EISENMENGER SYNDROME IN ADULTS

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Internal Medicine Grand Rounds

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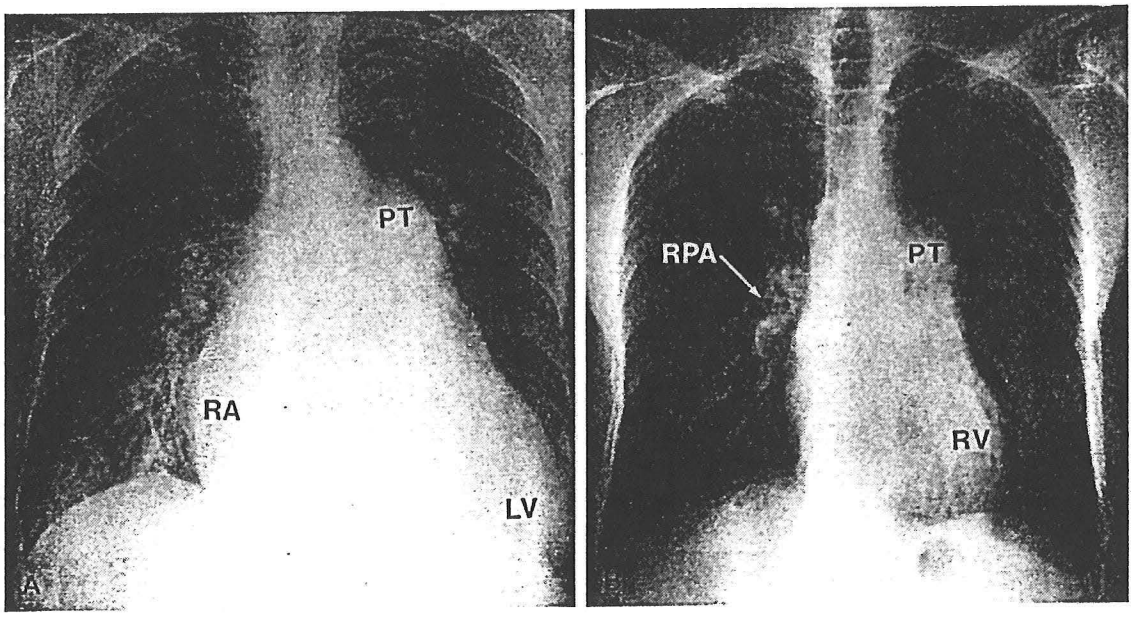

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Introduction

In 1897, Vicktor Eisenmenger described a patient with cyanosis and dyspnea since infancy who died at age 32 years of massive hemoptysis; postmortem examination showed a ventricular septal defect and severe pulmonary vascular disease [1]. In 1958, Paul Wood coined the term "Eisenmenger complex" to describe "pulmonary hypertension at the systemic level due to a high pulmonary vascular resistance, with reversed or bidirectional shunting through a large ventricular septal defect" [2]. Subsequently, the term Eisenmenger syndrome has been used to describe pulmonary vascular disease and cyanosis resulting from any systemic-to-pulmonary circulation connection (i.e., atrial septal defect, ventricular septal defect, patent ductus arteriosus, or aortopulmonary window).

In patients with intracardiac shunting, blood initially shunts from the systemic to the pulmonary circulation (so-called left-to-right shunting), since the resistance in the former is higher. If the defect is large and the left-to-right shunting sustained (e.g., over months to years), exposure of the pulmonary vasculature to systemic arterial pressure and/or increased blood flow leads to progressive morphologic changes in the microvasculature (Figure 1), including arteriolar medial hypertrophy, intimal proliferation and fibrosis, and capillary and arteriolar occlusion. Eventually, plexiform lesions and necrotizing arteritis occur [3], with resultant obliteration of pulmonary arterioles and capillaries and increased pulmonary vascular resistance. The classification of structural changes in the pulmonary artery by Heath and Edwards is used to assess the reversibility of pulmonary vascular changes. (Figure 2). When pulmonary vascular resistance (and pulmonary arterial pressure) finally approaches systemic vascular resistance (and systemic arterial pressure), reversal of the shunt occurs.

Figure 1. Pathophysiology of Eisenmenger Syndrome

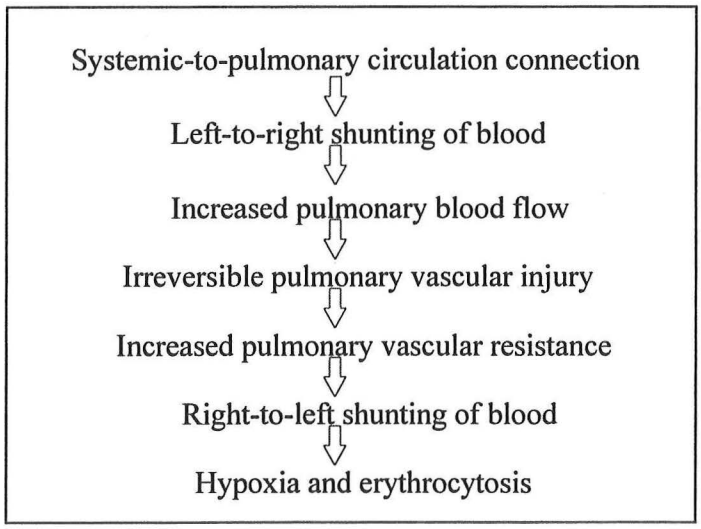


Figure 2. Heath-Edwards Classification of Structural Changes in Pulmonary Arteries

Grade 1 - Medial hypertrophy
Grade 2 - Medial hypertrophy/intimal hyperplasia
Grade 3 - Arteriole obliteration
Grade 4 - Arteriole dilatation (plexiform lesions)
Grade 5 - Angiomatous/cavernous lesions, hyalinization of intimal fibrosis
Grade 6 - Necrotizing arteritis

The pathophysiologic mechanisms responsible for the development of pulmonary microvascular changes in patients with Eisenmenger syndrome are not completely known. In experimental animals, pulmonary microvascular injury stimulates the production of elastase enzymes and growth factors (i.e., insulin-like growth factor-1 and transforming growth factor), which may cause medial hypertrophy, cellular intimal proliferation, progressive occlusion, and eventual destruction of small arterioles [4-6]. Endothelium-dependent pulmonary arteriolar relaxation is impaired, pulmonary endothelin production is increased, and plasma thromboxane B2 concentrations are elevated in patients with Eisenmenger syndrome, suggesting that endothelial dysfunction and/or platelet activation may play a causative role in this condition [7-11].

Figure 3. Proposed Etiologies For The Development of Pulmonary Vascular Disease

- Medial hypertrophy/intimal proliferation
  - Increased elastase enzymes
  - Increased growth factors (bTGF, ILGF-1)
- Pulmonary arteriolar vasoconstriction
  - Impaired endothelium dependent pulmonary arteriolar vasodilatation
  - Increased endothelin production
- Arteriolar thrombosis
  - Increased thromboxane

Clinical Presentation

Patients with Eisenmenger syndrome often give a history of transient pulmonary congestion in infancy as a result of a substantial pulmonary blood flow caused by a large left-to-right intracardiac shunt. Later in infancy or early childhood, as pulmonary vascular resistance increases, pulmonary blood flow declines, and symptoms of pulmonary congestion abate. When the shunt reverses (e.g., right-to-left shunting occurs), cyanosis and erythrocytosis develop (Figure 4). Less commonly, patients develop Eisenmenger syndrome in adulthood without obvious symptoms during childhood and seek medical attention because of progressive fatigue, dyspnea, and/or cyanosis.

Figure 4. Large Intracardiac Shunts: Natural Hx

Age	Presentation	Pathophysiology
Infancy	Pulmonary congestion	Right-to-left shunt ⇧ pulm blood flow
Childhood	Asymptomatic	⇧ PVR ⇩ pulm blood flow
Adulthood	Cyanosis Erythrocytosis	⇧⇧⇧ PVR Rt-to-left shunting

Eventually, most patients with Eisenmenger syndrome experience one or more of the following: (a) symptoms of a low systemic output (i.e., dyspnea on exertion, fatigue, syncope); (b) subtle neurologic abnormalities (i.e., headache, dizziness, visual disturbances) due to erythrocytosis and hyperviscosity; or (c) symptoms of congestive heart failure (Figure 5). In addition, arrhythmias and hemoptysis are common, and the former may lead to sudden death. Hemoptysis is due to pulmonary infarction, rupture of an aneurysmally dilated pulmonary artery or thin-walled pulmonary arteriole, or bleeding diathesis, which often is manifest initially as mucosal (i.e., epistaxis, gingival) bleeding. Cerebrovascular accidents frequently occur as a result of hyperviscosity, paradoxical embolism, or a cerebral abscess.

Figure 5. Symptoms Associated With Eisenmenger Syndrome

Symptoms in 201 Eisenmenger Syndrome Pts
Saha et al, Int J Cardiol 1994;45:199

Symptoms	Frequency	Percentage
Dyspnea/effort intolerance	196	98
Palpitation	160	80
Edema	27	13
Hemoptysis	34	17
Syncope	15	8
Angina	9	5

Physical Examination

Physical examination of the patient with Eisenmenger syndrome reveals central cyanosis and nailbed clubbing. If systemic vascular resistance falls -- as may occur with hot weather, exercise, fever, or systemic infection -- the magnitude of right-to-left shunting and cyanosis increases. Patients with a patent ductus arteriosus may have normal, pink nailbeds on the right hand and cyanosis and clubbing of the left hand and feet (so-called "differential cyanosis"). This occurs because venous blood shunts through the ductus and enters the aorta distal to the right subclavian artery.

Figure 6. Eisenmenger Syndrome: Physical Examination

• Jugular venous pressure	normal
• Carotid pulse	normal (40%) diminished (60%)
• Lung fields	clear
• Peripheral edema	absent

The jugular venous pressure may be normal or elevated, with a prominent "v" wave, if tricuspid regurgitation is present. The arterial pulse is usually diminished or normal [2]. Signs of pulmonary hypertension, including a right parasternal heave, palpable pulmonary valve closure, a right-sided S4, and loud pulmonic component of the second heart sound, are uniformly present. The second heart sound may be single (e.g., with ventricular septal defect) or widely split (e.g., with atrial septal defect). A high-pitched, diastolic, decrescendo murmur of pulmonic regurgitation (Graham-Steele murmur) is often audible, and a holosystolic murmur of tricuspid regurgitation may occur when right heart failure intervenes. In many patients, a pulmonary ejection click and soft systolic ejection murmur are audible and are attributed to dilation of the main pulmonary artery. Murmurs usually associated with ventricular septal defect or patent ductus arteriosus are absent. The lung fields are clear, and peripheral edema is absent unless right ventricular systolic dysfunction ensues.

Figure 7. Eisenmenger Syndrome: Physical Examination

• Central cyanosis	70%
• Clubbing	70%
• Palpable PV closure	75%
• Right parasternal heave	100%
• Right-sided S4	100%
• Prominent P2	100%

Noninvasive and Invasive Evaluation

In the patient with Eisenmenger syndrome, the 12 lead electrocardiogram demonstrates right atrial enlargement as well as right ventricular or biventricular hypertrophy. Atrial arrhythmias are often present, especially in those with atrial septal defect. The chest radiograph usually reveals prominent, dilated central pulmonary arteries, with a reduction in the size and number of peripheral vessels. Calcification of the pulmonary arteries or ductus arteriosus, signifying atherosclerosis, may be visualized. Eisenmenger patients with ventricular septal defect or patent ductus arteriosus usually have a normal or minimally increased cardiothoracic ratio, whereas most with atrial septal defect have cardiomegaly [12], with dilation attributed to right ventricular enlargement due to previously increased flow [2].

Two-dimensional echocardiography is helpful in visualizing intracardiac defects and identifying associated cardiac or valvular abnormalities. Color-flow Doppler imaging usually can detect intracardiac shunting. However, since pulmonary and systemic arterial pressures are similar in patients with Eisenmenger syndrome, the pressure gradient and flow across the intracardiac defect may be small and, therefore, difficult to visualize by color-flow Doppler imaging [13]. In such patients, contrast echocardiography should be performed. An intravenously injected contrast agent (e.g. agitated normal saline, indocyanine green, or hydrogen peroxide) quickly appears in the left heart chambers when a right-to-left intracardiac shunt is present, and the magnitude of intracardiac right-to-left shunting is assessed qualitatively as small, moderate, or large; however, it cannot be quantitated precisely [14-15]. Transesophageal echocardiography can be performed safely in patients with Eisenmenger syndrome and is superior to the transthoracic approach for detecting atrial septal abnormalities or patent ductus arteriosus [13,16]. It is valuable for evaluating patients with unexplained pulmonary hypertension and can identify patients with cyanosis and normal pulmonary arterial pressure (Figure 8). It should be performed in patients with Eisenmenger syndrome being considered for lung transplantation, since it provides additional diagnostic information (i.e., additional unsuspected intracardiac defects, unrecognized intracardiac shunts, proximal pulmonary artery thrombus, etc.) in approximately 25% of subjects that may alter surgical intervention [16,17].

Fig 8. Cyanotic Heart Conditions With Normal Pulmonary Arterial Pressures

1. Tetralogy of Fallot
2. Ebstein's abnormality
3. ASD or VSD with pulmonic stenosis
4. IVC blood preferentially directed across an ASD or patent foramen ovale (i.e., intact eustachian valve or post pneumonectomy)

In patients with suspected Eisenmenger syndrome, cardiac catheterization should be performed (a) to detect, localize, and quantitate intracardiac shunting and (b) to determine the severity of pulmonary vascular disease [15] (Figure 9). The assessment of pulmonary vascular resistance before and after administration of a pulmonary arteriolar vasodilator (i.e., 100% oxygen or nitric oxide via inhalation; tolazoline, adenosine triphosphate, or prostacyclin intravenously) can discriminate those with fixed, irreversible pulmonary hypertension -- in whom surgical repair of the

cardiac defect is associated with excessive morbidity and mortality -- from those with reversible pulmonary hypertension, who may benefit from surgical repair [22,23]. Cardiac catheterization is invasive. Since radiographic contrast material is hypertonic and a systemic arterial vasodilator, its administration to the patient with Eisenmenger syndrome may cause hypotension, hypoxemia, increased blood viscosity, or thrombosis, particularly in those with erythrocytosis.

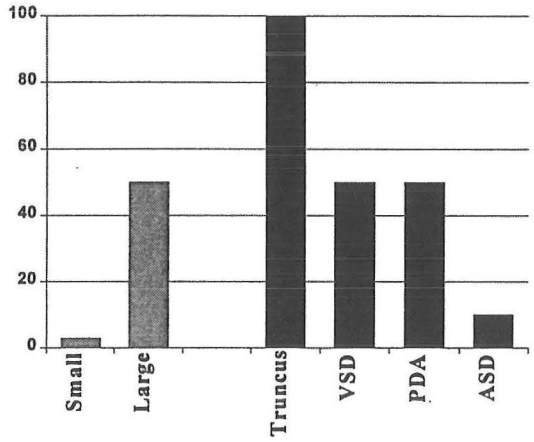
Figure 9. Cardiac Catheterization in The Pt With Eisenmenger Syndrome

- Determines the presence, site, and magnitude of intracardiac shunting
- Assesses the severity of pulmonary vascular disease
- Discriminates between patients with fixed, irreversible pulmonary hypertension from those with reversible pulmonary hypertension
- Identifies associated cardiac defects

Natural History: Course and Prognosis

The incidence of congenital heart disease is approximately 1%. About 8% of patients with congenital heart disease and 11% with left-to- right intracardiac shunting develop Eisenmenger syndrome [1,24]. Congenital heart defects that may result in Eisenmenger syndrome include ventricular septal defect, atrioventricular defect, patent ductus arteriosus, atrial septal defect, d-transposition of the great vessels, and surgically created aortopulmonary connections. The likelihood of developing Eisenmenger syndrome depends on the size and location of the intracardiac defect (Fgiure 10). In patients with ventricular septal defect, 3% with a small- or moderate-sized ($\leq$ 1.5 cm in diameter) and about half with a large defect ($>$ 1.5 cm in diameter) develop Eisenmenger syndrome [25]. In subjects with a large defect, the Eisenmenger syndrome develops in nearly all those with truncus arteriosus, about half with ventricular septal defect or patent ductus arteriosus, and only about 10% with atrial septal defect [1,26]. Interestingly, patients with patent ductus arteriosus or ventricular septal defect who develop Eisenmenger syndrome have an earlier onset (80% during infancy) than those with atrial septal defect (90% during adulthood) [1].

Figure 10. Incidence of Eisenmenger Syndrome by Size and Site of Intracardiac Defect



The long-term prognosis of patients with Eisenmenger syndrome is substantially better than that of other conditions associated with pulmonary hypertension, such as primary pulmonary hypertension (Figures 11, 12) [27]. Patients with Eisenmenger syndrome have an 80% survival at 10 years, a 77% survival at 15 years, and a 42% survival at 25 years [25,28]. The prognosis is not influenced by the location of the intracardiac defect [1,27,28]. Variables associated with a poor long-term outcome are syncope, elevated right heart filling pressures, and severe hypoxemia (systemic arterial saturation $< 85\%$) [28]. These conditions identify patients with advanced pulmonary vascular disease, severely impaired right ventricular function, decreased cardiac output, and/or inadequate oxygenation. Most subjects with Eisenmenger syndrome die of sudden cardiac death [24,28-30], probably from a ventricular arrhythmia. Other frequent causes of death include congestive heart failure, hemoptysis, brain abscess, thromboembolism, and complications of pregnancy or noncardiac surgery (Figure 13).

Figure 11. Actuarial survival curve for 188 Eisenmenger pts (Ref 92)

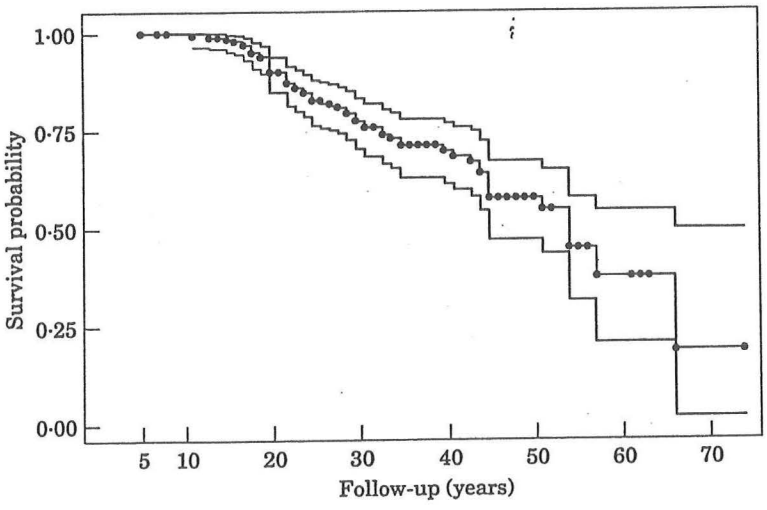


Figure 12. Survival of 94 adults with PPH or Eisenmenger Syndrome (Ref 27)

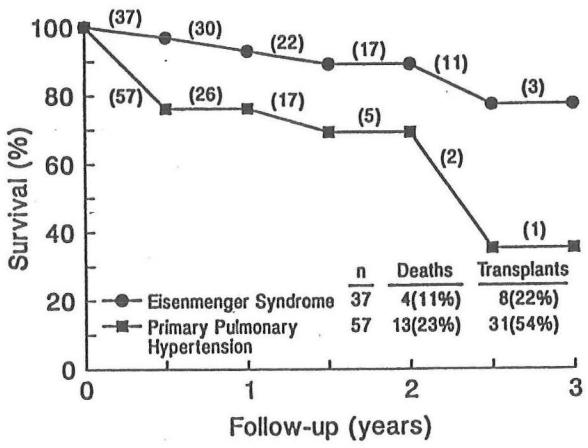
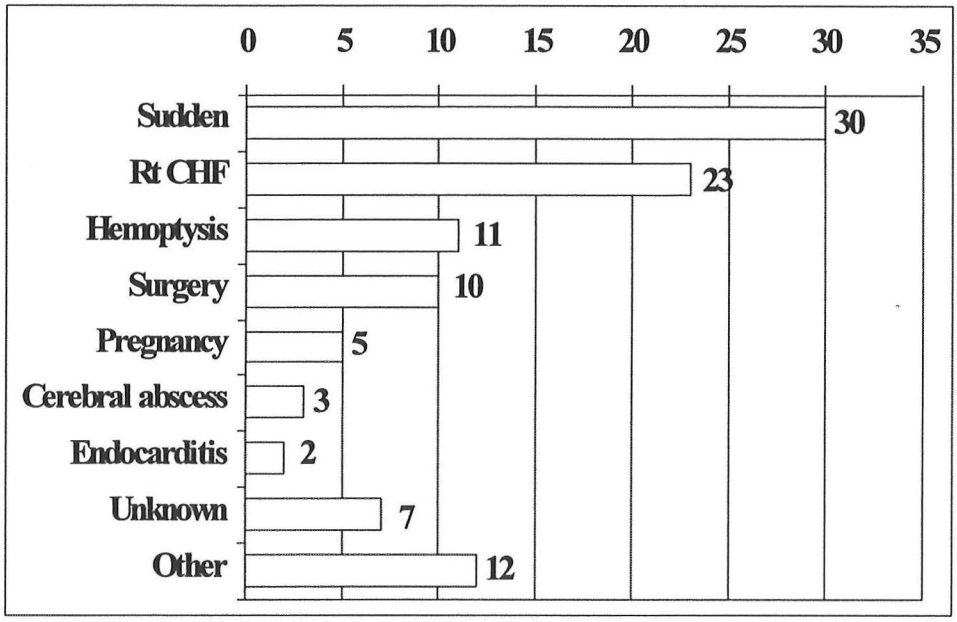


Fig 13. Eisenmenger Syndrome: Cause of Death (Ref 28)



Management

A. Medical: Once Eisenmenger syndrome has developed, closure of the systemic to pulmonary connection hastens mortality. Thus, efforts have been directed toward identifying medical therapies that can decrease the elevated pulmonary vascular resistance, right-to-left shunting, cyanosis, morbidity, and mortality associated with Eisenmenger syndrome. Unfortunately, these have been disappointing. Administration of a calcium channel blocker to the patient with Eisenmenger syndrome acutely decreases systemic arterial pressure and increases right-to-left shunting [31], which may lead to syncope and sudden death. The long-term hemodynamic effects of prolonged calcium channel blocker administration in adults with Eisenmenger syndrome are unknown, but studies have shown no benefit in children > 9 years old [32]. A small randomized study of adults with Eisenmenger syndrome suggested modest improvement of exercise capacity after nifedipine therapy for 4 weeks [31]. However, since injudicious administration of calcium channel blockers may cause syncope and sudden death, we do not recommend these agents.

Long-term home oxygen therapy was reported to improve survival in children with congenital heart disease and concomitant pulmonary vascular disease in a small nonrandomized study [33], but there are no data in adults with Eisenmenger syndrome. Home oxygen therapy is not routinely recommended but may be helpful in patients with profound hypoxemia and dyspnea at rest or with limited activity.

The mainstay of medical therapy is to avoid medications that have not proven to be beneficial (i.e., calcium channel blockers, antiplatelet agents, or anticoagulants) and may cause complications, such as systemic arterial hypotension, worsening cyanosis, increased hyperuricemia, or hemorrhage. Patients with lesions considered at high risk for infective endocarditis (i.e., ventricular septal defect, patent ductus arteriosus, systemic-to-pulmonary shunts, etc.) should be given instructions regarding antibiotic prophylaxis before undergoing a procedure that may cause bacteremia [34].

Figure 13. Drugs Which Are Potentially Harmful to Eisenmenger Patients

Nonsteroidal anti-inflammatory drugs
Diuretics
Estrogens (including contraceptive pills)
Danazol
Fertility hormones (used for in vitro fertilization)
Systemic vasodilators
Anesthetic induction agents

B. Phlebotomy: Shunting of blood from the venous to the systemic circulation results in systemic hypoxemia and secondary erythrocytosis. As the number of red blood cells (e.g., hematocrit) increases, the blood viscosity increases commensurately, and eventually blood flow and oxygen transport decline [35] (Figures 13, 14).

Figure 13. Relation of whole blood viscosity measured in a capillary viscometer and at shear rates for aorta (120 sec^{-1}) and arteriole (12 sec^{-1}) (Ref 35)

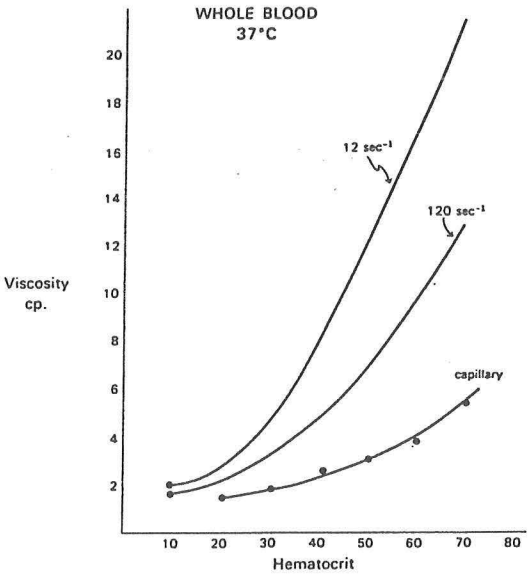
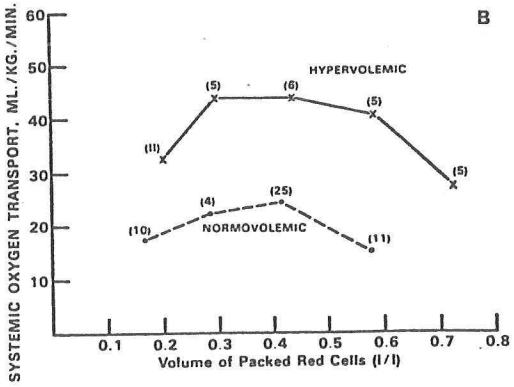


Figure 14. Arterial O2 transport at different volume of packed red cells and in normovolemic and hypervolemic conditions (Ref 35)



Patients with hyperviscosity may experience headache, fatigue, dizziness, visual disturbances, anorexia, or lethargy related to impaired tissue oxygenation. Phlebotomy without adequate volume replacement may worsen symptoms and further reduce cardiac output, oxygen delivery, and cerebral perfusion. However, isovolumetric reduction of the hematocrit increases cardiac output and systemic oxygen transport, decreases systemic vascular resistance, and improves symptoms at rest and during exercise [36,37].

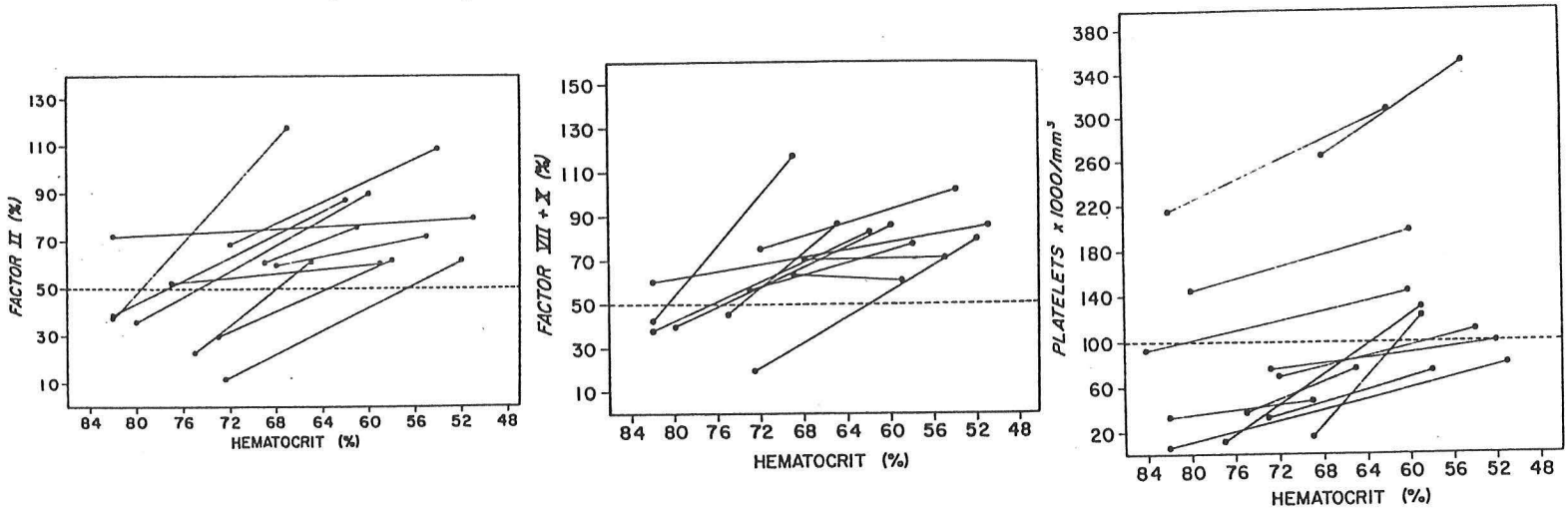
Fig 15. Effects of Hematocrit Reduction in Pts With Polycythemia 2° to Cyanotic CHD (Ref 36)

	Before	3d_after	14d_after
Hgb (gm/dl)	66	58*	58*
Cardiac index (L/m/m2)	2.2	2.9*	2.9*
O2 uptake (ml/min)	325	358*	375*
Max ETT (kpm/min)	333	500*	483*

p<0.01, compared to before

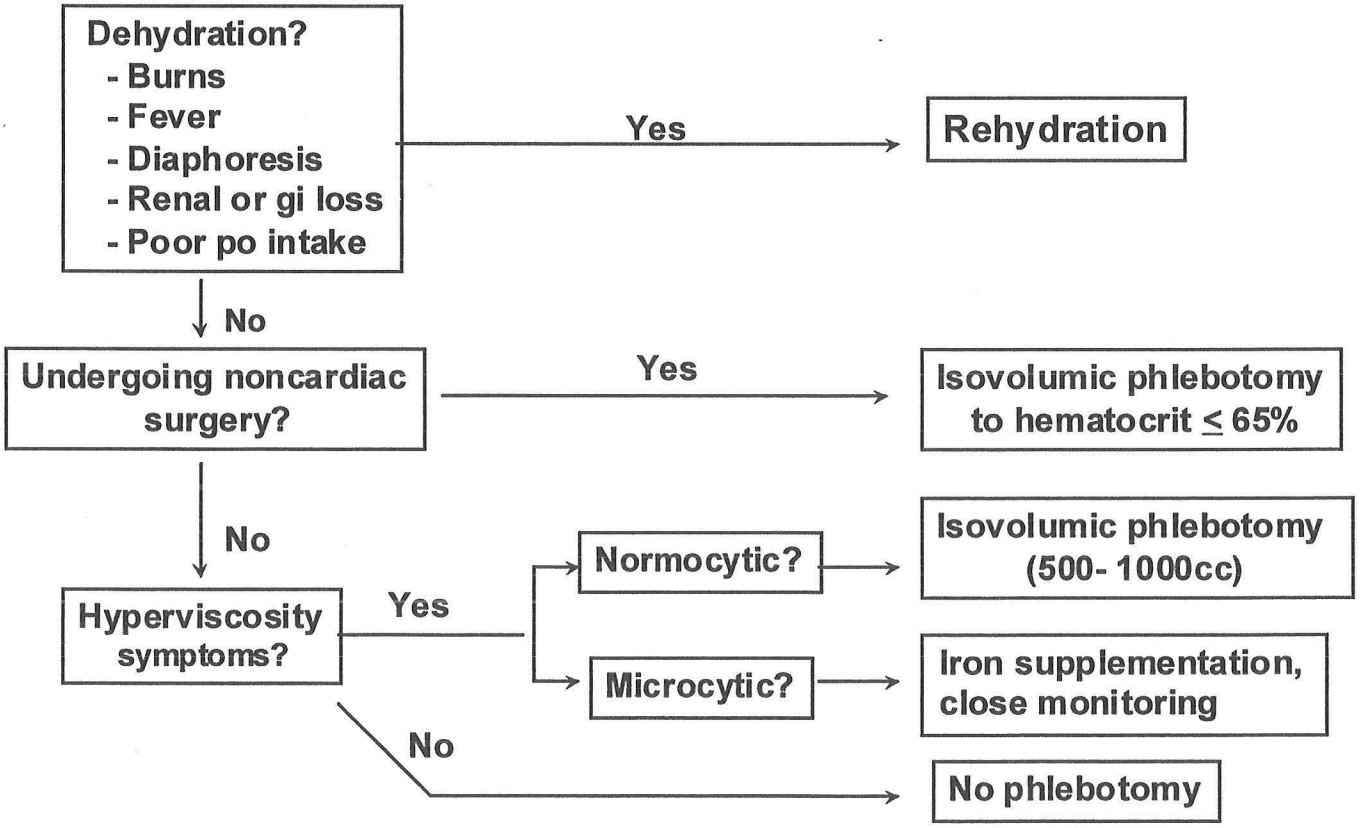
Hemodynamic and clinical improvement are usually evident within 24 hours [38]. Isovolumetric reduction in red blood cell mass also corrects the thrombocytopenia, platelet dysfunction, and various coagulation abnormalities commonly observed in polycythemic patients with cyanotic congenital heart disease [39,40] (Figure 16) . The mechanism underlying these benefits is not understood, but it is possibly related to increased oxygen delivery to the liver and bone marrow.

Figure 16: Reduction in hematocrit corrects depletion of factor II , VII + X, and platelets in pts with cyanotic CHD (Ref 39). Dotted line shows lower limits of normal



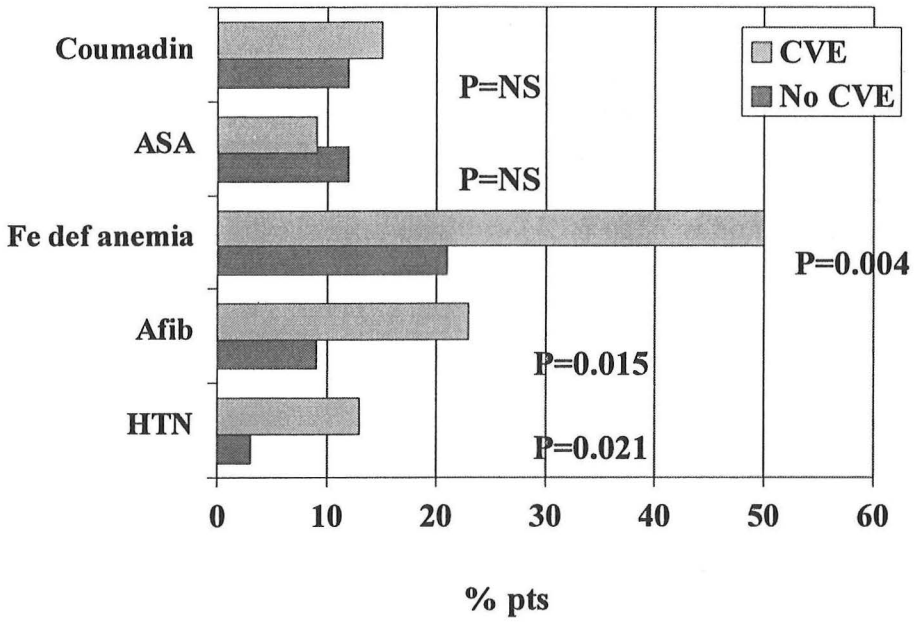
In adults with Eisenmenger syndrome and associated hyperviscosity, phlebotomy can be performed safely on an outpatient basis by removing 500 ml of blood in 30 to 45 minutes with infusion of an equal volume of isotonic saline [38]. Alternatively, salt-free albumin, dextran, or fresh frozen plasma may be used for volume replacement with similar efficacy but at a higher cost, risk of anaphylaxis, and/or exposure to blood-borne pathogens. Blood pressure should be monitored frequently throughout the phlebotomy, with careful avoidance of hypotension. Phlebotomy should be performed in the erythrocytotic patient with symptomatic hyperviscosity*; it is not indicated in those with an elevated hematocrit without symptoms of hyperviscosity* (Figure 17).

Fig 17. Management of the Eisenmenger Syndrome Pt With Erythrocytosis



In addition, it is recommended in those with severe erythrocytosis (hematocrit $\geq$ 65%) and bleeding diathesis undergoing cardiac or noncardiac surgery to decrease perioperative bleeding complications [39,40]. Although phlebotomy can be repeated if symptoms fail to improve, removal of >2 units of blood over a 2-day period is rarely required. The goal of phlebotomy is to relieve hyperviscosity symptoms, not to obtain a prespecified hematocrit. If symptoms of hyperviscosity persist despite multiple phlebotomies, iron deficiency should be suspected. As the mean corpuscular volume declines, the red blood cell becomes less deformable, and blood viscosity increases [41], which increases the risk of a cerebrovascular accident (Figure 18). Iron replacement therapy is indicated in patients with biochemical evidence of iron deficiency (decreased serum iron, ferritin, and transferrin saturation) or microcytosis. Patients on iron replacement therapy should be monitored closely, since the hematocrit may rise rapidly, resulting in hyperviscosity [42].

Figure 18. Factors Associated with CVA in Adults With Cyanotic CHD (Ref 69)



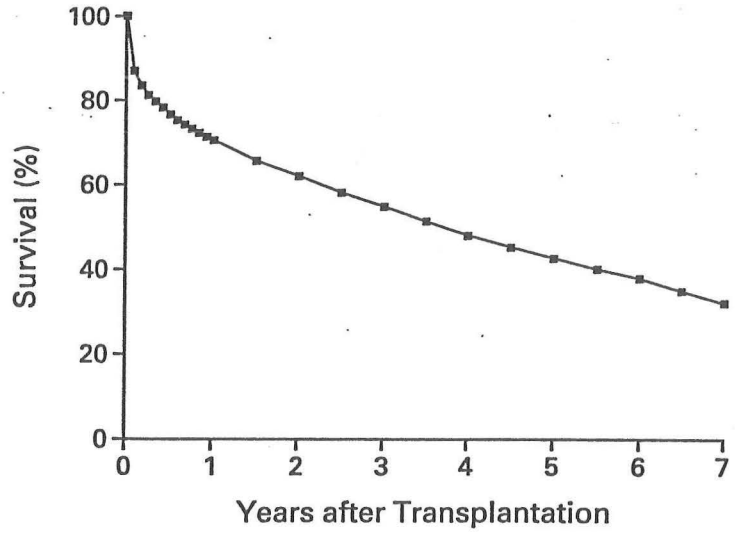
C. Transplantation: Eisenmenger syndrome was considered terminal until combined heart-lung transplantation was introduced by Reitz and associates in 1982 [43]. In 1990, Fremes et al [44] reported the first successful single lung transplantation (with closure of a patent ductus arteriosus) in a patient with Eisenmenger syndrome. Subsequently, others [45-48] reported successful single or bilateral lung transplantation and closure of intracardiac defects, with an immediate and sustained decline in

pulmonary arterial pressure and resistance, a rapid recovery of right ventricular function (within 3 months), and eventual regression of right ventricular hypertrophy (within 1 year) [46,47,49,50]. Lung transplantation has several advantages over combined heart-lung transplantation, including better donor organ availability (with shortened transplant waiting time) as well as avoidance of transplant coronary vasculopathy and cardiac allograft rejection [51]. In short, lung transplantation with repair of congenital cardiac defects is the preferred treatment in patients with Eisenmenger syndrome with (a) normal left ventricular systolic function, (b) absence of coronary artery disease or severe left-sided valvular disease, (c) a "simple" congenital cardiac defect (e.g. atrial septal defect, ventricular septal defect, or patent ductus arteriosus), and (d) a right ventricular ejection fraction >0.10 [52].

For patients undergoing lung transplantation, the selection of single or bilateral lung replacement depends on the experience and preference of the transplant center. Compared to bilateral lung transplantation, single lung transplantation is associated with reduced operative blood loss, decreased lung allograft ischemic time, and better usage of donor organs. In comparison to single lung transplantation, bilateral lung transplantation is associated with less ventilation/perfusion mismatch, better pulmonary function and gas exchange, and higher exercise capacity [48,53]. Patients undergoing single lung replacement are more likely to have reperfusion edema postoperatively -- since most of the cardiac output is directed to the transplanted lung -- and less likely to tolerate chronic graft rejection and obliterative bronchiolitis. Bilateral lung transplantation is preferred if the remaining lung is a potential source of infection (i.e. recurrent pneumonia, cystic fibrosis, or bronchiectasis).

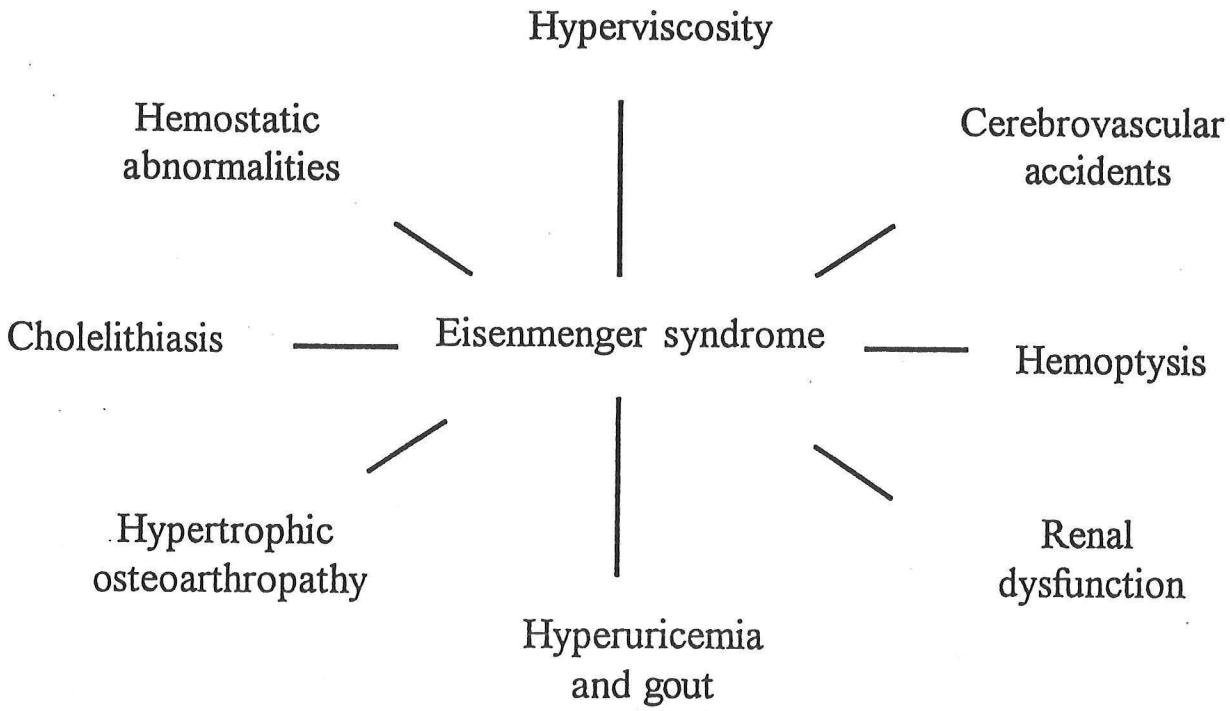
The short-term (1 year) actuarial survival of adults undergoing single or bilateral lung transplantation is 70 to 80%, and long-term results are less favorable, with less than 50% of patients alive 4 years after transplantation [48,54-57] (Figure 19). Heart-lung transplant recipients have a 1 year actuarial survival of 60 to 80% and a 10-year survival of $< 30\%$ [48,51,54].

Figure 19. Actuarial Survival After Lung Transplantation (Single and Double Lung, n=7021) (Ref 93)



Since many patients with Eisenmenger syndrome survive 25 years or longer, a determination of the appropriate time for transplantation is sometimes problematic. The indications for lung or heart-lung transplantation vary widely among transplant centers. In general, patients with adverse prognostic factors (i.e., syncope, refractory right heart failure, poor exercise tolerance, advanced functional class, or severe hypoxemia) have poor short-term survival and, therefore, should be considered for transplantation [28,58]. Absolute contraindications to heart-lung or lung transplantation include (a) active infection or malignancy, (b) current cigarette smoking or substance abuse, (c) medical non-compliance or psychiatric illness, (d) severe systemic illness (renal, liver, or central nervous system dysfunction), (e) morbid obesity or cachexia, and (f) advanced age ($>$ 60 years for lung and $>$ 50 years for heart-lung). Relative contraindications to transplantation include (a) glucocorticosteroid dependence ($>$ 10 mg of prednisone per day), (b) previous sternotomy, thoracotomy, or pleurodesis, (c) mechanical ventilation, (d) severe osteoporosis or skeletal abnormalities, and (e) recurrent pulmonary embolism [55,59].

Figure 20: Complications Associated With Eisenmenger Syndrome



Complications (Figure 20): Recognition and Management

A. Hemostatic abnormalities: Multiple hemostatic abnormalities have been described in patients with congenital heart disease with cyanosis or pulmonary hypertension, including (a) thrombocytopenia; (b) prolonged bleeding, prothrombin, or partial thromboplastin times; (c) deficient vitamin K dependent clotting factors; and (d) abnormal fibrinolysis [60-62]. Although the cause of these defects is not completely understood, an "acquired" type II-like von Willebrand factor (vWF) abnormality -- presumably from defective synthesis or abnormal degradation of vWF by dysfunctional pulmonary vascular endothelium -- has been described and may partially account for the bleeding diathesis [63-65].

Since hemorrhage in patients with Eisenmenger syndrome is usually mild and primarily mucocutaneous in location, supportive or symptomatic treatment is usually adequate. Replacement therapy with coagulation factors is indicated if massive or life threatening hemorrhage occurs, and desmopressin may be beneficial in patients with acquired vWF abnormalities. Antiplatelet agents (e.g., aspirin) and anticoagulants should be avoided in these patients, since they increase the risk of massive or life threatening hemorrhage.

B. Hyperviscosity Syndrome and Cerebrovascular Events: Infants, children, and adults with cyanotic congenital heart disease have a high incidence of cerebrovascular events [66-69], primarily because the associated erythrocytosis leads to increased blood viscosity and decreased cerebral blood flow. Interestingly, patients with microcytic, hypochromic erythrocytosis have a higher blood viscosity than those with erythrocytosis who are not iron deficient. Independent risk factors for cerebrovascular events include hypertension, atrial fibrillation, phlebotomy, and microcytosis, with the latter condition being the strongest [69]. As a result, phlebotomy should be reserved for the patient with symptoms of hyperviscosity (i.e., increasing fatigue, dyspnea, headache, hemoptysis); it should not be performed for stroke prophylaxis in the absence of other indications. Microcytosis and iron deficiency should be corrected promptly with ferrous sulfate administration (325 mg/day orally) with close monitoring of red blood cell indices.

Therapy of ischemic stroke is supportive and symptomatic. Decisions regarding the initiation of antiplatelet or anticoagulant therapy should be individualized, since these patients are at increased risk of bleeding. Anticoagulation should be initiated when paradoxical embolism is the source of stroke. Since patients with Eisenmenger syndrome are at increased risk for developing brain abscess, blood should be obtained for culture in those with suspected cerebral embolism to exclude bacteremia, especially if a recent invasive procedure was performed or a focus of infection is identified. Empiric antibiotic therapy should be considered until the results of blood cultures are available, even in the absence of radiologic evidence of a brain abscess on the initial

computed tomographic scan [70]. Once blood cultures are known to be sterile and there is no evidence of a brain abscess on repeated radiographic imaging, antibiotics can be discontinued.

C. Hemoptysis: Expectoration of blood frequently prompts medical evaluation of the patient with Eisenmenger syndrome. Although most episodes are self limited, an occasional patient may have massive hemoptysis that leads to sudden death. The evaluation and treatment of hemoptysis is complex, since multiple etiologies may be responsible. Potential etiologies and therapies are outlined in Figure 21.

Figure 21. Causes of and Therapy For Hemoptysis in Patients With Eisenmenger Syndrome

Cause	Therapy
Bronchitis	Antimicrobial therapy, cough suppression
Pulmonary embolization	Anticoagulation, inferior vena caval filter
Bleeding diathesis	Platelet or fresh frozen plasma infusion desmopressin infusion
Rupture of aortopulmonary collaterals	Percutaneous catheter embolization
Pulmonary artery or arteriole rupture	Balloon tamponade; surgical repair Pulmonary artery ligation Embolization of arteriole with percutaneous catheter

D. Gout: Hyperuricemia is common in patients with cyanotic congenital heart disease, due to increased production and decreased renal clearance of uric acid; however, clinical gout (i.e., acute gouty arthritis or uric acid nephrolithiasis) is rare [38]. In contrast, arthralgias are common and are due to hypertrophic osteoarthropathy. If gouty arthritis occurs, intravenous colchicine is the treatment of choice, since it is effective and has less gastrointestinal side effects than the oral form. Oral corticosteroids are reasonable alternatives. Nonsteroidal anti-inflammatory agents should generally be avoided, as they interfere with platelet function and hemostasis. Allopurinol or low-dose oral colchicine is recommended for prophylaxis of gouty arthritis.

E. Cholelithiasis: Patients with Eisenmenger syndrome and erythrocytosis are at increased risk of developing calcium bilirubinate gallstones and cholecystitis, presumably from an elevated concentration of unconjugated bilirubin in bile secretions as a result of the increased red blood cell mass [38]. Those with asymptomatic cholelithiasis should be observed and managed expectantly. Conversely, early surgery should be performed in the patient with active cholecystitis. Optimal management of the patient with symptomatic cholelithiasis (in the absence of cholecystitis) is not known.

F. Hypertrophic osteoarthropathy: Arthralgias are common in patients with Eisenmenger syndrome and are often a manifestation of hypertrophic osteoarthropathy, a syndrome characterized by excessive proliferation of the skin and osseus tissue of the extremities. This results in digital clubbing of the fingers and toes and periostitis in the metacarpal, metatarsal, and long bones of the forearms and legs. Mild or moderate arthralgias of the knees and ankles are the most commonly noted symptoms, and synovial effusions are frequent. Generally, the symptoms do not warrant treatment; however, salsalate may be used if arthralgias are severe [38].

G. Renal Dysfunction: Over one third of adult patients with cyanotic congenital heart disease have evidence of glomerulopathy (i.e., proteinuria, elevated serum creatinine, or abnormal urinalysis with hematuria, sterile pyuria, or casts) [71]. Diminished renal blood flow and glomerular filtration rate, azotemia, abnormal uric acid secretion, and nephrotic syndrome also occur, with the incidence of renal abnormalities increasing with the degree and duration of cyanosis and accompanying erythrocytosis. The serum creatinine concentration may not adequately reflect the severity of renal dysfunction in Eisenmenger patients. It is important to avoid drugs which may further impair renal function (i.e., nonsteroidal anti-inflammatory agents) and to administer intravenous fluids when these patients receive a radiographic contrast agent.

Special Considerations

A. Travel To, or At, High Altitude: Travel to high-altitude may pose a major risk to patients with Eisenmenger syndrome due to decreased inspired oxygen tension [72]. Hypoxic pulmonary vasoconstriction may cause worsening pulmonary hypertension, increased right-to-left shunting, systemic arterial desaturation, and acute right heart failure. Although patients with Eisenmenger syndrome may tolerate breathing air with a lower inspired oxygen tension at rest, even modest exercise may precipitate severe hypoxemia and dyspnea, thereby making travel to high-altitude prohibitive [73]. In contradistinction, high-altitude travel in commercial pressurized aircraft is usually well tolerated and safe for patients with Eisenmenger syndrome provided they receive supplemental oxygen and careful oximetric monitoring [74]. There are no published data regarding the safety of air travel for those not given supplemental oxygen.

B. Pregnancy: Pregnancy in the patient with Eisenmenger syndrome is associated with substantial risk to the fetus and mother. Spontaneous abortion occurs in 20 to 40% of pregnancies, premature delivery in 50%, and term delivery in only 25% [75,76]. At least 30% of the infants born have evidence of intrauterine growth retardation, and perinatal mortality is high (8 to 28%) [75,76].

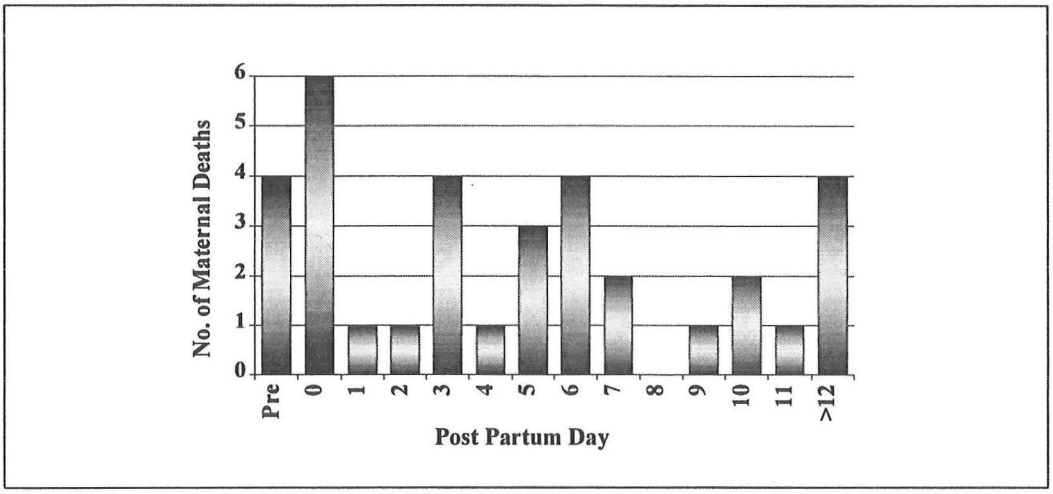
Figure 22. Pooled Data from Studies of Pregnant Pts With Eisenmenger Syndrome

Variable	Patients
Total pts, n	70
Pregnancies, n	98
Mortality rate, n/n (%)	31/70 (44%)
ASD	6/16 (38%)
VSD	18/40 (45%)
PDA	8/19 (42%)
Mortality by delivery	
Vaginal	20/60 (33%)
Cesarean section	7/15 (47%)

The maternal mortality is approximately 45% for women with Eisenmenger syndrome (Figure 22) [75-84], with death usually occurring during delivery or within 1 week postpartum and less frequently later (up to 1 month) (Figure 23). Most deaths are attributed to thromboembolism (44%), hypovolemia (26%), or preeclampsia (18%) [75,76]. In the pregnant patient with Eisenmenger syndrome, mortality is similar with Cesarean section and vaginal delivery (47% and 33%, respectively) and substantially higher than with spontaneous abortion (6%) [75-84]. Maternal mortality is similar with Eisenmenger syndrome from ventricular septal defect, patent ductus arteriosus, or atrial septal defect (Figure 22). Because of the substantial maternal risk, the pregnant patient

with Eisenmenger syndrome should be advised to have an elective abortion without delay.

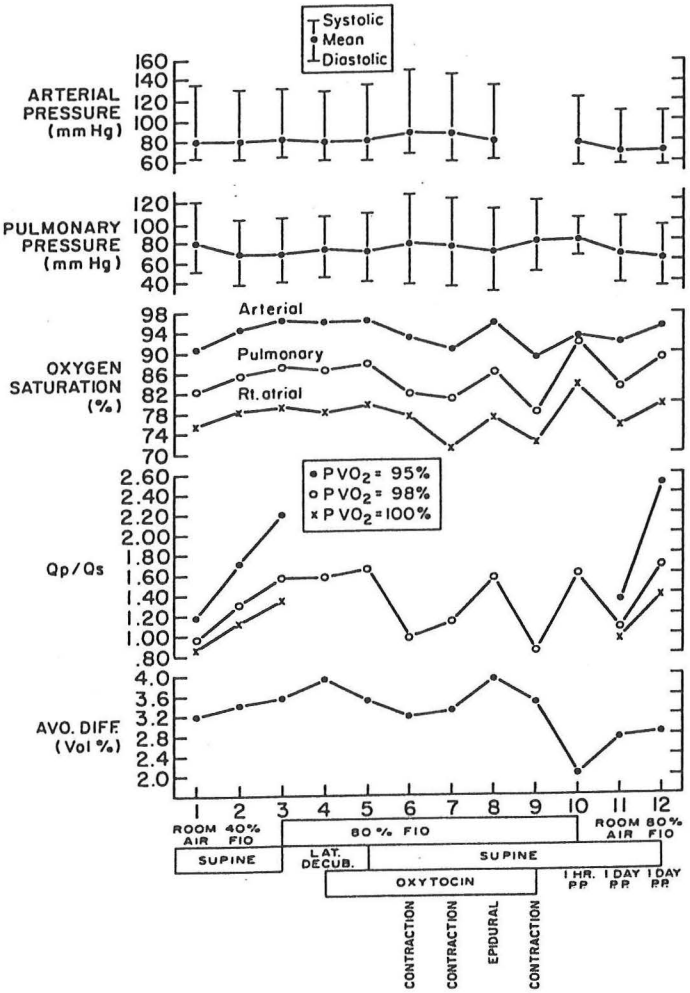
Fig 23. Timing of Maternal Deaths (Pooled Data)



For the patient who declines elective abortion, coordination of a multidisciplinary team, consisting of an obstetrician, cardiologist, social worker, anesthesiologist, and neonatologist, is essential for enhancing fetal and maternal health during pregnancy, delivery, and pueperium. The pregnant patient with Eisenmenger syndrome should be hospitalized after the 20th week of pregnancy -- or earlier if clinical deterioration occurs -- for close observation. If dyspnea occurs, supplemental oxygen should be administered to decrease any reversible component of pulmonary arterial hypertension and right-to-left shunting (Figure 24). Congestive heart failure should be treated with digoxin and diuretics. At the time of delivery, the patient should be transferred to an intensive care area for close hemodynamic monitoring (i.e., radial arterial cannulation, continuous pulse oximetry, and electrocardiographic monitoring). Supplemental oxygen should be administered because of its beneficial effect on pulmonary vascular resistance and shunt flow [85]. Since placement and maintenance of a flow-directed, balloon-tipped catheter in the pulmonary artery is difficult and associated with a high incidence of catheter-related complications, we do not recommend routine placement of such a catheter. Careful assessment of the patient's volume status, systemic arterial pressure and oxygen saturation, and hematocrit usually provides sufficient information to guide management.

To avoid the risks associated with anesthesia, vaginal delivery is preferable to Cesarean section. Excessive blood loss and hypotension increase right-to-left shunting and cyanosis and should be treated promptly with parenteral volume replacement and vasopressers. The second stage of labor should be shortened by elective low forceps delivery, as frequent uterine contractions in this stage may cause a decreased ratio of pulmonary to systemic blood flow [85].

Figure 24. Hemodynamic Changes During Vaginal Delivery in A Patient With Eisenmenger Syndrome (Ref 75)



Routine anticoagulation in the pregnant patient with Eisenmenger syndrome is controversial. Some studies [76,84] report improved maternal outcome when heparin is initiated in the second trimester of pregnancy. When administered immediately after delivery, however, excessive bleeding, hypotension, and maternal death may occur [86,87]. We recommend that subcutaneous heparin be initiated during the 20th week of pregnancy -- ensuring that the activated partial thromboplastin time 6 hours after injection is greater than 2 times control -- and discontinued immediately before planned delivery. It should be reinstituted as soon as feasible (e.g., 1 or 2 days) after delivery with close monitoring of the coagulation profile. Warfarin therapy can be started before hospital discharge and continued for 6 to 8 weeks postpartum.

Prevention of pregnancy and contraceptive counseling are extremely important for the woman with Eisenmenger syndrome. Oral contraceptives are contraindicated because of the increased risk of thromboembolic complications associated with their use. Barrier methods, such as condom and diaphragm, have an unacceptably high

failure rate. The safest and most effective method of contraception is tubal ligation. Alternative methods are intramuscular injection of medroxyprogesterone every 3 months or subcutaneous placement of a levonorgestrel implant.

C. Noncardiac Surgery: Since noncardiac surgery in the patient with Eisenmenger syndrome is associated with a high perioperative mortality (up to 19%), it should be avoided, if possible [88]. When it is necessary, the patient should be monitored closely and carefully during anesthesia induction and postoperatively. The anesthetic technique least likely to decrease the patient's systemic blood pressure and vascular resistance should be employed, since such changes increase the magnitude of right-to-left shunting and cyanosis. Surgery should be performed under local anaesthesia when feasible (i.e., dental, ophthalmic, or simple outpatient surgery). Otherwise, the choice of general or epidural/spinal anesthesia is controversial. Although the latter technique causes sympathetic blockade, which may cause systemic arterial vasodilation and hypotension, many of the agents used for induction and maintenance of general anesthesia depress myocardial function and reduce systemic vascular resistance. Both techniques have been used successfully in patients with Eisenmenger syndrome undergoing noncardiac surgery [77,88-90], but they have not been compared in a randomized study. In our opinion, it is most important that anesthesia for noncardiac surgery be administered by a cardiac anesthesiologist with experience in patients with Eisenmenger syndrome.

Prolonged fasting and volume depletion should be avoided preoperatively and treated promptly with intravenous fluids. Endocarditis antibiotic prophylaxis should be considered, and all intravenous lines should be equipped with a device to filter air bubbles to prevent paradoxical air embolism. Systemic arterial hypotension should be treated aggressively with an alpha-adrenergic agonist (such as methoxamine, metaraminol, or phenylephrine) and/or intravenous volume replacement, if the patient is hypovolemic. It is imperative that blood loss be minimized and excessive bleeding promptly treated with blood products. A "normal" hematocrit may not provide adequate arterial oxygenation in some patients with Eisenmenger syndrome; the hematocrit must be maintained higher. An intra-arterial cannula should be inserted for close monitoring of systemic arterial pressure and oxygenation. Routine insertion of an indwelling pulmonary arterial catheter is not recommended (see discussion of its use during pregnancy). Postoperatively, the patient should be observed closely in an intensive care unit. Early ambulation following surgery is desirable to prevent thromboembolism, and subcutaneous heparin should be considered when prolonged immobilization is anticipated [91].

Conclusions

Eisenmenger syndrome is characterized by an elevated pulmonary vascular resistance and right-to-left shunting of blood through a systemic to pulmonary circulation connection. Most patients with Eisenmenger syndrome survive for 20 to 30 years. The hemostatic changes associated with it may lead to thromboembolic events, cerebrovascular complications, or hyperviscosity syndrome. Erythrocytosis is present in most patients; however, excessive phlebotomy may cause microcytosis and exacerbate the symptoms of hyperviscosity. Other complications associated with Eisenmenger syndrome include hemoptysis, gout, cholelithiasis, hypertrophic osteoarthropathy and decreased renal function. Pregnancy or noncardiac surgery is associated with a high mortality rate in patients with Eisenmenger syndrome.

Since most pediatric patients with Eisenmenger syndrome survive to adulthood, primary care physicians should have a thorough understanding of the syndrome, associated complications, and medical and surgical management, especially with regard to the appropriate timing of phlebotomy and lung (or heart-lung) transplantation. In addition, Eisenmenger patients should undergo routine follow-up at a tertiary care center that has physicians and nurses with special expertise in congenital heart disease. In the Eisenmenger patient with pregnancy or noncardiac surgery, a multidisciplinary approach should be used to reduce the excessive mortality associated with these conditions.

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