

# **Eisenmenger Syndrome & Cyanotic Congenital Heart Disease**

## **Long-term Effects of Hypoxemia in the Adult with CHD**

### **What the ICU Bedside Nurse Needs to Know**

Nancy Rudd, RN, MS, CPNP-PC/AC;  
Children's Hospital of Wisconsin

Lindsey Fox, RN, MSN, ANP-AC;  
Children's Hospital of Wisconsin

#### **Introduction**

Cyanosis by definition is a bluish discoloration due to the presence of an increased quantity of desaturated hemoglobin in the tissues.

In our current era of congenital heart disease, cyanosis is generally due to right-to left shunting through congenital defects, blood bypassing the pulmonary alveoli, or due to acquired intrapulmonary shunts.

However, in adults with congenital heart disease, the presence of long-standing cyanosis is the result of a nonrestrictive intracardiac or extracardiac communication with consequent increased pulmonary blood flow and transmission of systemic or near systemic pressures to the pulmonary arteries leading to the development of irreversible pulmonary vascular disease.

Eisenmenger syndrome is term used to describe a physiologic state that begins with the presence of a left-to-right shunt. This results in a net increase in pulmonary blood flow eventually leading to the development of pulmonary vascular disease and increased pulmonary vascular resistance. The increase in pulmonary vascular resistance results in a rise in pulmonary artery pressure. Pulmonary arterial hypertension causes reversal of flow through the shunt because right heart pressure exceeds left heart pressure and right-to-left shunting of blood occurs. With right-to-left shunting, de-oxygenated blood returning to the right side of the heart, passes through a communication such as a VSD or PDA to the left side of the heart and is pumped to the body resulting in cyanosis.

#### **Eisenmenger Syndrome**

In 1897, Eisenmenger described a syndrome in which pulmonary vascular disease developed in patients with a nonrestrictive ventricular septal defect. The triad of systemic-to-pulmonary communication, pulmonary vascular disease and cyanosis is called Eisenmenger syndrome. The term Eisenmengers now includes patients with any congenital intracardiac or extracardiac shunt that results in the development of pulmonary vascular obstructive disease.

The diagnosis of Eisenmenger syndrome implies that the development of pulmonary vascular disease is a consequence of increased pulmonary blood flow, and requires the exclusion of other causes of pulmonary hypertension such as connective tissue diseases, HIV infection, portal hypertension, pulmonary veno-occlusive diseases, or drug or toxin induced arterial hypertension.

The risk of developing the Eisenmenger syndrome appears to be determined by the size of the initial left-to-right shunt and the volume of pulmonary blood flow, with larger shunts having increased risk. In addition, however, the type of defect is important. Only about 10 percent of patients with unrepaired atrial septal defects develop the Eisenmenger syndrome, compared to 50 percent of patients with unrepaired ventricular septal defects and nearly all patients with unrepaired truncus arteriosus. In some cases, the

diagnosis of Eisenmenger syndrome is not established until adulthood when overt signs of pulmonary hypertension such as syncope, atrial and ventricular arrhythmias, and right and left heart failure develop.

Since the introduction of surgical correction of congenital heart defects such as ASD and VSD in the 1970s the prevalence of Eisenmenger syndrome has declined but not disappeared. Life expectancy for this group of patients was described in one large study of 188 patients diagnosed with Eisenmenger syndrome. Findings included 75% of patients were alive at age 30, 70% at age 40, and 55% at age 50. From the study, it was clear that patients with more complex diseases did worse than those with simpler lesions such as ASD, VSD, and PDA. Many adolescents and adults with Eisenmenger syndrome do well until their third decade of life, but then become more symptomatic. Strong predictors for death in retrospective studies include syncope, age of presentation, or symptoms, deterioration in ability index or poor functional class, supraventricular arrhythmias, elevated right atrial pressures, low oxygen saturation (defined as less than 85%), renal insufficiency, severe RV dysfunction, and trisomy 21.

### **Associated Lesions - Eisenmenger syndrome**

Eisenmenger syndrome may occur as result of primary congenital heart lesions or secondary to surgically created communications between the systemic and pulmonary circulations.

- **Congenital Heart Defects:** Although the most common defects associated with the development of Eisenmenger Syndrome are ventricular septal defects (33 percent), atrial septal defects (30 percent), and patent ductus arteriosus (14 percent), (Blieden, 1984) the development of Eisenmenger syndrome may be associated with a variety of forms of congenital heart disease.
  - ***Isolated lesions without pulmonary outflow tract obstruction***
    - ASD
    - VSD
    - PDA
    - PAPVR
  - ***Complex lesions without pulmonary outflow tract obstruction***
    - AVSD
    - D-TGA
    - L-TGA with nonrestrictive VSD
    - Truncus Arteriosus
  - ***Large aortopulmonary connections***
    - Aortopulmonary window
    - Aortopulmonary collaterals in patient with PA
- **Surgically-created Palliative Communications:** Creation of a communication or shunt between the systemic and pulmonary circulation was a palliative procedure performed mainly in past decades to augment pulmonary blood flow and relieve cyanosis in setting of complex CHD not easily amenable to complete repair such as TOF, PA, TA and single ventricle anatomy.
  - Potts shunt
  - Waterson shunt
  - Blalock-Taussig shunt

### **Clinical Assessment**

Physical examination of the patient with Eisenmenger syndrome generally demonstrates pulmonary arterial hypertension, central cyanosis and digital clubbing of all extremities. However, in some cases the pattern and degree of cyanosis and clubbing may depend upon the patient's hemodynamic status and the cardiac anatomy. An often discussed example is the patient with a patent ductus arteriosus and Eisenmenger syndrome, in whom the right-to-left shunt through the ductus typically delivers unoxygenated blood distal to the left subclavian artery. This can result in differential cyanosis and clubbing that may be more pronounced in the lower extremities. Signs of pulmonary artery hypertension include a right ventricular impulse and a palpable pulmonary closure sound (P2) on palpation of the precordium. On auscultation, there is usually no murmur, but an ejection sound is common due to dilatation of the pulmonary artery.

With progressive right heart failure, additional clinical findings may develop: The mean jugular venous pressure increases resulting in jugular venous distension. The increase in pulmonary venous pressure can also lead to the development of hepatomegaly, peripheral edema, and ascites. Murmurs of tricuspid and pulmonic regurgitation become audible. Tricuspid regurgitation in this setting is secondary to dilatation of the tricuspid annulus and right ventricle, and is not a sign of valve disease

### **Diagnostic Evaluation**

Evaluation for congenital heart disease related pulmonary arterial hypertension should include:

- noninvasive assessment of cardiopulmonary anatomy and function via echocardiogram
- pulse oximetry with and without oxygen to as well as upper and lower extremity oximetry looking for differential cyanosis
- ECG may demonstrate right or biventricular hypertrophy, evidence of right atrial abnormality, or ST-T wave changes
- chest x-ray usually shows dilation of central pulmonary arteries and cardiomegaly
- cardiac catheterization with potential for vasodilator testing should be performed in a center with expertise in managing congenital heart disease and related pulmonary arterial hypertension

### **Associated Complications and Management**

In the presence of chronic hypoxemia, these patients develop a wide range of long-term complications involving multiple different organ systems.

- Secondary Erythrocytosis
  - Patients develop secondary erythrocytosis due to increased erythropoietin productions in response to long-standing hypoxemia. This is a physiologic response, since the cyanotic blood stimulates the bone marrow to produce more red blood cells in an attempt to improve tissue oxygenation. Stable erythrocytosis at an appropriate level develop in some patients, however, often hematopoiesis increases dramatically and the hemoglobin rises to over 20 g/dL with a hematocrit of more than 65 percent. Symptoms of hyper viscosity may develop, such as headache, loss of concentration, muscle weakness, and fatigue. Of note, intravascular volume depletion can cause these same symptoms and must be excluded.
  - Hyperviscosity symptoms can be avoided by maintaining adequate hydration, avoiding prolonged NPO times (consider giving maintenance IV fluids while NPO), and diagnosing and treating iron deficiency (see section below on anemia).
  - Phlebotomy in patients with Eisenmenger syndrome and secondary erythrocytosis should be used conservatively and not solely to achieve a target hematocrit. Phlebotomy should be performed ONLY in patients with intrusive symptoms of hyper viscosity such as headache, loss of concentration, muscle weakness, and fatigue, and then only with caution in the setting of iron deficiency (see Anemia section below). Some experts also recommend preoperative phlebotomy to improve hemostasis.

- The 2008 ACC/AHA guidelines on phlebotomy recommend:
  - Therapeutic phlebotomy for hemoglobin greater than 20 g/dL and hematocrit >65 percent, associated with headache, increasing fatigue, or other symptoms of hyper viscosity in the absence of dehydration or anemia.
- Repeated routine phlebotomies are NOT recommended because of the risk of iron depletion, decreased oxygen-carrying capacity, and stroke.
  - The phlebotomy procedure should be carried out slowly with simultaneous infusion of isovolumic fluid. Frequent phlebotomies and iron deficiency anemia should be avoided, since rebound erythropoiesis can occur, with production of iron deficient red blood cells (microspherocytes). There is debate about a potential increase in risk of cerebrovascular events in patients with rebound erythropoiesis and microspherocytosis. Microspherocytes have reduced oxygen carrying capacity as well as increased rigidity and fragility. As a result, there is an increase in whole blood viscosity and possible development of symptoms of iron deficiency anemia such as exercise intolerance, weakness, headache, irritability, and fatigue.
- Anemia
  - Symptomatic anemia can occur in cyanotic patients and is most often due to iron deficiency resulting from rebound erythrocytosis or bleeding.
  - The 2008 ACC/AHA guidelines recommend avoidance of iron deficiency in patients with cyanotic heart disease and/or Eisenmenger syndrome.
  - The treatment of iron deficiency is iron therapy.
    - Iron should be administered with care since iron supplementation may lead to rapid increases in red cell mass.
    - Although there are no specific data regarding timing, some sources recommend that iron supplementation be instituted when the mean corpuscular volume is less than 82, since microspherocytes may increase the cerebrovascular risk.
    - Iron should be discontinued when the hematocrit begins to rise, usually within 7 to 10 days.
- Hemostasis
  - Eisenmenger patients are at risk for both bleeding and thrombotic hematologic issues.
  - Prolonged periods of immobilization should be avoided in these patients.
  - Cyanotic patients have an increased risk of hemorrhage due to a number of hematologic abnormalities documented in up to 20 percent of patients. These include:
    - Abnormal platelet function
    - Elevations in the prothrombin and partial thromboplastin times
    - Thrombocytopenia.
  - These patients all have low levels of circulating vitamin K dependent clotting factors, factor V, and von Willebrand factor.
  - Bleeding in this population is usually mild and self-limiting, but can be life threatening.
  - Pulmonary bleeding and menorrhagia are the most frequently reported in this population (see below).
  - Most recommend that anticoagulants and antiplatelet drugs be avoided in these patients unless clear indications arise.
  - Anticoagulation is not routinely recommended for patients with cyanotic heart disease but exceptions to this rule include:

- Atrial fibrillation
- Documented pulmonary thrombosis or embolism
- Mechanical heart valves or pacemaker leads in right side of heart
- Deep venous thrombosis

For example, in the case of recurrent atrial arrhythmias in the presence of a right-to-left shunt, the risk of paradoxical emboli is relatively high. Some treat these patients with aspirin, however, currently there is no clear data indicating that warfarin or aspirin reduce the incidence of clot formation, pulmonary infarct, or ischemia in this patient population. In addition, there is no clear data indicating that warfarin in this population improves mortality or morbidity. As a result, the risk for bleeding clearly needs to be weighed against the risk for thrombus formation in each individual. In general, most major adult congenital heart centers do not put these patients on Coumadin.

- Pulmonary Bleeding
  - Intrapulmonary hemorrhage, which is a serious and life-threatening problem for Eisenmenger and other cyanotic patients and can reflect rupture of the pulmonary trunk or a bronchial artery.
  - Hemoptysis is external bleeding and does not directly correlate with the extent of pulmonary hemorrhage.
  - Bronchoscopy should be avoided as it is associated with significant risk and rarely discloses the cause of hemoptysis.
  - CT angiography should be performed to determine the presence and extent of intrapulmonary hemorrhage.
- Menorrhagia
  - A common problem in women with cyanotic heart disease and, if severe, can lead to iron deficiency anemia.
  - Suppression of menorrhagia with hormonal stimulation is often helpful.
  - However, hysterectomy is occasionally required.
- Renal Dysfunction
  - Several studies have demonstrated that cyanotic kidneys do not function normally despite having normal serum creatinine.
  - Often these patients have a relatively low GFR.
  - Renal dysfunction in cyanotic patients is primarily manifested as hyperuricemia and proteinuria.
  - The 2008 ACC/AHA guidelines recommendations:
    - Uric acid and creatinine levels are assessed at least yearly in Eisenmenger syndrome patients.
    - Drugs that can impair renal function, such as ACE inhibitors, diuretics, and NSAIDs should be avoided or used with caution.
    - If administration of radiographic contrast agent is planned, the glomerular filtration rate should be assessed.
    - Intravenous fluids administered as appropriate and other precautions considered.
- Hyperuricemia
  - Among patients with cyanotic congenital heart diseases, the serum uric acid rises in proportion to the degree of hypoxemia.

- Hyperuricemia can lead to gout but rarely to renal failure, since the hyperuricemia is primarily due to reduced excretion rather than increased production.
- Therapy is not necessary in asymptomatic patients.
- For patients who do develop gout, allopurinol and colchicine are preferred treatment options over nonsteroidal anti-inflammatory drugs as they may interfere with platelet function and may impair renal function.
- Gallstones
  - Increased red blood cell turnover and subsequent production of unconjugated bilirubin can result in gallstones.
  - The major risk of cholelithiasis is the development of acute cholecystitis with the need for emergency surgery.
  - Surgery is not recommended until patients become symptomatic.
- Orthopedic
  - Orthopedic problems, such as scoliosis, are present in approximately 25 to 30 percent of patients with congenital heart disease, many of those with cyanotic heart disease.
  - Scoliosis
    - The etiology is unknown but can be disabling.
    - Can contribute to increased cyanosis and functional incapacity due to pulmonary restriction.
    - May require consideration of high-risk surgical intervention.
  - Hypertrophic osteoarthropathy
    - Periostitis is associated with this condition.
    - Causes aching and tenderness of long bones of the body.
- Arrhythmias
  - Patients are at increased risk for significant atrial and ventricular arrhythmias.
  - Supraventricular tachyarrhythmias, specifically atrial flutter, atrial fibrillation and ectopic atrial tachycardia are common.
    - These arrhythmias often lead to clinical deterioration and a return to sinus rhythm is imperative.
    - Often this is best achieved with cardioversion, however, in hemodynamically stable patients, a trial of amiodarone may be an option.
    - All antiarrhythmics can be proarrhythmic and their effects on a hypertensive, hypertrophied, cyanotic ventricle are not well known.
    - Amiodarone has been most frequently used and likely is the least proarrhythmic of all available medications.
  - Ventricular arrhythmias although less common can cause significant hemodynamic compromise.
  - Unfortunately, data on the use of antiarrhythmics or AICDs in this patient population is limited.
- Respiratory
  - Many patients with Eisenmenger syndrome are wrongly diagnosed with obstructive airway disease.
  - Typically, these patients have severely dilated main pulmonary arteries.
  - The distant pulmonary arteries are also under significantly elevated pressure.
  - It is speculated that these large, dilated, hypertensive pulmonary arteries compress the small adjacent airways resulting in air trapping.

- This often leads to a false diagnosis of obstructive airway disease when in fact, the cause is mechanical compression secondary to large hypertensive pulmonary arteries.
- Neurologic
  - Patients with cyanotic heart disease are at risk for neurologic complications in the setting of paradoxical cerebral emboli which may lead to stroke or brain abscess.
  - Atrial arrhythmias and transvenous pacing leads may increase the risk of thrombosis.
- Endocarditis prophylaxis
  - These patients are at increased risk for endocarditis.
  - The 2007 AHA guidelines on the prevention of infective endocarditis recommend antimicrobial prophylaxis for all patients with unrepaired cyanotic congenital heart disease.
  - If endocarditis develops, this patient population is prone to having embolization to their lung. Therefore, if these patients develop fever that is unexplained, blood cultures along with ESR and CRP should be obtained prior to starting antibiotics.

### **Medical Treatment Options:**

- Pulmonary Vasodilators
  - Until recently, management strategies for patients with Eisenmenger syndrome have been limited to palliative and supportive options.
  - More recently, pulmonary vasodilator agents have emerged as targeted treatment therapy options.
  - The 3 currently utilized classes of pulmonary vasodilating agents used in this population are:
    - Prostacyclin and prostacyclin analogs
    - Endothelin receptor antagonists
    - Phosphodiesterase inhibitors
  - Pulmonary arterial hypertension targeted treatments have been shown to improve functional capacity and quality of life in Eisenmenger patients.
    - The Bosentan Randomized Trial of Endothelin Antagonist Therapy – 5 (BREATHE-5) is the first placebo-controlled study in Eisenmenger patients to show improved exercise capacity and functional class (Galie, 2006).
    - An open-label uncontrolled study reported improved NYHA functional class and systemic arterial oxygen saturations following 6 months of sildenafil, a phosphodiesterase inhibitor, administration however no improvement in 6-minute walk was found (Chau,2007).
    - A retrospective report on epoprostenol therapy given to Eisenmenger patients for 3 months resulted in improved functional class, increased oxygen saturation, decreased pulmonary vascular resistance, and improved 6-minute walk distance (Fernandes 2003).
    - A study published in 2010 detailed use of advanced therapies including bosentan, sildenafil, and epoprostenol individually and in combination, and outcomes included an associated lower risk of death with these advanced therapies (Dimopoulos, 2010).
- Oxygen
  - Use of inhaled oxygen in this patient population is controversial.
  - Administration of high-level inhaled oxygen does raise the systemic arterial oxygen saturation. However, it does not have any effect on the degree of right-to-left shunting.
  - Some patients, however, do report benefit from oxygen.

- This needs to be weighed against the risk of chronic oxygen toxicity as well as the known drying effect that chronic oxygen has on the nasal mucosal membrane and tracheobronchial tree.
- This drying effect of inspired oxygen can lead the nocturnal cough with greater interference of sleep and potential risk for pulmonary hemorrhage.

### **Prophylactic Management Strategies:**

- Phlebotomy procedure, if indicated, should be carried out slowly with simultaneous infusion of isovolumic fluid
- Use of an air filter on all intravenous lines to eliminate risk of systemic air emboli
- Avoidance of dehydration
- Avoidance of iron deficiency
- Avoidance of drugs that impair renal function
- Administration of influenza vaccine annually and pneumococcal vaccine every 5 years
- Encourage fitness maintenance by patients remaining active within their abilities and minimizing use of wheelchairs and other aids when possible
- These patients often develop significant right heart failure. As a result, these patients may require small doses of diuretics. This, however, clearly needs to be balanced with maintaining adequate preload. These patients have fixed pulmonary hypertension and as a result, the amount of pulmonary blood flow directly relates to the overall stroke volume and cardiac output. In the setting of dehydration, there is decreased pulmonary blood flow with more right-to-left shunting, more cyanosis, more hypoxia and associated increased symptoms.

*The following considerations were noted in the 2008 ACC/AHA guidelines:*

- During long-distance flights, cyanotic patients should drink nonalcoholic and noncaffeinated fluids to avoid dehydration and the diuretic effects of alcohol and caffeine. Supplemental oxygenation may be considered.
- Competitive sports should be avoided in cyanotic patients.
- Maternal and fetal outcomes are adversely affected in cyanotic patients (see below).
- Given the high risk of hospitalization and/or surgery in patients with cyanotic heart disease, these patients should be seen and followed by an adult congenital heart disease specialist.
- Adult patients with cyanotic heart disease should be seen at least annually by an adult congenital heart disease specialist.

### **Special Considerations**

- Life expectancy is generally more severely reduced in Eisenmenger patients with complex congenital heart disease than in those with simple lesions.
- Eisenmenger patients have a better life expectancy than patients with primary pulmonary hypertension (PPH) who have similar hemodynamics.
- The majority of Eisenmenger patients die suddenly. The most common cause of death is massive hemoptysis secondary to intraparenchymal hemorrhage, rupture of an aneurysm, erosion of bronchial collateral, dissection of ascending aorta, or massive pulmonary infarct.
- Pregnancy for women with a right-to-left shunt and pulmonary vascular disease poses extreme risk to the mother and fetus. The fall in peripheral vascular resistance that occurs during pregnancy increased the shunting and exaggerates the cyanosis. Any fall in blood pressure or episode of blood loss can result in sudden death. Maternal mortality rates are reported at >50%. Termination of pregnancy is strongly advised. If the women decides to proceed with pregnancy

again advice, coordinated care with an adult congenital heart disease specialist and high-risk obstetric team is essential.

- General anesthesia and sedation can be risky in this population therefore non-essential surgery or interventional procedures should be avoided.

#### **REFERENCES:**

Blieden, L. C., Moller, JH. (1984). Small ventricular septal defect associated with severe pulmonary hypertension. *Br Heart J*, 52, 117.

Bolger, A. P., Sharma, R., Li, W., et al. (2002). Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation*, 106, 92.

Chau, E. M., Fan, K. Y., Chow, W. H. (2007). Effects of chronic sildenafil in patients with Eisenmenger syndrome versus idiopathic pulmonary arterial hypertension. *Int J Cardiology*, 120, 301-5.

Dimopoulos, K., Inuzuka, R., Goletto, S., Giannakoulas, G., Swan, L., Wort, S. J., Gatzoulis, M. A. (2010). Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. *Circulation*, 121(1), 20.

Dimopoulos, K., Wort, S. J., Gatzoulis, M. W. (2014). Pulmonary hypertension related to congenital heart disease: a call for action. *Eur Heart J*, 35, 691-700.

Eisenmenger, V. (1897). Die Angeboren Defect der Kammer scheiderwand des Herzens. *Z Klin Med Suppl*, 32, 1.

Fernandes, S. M., Newburger, J. W., Lang, P., et al. (2003). Usefulness of epoprostenol therapy in the severely ill adolescent/adult with Eisenmenger physiology. *Am J Cardiology*, 91: 632-5.

Fukushima, H. (2015). Update on medical treatment of patients with Eisenmenger syndrome. *Int Heart J*, 56 suppl, S4-S7.

Galie, N., Beghetti, M., Gatzoulis, M. A., Granton, J., Berger, R. M., Lauer, A., Chiossi, E., Landzberg, M. J. (2006). Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation*, 114, 48-54.

Gatzoulis, M. A., Webb, G. D., Daubeney, P. E. I. (2010). *Diagnosis and Management of Adult Congenital Heart Disease* (2nd ed.). St. Louis, MO: Elsevier.

Granton, J. T., Rabinovitch, M. (2002). Pulmonary arterial hypertension in congenital heart disease. *Cardiol Clin*, 20, 441.

Mikami, T., Kudo, T., Sakurai, N., et al. (1984) Mechanisms for development of functional tricuspid regurgitation determined by pulsed Doppler and two-dimensional echocardiography. *Am J Cardiol*, 53, 160.

Ohuchi, H., Takasugi, H., Ohashi, H., et al. (2003). Stratification of pediatric heart failure on the basis of neurohormonal and cardiac autonomic nervous activities in patients with congenital heart disease. *Circulation*, 108, 2368.

Saha, A., Balakrishnan, K. G., Jaiswal, P. K., et al. (1994). Prognosis for patients with Eisenmenger syndrome of various aetiology. *Int J Cardiol*, 45, 199.

Warnes, C. A., Williams, R. G., Bashore, T. M., et al. (2008). ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*, 118, e714-833.

Reviewed/Revised  
10/2015  
N. Rudd