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TOPICAL REVIEW

Eisenmenger syndrome – a unique form of pulmonary arterial hypertension

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Abstract: In 5–10 % of adults with congenital heart disease (left-to-right shunt defects), pulmonary arterial hypertension (PAH) can develop with variable severity. An extreme manifestation of PAH in this setting is known as the Eisenmenger syndrome. It represents not only PAH associated with congenital heart disease, but also a multi-systemic disorder, presented by variety of complications (cyanosis, bleeding, thrombotic diathesis, high risk of bacterial endocarditis or cerebral abscess, ischemic complications, hepatic and renal involvement, congestive heart failure and sudden death).
Authors concisely identify the underlying pathophysiological and hemodynamic aspects of Eisenmenger syndrome and focus on the clinical presentation. Eisenmenger syndrome represents a unique form of PAH with many differences. The preserved right ventricular function seems to play the key role in a better survival of these patients compared to other forms of PAH.
To achieve a satisfactory prognosis and life-quality in patients with Eisenmenger syndrome it is necessary not only to treat their hemodynamic features (PAH and/or ventricular dysfunction) but also to adequately manage and prevent all the multi-systemic complications resulting from this disease. This often needs a care in specialized centers with multi-disciplinary approach *(Tab. 2, Fig. 6, Ref. 17)*. Full Text (Free, PDF) *www.bmj.sk.*
Key words: congenital heart defects, pulmonary arterial hypertension, Eisenmenger syndrome, right ventricular function.

Pulmonary arterial hypertension (PAH) can have a wide spectrum of etiological reasons. It may be present also **in association with congenital heart defects** (1), where the elevated pulmonary artery pressure and pulmonary vascular resistance develops as a result of an increased pulmonary blood flow due to a communication between the systemic and pulmonary circulation.

Definition

Eisenmenger syndrome is an extreme manifestation of the above mentioned setting and represents a distal endpoint of the spectrum of congenital heart defects and PAH with already irreversible pulmonary vascular changes. It is defined: 1) by the presence of a communication between the two circulations with right-to-left (pulmonary-to-systemic) or bidirectional shunting and 2) by the high pulmonary artery pressure that reaches at least 2/3 of the systemic pressure (but it often exceeds the level of systemic pressure) (2).

Eisenmenger syndrome is the only type of PAH, where its development is preventable by an early closure of the underlying defect. On the other hand, once it develops, the closure of the present defect is contraindicated. Eisenmenger syndrome represents a specific form of PAH, as these patients, compared to idiopathic PAH, act often in a different and unique way.

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History

A patient with pulmonary hypertension and a large ventricular septal defect was first described by Viktor Eisenmenger back in 1897 (3) and in 1958 Paul Wood (4) first used the term Eisenmenger's complex or syndrome for *pulmonary hypertension at systemic level due to high pulmonary vascular resistance with reversed or bidirectional blood flow through a defect.*

In fact, already at that time he understood, that *it matters very little, where the shunt occurs* – a large communication between the systemic and pulmonary circulation at any level could lead to same hemodynamic condition. But on the other hand, *the size of the defect* was still important: in his autopsy cases the smallest defects causing pulmonary hypertension occurred at the aorto-pulmonary level (>0.7 cm) and the largest occurred at the atrial level (>3.0 cm).

Background

In Eisenmenger syndrome, the presence of a non-restrictive systemic-to-pulmonary connection without pulmonary outflow tract obstruction is crucial.

Tab. 1. The main features of the congenital heart defect important for the development of pulmonary arterial hypertension (modified from Galic N. Classification of patients with congenital systemic-to-pulmonary shunt associated with pulmonary arterial hypertension: Current status and future directions. In: Beghetti M, Barst RJ, Naeije R, Rubin LJ. Pulmonary arterial hypertension related to congenital heart disease. Munich; Elsevier GmbH, Urban & Fischer Verlag 2006: 11–17).

The site of the defect
- atrial - ventricular - aorto-pulmonary level
The size of the defect
- small to moderate (atrial ≤ 2.0cm, ventricular ≤ 1.0cm) - large (atrial > 2.0cm, ventricular > 1.0cm)
The type of the defect
- simple (atrial septal defect, ventricular septal defect, persistent arterial duct, aorto-pulmonary window) - combined (defects at more sites) - complex (truncus arteriosus, atrio-ventricular septal defect, single ventricle complexes) - presence of aorto-pulmonary collaterals
Associated extra-cardiac abnormalities
- especially genetic syndromes (like Down syndrome)
Presence / absence of correction, time and type of correction
(not forgetting the presence of surgically created aorto-pulmonary anastomoses)

For the development and onset of irreversible pulmonary vascular disease following factors are important (5, 6) – the site of the defect (pre- or post-tricuspid), the size and the type of the defect, associated extra-cardiac abnormalities and the presence or absence of correction, as well as the time and type of correction (Tab. 1).

A wide spectrum of defects can lead to pulmonary hypertension, although some defects are at a higher risk. About 50 % of patients with a large ventricular septal defect and almost 100 % of complex heart defects with an unobstructed pulmonary flow are at risk of developing the Eisenmenger syndrome, on the other hand it is only in 10 % of patients with atrial septal defects (7).

The development of irreversible pulmonary vascular changes may occur within the first two years of life when a large defect at the aorto-pulmonary or ventricular level (post-tricuspid) is present. In contrast, if the pulmonary hypertension develops due to a large defect at the atrial level (pre-tricuspid), in most cases it occurs much later, during adulthood (Fig. 1).

Development of pulmonary hypertension

In the presence of a defect between the systemic and pulmonary circuit at any level, blood shunting occurs according to the current pressure difference between the two communicating sites. Prenatally, the normal hemodynamic situation allows right-to-left shunting through the foramen ovale and the arterial duct.

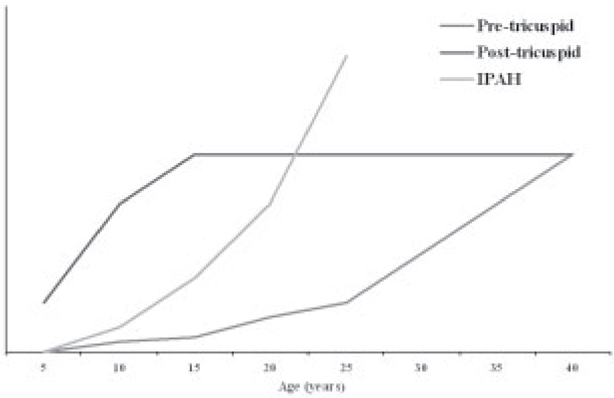


Fig. 1. Time-line of pulmonary hypertension development in patients with post-tricuspid and pre-tricuspid defects compared to patients with idiopathic pulmonary arterial hypertension.

After postnatal adaptation changes, the pressure in the pulmonary (venous) circuit physiologically decreases. So in a "normal" hemodynamic situation the pressure in the pulmonary circuit is lower than in the systemic circuit and in the presence of the defect a left-to-right shunting occurs (Fig. 2a). Due to the shunting this means an increased pulmonary blood flow (Qp) compared with the systemic flow (Qs). Long-lasting increased Qp:Qs >1.5 (especially together with pressure overload) leads to pulmonary vascular reaction. The structural remodeling of the pulmonary vascular bed starts early in childhood, is progressive (2) and leads to irreversible changes of small pulmonary arteries (plexiform lesions with hypertrophy of media and intimal proliferation and fibrosis, finally with necrotizing arteritis of arterioles and small pulmonary arteries).

The development of pulmonary vascular disease increases pulmonary vascular resistance and pulmonary arterial pressure. For a short time the pressure between the two circuits may be equal with virtually no shunting (Fig. 2b) but with the progression of the disease, when the pressure at the pulmonary (venous) side of the defect reaches or exceeds systemic values, the previously left-to-right shunt changes to right-to-left (Fig. 2c). This is the point where we speak of Eisenmenger syndrome.

Clinical models of pulmonary hypertension

There are 3 models of possible development of pulmonary hypertension in Eisenmenger syndrome. When managing an adult patient with Eisenmenger syndrome, the clue that can help is the patient's past medical history (2).

– Congestive heart failure during infancy/childhood, cyanosis developing later

After postnatal physiological decrease of pulmonary vascular resistance a large left-to-right shunt occurs. Due to the increased pulmonary blood flow symptoms of congestive heart failure can be found (tachypnea and/or dyspnea, failure to thrive, heart murmur, hepatomegaly etc.), but *no signs of cyanosis.* With this condition, changes of the pulmonary vascular bed start sooner or later, gradually increasing pulmonary arterial pressure. At one

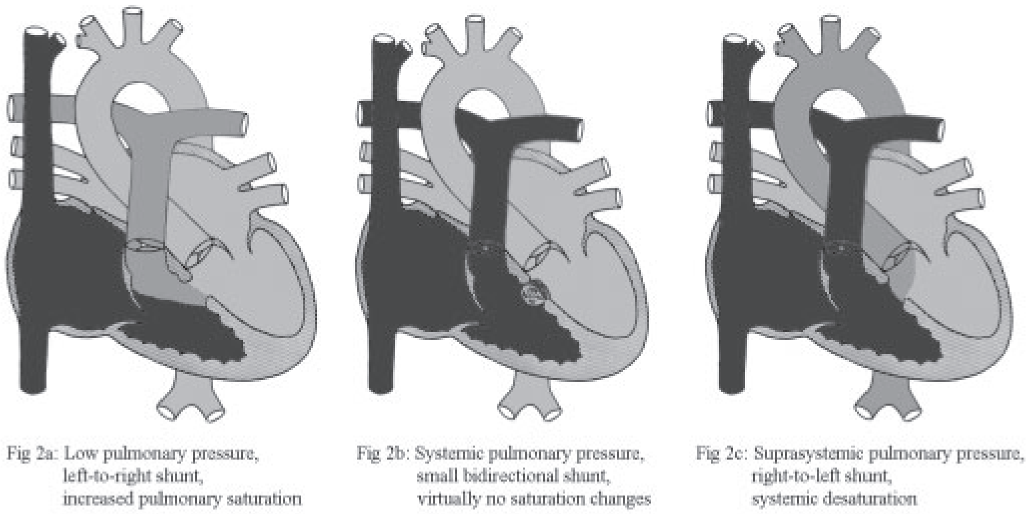


Fig. 2. Hemodynamic considerations in Eisenmenger syndrome development – shunt flow across the defect according to the level of pulmonary arterial pressure.

point, the patient's clinical status seemingly improves for a short period of time and the heart murmur disappears, which can lead to the misinterpretation of a spontaneous defect closure. Hemodynamically it represents a temporary balanced situation, where an aligned pressure in both circuits causes that there is virtually no blood shunting. When the pulmonary arterial pressure exceeds the systemic level, the shunt will change to right-to-left. At this time the patient *will develop cyanosis and hypoxia, fatigue and continuously decreasing exercise tolerance.* Heart murmur can be again audible. From this point onwards all symptoms are progressive with time.

This model is typical **for post-tricuspid defects**, more prominent when a defect at the aorto-pulmonary level is concerned. And of course, the larger the defect, the sooner it comes to irreversible pulmonary hypertension.

– Low level of symptoms during childhood, PAH symptoms in adulthood

Patients even with a large **pre-tricuspid defect** often lack any symptoms during childhood and only later *in adulthood they complain of fatigue, decreased exercise tolerance and mostly mild- or exercise-induced cyanosis*. The development of pulmonary hypertension without any pressure overload is not obligatory and so other factors (genetic?) may play an important trigger role in these patients.

– Cyanosis through childhood, progressive with time

In patients with the Eisenmenger syndrome, the *presence of cyanosis from the beginning* **without any surgical intervention** most probably means a **complex cyanotic congenital heart defect with an increased pulmonary blood flow** (i.e., pulmonary atresia with large aorto-pulmonary collaterals, single ventricle complex without pulmonary flow obstruction, etc.).

On the other hand, a cyanotic adult patient **after a surgical intervention** directs to a cyanotic defect **with initially a low pulmonary blood flow who had surgically created an aorto-pulmonary shunt.** Previously used Potts or Watterston shunts often represented a large non-restrictive aorto-pulmonary communication that could soon lead to irreversible pulmonary vascular disease.

It is necessary to understand the mechanisms of PAH development in every patient, as it plays a crucial role in further prognosis.

Survival

According to multicentric studies, 5–10 % of all patients with congenital heart defects and 19 % of patients with cyanotic heart defect develop PAH. The estimated prevalence of Eisenmenger syndrome among contemporary adult congenital heart disease population is 4 % (7, 8). With the improvement of pediatric cardiology and cardiac surgery during the last decades (with a better diagnosis and sooner performed definitive correction of lesions) it can be expected that their number in future will decrease.

Patients with Eisenmenger syndrome are in many ways different from patients with idiopathic pulmonary hypertension (IPAH). Despite severe morbidity (cyanosis is causing multi-systemic disorders), the survival in patients with Eisenmenger syndrome is strikingly better then in patients with idiopathic PAH – a 5 year survival >80 % compared to a 3 year survival <20–30 % (7, 8, 9). Despite better outcome compared to IPAH patients, the life-expectancy of Eisenmenger patients is significantly reduced compared to normal population. Only 75 % of patients with Eisenmenger syndrome reach 30 years, 70 % reach 40 years and 55 % reach 55 years of age. The mean life-expectancy of patients with simple defects is 32.5±14.6years, in complex defects 25.8±7.9 years (8).

Right ventricle in Eisenmenger syndrome

The crucial question is why despite similar histopathological and pathophysiological pulmonary changes Eisenmenger patients do clinically much better compared to other forms of PAH. The clue seems to be the right ventricle (RV). The intergrity of RV function rather then the degree of pulmonary vascular damage seems to be the main determinant for survival as well as for presentation of clinical symptoms in PAH. The RV in Eisenmenger patients is often described as unique (10).

For the function of the ventricles (both left and right), volume and pressure characteristics play an important role as well as interventricular interdependence.

A normally thin-walled right ventricle (RV) physiologically works in a low-pressure circulatory system. RV can better cope with volume load; on the other hand it does not tolerate a sudden pressure increase very well. Already a mild increase in pulmonary artery pressure happening in a short period of time causes a significant deterioration of RV output. A pressure that the right ventricle can generate in situation of an acute pressure overload is not more 50–60 mmHg.

Chronic RV adaptation to pressure overload is better and includes spherical and morphological remodelation with RV hypertrophy (wall thickness >5 mm). Beside that RV is getting dilated, its shape is changing to a more balloon-like and the heart is rotating to the left. The RV pressure increase is shifting interventricular septum to the left and the left ventricle is changing to a D-shape. Further increase of RV pressure leads to further RV dilatation, secondary dilatation of the tricuspid annulus – and this again leads to progression of tricuspid regurgitation, right atrial and right ventricular dilatation and consequently to right heart failure.

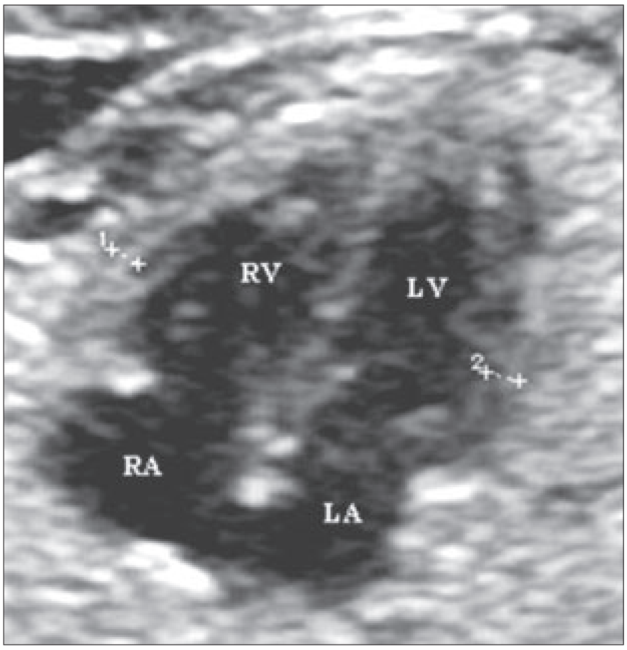
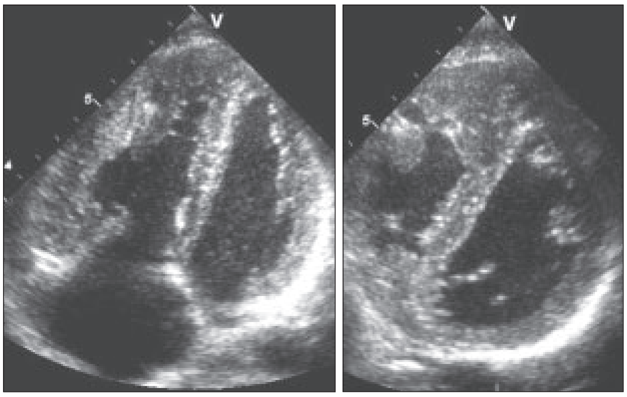


Fig. 3. Apical 4-chamber view, prenatal echocardiographic picture of a normal heart, similar right and leaft ventricular wall thicknes (LA – Left Atrium, LV – Left Ventricle, RA – Right Atrium, RV – Right Ventricle).



a) Apical 4-chamber view, right ventricular hypertrophy and dilatation b) Parasternal short axis view, mid-position of the interventricular septum

Fig. 4. Echocardiographic picture of a patient with Eisenmenger syndrome.

A decrease of RV output influences also the left heart – which means a decreased left ventricular filling volume and insufficient left ventricular output.

In **Eisenmenger syndrome,** the RV gives a specific picture compared to other forms of PAH. The presence of a defect with a right-to-left shunt is the first of all pressure off-loading the right ventricle (**a "pop-off valve"**). Although the pulmonary arterial pressure is high, the RV has better options for adaptation to the situation. This is especially prominent in post-tricuspid defects. On the other hand in pre-tricuspid shunts, where pulmonary hypertension (if at all) develops later in adulthood (after a period of normal pulmonary pressure), the RV picture seems to be more similar to idiopathic PAH.

The presence of the right-to-left shunting is supplying the systemic circulation also with some additional volume. So the left ventricle is able to **maintain a sufficient resting systemic cardiac outpu**t, although of course, at the price of systemic desaturation.

Pressure overload in Eisenmenger syndrome leads to severe RV hypertrophy. In fact, the right ventricle in Eisemenger syndrome is often described as the **"fetal phenotype"**, comparing its hypertrophy to the prenatal picture (Fig. 3), where both ventricles physiologically act under systemic pressure conditions (6, 8, 10). This is present especially in post-tricuspid shunts, where the RV pressure overload is preserved from the newborn period and the ventricle is considered as "trained" for this high-pressure condition.

In the presence of a shunt in the Eisenmenger syndrome, both ventricles act together as one entity throughout the cardiac cycle – **a ventricular interdependence** of both ventricles is present. RV dilatation is less prominent than in other forms of PAH, interventricular septum is more in the mid-line position (Fig. 4), severe tricuspid regurgitation and RV failure usually occur later.

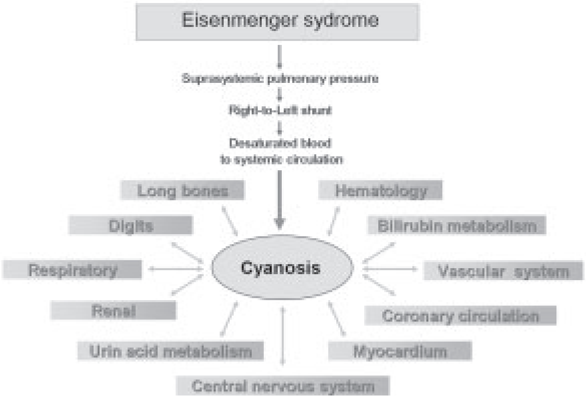


Fig. 5. Eisenmenger syndrome – a multi-systemic disorder.

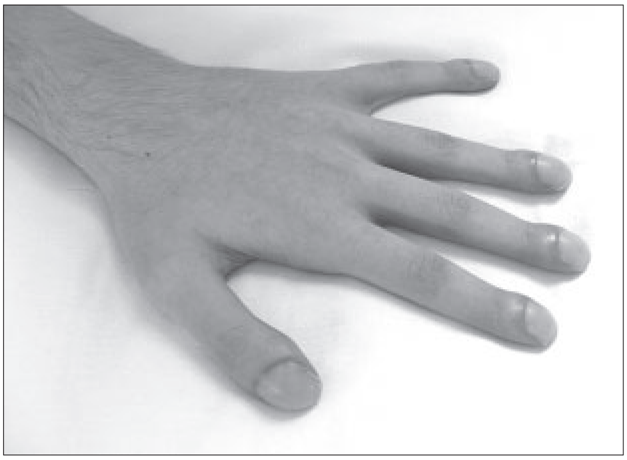


Fig. 6. Hour-glass deformation of fingertips as a result of cyanosis.

So it is clear that in patients with Eisenmenger syndrome the high pulmonary arterial pressure is usually well tolerated. This most probably plays the crucial role for their better survival compared to idiopathic PAH or other forms of PAH. The exact mechanisms underlying the preserved right ventricular function over decades are poorly understood. Further studies with imaging techniques, such as cardiac MRI and tissue Doppler echocardiography, and potential surrogate markers for right ventricular function, such as brain natriuretic peptide, the 6 min walk test, and autonomic nervous activity, are clearly warranted.

A multi-systemic disease

Despite so good cardiac and hemodynamic situation, most patients with Eisenmenger syndrome are symptomatic. Most of the symptoms are a direct consequence of severe cyanosis and/ /or pulmonary hypertension. Cyanosis is not merely systemic arterial desaturation but it triggers many adaptive and also pathological mechanisms. Eisenmenger syndrome can be described as a multi-systemic body dysfunction that can cause various multi-systemic complications (Fig. 5) (6, 11, 12, 13).

– **Hematology**. Chronic hypoxemia stimulates the production of red blood cells. Microcytes due to iron deficiency are typically found. Secondary eryhrocytosis and increased hematocrit cause **hyperviscose syndrome**. Because of this, together with hemodynamic reasons (dilated chambers, arrhythmias, the presence of prothrombotic materials etc.), Eisenmenger patients are at a high risk for **thrombosis.** On the other hand, the presence of thrombocytopenia and coagulation factors deficiency can cause **bleeding** (cerebral, gastrointestinal etc.).

– **Cerebrovascular events.** Stroke or transient ischemic attack can occur due to hyperviscose syndrome or thrombosis. Right-to-left shunt can be the reason for paradoxical embolisation from the venous system. In Eisenmenger patients, there is also a high incidence of **brain abscess**.

– **Vascular system.** Hyperviscosity in the peripheral vascular system leads to shear stress and releases endothelial nitric oxide and prostaglandin. Enhanced vasodilatation can cause increased **risk for syncope**.

– **Coronary circulation.** The same mechanism of vasodilatation leads to elongation, tortuous or aneurysm deformations of coronary arteries. In addition, the arterial oxygen extraction of 70 % is required for basal myocardial function. In most Eisenmenger patients, the aortic oxygen saturation is substantially lower and the ventricular mass is considerably higher which means that the myocardium is not able to cover its metabolic needs. This leads to a compensatory higher basal coronary flow but a decreased flow reserve.

– **Respiratory system.** At rest there is a balance between oxygen supply and demand but there is virtually no reserve during exercise.

– **Bilirubin metabolism.** Erythrocytosis has also an impact on production of non-conjugate bilirubin and this can lead to cholecystitis and/or presence of gallstones.

– **Renal/rheumatologic complications.** The presence of hyperuricemia, glomerular dysfunction, proteinuria and urate nephropathy is frequent and can lead to renal failure and/or gout.

– **Skeletal changes.** Eisenmenger patients often come to connective tissue proliferation of fingertips, with collagen deposit formation, capillary dilatation and lymphocytes infiltration – so called **hourglass-like deformation** (Fig. 6). Long bones are also affected, hypertrophic osteoarthopathy can be found.

– Symptoms of **heart failure** (hepatomegaly, peripheral edema) are mostly present in advanced disease. However **arrhythmias**, believed to be a result of a failing heart, are in Eisenmenger syndrome common also in early phase. They are poorly tolerated and often a cause of morbidity and mortality (11, 14).

Clinical evaluation

When first evaluating an adult patient with Eisenmenger syndrome it is necessary – to **confirm the diagnosis of severe PAH**, to identify correctly the underlying **heart lesions** and the patient's contemporary **hemodynamic situation**, to **exclude any other**

Tab. 2. Diagnostic methods used in Eisenmenger syndrome (modified from R. Krishna Kumar RK, Sandoval J. Advanced pulmonary vascular disease: the Eisenmenger syndrome. Cardiol Young 2009; 19 (E-Suppl 1): 39–44).

	Diagnostic method	Reasons
Cardiac diagnosis	ECG, 24-hour Holter monitoring	Detecting enlaged RA,RV and arrhythmias - atrial flluter / extrasystoles common
	Chest X-ray	Cardiac size / shape and lung fields - to understand cardiac remodeling and associated (respiratory) disorders
	Trans-thoracic echocardiography Trans-esophageal echocardiography	Diagnosis of the underlying heart defect, assessment of pulmonary artery pressure, assessment of ventricular size / function and valve competences
Hypoxia / Lung disease	Measurement of oxygen saturation	Assessment of severity of hypoxemia
	Arterial blood gas	↑ PCO_2 may suggest underlying lung disease
	Pulmonary function tests	Impaired lung function can substantially elevate PVR and contribute to hypoxia
Functional status	Exercise testing	Oxygen consumption of < 10.4ml/min/m² is associated with poor prognosis in idiopathic PAH
	Six-minute walking test (6MWT)	Simple and reproducible measurement of functional capacity
Multi-systemic disorders	Complete blood counts	Hemoglobin and hematocrit estimation, mean corpuscular volume and mean corpuscular hemoglobin concentration
	Serum ferritin and transferring saturation	To identify iron deficiency
	Liver and renal function tests, serum uric acid	To evaluate commonly affected organs, renal dysfunction common with advancing disease
PAH	Cardiac catheterization and Angiography	Measurement of PAP and PVR; response to vasodilators, analysis of the capillary network and proximal arteries and veins (thrombosis / stenoses)
Additional information	Magnetic resonance imaging (MRI)	Anatomic definition, assessment of ventricular function, estimation of flows and resistances
	Chest computed tomography (CT)	Identification of intrapulmonary thrombi, assessment of pulmonary arteries, pulmonary veins and lung parenchyma pathology

causes of hypoxia and (potentially reversible) causes of increased pulmonary vascular resistance, to evaluate any non-cardiac **multi-organ dysfunction** and to estimate the patient's baseline **functional status and RV function** (12).

During the initial evaluation but also through the follow-up, a wide spectrum of diagnostic tools is to be applied (Tab. 2) to be able to define their contemporary status – cardiac as well as any potential non-cardiac dysfunctions.

Long-term management

Due to the a relatively good clinical status and preserved RV function, the patients with Eisenmenger syndrome usually can lead an adequate, though symptomatic lives until their middle age. A successful survival beyond 50 years demands an optimal care from a well-informed cardiologist and also a team of other specialists (11, 15). An optimal care of the patients means that they need to be seen regularly (at least 1–2 times per year) to be able discover the point of their clinical deterioration, but beyond that to prevent high risk complications that can cause sudden death (especially in connection with life threatening bleeding or thromboembolic events) regardless their clinical status. As many as 20 % of deaths in Eisenemenger patients may be related to management errors (11).

In this connection it is important to consider some of the most frequent issues (6, 11, 15).

– Life style. Although they invariably have marked limitations in exercise tolerance, many patients with Eisenmenger syndrome are able to lead reasonably normal lives. Activities and occupation are directed by the patients themselves and therefore adequate education and counseling is particularly important.

– Pregnancy and delivery. This is associated with a substantial risk of maternal and fetal mortality. For the mother, thrombosis and/or bleeding events, RV failure and extensive systemic O_2 desaturation may be the major complications; the most dangerous period being the time of delivery and 1–2 weeks postpartum, when the risk of death is the highest. For the fetus, severe systemic desaturation is a high risk for developing either multi-systemic congenital malformations or can lead to progressive growth retardation and even to death. Due to this, pregnancy should be strictly avoided. It is needed to explain to young women with Eisenmenger syndrome all the risk factors extensively and if possible, to do so as soon as the diagnosis is confirmed.

In connection with this issue, the question of an optimal **contraception** is also important, as standard oral estrogen contraceptives are associated with a risk of thrombosis and laparoscopic sterilization carries the risk of general anesthesia. The best options include progestogen impregnated intrauterine coils and subdermal progesterone implant.

– **Dehydratation.** Due to the secondary erythrocytosis and hyperviscose syndrome, the patients with Eisenmenger syndrome are at a very high risk of dehydration. A sufficient fluid intake is therefore substantial, especially in hot weather. On the other hand, any situation with an extensive loss of fluid (like sauna) should strictly be avoided.

– **Air-traveling.** Already in the altitudes above 2500 m is the air oxygen saturation decreasing and during air-traveling in 10 000 m a physiological decrease in blood O_2 saturation of about 5–10 % can be found. This desaturation is tolerated by patients quite well. Other risk factors associated with long traveling are dehydratation and immobilization, with the danger of developing thrombotic complications. So any long-flights theoretically can be undertaken but dehydration and immobilization should be prevented, and oxygen supply should be prearranged if necessary.

– **Prophylaxis of endocarditis.** With a high risk of brain abscess formation and other possible infective complications in these patients a close attention to oral/dental hygiene and prophylaxis of bacterial endocarditis is mandatory. **Annual immunization** against influenza and pneumococcal infections are considered very useful.

– **Non-cardiac surgery.** For the patient, even a simple surgery may present a substantial risk, so if possible, the patient should be prepared. This is an indication for phlebotomy with the aim to achieve lower hematocrit level during surgery. It is also necessary, if possible, to compensate any hemocoagulation abnormalities to minimize bleeding or thrombotic complications.

There are no specific anesthesia protocols recommended for patients with Eisenmenger syndrome. It is therefore necessary for the anesthesiologist to understand the specific hemodynamic situation of this disease. It is very helpful if the anesthesiologists have some experience with such patients, so it may be reasonable to manage these patients in specialized centers.

In a patient with Eisenmenger syndrome, a careful attention and close monitoring throughout the surgery and in the early postoperative period is necessary. Inhalational agents that are associated with a reduction of systemic vascular resistance lead to an increase of the right-to-left shunt with further decline in systemic O_2 saturation. Additional issues include the risk of bleeding and rapid changes in intravascular volume that are not tolerated by the patients so well.

– **Hemodilution.** Secondary erythrocytosis is often well tolerated; even hematocrit levels around 65 %. Repeated phlebotomy on the other hand often worsens iron deficiency and is associated with an increased risk of stroke and paradoxically also with further reduction in exercise tolerance. Hemodilution should be therefore strictly used only in patients with symptoms resulting from hyperviscosity (headaches, dizziness, syncope, blurry vision, arthralgia, worsening of dyspnea). After phlebotomy, a sufficient immediate volume supply is necessary. And of course, iron substitution is crucial.

– **Anticoagulation therapy.** Routine anticoagulation is controversial in patients with the Eisenmenger syndrome. Secondary erythrocytosis with hyperviscosity, a high risk of pulmonary arterial thrombosis or other thromboembolic complications and a frequently present finding of chronic atrial flutter or fibrillation are the "pros" for anticoagulation. On the other hand, these patients are at risk for bleeding episodes, which represents a strong "contra". As there is no clear evidence supporting the benefit of chronic anticoagulation in the specific setting of the Eisenmenger syndrome, this should not be considered without precise monitoring.

– **Oxygen therapy.** Despite expectations, a long-term nocturnal oxygen therapy did not show to improve symptoms, exercise capacity or outcome in adult patients with the Eisenmenger syndrome. It can be used individually, when considered.

– **Conventional and specific therapy.** Conventional therapy (cardiotonics and diuretics) is dealing with the heart failure symptoms, though it often does not have a significant effect on patients' survival, exercise tolerance, nor symptom-relieve, and of course it does not affect the underlying PAH at all.

Due to a better understanding of the pathophysiological pulmonary processes in PAH, in the last years a new hope appeared – so called specific therapy (16, 17). The aim is to affect PAH through a targeted impact, influencing endothelial dysfunction in one or more pathways. As well as in other forms of PAH, the specific therapy is a hot topic also in the Eisenmenger patients.

Conclusion

The patients with Eisenmenger syndrome represent a group of PAH with a specific and challenging pathophysiology. A surprisingly good RV adaptation for the high pressure overload with a preserved RV function seems to be the key feature enabling a significantly better long-term survival and better clinical status of the Eisenmenger patients compared to other forms of PAH. In these patients, the RV is often decribed as unique – because of its more prominent hypertrophy, better functioning interventricular interdependence (both ventricles acting as one entity with less prominet shifting of the interventricular septum) and because of a presence of a "pop-off valve" that enables an off-load for the RV preventing it from failure and means also an additional volume supply to the left ventricle through the right-to-left shunting, therefore maintaining a sufficient resting systemic cardiac output.

On the other hand, these patients are symtomatic from their young age, and symptoms result mostly from compensatory adaptation (or maladaptation) mechanisms due to severe cyanosis.

The Eisenmenger syndrome has to be considered not only as PAH but as a multi-systemic disease as well. The prognosis is determined by a high-quality long-term management, optimally in expert centers. These patients need a multi-disciplinary aproach, besides cardiology also hematology, neurology, infectology, anesthesiology, gynecology, psychology and other specialized consulting. It is crucial to be able to treat their high risk complications correctly, as these lead to a sudden death rather RV dysfuction or PAH. With an adequate management and careful prevention of expected complications, the survival in these patients may reach 70 years or even longer.

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