The Adult Patient with Eisenmenger Syndrome: A Medical Update After Dana Point
Part I: Epidemiology, Clinical Aspects and Diagnostic Options

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Abstract: Eisenmenger syndrome is the most severe form of pulmonary arterial hypertension and arises on the basis of congenital heart disease with a systemic-to-pulmonary shunt. Due to the chronic slow progressive hypoxemia with central cyanosis, adult patients with the Eisenmenger syndrome suffer from a complex and multisystemic disorder including co-agulation disorders (bleeding complications and paradoxical embolisms), renal dysfunction, hypertrophic osteoarthropa-thy, heart failure, reduced quality of life and premature death.

For a long time, therapy has been limited to symptomatic options or lung or combined heart-lung transplantation. As new selective pulmonary vasodilators have become available and proven to be beneficial in various forms of pulmonary arte-rial hypertension, this targeted medical treatment has been expected to show promising effects with a delay of deteriora-tion also in Eisenmenger patients. Unfortunately, data in Eisenmenger patients suffer from small patient numbers and a lack of randomized controlled studies.

To optimize the quality of life and the outcome, referral of Eisenmenger patients to spezialized centers is required. In such centers, specific interdisciplinary management strategies of physicians specialized on congenital heart diseases and PAH should be warranted.

This medical update emphasizes the current diagnostic and therapeutic options for Eisenmenger patients with particularly focussing on epidemiology, clinical aspects and specific diagnostic options.

Keywords: Cardiovascular diseases, adult congenital heart defects, pulmonary hypertension, Eisenmenger syndrome, follow-up studies, Competence Network for Congenital Heart Defects.

1. INTRODUCTION

The revised classification system defined during the 3rd World symposium on PAH held in 2003 in Venice, Italy, included several improvements over the former 1998 Evian Classification system [1].

Slight modifications were proposed during the 4th World symposium on PAH held 2008 in Dana Point, USA (Table **2**), also being reflected in the ESC-Guidelines for diagnosis and treatment of pulmonary hypertension [2], which have significant impact on the management strategies of PAH in congenital heart disease (Table **1**).

Overall, the classification system of pulmonary hypertension can be summarized as:

o   WHO Group I - Pulmonary arterial hypertension (PAH)

o   WHO Group II - Pulmonary hypertension associated with left heart disease

o   WHO Group III - Pulmonary hypertension associated with lung diseases and/ or hypoxemia

o   WHO Group IV - Pulmonary hypertension due to chronic thrombotic and/ or embolic disease

o   WHO Group V - Miscellaneous.

Congenital cardiac anomalies, associated with PAH, are represented in Group 1 in this clinical classification system.

Until recently pulmonary arterial hypertension (PAH) was defined by a mean pulmonary artery pressure (PAP) of more than 25 mmHg at rest or more than 30 mmHg during exercise. A short time ago, a new grading has been proposed during the 4th World symposium on PAH 2008 in Dana Point, USA [3]. Now, the preassigned upper limit of the normal mean PAP at rest will be 20 mmHg, while 21-24 mmHg is termed "borderline-PAH", and a mean PAP of more than 25 mmHg as "manifest" PAH [4]. Pulmonary ar-tery wedge pressure, cardiac output and the derived parame-

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Table 1.   Management Algorithm for Pulmonary Arterial Hypertension in Congenital Heart Disease Patients (mod. ESC-Guidelines [2])
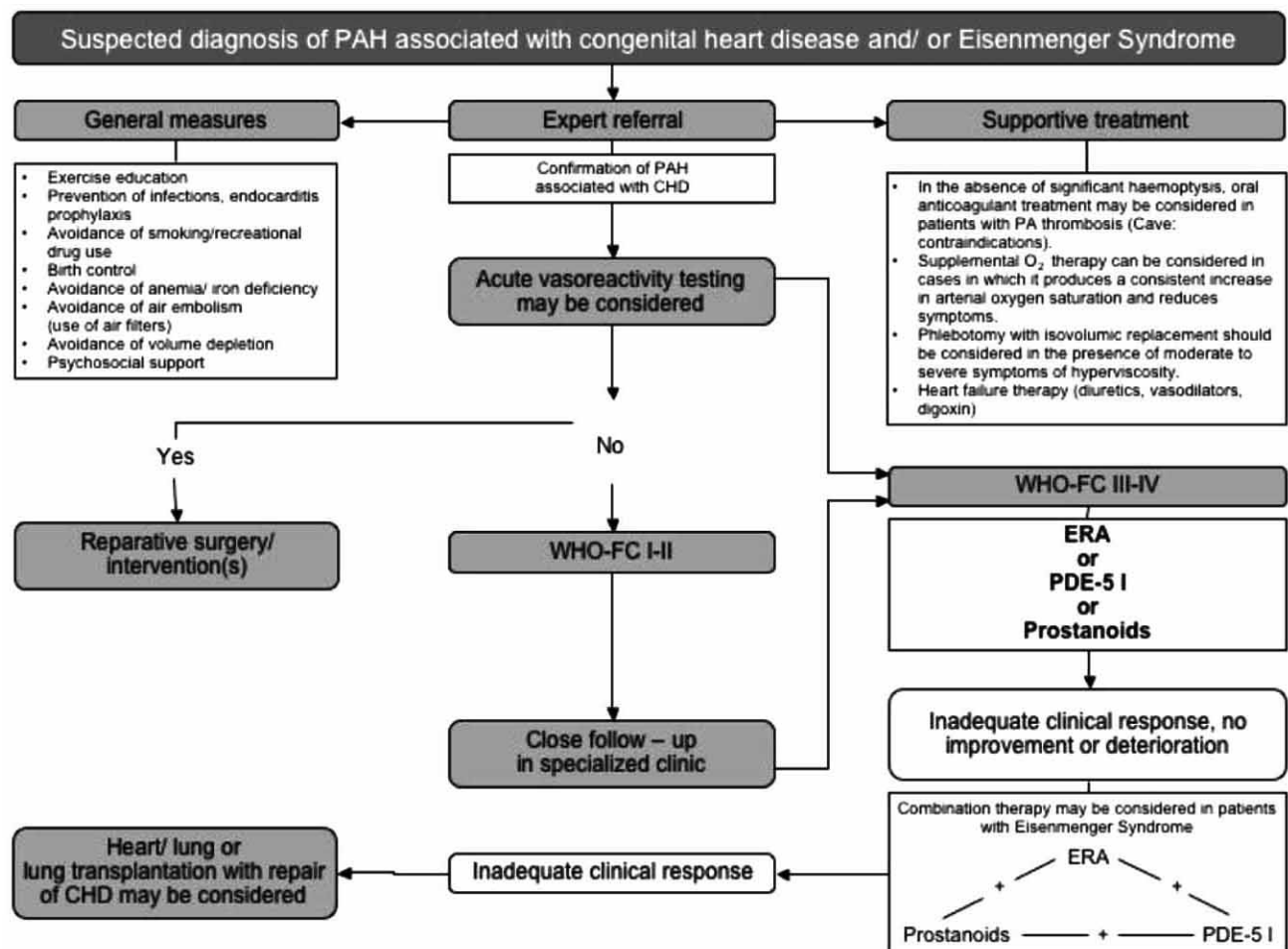
ters will not be taken into account, and PAH during exercise will not any longer be used for defining PAH.

The most severe form of PAH related to congenital cardiac anomalies (CCD) is called Eisenmenger Syndrome (ES).

The first clinical description originates from the Viennese physician Victor Eisenmenger (29. Jan. 1864 - 11. Dec. 1932). In 1897 he reported on a 32-year-old man with cyanosis and dyspnea since infancy [5, 6]. This patient had a reasonably active life until 3 years before his death, when dyspnea increased and right heart failure began. He succumbed suddenly after massive hemoptysis. Autopsy revealed a non-restrictive membranous malalignment ventricular septal defect (VSD), marked right ventricular hypertrophy, an overriding aorta, and atheromatosis of the major pulmonary arteries. In this paper neither pulmonary artery pressure nor pulmonary vascular disease were discussed [6].

During 60 years following Eisenmenger´s report only little insight was gained into the pathophysiology of this disease. In 1951 Paul Wood referred for the first time to the pathophysiology of Eisenmenger syndrome (ES) or pulmonary hypertension with reversed shunt, and in 1958 refined ES as "pulmonary hypertension due to a high pulmonary

vascular resistance (PVR) with reversed or bidirectional shunt at aorto-pulmonary, ventricular or atrial level".

Pulmonary arterial hypertension and pulmonary vascular disease are induced by uncorrected congenital cardiac anomalies with a primary left-to-right shunt. Over time, vascular changes, and a decrease of the overall cross-sectional area develop in the pulmonary arteriolar bed. When two thirds of the pulmonary vascular bed is compromised, pulmonary resistance and pressure increase.

Secondary to the elevated pulmonary artery pressures, the left-to-right shunt converts into a right-to-left shunt, resulting in desaturation of systemic arterial blood and **cyanosis**.

Today, ES indicates **any** large congenital cardiac defect, no matter where it is located, permitting increased pulmonary blood flow and transmission of elevated pressure to pulmonary circulation, causing a balanced or predominant right-to-left shunt secondary to a fixed and markedly elevated pulmonary vascular resistance. Hemodynamically, Eisenmenger syndrome (ES) is defined as an elevation of the pulmonary vascular resistance to 12 Wood Units or to a pulmonary-to-systemic resistance ratio equal to or greater than 1.0 [7].

Table 2.   **Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008) [3]**

Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. **Heritable**
1.2.1. **BMPR2**
1.2.2. **ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)**
1.2.3. **Unknown**
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. **Schistosomiasis**
1.4.6. **Chronic hemolytic anemia**
1.5 Persistent pulmonary hypertension of the newborn
1′. **Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**
2. Pulmonary hypertension owing to left heart disease
2.1. **Systolic dysfunction**
2.2. **Diastolic dysfunction**
2.3. Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. **Other pulmonary diseases with mixed restrictive and obstructive pattern**
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. **Pulmonary hypertension with unclear multifactorial mechanisms**
5.1. **Hematologic disorders: myeloproliferative disorders, splenectomy**
5.2. **Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis**
5.3. **Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders**
5.4. **Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis**

Main modifications to the previous Venice classification are in **bold**.
ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; HIV = human immunodeficiency virus.

For a very long time severe pulmonary hypertension in ES was believed irreversible and treatment was only symptomatic. Recent advances in the medical treatment, however, may potentially reduce pulmonary artery resistance, reverse the process and improve clinical condition and survival in selected patients with systemic pressures in the pulmonary artery. Recent data on vasodilator treatment for PAH show that nearly one third of Eisenmenger patients maintain some degree of pulmonary vasoreactivity to inhaled NO [8], and even some reverse remodeling due to antiproliferative effects of endothelin receptor antagonists may occur [9].

However, long-term results of this approach are lacking. It has to be kept in mind that pharmacological treatment of PAH in patients with persisting shunt lesions may even be precarious. This is completely different from people with idiopathic forms of PAH (iPAH). If the underlying defect remains uncorrected, the pharmacologically induced reduction of pulmonary vascular resistance may induce increased pulmonary flow, and even an increased pressure and shear stress, which, in turn, may intensify anatomic vascular changes. This may put the patients with persisting shunts into a high risk group and, perhaps, the long-term prognosis may worsen and become comparable with that of iPAH patients.

Moreover, the prognosis of the rare, primarily inoperable patients with a congenital cardiac defect (CCD) and a shunt who can be repaired after a positive response to pharmacotherapy is also uncertain. It is still unknown, if his 'natural' or unnatural history can be affected favorably, or, if his prognosis becomes worse and also converges to that of a patient with idiopathic forms of PAH.

2. EPIDEMIOLOGY, NATURAL HISTORY AND CLINICAL COURSE

The development of ES depends on the size of the shunt lesion and concomitant factors, such as the presence of Down syndrome.

Eisenmenger physiology is commonly established during the first one or two years of life if the shunt is aortopulmonary or interventricular. The risk to develop ES depends on the size and location of the shunt lesion. It may occur in congenital anomalies with a left-to-right shunt big enough to allow equalization of pressure between both ventricles and/ or pulmonary artery, and not in patients with small shunts or septal defects associated with significant pulmonary stenosis. Particularly susceptible are patients with VSD, complete AV-septal defect, patent ductus arteriosus (PDA), aorto-pulmonary window, D-transposition of the great arteries and a VSD as well as a truncus arteriosus. Major previously used systemic-to-pulmonary artery shunts such as Waterston- or Pott-shunts may also be associated with the development of ES. Large defects at the atrial level may also cause pulmonary hypertension, but usually less often, and not until the second or third decade of life.

The **prevalence** of ES is not known. According to historical data, about 8% of patients with congenital cardiac disease and 11% of those with left-to-right shunts develop the ES [10, 11]. Recent data are derived from the CONCOR (CONgenital COR vitia) registry, a nationwide registry of adult patients with congenital heart defects in the Netherlands [11]. The prevalence of PAH among 5970 registered adults with congenital heart disease (CHD) was 4.2%, one percent of all registered patients had the ES. Of 1824 patients with a septal defect and therefore prone to PAH, in the registry 112 patients (6.1%) had PAH. Of these patients, 58% had the ES. Among the patients with a previously closed septal defect, 30 had PAH (3%).

The natural history of ES is comprised of a long symptom-free time period. Patients have adjusted to a lower exercise capacity since childhood. Patients may even do well throughout adolescence and early adulthood. Many become symptomatic during their 30s and gradually develop complaints and complications, particularly cyanosis, exercise intolerance, dyspnea upon exertion, syncope, chest pain, stroke or brain abscesses, right sided congestive heart failure,

hyperviscosity complications, pulmonary hemorrhage/ hemoptysis and endocarditis. Rhythm disturbances, particularly atrial fibrillation, corresponds to clinical deterioration and right heart failure. According to historical data, patients with ES usually die between 30 and 35 years [7]. However, survival to late adulthood has been reported.

Importantly, prognosis of patients with spontaneous ES is by far better than the prognosis of patients with idiopathic forms of PAH, although there are many similarities regarding the histological changes [12], Fig. (**1**). The ventricular remodeling in patients with ES differs from that in patients with idiopathic pulmonary hypertension [13, 14]. The better prognosis of Eisenmenger patients is believed to be to the fact that the subpulmonary ventricle has been exposed to high pressures and has been primed since birth; it is better adapted because of the long-standing volume and pressure overload. Furthermore, regression of the physiologic right ventricular hypertrophy does not occur and the right-to-left shunt serves as an excess flow valve.
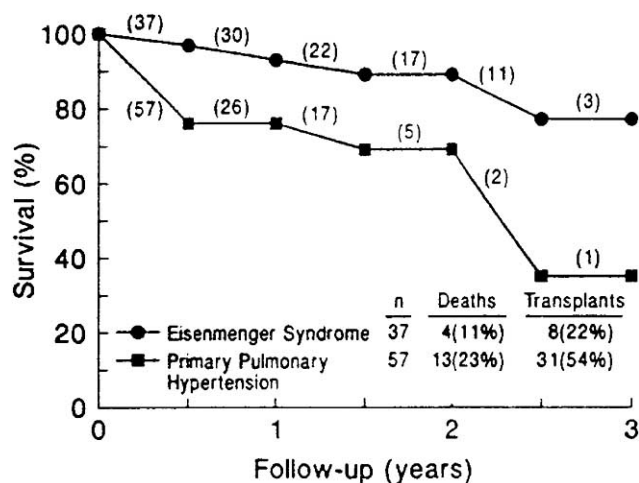

Fig. (1). Kaplan-Meier survival of patients with Eisenmenger syndrome and PPH [12].

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The actuarial survival rate is 80% at 10 years, 77% at 15 years 42% at 25 years [15, 16]. Most Eisenmenger patients die from sudden cardiac death, congestive heart failure, hemoptysis, cerebral abscesses, thromboembolic events, from complications during pregnancy or due to noncardiac surgery [17].

3. ANATOMY AND PATHOPHYSIOLOGY

3.1. Anatomy

The Eisenmenger physiology is part of the spectrum of unoperated CHD, as mentioned above, but may also develop despite surgical repair of the underlying cardiac anomaly.

Pulmonary vascular resistance plays the key role. Paul Wood's strict definition of ES as severe systemic cyanosis due to reversal of the shunting at atrial, ventricular or great artery level theoretically excludes common atrium and anomalous pulmonary venous drainages, single ventricle, and truncus arteriosus. In these cases, cyanosis does not result from shunt reversal, but is the consequence of obligate intracardiac mixing of desaturated and oxygenised blood. This aspect is important for proper management of these diagnoses.

While the process to ES is usually interrupted with early surgical repair of the shunting lesion, pulmonary vascular disease may progress in late repair and individual cases. As a consequence, a hemodynamic situation similar to iPAH may result.

3.2. Pathophysiology

The presence of an increased pulmonary blood flow and transmission of systemic pressure to the pulmonary arteries - due to a nonrestrictive communication at any level between the systemic and pulmonary circulation- are the driving forces for the development of reactive pulmonary hypertension, which is followed by irreversible pulmonary vascular disease.

As a matter of principal, in patients with a primary left-to-right shunt, the physiologic decrease of pulmonary vascular resistance early after birth results in an increased left-to-right shunt (right-to-left shunting in transposition or mixed flow in single ventricle). It is likely that in patients with a large communication high flow causes mechanical stretch and intimal tears. Moreover, it produces progressive structural abnormalities and histological changes in the pulmonary vasculature, which are accompanied by an increased production of intrinsic elastase and vascular endothelial growth factors. Endothelial and medial hypertrophy and pulmonary occlusive lesions can progress further [18, 19]. Furthermore, endothelin concentrations and serum thromboxane levels increase and induce endothelial dysfunction and platelet activation [20, 21]. Complex pathobiological processes cause pulmonary obstructive lesions and pulmonary hypertension can develop, which result in decreased pulmonary blood flow in turn [22].

As long as PVR is lower than the systemic vascular resistance, a predominant left-to-right shunt is present. Particularly in children this situation is associated clinically with congestive heart failure.

As structural changes in the pulmonary artery progress and pulmonary vascular resistance rises, symptoms of congestive heart failure disappear, and right-to-left shunt develops at the atrial, ventricular or the level of the great arteries. Cyanosis may initially be observed only on effort, but over time, cyanosis manifests at rest (ES).

The effect of the **shunt** depends on the exact **location and its size** (Table **3**, **4**). Shunts may cause different loading conditions and exert strain on the pulmonary vascular tree and the subpulmonary ventricle, and thus modify morbidity and mortality.

Table 3. **Anatomic-Pathophysiologic Classification of Congenital Systemic-to-Pulmonary Shunts Associated With Pulmonary Arterial Hypertension (Modified From Venice 2003) [3]**

Anatomic-Pathophysiologic Classification of Congenital Systemic-to-Pulmonary Shunts Associated With Pulmonary Arterial Hypertension (Modified From Venice 2003)

1. Type
1.1. Simple pre-tricuspid shunts
1.1.1. Atrial septal defect (ASD)
1.1.1.1. Ostium secundum
1.1.1.2. Sinus venosus
1.1.1.3. Ostium primum
1.1.2. Total or partial unobstructed anomalous pulmonary venous return
1.2. Simple post-tricuspid shunts
1.2.1. Ventricular septal defect (VSD)
1.2.2. Patent ductus arteriosus
1.3. Combined shunts (describe combination and define predominant defect)
1.4. Complex congenital heart disease
1.4.1. Complete atrioventricular septal defect
1.4.2. Truncus arteriosus
1.4.3. Single ventricle physiology with unobstructed pulmonary blood flow
1.4.4. Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
1.4.5. Other

2. Dimension (specify for each defect if >1 congenital heart defect)
2.1. Hemodynamic (specify Qp/Qs)*
2.1.1. Restrictive (pressure gradient across the defect)
2.1.2. Nonrestrictive
2.2. Anatomic
2.2.1. Small to moderate (ASD ≤2.0 cm and VSD ≤1.0 cm)
2.2.2. Large (ASD >2.0 cm and VSD >1.0 cm)

3. Direction of shunt
3.1 Predominantly systemic-to-pulmonary
3.2 Predominantly pulmonary-to-systemic
3.3 Bidirectional

4. Associated cardiac and extracardiac abnormalities

5. Repair status
5.1. Unoperated
5.2. Palliated (specify type of operation[s], age at surgery)
5.3. Repaired (specify type of operation[s], age at surgery)

*Ratio of pulmonary (Qp) to systemic (Qs) blood flow.

I. Shunt at Atrial Level

Partial and total anomalous pulmonary venous drainage, sinus venosus defects, atrial septal defects, and common atrium:

These defects deliver mainly large blood volumes without an increase of pressure and without shear stress to the pulmonary endothelium.

In **abnormally draining pulmonary veins**, the shunt is fixed due to the abnormal connection.

In **atrial septal defects**, the shunt volume can be large and may cause right heart dilatation. The amount of left-to-right shunt correlates with right ventricular diastolic compliance and will decrease with increasing right ventricular stiffness. If PVR increases in the 3rd and 4th decade, an additional

pressure load develops, and right ventricular myocardium may fail. Hence, cyanosis may worsen by the increased right-to-left shunt due to increased right ventricular filling pressure overload.

II. Shunt at Ventricular Level

Atrio-ventricular and ventricular septal defects, and single ventricle:

These defects deliver volume and, depending on size, pressure. In systole, the volume is directly ejected into the great arteries and depends on the R_p:R_s ratio and the ejecting power of the ventricles and ends with closure of the semilunar valves. There may be a different shunt direction and volume in early and late diastole, which depends on ventricular compliance. This explains the angiographic and hemodynamic findings of left-to-right shunting during systole and right-to-left shunting in diastole in the presence of a hypertrophied and stiff right ventricle.

The atrio-ventricular septal defect adds the atrial shunt physiology to this, i.e. contributes the volume load causing ventricular dilatation. In case of a large defect, the high pressure postnatally maintains a high, near systemic PVR, avoiding severe cyanosis and also avoiding transient heart failure. Cyanosis may not be marked and is discovered only when PVR becomes suprasystemic.

III. Shunt at Arterial Level

Aortopulmonary window, persistent ductus arteriosus, and truncus arteriosus:

All shunts at arterial level deliver blood flow and systemic pressure to the pulmonary vascular tree continuously during both systole and diastole and are therefore associated with an early and rapidly progressive rise of pulmonary vascular resistance.

Size of Shunt

Restriction versus large defects:

Below a certain size, the exact diameter of the defect does matter. The threshold is 2-3 cm at atrial level (limiting Q_p:Q_s ratio to 4-6-fold), and 1-1.5 cm at ventricular level (limiting Q_p:Q_s ratio to 3-4 fold), and 0.5-0.7 cm at arterial level [23].

On the contrary, if the entire septum is almost absent (e.g. in common atrium, single ventricle, truncus arteriosus), then complete mixing of the venous and arterialised blood occurs, and the resulting saturation is a function of the Q_p:Q_s ratio and is equal in both great arteries, with univentricular heart function.

Eisenmenger physiology may occur not only in unoperated patients, but also postoperatively if communications between the systemic and pulmonary circulation persist. Surgically created systemic arterial to pulmonary shunts (Waterston- and Pott-shunts, and rarely Blalock-Taussig anastomosis) improve oxygen saturation, but at the expense of volume loading of the systemic ventricle. Blood flow through these non-restrictive shunts is frequently difficult to control and may result in pulmonary vasculopathy during follow-up, especially in adult patients.

Table 4.   Clinical Classification of Congenital Systemic-to-Pulmonary Shunts Associated to PAH [3].

Table 5	Clinical Classification of Congenital Systemic-to-Pulmonary Shunts Associated to PAH
A. Eisenmenger syndrome	Includes all systemic-to-pulmonary shunts resulting from large defects and leading to a severe increase in PVR and a reversed (pulmonary-to-systemic) or bidirectional shunt; cyanosis, erythrocytosis, and multiple organ involvement are present
B. PAH associated with systemic-to-pulmonary shunts	Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunt is still prevalent, and no cyanosis is present at rest
C. PAH with small defects	Small defects (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography); clinical picture is very similar to idiopathic PAH
D. PAH after corrective cardiac surgery	Congenital heart disease has been corrected, but PAH is still present immediately after surgery or recurs several months or years after surgery in the absence of significant postoperative residual lesions

PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance.

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3.3 Differences to Idiopathic Pulmonary Arterial Hypertension

Stimulus Known

In contrast to idiopathic PAH, the cause for the development of increased PVR in patients with CHD is known and monitored. In some patient groups, however, the increase in PVR seems to be out-of-proportion to the stimulus, such as in children with persistent small ducts or insignificant atrial septal defects or transposition that is operated on in a timely fashion.

Age Distribution

Idiopathic PAH can present at any age and seems to occur as early as in the first months of life and as late as in the seventh decade. Pediatric iPAH shows a progressive course, which only recently has been modified by available new drug treatments. In contrast, the development of increased PVR in CHD appears somewhat more predictable, being avoidable by surgical repair before 6 months of age and showing decades-long stability in ES.

Right Ventricular Remodeling/Function

The right ventricle can chronically adapt to a large extent to increased afterload and maintain cardiac output until contractility decreases. The subpulmonic ventricle in CHD may be congenitally malformed with different positions of atrioventricular and semilunar valves, hypoplasia or hypertrophy of the inflow, trabecular and infundibular portion or the subpulmonic ventricle, and it may be surgically altered due to myocardial incisions and intraventricular and septal repair, conditions which affect contraction.

4.   CLINICAL PRESENTATION AND PHYSICAL EXAMINATION

Patients with ES often have a history of pulmonary congestion during infancy due to the left-to-right shunt with increased pulmonary blood flow. With increasing pulmonary vascular resistance, the pulmonary flow declines and pulmonary congestion decreases. The shunt will reverse and the patients become cyanotic with further increase in pulmonary vascular resistance.

Typical clinical signs and symptoms of adults with ES are dyspnea on exertion, fatigue, syncope due to low systemic cardiac output, neurologic abnormalities (e.g. headache, dizziness, visual disturbances) due to secondary erythrocytosis and hyperviscosity, congestive right heart failure, arrhythmias, hemoptysis due to pulmonary infarction, rupture of a dilated pulmonary artery or a thin-walled pulmonary arteriole, bleeding due to coagulation abnormalities or thrombocytopenia, and cerebrovascular accidents due to hyperviscosity, paradoxical embolism, or a cerebral abscess.

4.1. Physical Examination

Physical examination reveals central cyanosis and clubbing. In case of a PDA differential cyanosis may occur, if desaturated blood enters the aorta distal to the left subclavian artery. The arterial pulse is often normal or diminished. The jugular venous pulse is normal without right heart failure, or reveals mild to moderate systemic venous pressure elevation with a prominent "a"-wave. In tricuspid regurgitation, the jugular venous pressure may be elevated and shows a prominent "v" wave, Fig. (**2**).

A parasternal lift from the right ventricle is palpable in almost all patients. The left ventricular apical impulse is usually absent due to a posterior displacement. At the upper left sternal border a prominent main pulmonary artery impulse is present and a tactual closure of the pulmonary valve.

On auscultation many adults have a pulmonary ejection sound early in systole, and a loud 4th heart sound. The pulmonary component of the second heart sound is usually loud and single in the presence of non-restrictive ventricular septal defect. The widely and fixed split S2 persists in patients with an ASD. There is usually a spindle-shaped systolic murmur in the pulmonary area. An isodynamic holosystolic murmur of tricuspid regurgitation, which increases its intensity in inspiration may occur at the left lower parasternal border. In case of pulmonic regurgitation a decrescendo murmur (Graham Steell murmur) is audible early in diastole over the left upper parasternal border. Murmurs of a ventricular septal defect or a patent ductus arteriosus are lacking in patients with severe pulmonary hypertension. A third heart sound as well as hepatosplenomegaly or a pulsatile liver occur with right heart failure.

Fig. (2). Elevated jugular venous pressure and prominent "v" wave in right heart failure and severe tricuspid regurgitation.

4.2. ECG

ECG shows right atrial enlargement (P-dextroatriale), right axis deviation, and right ventricular hypertrophy, including tall R wave in $V_{1/2}$, deep S waves in $V_{5/6} \pm$ ST- and T-wave abnormalities. Sometimes, these alterations are superimposed by ECG signs of the underlying cardiac defect (e.g. left or biventricular hypertrophy in univentricular hearts, transposition of the great arteries (TGA), truncus arteriosus). Left axis deviation is typically seen in complete or incomplete AV-septal defects. Atrial or ventricular arrhythmias are often present, particularly in the presence of heart failure. A first-degree AV-block is common in AV-septal defects.

4.3. Lab-Studies

Pulse oximetry depicts decreased oxygen saturations in the cyanotic patient. Secondary erythrocytosis and hematocrit levels greater than 65% are present in most Eisenmenger patients as an adaptation to the low level of circulating oxyhemoglobin. Mean corpuscular hemoglobin and mean corpuscular volume may be low in iron deficient states (microcytosis, hypochromasia). However, despite of iron deficiency hypochromasia and microcytosis are not as frequent as expected, whereas hyperchromasia and macrocytosis are relatively common [24]. Furthermore, many patients present with hyperhomocysteinemia, possibly related to folate or B-vitamin deficiencies [24].

For full evaluation of iron metabolism, serum ferritin and serum transferrin must be assessed in addition to the erythrocyte indexes and perhaps the soluble transferrin receptor, which is proportional to cellular iron requirements [24]. Uric acid and bilirubin levels are usually increased.

4.4. Chest-X-Ray

Chest-x-ray varies with the underlying lesion, the magnitude of the shunt and the duration of pulmonary vascular changes. Usually it reveals prominent, dilated main and branch pulmonary arteries. The peripheral pulmonary vessels are diminished in size and number (pruning), Fig. (**3**). Calcification of the pulmonary arteries or ductus arteriosus may be visible.

Fig. (3). Chest-x-ray in ES with prominent, dilated main and branch pulmonary arteries and diminished size and number of peripheral vessels (pruning).

Patients with the ES due to VSD or PDA have usually a cardiothoracic ratio, which is normal or mildly increased. The left atrium and the left ventricle are not enlarged in patients with ES due to a previous left-to-right shunt at ventricular level or at the level of the great arteries. In contrast, patients with ASD have cardiomegaly due to a volume-overloaded right atrium and ventricle. Biventricular enlargement can be seen in TGA, truncus arteriosus, or univentricular hearts.

5. MODERN IMAGING (ECHO, MRI, CT)

5.1. Echo

Transthoracic echocardiography (TTE) is the first-line imaging modality in the diagnosis of ES. Hemodynamic as-

sessment can be performed using spectral and color flow Doppler. Pulmonary artery pressures are estimated by the following equations:

- **systolic PAP = 4 v_{TR}^2 + RAP**, where v_{TR} equals the peak velocity of the jet of tricuspid regurgitation on continuous wave Doppler (in m/s), provided there is no pulmonary stenosis [25]; RAP is estimated by the size and the diameter change of the inferior vena cava during a "sniff" test [26]

- **diastolic PAP = 4 $v_{PR\text{-}dia}^2$ + RAP**, where $v_{PR\text{-}dia}$ equals the end-diastolic velocity of the pulmonary regurgitation jet [27]

- **mean PAP = 4 $v_{PR\text{-}max}^2$**, where $v_{PR\text{-}max}$ equals the maximum velocity of the pulmonary regurgitation jet

Two-dimensional anatomy is characterized by signs of chronic right ventricular pressure overload. The right ventricular wall thickness is increased and there is flattening of the interventricular septum in systole as right ventricular pressure equals left ventricular systolic pressure. Initially right ventricular systolic function is preserved, but with more advanced disease the right ventricle will dilate, hypokinesis will occur, and eventually the right ventricle will fail.

There are several limitations in the evaluation of size, systolic function and mass of the right ventricle by transthoracic echocardiography. The American Society of Echocardiography has published recommendations for the evaluation of the size of the right ventricle, which rely on linear dimensions and surface measurements in the apical four-chamber view [28]; volumetric measurements cannot be performed accurately because of the complex geometry of the right ventricle. Hence, surrogate markers of right systolic ventricular function, such as fractional area shortening, tricuspid annular motion and systolic tissue Doppler velocities, are used in daily routine practice to describe right ventricular systolic function.

Three-dimensional TTE may circumvent some of the limitations in the volumetric assessment of the right ventricle in the future, but preliminary experience indicates that this technique is not applicable yet to all adult patients [29].

Two-dimensional TTE may also demonstrate the underlying cardiac defect, such as an ASD, large nonrestrictive VSD, AV-septal defect, PDA, AP-window or even more complex anomalies.

Color flow Doppler will document the flow-velocity, bidirectional or right-to-left shunt across the defect. However, the diagnosis of the defect may be difficult in adults due to poor acoustic windows and the equalization of pressures in the systemic and pulmonary circulations.

Transesophageal echocardiography may be useful in patients with ES to rule out thrombi in the presence of atrial fibrillation prior to cardioversion [30] or in search of vegetations when endocarditis is suspected [31]; however, low oxygen saturation levels in these patients, and the potential need for sedation makes this examination uncomfortable and alternative imaging modalities should be considered if TTE is inconclusive. Meticulous monitoring and surveillance by an experienced team (incuding a cardiac anesthetist) is critical.

5.2. Cardiac Magnetic Resonance (CMR)

Cardiac Magnetic Resonance (CMR) provides unrestricted access to the chest without exposure to ionizing radiation. Thus it is ideally suited for longitudinal follow-up of adult CHD patients. CMR provides information on ventricular size and function regardless of chamber geometry, flow volumes, tissue characterization, viability and myocardial perfusion [32].

In patients with ES, CMR has incremental value over TTE with regard to the evaluation of size, systolic function and muscle mass of the right ventricle, the assessment of the main and branch pulmonary arteries, and to exclude congenital cardiac defects that were not recognized during the echocardiographic examination (e.g. PDA, aorto-pulmonary collateral vessels).

In order to evaluate the right ventricle a stack of multiple transaxial cines is acquired, and analyzed using contemporary CMR software. Although time consuming, right ventricular volume measurements can be performed with good accuracy and reasonable reproducibility, particularly if contour data have been stored in a database and are available for comparison at the time of follow-up studies. Reference results for right ventricular volumes and systolic function, according to age and gender have been published [33]. Furthermore, CMR is also capable to evaluate right ventricular mass; these measurements are still labor intensive and used at present mainly for research purposes at the present time [34].

However, CMR does have limitations when it comes to measure velocities of narrow regurgitant tricuspid or pulmonary jets, and is thus unlikely to estimate pulmonary pressures accurately.

5.3. Computed Tomography (CT)

Computed Tomography (CT) provides excellent spatial resolution and it has been shown that **CT angiography of the pulmonary arteries (CTPA)** has good sensitivity in the diagnosis of pulmonary embolism [35]. Furthermore, it is known since Wood's necropsy series that Eisenmenger patients may develop thrombi in the pulmonary arteries. Thus, several recent studies have used this imaging modality to examine the prevalence and risk factors for pulmonary arterial thrombosis in patients with ES [36, 37].

In these studies CT and CTPA showed enlargement, thrombosis, and mural calcification of the pulmonary artery and its proximal branches. Within the lung parenchyma, embolic infarction, hemorrhage, neovascularity, lobular ground glass opacification, and hilar and intercostal collaterals were recognized. In Eisenmenger patients, neovascularity, lobular ground glass opacification, and hilar and intercostal collaterals were more prevalent than in acyanotic pulmonary hypertension (see also Part III "1.2.2 Bleeding and thrombotic diathesis").

Although CT and CTPA help us to diagnose in situ thrombosis in patients with ES, the lack of prospective data to establish the usefulness of anticoagulation in this patient group, and the exposure to a marginal dose of ionizing radia-

tion, precludes a recommendation to implement this imaging modality in this group of patients on a regular basis.

6. EXERCISING/CARDIOPULMONARY EXERCISE TEST (CPET)

Exercise Physiology of the Pulmonary Circulation

Pulmonary blood flow has different characteristics from the systemic circulation:

– Pulmonary vessels have a low basal tone;

– Numerous extraordinary, short and thin-walled arterioles with a low resistance;

– Sympathetic vasomotor nerves have no clear physiological role;

– Ventilation has an important impact on pulmonary vascular resistance;

– Metabolic factors have no physiological role, except for oxygen, carbon dioxide and hydrogen that cause an opposite effect on the lung vessels than in the systemic vasculature;

– Metabolic demands of the bronchi are met by a separate bronchial arterial supply. That supply is part of the systemic circulation, causing a minor shunt by drainage into the pulmonary veins.

At rest, mainly the basal lung areas are perfused due to orthostasis. To prevent shunting in the most basal areas the Euler-Liljestrand [38] reflex causes a regional vasoconstriction in hypoxic alveolar areas and redirects pulmonary blood flow to the better ventilated areas. In healthy people there is a large pulmonary blood flow reserve. This can be promoted by stimulating endothelial factors like nitric oxide and prostaglandins, or by relaxing the vascular smooth muscle cell directly.

During exercise endothelial nitric oxide production, measured by exhaled nitric oxide, rises in proportion to ventilation [39] Pulmonary vascular resistance declines to limit elevation of the mean pulmonary pressure. While Oelberg [40] found no increase of the systolic tricuspid regurgitation velocity (TRV) as a non-invasive substitute for the systolic right ventricular pressure, other studies reported on a moderate increase of the TRV [41, 42]. Especially in athletes the previous definition of pulmonary hypertension in the ESC-Guidelines of 2004 [43] with a mean PAP of more than 30 mmHg at exercise is often met [41]. Some of these subjects are merely pre-symptomatic and at high risk to develop PAH later. Others, maybe, are not. Therefore, PAP at exercise was deleted from the diagnostic criteria in the current guidelines [2].

Exercise Physiology in Pulmonary Arterial Hypertension

In patients with pulmonary vascular disease, pulmonary vascular resistance does not display the physiologic decline during exercise. Even in asymptomatic genetic carriers of a familial form of primary pulmonary hypertension, a pathological rise of pulmonary artery systolic pressure could be found [44]. Also patients with atrial septal defect show a decrease in exercise capacity correlating with the extensive

increase of systolic pulmonary pressure during exercise [40]. Patients after repair of a ventricular septal defect showed an increase in mean arterial pulmonary pressure and a failure to decrease pulmonary vascular resistance if there was an elevated pulmonary vascular resistance prior to surgery, or if surgery was performed too late [45].

In patients with ES the unrestrictive bidirectional shunt prevents suprasystemic right ventricular pressure and enables left ventricular filling. A right-to-left shunt at atrial level even augments left ventricular filling and may prevent heart failure during exercise, however, at the expense of cyanosis during exercise [46].

The amount of right to left shunting through a large, unrestrictive ventricular septal defect depends on the ratio of pulmonary to systemic vascular resistance (R_p/R_s). In Eisenmenger patients systemic vascular resistance decreases substantially during exercise, whereas pulmonary vascular resistance decreases inadequately. The ratio of pulmonary to systemic vascular resistance, which might be less than 1 at rest, increases to more than 1 during exercise. Severe cyanosis reaching saturations of less than 50% causes dyspnea and makes patients stop exercise [46].

In addition to the findings in patients with pulmonary hypertension without shunt (reduced peak work load, oxygen uptake ($V'O_2$), oxygen pulse, heart rate, ventilation, systolic blood pressure, ventilatory threshold, $V'O_2$ to work load slope, and $V'O_2$ to heart rate slope; increased ratio of ventilatory threshold to peak $V'O_2$ and especially the $V'E/V'CO_2$ slope [47-49]), the right-to-left shunting in Eisenmenger patients provokes a further increase in the $V'E/V'CO_2$ slope [50], a further increase in end-tidal partial pressure of O_2, a further decrease in end-tidal CO_2, an increase in the respiratory exchange ratio ($V'CO_2/V'O_2$) [51], and a decline of the oxygen pulse. Despite low arterial oxygen saturation, only few patients report on central nervous symptoms like dizziness. However, ECG repolarization abnormalities, including T-wave inversion or ST-segment depression, similar to those seen in ischemic heart disease, are common.

PAH and Sports

As many congenital cardiologists have seen pulmonary hypertensive crises in the postoperative management of patients with pulmonary hypertension [52], they fear to provoke a pulmonary hypertensive crisis by exercise. However, during laboratory exercise tests these events are hardly reported [47]. Moreover, none of the 61 deaths Daliento *et al* [53] reported on were related to sporting activities.

Nevertheless, for Eisenmenger patients a recent recommendation for participation in competitive and leisure sport [54] allows only low dynamic sport leisure activities and forbids competitive sports. Patients with ES may not perform scuba diving. Decompression in commercial airlines causes less desaturations than sports [55]. Patients report on travelling frequently and safely [56] (see also Part III "1.9 Travel to high altitude / Air flight").

Exercise Training as a Therapeutic Concept in PAH

Regular exercise training improves endothelial function in systemic vessels even in severe heart failure patients [57]

and improves survival [58]. An animal model [59], trying to translate these improvements to the pulmonary vessels, failed to show positive effects of exercise training to pulmonary hypertensive rats.

However, patients with idiopathic or chronic thromboembolic pulmonary hypertension [60] had a benefit from exercise training in respect to an increased six minute walking distance, peak $V'O_2$, ventilatory threshold, and peak achieved work load. Additionally, quality of life improved. No adverse events were reported. Nevertheless, changes in the hemodynamics could not be found. Perhaps, exercise training may mainly result in an improvement of the peripheral exercising muscles, and not of the pulmonary vascular bed [61]. Evidence of improved survival is lacking.

7. HAEMODYNAMICS/CARDIAC CATHETERIZATION

The main purpose in cardiac catheterization of a patient with ES is to determine vascular physiology and to assess pulmonary vascular reactivity to vasoactive substances such as oxygen, nitric oxide and prostacyclin. Based on these measurements therapeutic decisions on treatment with vasoactive substances, catheter interventions, or surgery can be made.

In the following, a practical guideline is given how to acquire relevant hemodynamic data for decision making in PAH due to congenital cardiac lesions and to discuss potential pitfalls in the interpretation of the measured data [62, 63].

Cardiac Catheterization

Patients are often examined with mild conscious sedation, breathing spontaneously, to avoid hemodynamic side effects of general anesthesia. A CO_2 value < 45 mmHg is acceptable during the examination. Higher CO_2 values may significantly alter vascular resistance. To obtain exact data, oxygen consumption (VO_2) is measured by the polarographic method. The tables of LaFarge and Mietinnen [64] were relying on healthy young individuals and hence tend to overestimate oxygen consumption. For this reason these table values are not acceptable to determine accurate data in adults with ES.

Usually, a femoral vein and artery are used for vascular access. An end open balloon catheter (pulmonary venous wedge catheter) is placed distally into a pulmonary artery. Systemic arterial pressures and oxygen saturations are assessed *via* the femoral artery or the aorta.

Blood samples are collected in the superior and inferior vena cava, the pulmonary artery, the left atrium (pulmonary venous wedge position) and in the systemic artery.

Measurement is carried out in several conditions: room air, 20-40 ppm nitric oxide, 100% oxygen and nitric oxide 20-40 ppm, inhaled prostacyclin. Every substance needs to be applied for at least ten minutes in a steady state. In each condition pressures are recorded in the right atrium, left atrium (pulmonary venous wedge position), pulmonary artery, and the aorta. Blood samples are collected in the superior and inferior vena cava, the pulmonary artery, the left atrium (pulmonary venous wedge position) and the aorta. The oxygen saturation of the blood probes is measured using a spectrophotometric method.

Oximetry

Oxygen saturation is the proportion of oxygen bound to hemoglobin divided by the oxygen capacity:

O_2 saturation = (O_2 content - dissolved O_2) x 100 / O_2 capacity.

The **oxygen content** is the total amount of oxygen present in a blood sample. It is a combination of the oxygen bound to hemoglobin plus the dissolved oxygen.

The **oxygen capacity** (in mL O_2/L) can also be calculated by multiplying the hemoglobin (in g/dL) by 13.6. This is because each gram of hemoglobin in a liter of blood will combine with 13.6 mL of oxygen when the hemoglobin is fully (100%) saturated [65].

In contrast to the measurement of oxygen content by the original method of Van Slyke [66] the contemporarily used spectrophotometric method for oxygen saturation assessment does not measure the dissolved oxygen present in the probe. Under room air condition this is negligible, since the amount of dissolved oxygen is only about 1% of the amount of oxygen combined with the hemoglobin (0.03 mL/O_2/mmHg in 1.0 L of blood). However, if the patient breathes 100% oxygen the amount of dissolved oxygen rises significantly. Additional assessment of the pO_2 by blood gas analysis enables to take the dissolved oxygen into consideration. Blood flow can then be calculated using the formulas in Table **5**.

Table 5.   Calculations for Hemodynamic Assessments

Q_p	=	VO_2 / PVO_2 - PaO_2	=	VO_2 / [(PV_{sat} - PA_{sat}) (O_2 capacity)]
Q_s	=	VO_2 / SAO_2 - MVO_2	=	VO_2 / [(SA_{sat} - MV_{sat}) (O_2 capacity)]
Q_{ep}	=	VO_2 / PVO_2 - MVO_2	=	VO_2 / [(PV_{sat} - MV_{sat}) (O_2 capacity)]
Q_p/Q_s	=	(SA_{sat} - MV_{sat}) / (PV_{sat} - PA_{sat})		
Left-to-right shunt	=	Q_p - Q_{ep}		
Right-to-left shunt	=	Q_s - Q_{ep}		
O_2 capacity = 13.6 x gm Hb/dL				

Legend: Q_p = pulmonary blood flow, Q_s = systemic blood flow, Q_{ep} = effective pulmonary blood flow, VO_2 = oxygen consumption, PV_{sat} = pulmonary venous O_2 saturation, PA_{sat} = pulmonary arterial O_2 saturation, SA_{sat} = systemic arterial O_2 saturation, MV_{sat} = mixed venous O_2 saturation.

Resistance

To calculate **vascular resistances** Ohm's and Hagen Poiseuille's laws are applied. It is of note that vessel radius enters the denominator of the formula in the forth power. Hence, a smaller vessel diameter, as seen in pulmonary vascular disease, has significant impact on pulmonary vascular resistance (Table **6**).

Table 6. Calculations for Assessment of Vascular Resistances

R_p =	mPAP - mPVP / Q_p
R_s =	mAOP - mRAP / Q_s

Legend: R_p and R_s = pulmonary and systemic vascular resistance. mPAP = mean pulmonary arterial pressure, mPVP = mean pulmonary venous (left atrial, pulmonary venous wedge) pressure, mAOP = mean systemic arterial pressure, mRAP = mean right atrial pressure

The resistance is expressed in mm Hg x minute x 1-1 (hybrid resistance units or Wood units) [67]. Multiplying by 80 converts Wood units to the centimeter-gram-seconds system, where units are dynes x seconds x cm^{-5}.

Normal **systemic resistance (R_s)** is 13 to 18 units x m^2. Normal **pulmonary arteriolar resistance (R_p)** is less than 2 units x m^2.

It is important to note that for **indexing Wood units to body surface area**, they need to be multiplied (!) by BSA [68].

Interpretation of the Hemodynamic Results

Q_p, Q_s, R_p and R_s are calculated in all conditions. In general, patients with Eisenmenger reaction pulmonary arterial pressures equal systemic arterial pressures due to the large communication between the systemic and pulmonary circulation. The severity of pulmonary arteriopathy is expressed by the pulmonary vascular resistance and the reactivity to vasoactive substances.

In adults with this disease under room air R_p is equal to or greater than R_s. This results in moderate to severe right-to-left shunt with subsequent cyanosis. If however, after exposure to oxygen and nitric oxide, R_p falls to below 5 units x m^2 and a resistance ratio of less than 0.4/1, this would result in significant left-to-right shunt. It is possible that in this case pulmonary pressure and eventually pulmonary vascular resistance will diminish with repair of this lesion [69].

Most patients with Eisenmenger reaction, however, are beyond the point to consider corrective therapy. An R_p of > 10 units x m^2 and R_p/R_s of greater than 0.7/1 usually indicates that corrective treatment (surgery/ catheter intervention) is associated with an increased risk for morbidity and mortality. These patients will not benefit from this approach. If however, R_p or R_p/R_s drops by more than 20% during exposure to oxygen and nitric oxide, medical treatment with vasoactive agents is indicated and may result in significant improvement of quality of life.

8. ACKNOWLEDGEMENT

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