>[318,319]</sup> In addition, genetic predisposition can be also involved as this complication affects only a minority of HIV-infected patients. The absence of BMPR2 mutation in a subset of 30 tested patients with HIV-associated PAH suggests that other susceptibility factors are involved.<sup>[320]</sup>

In patients without HIV infection, a recent report linked infection with human herpes virus 8 (HHV-8) to 'primary' pulmonary hypertension.<sup>[321]</sup> The seroprevalence of HHV-8 remains high in populations at risk for HIV, such as homosexual men in San Francisco.<sup>[322]</sup> For patients with HIV, HHV-8 may thus be a causative agent for pulmonary hypertension. However, this theory has not yet been demonstrated.

**Clinical picture and investigations:** HIV-related PAH shows similar clinical, hemodynamic and histological findings as IPAH, and it does not appear to be related to the route of HIV transmission nor to the degree of immunosuppression.<sup>[323]</sup> HIV patients may also be infected by hepatitis B and C viruses, and a concomitant liver disease may be present.

Echocardiographic screening for the detection of PH in patients with HIV infection is required in symptomatic patients. A careful exclusion of other causes of PH, such as left-heart and parenchymal lung and liver diseases, is necessary. RHC is recommended in all cases of suspected PAH associated with HIV infection to confirm the diagnosis, determine severity and rule out left-sided heart disease.

Mortality of patients with HIV-associated PAH is mainly related to PAH itself, rather than to other complications of HIV infection.<sup>[323]</sup> PAH is an independent predictor of mortality in these patients.<sup>[314]</sup>

**Treatment:** In HIV-associated PAH, therapeutic options are less well established as compared to other forms of PAH. Treatment with oral anticoagulation should be individualized in this group of patients, based on the risk-benefit profile. Patients with low platelet count, active esophageal varices or with poor compliance should not receive anticoagulation. Furthermore, special attention should be given to drug-drug interaction once warfarin is introduced (if there is no contraindication).

The effect of CCBs on the course of HIV-IPAH remains unclear. In one small study, none of the five tested patients with known HIV-PAH responded to calcium-channel blockers, and four of them experienced intolerable side effects necessitating discontinuation of therapy.<sup>[324]</sup> One uncontrolled open study of six patients with severe HIV-associated PAH<sup>[143]</sup> suggests that continuous infusion of epoprostenol might be effective in improving functional status and hemodynamics up to 12-47 months. Lung transplantation is considered not advisable in this patient population.

Chronic treatment with inhaled iloprost in four HIV patients has been shown to improve the 6MWT distance and decrease pulmonary vascular resistance in all patients without serious adverse events or major interactions with the ongoing antiretroviral therapy.<sup>[325]</sup> However, none of these patients

were found to be responsive to the short-term NO inhalation challenge.

The effects of bosentan have been assessed in nonrandomized clinical trial of 16 patients with HIV-PAH and in NYHA class III-IV; the treatment resulted in clinical benefits with respect to 6MWT distance (+91 ± 60 m,  $P < 0.001$ ), NYHA class (14 patients improved), hemodynamics (cardiac index: +0.9 ± 0.7 L/min/m<sup>2</sup>,  $P < 0.001$ ), Doppler echocardiographic variables and quality of life at the end of 16 weeks.<sup>[326, 327]</sup>

The role of highly active antiretroviral therapy (HAART) in the management of HIV-associated PAH remains to be established. However, a recent report from the Swiss Cohort Study showed that pulmonary artery pressure increased in untreated patients but decreased in patients treated with HAART.<sup>[328]</sup> A beneficial effect on pulmonary hemodynamics was also observed in patients treated with nucleoside reverse transcriptase inhibitors.<sup>[314]</sup> A single study of long-term hemodynamic improvement with this treatment, without the associated use of any vasodilator agents, has been reported.<sup>[329]</sup>

Lastly, in a large single-center case series of 82 patients,<sup>[320]</sup> univariate analysis indicated that CD4 count (>212 cell/mm<sup>3</sup>), combination antiretroviral therapy and the use of epoprostenol infusion were associated with improved survival. However, on multivariate analysis, only CD4 lymphocyte count was an independent predictor of survival, presumably because the combination of antiretroviral therapy and epoprostenol infusion was strongly linked in this study population. The survival was worse in NYHA class III-IV patients that were treated with combination antiretroviral therapy (CART) only, compared with those who received CART and epoprostenol.

In summary, uncontrolled studies suggest that patients with severe HIV-associated PAH may respond favorably to the combination of antiretroviral therapy and epoprostenol, inhaled iloprost and possibly to bosentan. However, epoprostenol, as well as endothelin receptor antagonists and PDE-5 inhibitors, should be evaluated in this patient population in controlled randomized trials.<sup>[330]</sup>

It is also crucial and necessary to design multi-center prospective and well-conducted studies to definitively assess the beneficial effect of HAART in HIV-1-infected patients with PAH. Such studies are particularly important to assess the effects of HAART in HIV-1-infected patients with higher CD4 cell counts (i.e., >350 cells/mm<sup>3</sup>), for whom antiretroviral therapy might be deferred or started only in particular circumstances.

Physicians should be aware of possible PAH in patients with HIV infection that present with progressive shortness of breath and/or symptoms or signs of right-sided heart failure, as this condition increases morbidity and mortality. We recommend screening of these patients with transthoracic echocardiography.

#### **IV. Pulmonary arterial hypertension associated with connective tissue diseases**

PAH is a common manifestation of connective tissue diseases

(CTDs). In this respect, mainly patients suffering from systemic sclerosis (SSc),<sup>[331]</sup> systemic lupus erythematosus (SLE),<sup>[332]</sup> mixed connective tissue diseases (MCTDs),<sup>[333]</sup> and, to a lesser extent, rheumatoid arthritis, dermatomyositis and primary Sjogren's syndrome<sup>[334]</sup> are usually affected.

**Epidemiology:** PAH has been increasingly recognized as a common and severe complication of CTD. In a population-based approach, the prevalence of PH was 2.6% in over 3,500 investigated patients.<sup>[335]</sup> In the NIH Registry, among 236 cases of unexplained PH, about 8% of cases were associated with CTDs.<sup>[31]</sup> A recently finished registry study of PH in 722 patients with SSc in the United Kingdom showed a prevalence of about 12%.<sup>[331]</sup> In another series of 930 patients with SSc, the cumulative incidence was 13%,<sup>[336]</sup> and in the French registry, which included hemodynamic confirmation of PAH, it was calculated to be 10%.<sup>[337]</sup> Compared to SSc, PAH is less commonly seen in SLE (0.5-14%) and is a rare clinical finding in dermatomyositis and rheumatoid arthritis.

Compared with IPAH, patients with PAH secondary to CTD are usually women, older, have a significantly lower cardiac output and have a trend towards worse survival: 1-, 2- and 3-year survival rates were reported to be 45, 35 and 28% respectively, with a median survival of only 1 year following diagnosis.

Unfortunately, the risk factors for PAH development in CTDs are as yet unknown.

**Pathophysiology:** PAH occurring in association with CTD is pathologically similar to IPAH. The etiology of PAH in patients that have CTD is unknown. Cool and colleagues reported the presence of inflammatory cells surrounding the plexiform lesions in patients who had PAH related to limited sclerosis (previously known as CREST syndrome), possibly indicating an inflammatory mechanism.<sup>[338]</sup> Quismorio and colleagues found antinuclear antibody and rheumatoid factor within the cells of the pulmonary vasculature in two patients who had PAH related to SLE.<sup>[339]</sup> Others have reported IgG and complement fraction deposits in the vascular endothelium of patients who had SLE.<sup>[340]</sup> In some cases, pulmonary hypertension developing in patients with an underlying CTD can be attributed to pulmonary parenchymal disease, such as interstitial lung disease and pulmonary fibrosis. The parenchymal destruction results in hypoxia and thus pulmonary vasoconstriction. Thromboembolic disease due to an underlying hypercoagulable state associated with some forms of CTD can also result in pulmonary hypertension. However, these abnormalities do not adequately explain the vascular remodeling and severe arterial pulmonary pressure elevation typical of most cases of PAH associated with CTD. Raynaud's phenomenon is commonly reported in patients who have scleroderma, SLE and MCTD. The presence of pulmonary hypertension in patients who have SLE and limited sclerosis with Raynaud's phenomenon is common. The perceived association between Raynaud's phenomenon and PAH has led to the 'pulmonary Raynaud's' hypothesis, in which pulmonary arterial vasospasm is believed to contribute to the development of pulmonary hypertension.

Severe PAH is a potentially devastating manifestation of MCTD

and is usually associated with high morbidity and mortality. Esther and colleagues performed a prospective evaluation of pulmonary function in 26 patients that had MCTD. Twenty of the 26 patients had a decreased DLco on pulmonary function tests. Nine of the patients underwent RHC, and 7 were diagnosed with PAH.<sup>[341]</sup> Weiner-Kronish and colleagues reported on a series of 5 patients with MCTD and pulmonary pathology. Three of the 5 patients had severe PAH.<sup>[342]</sup> Autopsy series have demonstrated medial hypertrophy, intimal proliferation and plexiform lesions, as have been observed in scleroderma-associated PAH and IPAH.<sup>[343]</sup>

**Diagnosis:** Echocardiographic screening for the detection of PH has been suggested to be performed yearly in asymptomatic patients with the scleroderma spectrum of diseases<sup>[32]</sup> and only in presence of symptoms in other CTDs. The rationale for screening asymptomatic patients is not clear as we do not have evidence that treatments are effective in this subset. In any case, the early detection of any PAH-related symptom should prompt a complete and careful echocardiographic assessment at any time and in any patient with CTD.

It is crucial to perform RHC for these patients to assess the vasoactive status and to rule out LVDD. This is usually achieved by a rapid infusion of 1 L of normal saline as a fluid challenge, as CTD patients often have significant risk factors for LVDD, e.g., hypertension, renal disease and older age.

The same diagnostic tools for other types of PAH apply for cases with connective tissue disease (see above), in addition to investigations directed to elucidate the underlying cause.

**Treatment:** Treatment of PAH associated with CTD mirrors the diagnosis and treatment for PAH of any other etiology. However, the prognosis of CTD patients with PAH, especially SSc, is substantially worse than that of patients with IPAH; and treatment appears more complex as compared with other forms of PAH.

The risk-to-benefit ratio of oral anticoagulation is not yet well established. Furthermore, the rate of acute vasoreactivity and of a long-term favorable response to CCBs treatment is suggested to be lower when compared with IPAH.

Therapeutic agents like prostacyclins or drugs that modulate the synthesis of nitric oxide and additional agents targeting the ET-1 signaling system are under ongoing investigation. Intravenous epoprostenol has been shown to be effective in a 3-month randomized trial of patients suffering from scleroderma spectrum.<sup>[124]</sup> It improved exercise capacity, symptoms and hemodynamics. However, no improvement in survival was observed.<sup>[124]</sup> Indeed, retrospective analyses have shown that the effect of intravenous epoprostenol on survival seems to be less in scleroderma patients as compared to IPAH patients.<sup>[81,335]</sup>

Prostacyclin application by another route, a continuous subcutaneous administration of treprostinil, was evaluated in a subset of 90 patients with PAH and CTD that were enrolled in a large randomized controlled trial. After 3 months, an improvement in exercise capacity, symptoms and hemodynamics was shown.<sup>[344]</sup>

Also, favorable results have been shown after using the endothelin receptor antagonists bosentan and sitaxsentan in patients with CTD-related PAH. The clinical efficacy of the dual ET-receptor antagonist bosentan was demonstrated in BREATHE-1:<sup>[163]</sup> 213 PAH patients (either idiopathic or associated with CTD) were randomized to placebo or bosentan. Compared with placebo, administration of bosentan improved exercise capacity as measured by the 6MWT distance, WHO functional class and the Borg dyspnea index and significantly improved the overall time to clinical worsening. In the subgroup of SSC patients included in this trial, bosentan just prevented deterioration and did not significantly improve exercise capacity (+3 m in the bosentan group versus -40 m in the placebo group). Interestingly, a recent post hoc analysis revealed that the survival rate has improved after first-line bosentan therapy also in this subset of patients: 82% after 1 year, 66.6% after 2 years and 63.5% after 3 years. However, it has to be considered that 16% of the patients received epoprostenol as an add-on therapy, and 14% received epoprostenol after the discontinuation of bosentan<sup>[163]</sup> (see above under bosentan section).

More recently, the selective ET-A receptor antagonist sitaxsentan has also shown favorable results in patients with PAH associated with CTD.<sup>[174]</sup>

Sildenafil was compared to bosentan in a randomized double-blinded study<sup>[204]</sup> of 26 patients with PH (WHO class III with idiopathic PAH or PAH associated with connective tissue disease). The patients were randomized to receive sildenafil 50 mg twice daily for 4 weeks and then 50 mg three times daily or bosentan 62.5 mg twice daily for 4 weeks and then 125 mg twice daily for 16 weeks. Baseline characteristics did not differ significantly between the treatment groups. Six-MWT distance and QOL score improved more significantly in sildenafil group compared to bosentan group (both groups were significantly better when compared with baseline values)<sup>[204]</sup> (see above under sildenafil section).

Lung transplantation is the last option for patients with severe PAH. However, the presence of CTD with possible multi-organ involvement may represent a contraindication for lung transplantation in advanced cases not responsive to medical treatment. Thus, each patient needs to be considered individually, and the risk-versus-the benefit issues should be carefully balanced in this patient population.

## V. Pulmonary arterial hypertension associated with sickle cell disease

Sickle cell disease (SCD) is one of most common genetic disorders in Saudi Arabia, with overall prevalence of sickle cell gene Hb AS of 7.36% and Hb SS of 1.06%.<sup>[345]</sup> It is an autosomal recessive disorder in which hemoglobin 'S' polymerizes when deoxygenated. This polymerization causes red cell rigidity and sickling. Rigid sickle cells become entrapped in the microcirculation, producing ischemia and propagating inflammatory, thrombotic and oxidant stress, which ultimately damages the membrane and produces extra-vascular and intravascular hemolytic anemia. However, PAH is associated with any chronic hemolytic anemia and not just with SCD.

Epidemiology: PAH is an increasingly recognized complication

of SCD. Gladwin *et al.* in a prospective trial employed noninvasive Doppler echocardiography to measure tricuspid regurgitant jet velocity (TRV) to estimate the pulmonary artery systolic pressure in adult patients with SCD.<sup>[346]</sup> PAH on echocardiogram was defined as TRV of 2.5 m/s or greater. Using this criterion, it was found that 32% of SCD patients had PAH. In addition, It was also observed that prevalence of PAH increases with age. In the '40-49 years' age group, the prevalence was 40%, which increased to 55-60% by age 50 years and above. In another prospective study of 60 patients followed at SCD center, the prevalence of PH was 30%.<sup>[347]</sup> A recent autopsy study suggests that up to 75% of SCD patients have histological evidence of PAH at the time of death.<sup>[348]</sup>

Furthermore, SCD patients with PH have significantly increased mortality rate as compared with patients without PAH. Sutton and colleague reported a 40% mortality rate at 22 months after diagnosis (odds ratio, 7.86; CI ratio, 2.63-23.4).<sup>[349]</sup> In another study, 2-year mortality due to PAH and SCD was reported as 17% as compared to 2% in SCD subjects without PAH.<sup>[350]</sup>

In the study by Castro *et al.*, SCD patients with PH (confirmed by RHC) had a 2-year mortality of 50% compared with a 'greater than 70%' survival at the end of a 10-year observation period in patients without PH.<sup>[351]</sup>

Risk factors for pulmonary hypertension: According to the NIH-Howard study, risk factors for PAH in SCD include older age, degree of hemolysis, systemic blood pressure, history of renal and heart disease, iron overload and cholestasis. On univariate statistical analysis, all markers of hemolytic anemia, including low hemoglobin (Hb) and hematocrit, high aspartate aminotransferase and high lactate dehydrogenase (LDH) levels, were associated with elevated pulmonary pressures. Increasing age was also a univariate predictor; patients with PH were significantly older than patients without PH (38 ± 19 years for patients with TRV ≥3.0 m/s, 39 ± 12 years for patients with TRV = 2.5-2.9 m/s and 34 ± 10 years for patients with TRV <2.5 m/s, *P* = 0.02). In men, a history of priapism was an independent factor associated with PH.<sup>[346]</sup>

The risk of PAH is not associated with Hb F level, the frequency of acute chest syndrome or painful vaso-occlusive crises or hydroxyurea treatment.

Pathogenesis: The pathogenesis of PH in SCD is probably multi-factorial.<sup>[352]</sup> It may be secondary to chronic intravascular hemolysis producing endothelial dysfunction, oxidant and inflammatory stress and scavenging of NO by cell-free plasma hemoglobin.<sup>[353,354]</sup>

Destruction of red blood cells (RBCs) also results in the release of arginase, which converts L-arginine (the substrate for NO synthesis) to ornithine. Elevated arginase activity, with the resultant decrease in arginine/ornithine ratio, is associated with elevated pulmonary artery pressures.<sup>[355]</sup>

In patients with SCD, plasma ET-1 levels, known to be associated with PAH (see above and disease pathology), are also increased in steady state and during crisis.<sup>[356]</sup> Pulmonary thromboembolism<sup>[357,358]</sup> and progressive endothelial damage with concentric pulmonary vascular intimal hyperplasia and

*in-situ* thrombosis<sup>[359]</sup> may also contribute to the pathogenesis of PH in SCD. A hypercoagulable state, including low levels of protein C and S, elevated levels of thrombin-antithrombin complexes and D-dimers and increased activation of tissue factor, is seen in patients with SCD in steady state.<sup>[345,360,361]</sup> This hypercoagulable state could potentially promote vascular obstruction. *In situ*, thrombosis is observed in both IPAH patients and in patients with SCD at autopsy.<sup>[350,358]</sup>

**Clinical features:** It is difficult to diagnose the presence of PAH in SCD; as common symptoms, such as exertional dyspnea and chest pain, are manifestations of SCD. A high index of suspicion for the disease is necessary. Patient with mild disease may not have any specific symptoms or signs; however, with increasing disease severity, patients may develop chronic dyspnea, hypoxemia and signs of PH. These patients usually tend to be older; have higher systolic arterial blood pressure, lower Hb levels, high bilirubin and LDH, lower SaO<sub>2</sub> and renal and liver impairment. These patients may also have received multiple transfusions, suggesting chronic intravascular hemolysis.<sup>[346]</sup>

**Diagnosis:** A high index of suspicion for the presence of PAH in SCD is important as the patient may present with nonspecific symptoms such as dyspnea. Moreover, it has been observed that even mild PAH in SCD is associated with a very high risk of death. Because of this, it is suggested that all patients with SCD should have screening with Doppler echocardiography. If TRV is found to be greater than 2.5 m/s, the situation should be further investigated [Figure 2].

Diagnostic evaluation follows the same guidelines as for other causes of PHT. Patients should undergo complete PFTs, V/Q scan and contrast-enhanced spiral CT chest. Most patients with SCD may have abnormal PFTs, showing airflow obstruction, restrictive pattern and/or abnormal DLco associated with hypoxemia. The latter may further exacerbate pulmonary hypertension.

Chronic thromboembolic pulmonary hypertension is a recognized complication of SCD and is a potentially surgically treatable condition (see below). This may be initially evaluated by V/Q scan and spiral CT; if abnormal, some authorities suggest investigating further with pulmonary angiography.

Pulmonary hypertension in SCD is a different and unique entity. SCD patients have anemia-induced high cardiac output status (usually around 10 L/min); interference with vasodilatation might further increase the cardiac output secondary to afterload reduction, which might ultimately worsen PH. This is poorly tolerated in SCD patients, who may develop symptoms with relatively mild PH as compared to patients with PH without SCD. Furthermore, these patients have more functional impairment and will show signs of fatigue on exertion, have significant shorter mean 6MWT distance and lower oxygen consumption during cardiopulmonary exercise testing.

**Management of SCD-related PAH:** There is a limited data on the specific management of patients with SCD and PH. Most of the recommendations are based on expert opinion or extrapolation from data derived from other forms of PH.

General approach usually includes (1) optimizing and intensification of disease treatment with hydroxyurea (with or without erythropoietin), hydration and transfusion; (2) treatment of associated condition; (3) oxygen therapy; (4) anticoagulation; and (5) targeted therapy with pulmonary vasodilator/ anti-remodeling agents.

#### **a. Intensification of sickle cell disease therapy**

Chronic intravascular hemolysis probably plays a pivotal role in the development of PH in SCD. In addition, significant worsening of PH during acute episodes of vaso-occlusive crisis and the acute chest syndrome have been reported.<sup>[362]</sup> Based on this observation, it is likely that maximization of SCD therapy would be beneficial by ameliorating the principal mechanism involved in the pathogenesis of PH. It is recommended that all patients with SCD and PH undergo maximization of therapy with hydroxyurea or simple/ exchange transfusions. Hydroxyurea has been shown to decrease pain, incidence of acute chest syndrome and overall mortality.<sup>[363,364]</sup>

Long-term transfusion therapy in patients with SCD reduces the synthesis of sickle cells and its pathological effects. The risks of most complications of the disease are reduced, including the risk of pulmonary events and central nervous system vasculopathy.<sup>[365,366]</sup>

#### **b. Treatment of associated conditions**

Aggressive search for associated conditions, such as iron overload, chronic liver disease, nocturnal hypoxemia and thromboembolic disorders, should always be undertaken given the availability of specific therapies.

#### **c. Oxygen therapy**

Oxygen desaturation, especially unrecognized nocturnal hypoxemia, should be pursued and treated.<sup>[367,368]</sup>

#### **d. Anticoagulation**

The potential benefits of warfarin therapy observed in patients with IPAH have to be weighed against the risk of hemorrhagic stroke in adults with SCD. However, the relatively low risk of hemorrhagic stroke [0.21 events per 100 patient years, compared with the high risk of death in patients with TRVs  $\geq 3.0$  m/s (16-50% 2-year mortality<sup>[26,369]</sup>)] supports anticoagulation in patients without a specific contraindication.

#### **e. Target therapy for pulmonary hypertension**

There is limited data on the specific efficacy and safety of selective pulmonary vasodilator in patients with SCD. Although there is well documented evidence for the beneficial effects of therapy with prostanoids [epoprostenol, treprostinil, iloprost, beraprost,<sup>[370]</sup> ET antagonists bosentan<sup>[371]</sup> and sitaxsentan<sup>[174]</sup> and possibly phosphodiesterase-5 inhibitors (sildenafil)<sup>[372,373]</sup>] in patients with other forms of PAH, yet treatment with these agents in SCD requires special consideration.

The systemic use of prostanoids produces significant systemic vasodilatation and increases cardiac output, raising concern for potential development of high-output heart failure in anemic patients. In addition, the risk of chronic intravenous line-related complications, such as thrombosis and sepsis, is probably higher in patients with SCD.

The main toxicity of ET-1 receptor antagonists is hepatocellular injury, which could limit their applicability in patients with SCD at risk for liver dysfunction (e.g., iron overload, hepatitis C). Another class effect of these agents is a dose-related decrease in Hb levels, usually in the range of 1 g/dl.<sup>[174]</sup>

Sildenafil has been shown to decrease pulmonary artery pressure and improve 6MWT distance in SCD patients with PAH. The main concern, however, is related to the potential for development of priapism in men with SCD.

### Summary

PAH is much more common in SCD than generally recognized and occurs in about one-third of patients with SCD. PAH probably results from intravascular hemolysis with cascade of events which follow. Even mild-to-moderate rise in pulmonary artery pressure can result in increased mortality and morbidity. Adult patients with SCD should be screened by echocardiography for presence of PAH. Intensification of specific SCD therapy, such as the use of hydroxyurea, simple/ exchange transfusion, oxygen therapy and treatment of infection and hydration, can limit the progression of disease. Specific therapy with vasodilators/ anti-remodeling agents should be considered in patients with more advanced disease.

## VI. Pulmonary arterial hypertension associated with sleep breathing disorders

### a. Epidemiology

Several studies have examined the relationship between sleep-disordered breathing and cardiovascular risk.<sup>[374]</sup> Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing, and it is associated with PAH. OSA is defined on the basis of apnea-hypopnea index (AHI) (the number of apneas plus hypopneas per hour of sleep). It is said to be present if AHI is greater than five with or without symptoms. Based on this definition, the prevalence of OSA is approximately 20%.<sup>[375,376]</sup> In contrast, only 3-9% have obstructive sleep apnea syndrome, defined as AHI greater than five accompanied by symptoms.<sup>[375]</sup> It is also reported that approximately 20% of OSA patients without any other cardiopulmonary diseases develop mild PH.<sup>[377,378]</sup> Alchanatis *et al.* reported that the emergence of PAH is related to old age, greater body mass index and low PaO<sub>2</sub> during wakefulness.<sup>[378]</sup>

### b. Pathogenesis

It is postulated that nocturnal hypoxia that accompanies respiratory events during sleep causes hypoxic pulmonary vasoconstriction, eventually leading to sustained PAH and subsequently right ventricular failure, i.e., cor pulmonale.

### c. Evidence-based

Although it has become clear that OSA alone may cause mild PAH, a coexisting cause of daytime hypoxia is necessary to produce sustained severe PH.<sup>[379-382]</sup> This is illustrated by the following studies:

1. In an observational study of 50 consecutive patients with OSA, patients with cor pulmonale were compared to those with normal right heart function.<sup>[379]</sup> There was no difference in the severity of OSA; however, patients with cor pulmonale had more severe nocturnal desaturation (76 vs. 90%) and poorer daytime PaO<sub>2</sub> (52 vs. 75 mmHg).

Severe nocturnal hypoxemia in the absence of daytime hypoxemia was not associated with cor pulmonale, suggesting that sustained hypoxemia (nocturnal and daytime) is necessary to cause cor pulmonale.

2. In another observational study of 27 OSA patients without cardiopulmonary diseases, mild PAH (<26 mmHg) was observed in 41% of the patients.<sup>[380]</sup> No patients were identified with severe PAH or cor pulmonale.
3. In a study comparing 90 patients with OSA, patients with a high AHI had a small but significant increase in right ventricular wall thickness.<sup>[381]</sup> There was no difference in right atrial size, right ventricular size or right ventricular function.
4. Kessler *et al.*<sup>[382]</sup> reported a descriptive analysis of prospectively collected data comparing the prevalence and degree of PAH in patients with obesity hypoventilation syndrome (OHS) plus OSA ( $n = 34$ ); patients with pure OSA ( $n = 220$ ); and patients with overlap syndrome, in which OSA coexists with chronic obstructive lung disease ( $n = 30$ ). PAH was more frequent in OHS patients than in pure OSA patients but not different from that in overlap syndrome patients. The mPAP in OSA patients was  $15 \pm 5$  mmHg, which is significantly less than that in OHS and overlap syndrome groups. Moreover, there were no significant differences between the three groups of patients in terms of severity of sleep apnea based on AHI.<sup>[382]</sup>
5. In a randomized study, 23 patients with severe OSA and 10 control subjects were evaluated.<sup>[383]</sup> Ten of OSA patients and none of the control subjects had PAH. The systolic pulmonary arterial pressure was  $29.8 \pm 8.8$  mmHg in OSA patients compared to  $23.4 \pm 4.1$  mmHg in control subjects (based on echocardiogram).

All the above studies suggest that OSA alone may be associated with mild PH, but it is unlikely to be a common cause of severe PAH and cor pulmonale.

### d. Treatment

Usually, there is no need for special treatment for the mild PAH associated with OSA. However, in the above-mentioned randomized cross-over study,<sup>[383]</sup> the use of continuous positive airway pressure (CPAP) was associated with a significant reduction in the systolic pulmonary arterial pressure - from  $29.8 \pm 8.6$  to  $24.0 \pm 5.8$  mmHg. Therefore, according to the current state of knowledge, CPAP, which is the standard therapy for patients with OSA,<sup>[384]</sup> is probably adequate to reduce pulmonary systolic pressure levels.

## VII. Chronic thromboembolic pulmonary hypertension

### a. Epidemiology

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening but potentially curable condition that should be considered in all patients with unexplained PAH. CTEPH is often misdiagnosed, and the true diagnosis may not be made until autopsy. It is characterized by single or recurrent pulmonary thromboemboli that obstruct or obliterate the pulmonary vascular bed, promoting increased PVR and progressive PAH and subsequently right-heart failure.<sup>[71,385-387]</sup> The involvement of pulmonary microvascular changes in the form of generalized pulmonary hypertensive arteriopathy has been defined relatively recently and is gaining increased recognition as a contributor to disease progression

in CTEPH.<sup>[388-390]</sup> Many patients with CTEPH present late in the course of disease with progressive dyspnea on exertion, hemoptysis and general clinical deterioration associated with right-heart dysfunction. Nonspecific symptoms and lack of medical history of previous venous thromboembolism (VTE) often complicate accurate diagnosis and, as a result, CTEPH is frequently misdiagnosed and is under-recognized in clinical practice.<sup>[391]</sup> The risk of death from right-heart failure in patients with undiagnosed or untreated CTEPH is high, with survival inversely related to pulmonary artery pressure at diagnosis. Mortality rate without treatment is approximately 70% among patients with an mPAP >40 mmHg, increasing to 90% at >50 mmHg.<sup>[387]</sup> Historically, the occurrence of CTEPH in patients diagnosed with acute pulmonary embolism (PE) has been considered rare. Data from autopsy studies estimated the overall incidence of CTEPH at 1-3% and at 0.1-0.5% in patients surviving acute PE. Approximately 600,000 individuals suffer from an acute pulmonary embolic event in the United States annually, and the annual number of new CTEPH cases in the United States is between 500 and 2,500. This may underestimate the true frequency of CTEPH because the disease is often misdiagnosed due to nonspecific symptoms and variable disease course.<sup>[392]</sup> A single-center prospective longitudinal study assessing symptomatic CTEPH in patients with acute PE but without prior venous thromboembolism has recently estimated the cumulative incidence of CTEPH to be 1.0% at 6 months after PE, 3.1% after 1 year, 3.8% after 2 years; and the overall post-PE incidence was approximately 3%.<sup>[393]</sup> CTEPH is often identified during diagnostic workup in patients with unexplained PH, many of whom lack medical history suggesting previous VTE. In a recent study in 142 consecutive patients with CTEPH, 90 (63%) had no previous history of symptomatic venous thromboembolism.<sup>[394]</sup>

### **b. Pathogenesis**

The pathogenesis of the disease has not yet been fully explained, and factors contributing to the development of CTEPH remain poorly defined.<sup>[390]</sup> The observation that the vast majority of those who suffer an acute PE do not go on to develop CTEPH<sup>[74,395]</sup> suggests that there are other factors that are important in the development of the disease. VTE is more common in the elderly, whereas CTEPH often affects younger adults.<sup>[396]</sup> CTEPH is difficult to replicate through induced PE in experimental studies, and there are striking differences between the organized thrombotic material removed during pulmonary thromboendarterectomy (PTEA) in CTEPH and that retrieved during embolectomy in patients with acute PE. In addition, many conditions that predispose to VTE do not seem to cause CTEPH, suggesting that the two conditions may be pathophysiologically unrelated. For instance, markers of congenital thrombophilia are considered as risk factors for VTE but are not prevalent in CTEPH.<sup>[397]</sup> No clear link has been established between CTEPH and the occurrence of abnormality in anti-thrombin, protein S, protein C or factor II or factor V Leiden.<sup>[398]</sup> Opinion on the pathogenesis and natural history of CTEPH is pointing more in favor of acknowledging that although organized central thrombi are the most likely disease-initiating event, progressive small pulmonary vessel arteriopathy may contribute to the long-term progression of PAH. Studies also suggest that local (*in-situ*) pulmonary thrombosis may contribute to disease progression, promoting the

stabilization and growth of thromboemboli.<sup>[399-401]</sup>

The current concept of CTEPH pathogenesis is based on gradual formation of organized thromboemboli after deep venous thrombosis and PE. One factor that may be involved in the pathogenic mechanism of the disease is an altered coagulation process, either inherited or acquired or a combination of both. In addition, a few case reports or small case series have suggested a link between CTEPH and some medical conditions, particularly splenectomy.<sup>[402]</sup> Prior splenectomy, ventriculo-atrial shunt and chronic inflammatory states are independent risk factors for CTEPH.

### **c. Diagnostic workup**

#### **1. V/Q scan**

If after history, physical examination, routine investigations and a transthoracic Doppler echocardiogram, a CTEPH is suspected, ventilation-perfusion (V/Q) lung scan should be ordered. V/Q lung scans of patients with CTEPH generally show one or more segmental-sized or larger mismatched perfusion defects.<sup>[55]</sup> A normal V/Q scan makes CTEPH unlikely to be the cause of PAH.<sup>[65,403]</sup> V/Q scanning showed sensitivity of 90-100% with specificity of 94-100% in differentiating between IPAH and CTEPH.<sup>[66]</sup> Although negative scan results are highly specific for absence of thromboembolism, false-positive scan results may occur with pulmonary artery sarcoma, large-vessel pulmonary vasculitis, extrinsic vascular compression, pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis.<sup>[64]</sup>

#### **2. Computed tomographic angiography (CTA)**

A spectrum of abnormalities on CT scanning has been described in patients with CTEPH, including right ventricular enlargement, dilated central pulmonary arteries, chronic thromboembolic material within the central pulmonary arteries, increased bronchial artery collateral flow, variability in the size and distribution of pulmonary arteries, parenchymal abnormalities consistent with prior infarcts and mosaic attenuation of the pulmonary parenchyma.<sup>[404-406]</sup> HRCT of the lung showing a mosaic pattern in CTEPH is very suggestive of the diagnosis. CT scan may also be useful in evaluating pulmonary parenchyma in patients with CTEPH and coexistent obstructive or restrictive lung disease, and in determining the extent of small-vessel involvement and likelihood of improvement after thromboendarterectomy.<sup>[73]</sup> With the advent of multi-slice CT and resolution approaching 0.5 mm in all planes, results for CTA match those obtained with conventional pulmonary angiography.<sup>[407,408]</sup> However, CTA has a 7% false-negative rate and so selective pulmonary angiography should be considered in certain cases with high clinical index and negative CTA study.

#### **3. Magnetic resonance angiography (MRA)**

Contrast-enhanced MR angiography (CEMRA) is an established alternative to CTA in all vascular beds beyond the coronary tree. MRI techniques can delineate anatomic abnormalities of the pulmonary arteries, including the presence of chronic thromboemboli.<sup>[409,410]</sup> In one report, the MRI diagnosis of chronic pulmonary thromboembolism matched the V/Q diagnosis in 92% of cases.<sup>[66]</sup> Contrast-enhanced three-dimensional magnetic resonance angiography may permit the detection of central chronic thromboembolic material

and may be equivalent to digital angiography up to the level of the segmental arteries.<sup>[411]</sup> Surgical intervention is largely limited to proximal and segmental vessels; and in a study by Kreitner and colleagues, CEMRA correctly predicted surgical success in 33 of 34 patients.<sup>[412]</sup> Pulmonary MRA may replace conventional angiography as the surgical 'road map' in patients being considered for surgery.

#### 4. Doppler echocardiography

Doppler echocardiography can provide information that may help differentiate between CTEPH and IPAH. In a retrospective unblinded study of 35 patients known to have either CTEPH (19 patients) or IPAH (16 patients), Doppler echocardiography-derived pulmonary pulse pressure normalized by sPAP or mPAP separated these two groups with a sensitivity of 95% and specificity of 100%. Cut off values were 0.77 and 1.35 for pulse pressure/systolic pressure and for pulse pressure/mean pressure respectively.<sup>[413]</sup>

#### 5. Pulmonary angiography

At present, pulmonary angiography remains the diagnostic procedure of choice for the evaluation of suspected CTEPH. By identifying occlusions and intravascular webs, it confirms the diagnosis and gives an indication of operability.<sup>[414-416]</sup> It can be performed safely regardless of the severity of PH. In some centers, pulmonary angiography is performed only in patients being considered for PTEA when an adequate surgical road map has not been provided by CT or MR. If pulmonary angiography has to be done, two views of each lung are essential to show pulmonary vascular anatomy in sufficient detail for surgical planning.

#### 6. Pulmonary angioscopy

Pulmonary angioscopy is invasive and expensive and carries a small but definite risk. Although it has been shown that angioscopy can predict hemodynamic outcome in patients with relatively mild PH and can confirm operability in patients with severe PH, noninvasive methods providing similar information are increasingly becoming available.<sup>[417]</sup> Pulmonary angioscopy is often important to be performed preoperatively before pulmonary thromboendarterectomy (PTEA) at the specialized center where surgery will take place.

#### d. Management

- i. Pulmonary thromboendarterectomy (PTEA)
- ii. Balloon angioplasty
- iii. Lung transplantation
- iv. Medical management

##### i. Pulmonary thromboendarterectomy (PTEA)

PTEA should be considered as the first line of treatment whenever possible. In patients in whom it can be applied, PTEA is potentially curative.<sup>[232,390,418]</sup> Based on a multidisciplinary team and a high level of surgical experience, the early mortality of pulmonary endarterectomy has become acceptably low. Long-term survival and quality of life of the patients after PTEA are excellent. CTEPH with thromboembolic defects at the main, lobar or proximal segmental level is characterized as having proximal disease and represents the main cases for operability.<sup>[419,420]</sup> Patients with significant PH but with little or no visible evidence of thromboembolic pathology are considered poor candidates for surgery.<sup>[420,421]</sup> A careful

preoperative assessment is mandatory, and the decision to undertake PTEA must be tailored to individual patients based on CTEPH type and on experience and the likelihood of successful outcome.

Factors which favor the decision to perform PTEA are:

- Proximal accessible lesions
- Patient consent
- Absence of major comorbidity
- mPAP >40 mmHg
- PVR >300 dyn-s-cm<sup>-5</sup>
- NYHA Class III/IV
- Surgical expertise

Currently, advanced age, concomitant cardiac disease (e.g., coronary artery disease), severe right ventricular failure, renal or hepatic insufficiency and malignancy with reasonable survival expectation are not considered absolute contraindications for the procedure. However, patients with severe left ventricular dysfunction or significant obstructive or restrictive lung disease are not accepted for surgery. All patients over 45 years of age should undergo coronary angiography before surgery to rule out coronary disease. If necessary, coronary artery bypass grafting can be performed at the time of pulmonary endarterectomy. Patients with supra-systemic pulmonary artery pressures and excessive elevation of pulmonary vascular resistance (>1,500 dynes-s-cm<sup>-5</sup>) are considered to be at a significantly high operative risk.<sup>[71]</sup>

#### PTEA procedure

The goals of the operation are restoration of lung perfusion and ventilation perfusion balance, reduction of right ventricular afterload and avoidance of a secondary vasculopathy in patent pulmonary arteries. The operation is performed using extracorporeal circulation and periods of circulatory arrest under deep hypothermia, as good visibility in a bloodless field is essential for accurate endarterectomy. Tricuspid valve repair is not necessary as tricuspid competence usually returns within days after successful pulmonary endarterectomy. Basic tenets of postoperative care are maintenance of adequate right ventricular function, organ perfusion, renal function, sufficient oxygenation and prevention of early pulmonary artery reocclusion.<sup>[232]</sup> Anticoagulation starting 3 months before the procedure and lifelong after endarterectomy is strongly recommended for all patients. Long-term survival, NYHA functional status and exercise capacity are significantly improved. Earlier referral to surgery might avoid the occurrence of a secondary vasculopathy and therefore further improve early and late results.

##### ii. Balloon angioplasty

Current evidence-based guidelines suggest considering balloon pulmonary angioplasty (BPA) as a possible option in patients with CTEPH deemed inoperable for PTEA or with significant residual postoperative PH. In a nonrandomized trial, BPA has been shown to reduce pulmonary artery hypertension in patients with CTEPH. The procedure is also associated with long-term improvement in NYHA class and 6MWT distance. BPA is a possible promising interventional technique that warrants randomized comparison with medical therapy in CTEPH patients who are not surgical candidates. At present, this is considered to be a controversial treatment option.

### iii. Lung transplantation (see above)

Lung transplant (LT) or heart-lung transplantation (HLT) may also be a viable option for some patients with inoperable CTEPH or postoperative persistent pulmonary hypertension.

#### Medical therapy

A substantial proportion of patients with CTEPH are considered inoperable due to significant distal thromboembolic pathology or are classified as representing poor candidacy for PTEA surgery due to concomitant vascular arteriopathy. Although survival in patients with CTEPH that do not undergo surgery has not yet been comprehensively followed up, prognosis in the absence of surgery is very poor, particularly in those with a mean PAP greater than 50 mmHg. The 5-year survival rate in this group of patients is as low as 10%.<sup>[387,421-423]</sup> Pharmacotherapy may be particularly useful in treating patients with predominant small-vessel disease that are poor candidates for surgery, or as bridging therapy in those where there is significant preoperative risk. Pharmacotherapy may be also beneficial in perioperative period to decrease surgical risks of PTEA. Post-surgery use trying to control persistent or recurrent PH also appears a distinct possibility. During initial studies, prostanoids, both IV and inhaled; the dual endothelin receptor antagonist bosentan; and the PDE-5 inhibitor sildenafil have all shown potential in the treatment of inoperable CTEPH. In these studies, these drugs have shown improvement in both hemodynamics and functional status.<sup>[8,11-15,28-30,52,53,90,95,101,120,126,129,131,135,138,145,146,154,164-168,169,171,172,176-178,194,198,202,206,218,219,222,226-228,233-238,240-244,252-253,259,260,269,270,274,275,287,298,301,305,307,309,424-434,435]</sup>

In an open-label multi-center study to evaluate the safety and efficacy of the dual endothelin receptor antagonist bosentan in patients with inoperable CTEPH, 19 patients were studied.<sup>[427]</sup> The primary end point was a change in PVR; the secondary end points included 6MWT distance, peak  $\text{VO}_2$ , NYHA functional class, serum levels of N-terminal-pro BNP and various other hemodynamic parameters. After 3 months of treatment with bosentan, PVR decreased from  $914 \pm 329$  to  $611 \pm 220$   $\text{dyne}\cdot\text{s}\cdot\text{cm}^{-5}$  ( $P < 0.001$ ). Functional class and peak  $\text{VO}_2$  remained unchanged, but 6MWT distance increased from  $340 \pm 102$  to  $413 \pm 130$  m ( $P = 0.009$ ); and serum NT-pro BNP levels improved from  $2,895 \pm 2,620$  to  $2,179 \pm 2,301$  ( $P = 0.027$ ). One patient died, presumably from influenza-A infection; and another patient experienced progressive fluid retention despite reduction of PVR. In another case series of 16 patients with inoperable CTEPH,<sup>[424]</sup> 6 months of bosentan treatment showed improvement in NYHA functional class by one class in 11 patients. Mean 6MWT distance increased from  $299 \pm 131$  m at baseline to  $391 \pm 110$  m at 6 months ( $P = 0.01$ ). In parallel, proBNP decreased from  $3,365 \pm 2,923$  to  $1,755 \pm 1,812$  pg/ml ( $P = 0.01$ ). Neither aspartate aminotransferase nor alanine aminotransferase changed significantly.

A subgroup analysis of a double-blind randomized placebo-controlled BENEFIT trial [Bosentan for inoperable chronic thromboembolic pulmonary hypertension (CTEPH) and post-pulmonary endarterectomy pulmonary hypertension] involving 157 patients in 26 centers in 13 countries was presented at the American Thoracic Society (ATS) meeting, 2007. It suggests that bosentan improves hemodynamics in both patients with inoperable CTEPH and those with persistent or recurrent PH after PEA. Of the 157 enrolled patients, 113 were

inoperable (bosentan,  $n = 55$ ; placebo,  $n = 58$ ) and 44 patients were post-PEA (bosentan,  $n = 22$ ; placebo,  $n = 22$ ). Significant reductions in PVR were observed in both groups. The mean treatment effect was  $-17.5\%$  ( $-27.0, -6.7$ ) in the inoperable group and  $-32.5\%$  ( $-44.4, -18.1$ ) in the post-PEA group. Mean 6MWT distance was unchanged in both groups. Improvements in the Borg dyspnea index were observed in the inoperable group but not in the post-PEA group. In the inoperable and post-PEA groups respectively, there were improvements in favor of bosentan on mean cardiac index [ $0.31$  ( $0.12, 0.50$ ) and  $0.25$  ( $-0.08, 0.57$ )  $\text{L}/\text{min}/\text{m}^2$ ], mean mPAP [ $-1.0$  ( $-3.9, 1.9$ ) and  $-6.4$  ( $-11.2, -1.7$ )  $\text{mmHg}$ ] and mean NT-pro-BNP [ $-654$  ( $-1170, -138$ ) and  $-526$  ( $-1054, 2$ )  $\text{ng}/\text{L}$ ].

The responses to continuous intravenous epoprostenol were evaluated in 9 CTEPH patients who subsequently underwent PTEA.<sup>[145]</sup> Cardiopulmonary hemodynamic parameters were determined prior to the initiation of epoprostenol, while on epoprostenol, prior to PTEA and after PTEA. Six patients treated for 2-26 months prior to PTEA experienced either clinical stability or improvement, which was associated with a mean reduction in PVR by 28%. Three patients treated for 3-9 months experienced clinical deterioration during epoprostenol administration, with a significant increase in PVR in 2 patients. Subsequent PTEA resulted in a highly significant improvement of cardiac index, mPAP and total PVR. Nagaya and co-workers<sup>[422]</sup> evaluated bridging treatment with intravenous epoprostenol for approximately 6 weeks before PTEA in 12 patients with severe CTEPH (PVR  $>1,200$   $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ ). Significant improvements were observed in PVR and cardiac output, but not in mPAP, during the preoperative period. Plasma BNP was also markedly decreased after treatment, suggesting improved right-heart function. Excellent post-PTEA outcome was observed, with further reductions in PVR and plasma BNP. However, it is not clear whether this was as a result of preoperative epoprostenol treatment, a successful surgical procedure or both. Ono and colleagues<sup>[429]</sup> evaluated oral beraprost sodium in inoperable patients with distal CTEPH in the absence of major vessel obstruction. Patients were divided into two treatment groups: one receiving oral beraprost and conventional therapy ( $n = 20$ ) versus one receiving conventional therapy alone ( $n = 23$ ). Overall, improvements in NYHA functional class were observed in 10 patients (50%) after oral administration of beraprost. In a subgroup of the patients, hemodynamics were evaluated after 2 ( $\pm 1$ ) months of treatment. In this subgroup, beraprost-treated patients showed significant improvements in mPAP and total PVR but not in cardiac output. Overall, the study suggested that 1- to 5-year survival may be improved with beraprost therapy when added to conventional treatment.<sup>[429]</sup>

Sildenafil has gained significant interest in this field. In an open-label study with an approximately 6-month follow-up, Ghofrani and co-workers<sup>[198]</sup> assessed sildenafil therapy in 12 patients with CTEPH with inoperable progressive distal disease and severe PH (PVRi,  $1,935 \pm 228$   $\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}\cdot\text{m}^2$ ; and mPAP,  $52.6 \pm 3.6$   $\text{mmHg}$ ). Acute vasodilator testing in these patients showed considerable vasoreactivity with both oral sildenafil and inhaled NO. After 6.5 ( $\pm 1.1$ ) months, 6MWT distance and PVR were significantly reduced, and significant changes were also seen in CI, mPAP and central venous pressure.

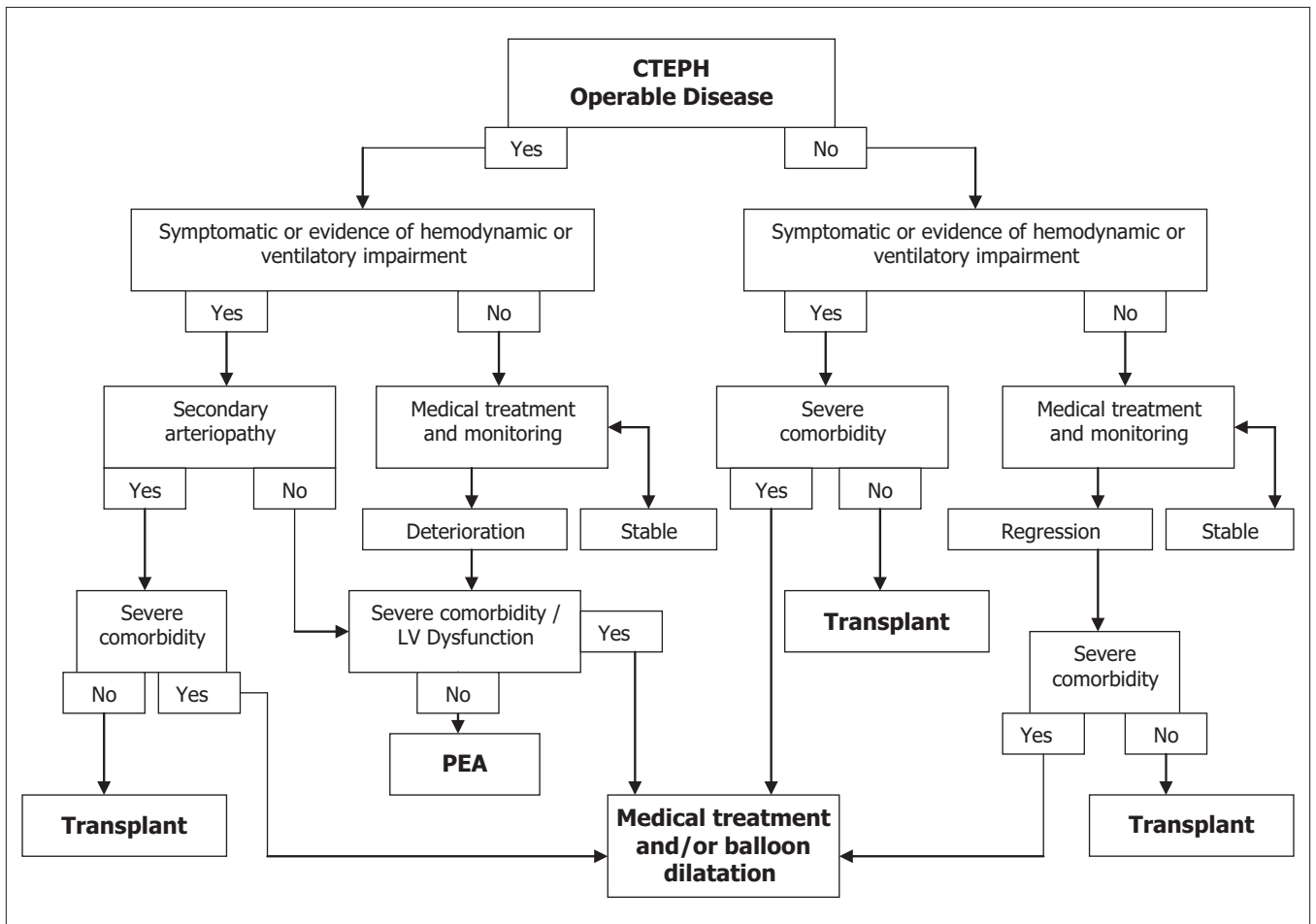


Figure 4: Algorithm for the management of CTEPH

More recently, Sheth and colleagues<sup>[428]</sup> reported a small study with sildenafil in six patients with severe, inoperable CTEPH and left ventricular dysfunction that were receiving anticoagulant therapy. Follow-up at 6 weeks showed beneficial effects of sildenafil on mPAP, mean capillary wedge pressure, Medical Research Council dyspnea scores and NYHA functional class.<sup>[428]</sup>

Many experts also agree that different combinations of prostanoids, endothelin receptor antagonists and PDE-5 inhibitors will play a major role in therapy in the future.<sup>[433,434]</sup> Randomized trials are needed to further assess the usefulness of these agents in this category of pulmonary hypertension. Two trials (COMPASS and EARLY) were presented at CHEST 2007, the annual meeting of the American College of Chest Physicians, in Chicago, USA, demonstrating that bosentan may be safe and effective as a combination therapy for the treatment of PAH. Data from both studies suggest that bosentan, when given in combination with sildenafil, is well tolerated and improves hemodynamics in PAH patients.

The role of intra-caval (IVC) filters to prevent venous thromboembolism (VTE) in patients with CTEPH is controversial. Some experts feel that IVC filtration may actually increase the incidence of pulmonary embolism (PE),

and controlled anticoagulation therapy is sufficient to combat recurrence of PE.

The algorithm for management of CTEPH is illustrated in Figure 4.

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