

AANA JOURNAL COURSE

Update for nurse anesthetists

2

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Eisenmenger syndrome: An anesthetic conundrum

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Eisenmenger syndrome is an insidious disease entity. This disease is characterized by an unrepaired congenital heart defect and left-to-right cardiac shunting. After many years of increased blood flow through the pulmonary system as a result of the shunting, damage to the pulmonary vessels occurs, culminating in severe pulmonary hypertension. The pulmonary hypertension eventually causes the cardiac shunt to reverse direction. The right-to-left shunt results in a very debilitated patient.

There is no known medical cure for this disease; the only

curative option is heart-lung transplantation or bilateral lung transplantation with repair of the patent heart defect. Because of the great strides in medical care, more patients with Eisenmenger syndrome require anesthesia. Maintaining the patient's systemic vascular resistance at the preoperative level is of paramount importance. Choosing the best anesthesia technique is difficult, at best.

Key words: Congenital heart defect, Eisenmenger syndrome, pulmonary hypertension, right-to-left cardiac shunt, systemic vascular resistance.

Objectives

At the completion of this course, the reader should be able to:

1. List the anatomic and physiologic factors involved in the development of Eisenmenger syndrome.
2. Describe complications commonly associated with Eisenmenger syndrome.
3. Name 2 medications useful in the treatment of Eisenmenger syndrome.
4. State the most important physiologic factors to consider in choosing the anesthetic technique for a patient with Eisenmenger syndrome.
5. Describe the monitoring requirements during anesthesia for a patient with Eisenmenger syndrome.

History

Documentation of severe pulmonary vascular disease in conjunction with a significant ventricular septal defect and right ventricular hypertrophy appeared in the medical literature in 1897.¹ The postmortem description was made by a little-known German physician, Viktor Eisenmenger, who would later become the physician for Archduke Ferdinand. The subject of the autopsy was a patient who had cyanosis

and dyspnea throughout life and died of massive hemoptysis at 32 years of age. For more than 50 years, the pathophysiologic entity that came to be known as Eisenmenger syndrome (ES) was defined, essentially, by Dr Eisenmenger's original observations.

In 1958, Paul Wood, MD, published data and observations that redefined ES. Wood's data and observations dictated that ES results from systemic pulmonary hypertension secondary to persistently elevated pulmonary vascular resistance (PVR). The elevated PVR eventually produced a bidirectional or completely reversed cardiac shunt through a significant ventricular septal defect.² Currently, the parameters by which ES is defined have been expanded to encompass pulmonary hypertension that develops as the result of any pulmonary-to-systemic circulation communication that produces a right-to-left shunt.³ Because of the tremendous advances in medical care, patients with ES, although still relatively rare, are more likely than in the past to need anesthesia care for cardiac or noncardiac surgical interventions.

Pathophysiology

Since the mid-1970s, many of the known congenital heart defects, such as atrial septal defect, ventricular septal defect, and patent ductus arteriosus, have been

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included in the development scheme of ES (Table 1).³ Statistically, congenital heart defects occur at a rate of 1% of live births. Of this 1%, ES eventually will develop in approximately 8% who have a congenital defect and 11% with a left-to-right shunt.⁴

The basic evolution involves one or more of the numerous defects present. Initially, the communication pathway or shunt allows blood flow from left-to-right, and oxygenated blood mixes with deoxygenated blood. The shunt is the product of a simple pressure gradient, as is any flow dynamic, from higher pressure to an area of lower pressure.

Initially, the systemic vascular resistance (SVR) is the higher pressure reservoir, whereas the pulmonary vascular resistance (PVR) is the lower pressure reservoir. The normal SVR value is 700 to 1,400 dynes/cm,⁵ and the normal PVR is 50 to 300 dynes/cm.⁵ As a result of the volume of the shunt, the stroke volume of the right ventricle is increased. The increased stroke volume produces shear forces within the microvasculature of the pulmonary system. The combination of the increased volume and shear forces, over time, results in damage to the walls of the pulmonary vasculature, in turn increasing the PVR.

As the PVR continues to increase, the left-to-right shunt volume eventually decreases, but the damage has been done. As the resistances of the 2 systems approach equality, the shunt volume decreases. When the resistances achieve equality (ie, PVR = SVR), the shunt flow essentially stops, that is, there is no pressure gradient across which flow can be initiated. However, the resistances of both systems are dynamic entities, varying on a beat-to-beat basis. Thus, as PVR and SVR vacillate around or near equality, cardiac shunting becomes bidirectional. When the PVR meets and eventually exceeds the SVR consistently, the shunt changes direction to that of the decidedly detrimental right-to-left shunt. At this point, deoxygenated blood mixes with oxygenated blood, producing chronic hypoxemia for all body tissues.

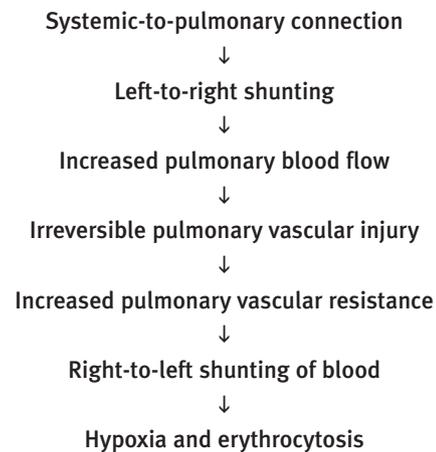
Eisenmenger syndrome is defined by the appearance of a bidirectional or completely reversed cardiac shunt in conjunction with a patent heart defect and pulmonary hypertension (Figure). When the cardiac shunt becomes bidirectional or has completely reversed, the damage to the pulmonary vasculature is considered too extensive to allow for surgical correction of the patent heart defect. Surgical correction at this time would be nullified by the development of cardiomegaly and right-sided heart failure as the heart tries to overcome the primary pulmonary hypertension that remains.

Experimental data indicate that injuries such as medial hypertrophy and progressive occlusion

Table 1. Congenital heart defects

Ventricular septal defect
Patent ductus arteriosus
Atrial septal defect
Atrioventricular septal
Double-outlet right ventricle
Tetralogy of Fallot
Transposition of the great vessels
Truncus arteriosus
Hypoplastic right defect heart
Univentricular heart

Figure. Pathophysiology of Eisenmenger syndrome⁴



observed in association with ES may be the result of the production of elastase enzymes and growth factors in the presence of pulmonary microvascular injury.⁵⁻⁷ Further experimental data point to malfunction or dysfunction of some of the pulmonary vascular endothelium or possibly activation of platelets.⁸⁻¹² Unfortunately, the exact details involved in the development of ES remain somewhat obscure.

Signs and symptoms

Eisenmenger syndrome is an insidious disease process. Rather than the days, weeks, or months of development that is more common in many chronic diseases, ES sometimes requires decades before fully manifesting. As stated, ES will develop in only 8% of people with congenital heart defects and 11% of people with a left-to-right shunt.⁴ This represents a small percentage of an already small percentage of the overall population. This malady does not seem to target any particular racial ethnic group or gender. Instead, the target population tends to arise most frequently from the population for whom prenatal care is suboptimal.

Table 2. Signs and symptoms of Eisenmenger syndrome

Dyspnea on exertion
Palpitations
Syncope
Cyanosis
Fatigue
Angina
Hemoptysis
Erythrocytosis or polycythemia

As such, the signs and symptoms of ES are relatively indistinguishable from those of a myriad of maladies, such as chronic obstructive pulmonary disease and congestive heart failure. Some of the signs and symptoms of ES include dyspnea on exertion, fatigue, palpitations, syncope, cyanosis, and hemoptysis (Table 2). In addition, some patients with ES may have clubbing of the digits. All of these signs and symptoms are the result of chronic hypoxemia. Another symptom of chronic hypoxemia is a proliferation of red blood cells, that is, polycythemia or erythrocytosis, as the body attempts to compensate for the chronic hypoxemia. As a result, patients with ES frequently have elevated hematocrit values, sometimes 60% or greater. The polycythemia makes the blood more viscous and can contribute to coagulopathies and other maladies, such as stroke and emboli.¹³

Current medical management

Eisenmenger syndrome is not typically diagnosed until the third or fourth decade of life, unless the patient becomes pregnant. The hemodynamic changes associated with pregnancy and fetal development hasten the deterioration of the cardiac shunt. The therapeutic treatment is termination of the pregnancy, but it is also one of the most difficult decisions such a patient will be required to make. Should the patient decide against pregnancy termination, maternal mortality in ES patients is approximately 45%.⁴

Eisenmenger syndrome is an incurable entity, except under relatively extraordinary circumstances, which involve transplantation of heart and lungs or bilateral lung transplantation in conjunction with repair of the patent congenital defect. Correction of the cardiac defect without concomitant lung transplantation serves only to hasten death.

Currently, medical management of this disease process focuses on modalities aimed at reducing the PVR, right-to-left shunting, cyanosis, morbidity, and mortality.⁴ Medical management must, of necessity, focus on avoidance of medications and treatments that have demonstrated detrimental effects in patients

with ES. For example, calcium channel blocking agents, while effective in reducing the PVR, produce an unacceptably greater reduction in the SVR. Therefore, the right-to-left shunt is worsened.

As stated, polycythemia is a part of ES. Hematocrit values between 60% and 75% occur. When patients become symptomatic, for example, they become more fatigued without increased activity, have more dyspnea, and experience headaches and hemoptysis, therapeutic phlebotomy may be used to help relieve associated symptoms. The initiation of therapeutic phlebotomy must be accompanied by careful, equal-volume fluid replacement of the blood withdrawn. The goal of phlebotomy is to reduce the mass of red blood cells and reduce the viscosity of the patient's blood. Special care must be taken to prevent hypotension throughout the procedure so as to not enhance the degree of right-to-left shunting that is present.^{4,13} Typically, about 500 mL can be safely withdrawn, but an equal volume of salt-free albumin, fresh frozen plasma, dextran, or isotonic saline solution must replace the volume removed.⁴

Administration of oxygen can be helpful in ameliorating chronic hypoxemia, dyspnea, and cyanosis. Long-term use of oxygen may continue to be palliative, but no studies have demonstrated beneficial effects on the length of survival.¹³

Aside from oxygen, patients with ES may be treated with oral and/or intravenous (IV) medications to try to reduce pulmonary resistance and help improve oxygenation. As is the case with long-term oxygen administration, the use of medications in the management of ES is more palliative. Two agents being studied for use in ES are sildenafil and L-arginine. Both agents are effective in decreasing pulmonary hypertension. In the body, L-arginine is converted to nitric oxide (NO). Nitric oxide has a well-documented ability to activate guanylate cyclase, which produces increased levels of cyclic guanosine monophosphate (cGMP). cGMP is instrumental in relaxing smooth muscles such as those found in the pulmonary vascular beds. Sildenafil inhibits the degradation of cGMP, thus fostering greater availability of cGMP, particularly in the lungs and corpus cavernosum.⁴

Recent reports have demonstrated that the administration of sildenafil works synergistically with inhaled NO to potentiate the effects of both within the NO-cGMP pathway.¹⁴⁻¹⁶ Combining sildenafil with L-arginine seems to enhance the NO-cGMP pathway without administering NO.

Another avenue of study involves newer medications: epoprostenol and bosentan. Epoprostenol is an analogue of prostacyclin. Prostacyclin and its analogues were first used in treating congenital heart defects and pulmonary vascular disease almost 30 years ago.¹⁷

Epoprostenol, introduced into the treatment milieu for patients with ES in the 1990s,¹⁸ has 2 primary pharmacologic actions: (1) direct vasodilatation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation and (2) facilitation of bronchodilation. Epoprostenol must be administered as a continuous infusion via permanent central venous access. The dosage range is 2 to 16 ng/kg per hour. A recently published study demonstrated tremendous improvement in exercise capacity, functional capacity, oxygen saturation, and hemodynamics.¹⁸

The most recently introduced medication to be used in the treatment of ES is bosentan. Bosentan is the first medication marketed in the newest drug classification: endothelin receptor antagonist. Endothelin-1 (ET-1) is a neurohormone that exerts its actions in the endothelium and the vascular smooth muscle. Elevated concentrations of ET-1 are found in conjunction with pulmonary arterial hypertension, a component of Eisenmenger syndrome. Bosentan binds to ET_A and ET_B receptors, with a somewhat greater affinity for the ET_A receptors. By binding to both endothelin receptors, bosentan has demonstrated reduction in PVR by almost 25% compared with placebo. The reduction in PVR by bosentan is credited with improving the functional status and oxygenation of patients with ES, after being administered for several months.¹⁹

Complications

Patients with ES are a subset of patients classified as having congenital heart defects. They are prone to develop any of several bleeding disorders or hemostatic abnormalities, including thrombocytopenia; increased bleeding, prothrombin, and partial thromboplastin times; loss of vitamin K-dependent clotting factors; abnormal fibrinolysis; and acquired type II von Willebrand factor abnormality; however, the cause for these abnormalities is unknown. As a result, abnormal and/or prolonged bleeding during or after a surgical procedure is a great concern. The blood lost must be carefully and equally be replaced to maintain the SVR as close to normal for the individual patient as possible to not contribute to degradation of the right-to-left shunting.

Another complication that may occur in patients with ES, as a subset of patients with congenital heart defects, is renal dysfunction. The occurrence of renal dysfunction is directly related to the severity and duration of cyanosis, hypoxemia, and erythrocytosis. The degree or extent of the renal dysfunction can range from diminished blood flow, with decreased glomerular filtration rate, to azotemia to nephrotic syndrome.⁴

One of the signs and symptoms of ES is also one of

Table 3. Hemoptysis: Causes and therapies in Eisenmenger syndrome⁴

Cause	Therapy
Bronchitis	Antimicrobial therapy; cough suppression
Pulmonary embolization	Anticoagulation; inferior vena caval filtration
Bleeding diathesis	Platelets or fresh frozen plasma; desmopressin infusion
Aortopulmonary collaterals rupture	Percutaneous catheter embolization
Pulmonary artery or arteriole rupture	Balloon tamponade; surgical repair; pulmonary artery ligation; embolization of arteriole with percutaneous catheter

the complications: hemoptysis. Hemoptysis may be the initial cause or concern for which the patient seeks treatment. It can result from hypoxemia and/or greater fragility of the pulmonary vasculature that ensues. Typically, the episode(s) of hemoptysis is relatively minor and self-limiting; however, as Eisenmenger originally observed, hemoptysis in this patient population can be massive and can be the cause of sudden death. Table 3 gives some of the causes of hemoptysis in ES along with relevant therapies.⁴

As noted in Table 4, 3 other relatively minor complications are closely associated with ES. Cholelithiasis, hypertrophic osteoarthropathy, and gout may occur. These complications are directly related to the extent of erythrocytosis the patient experiences.

Anesthetic considerations and management

Every patient who enters the operating suite for care presents a unique challenge for anesthetists. When a patient arrives who also has ES, anesthetists are presented with a challenge so unique that it may well be a true conundrum. By the very nature of the disease process, a detrimental right-to-left cardiac shunt already exists. The directionality of the shunt flow has shifted, over time, from a less detrimental flow (the left-to-right flow) as the result of the development of pulmonary hypertension and ever-increasing PVR. The first concern for the anesthetist is to make every attempt to relieve as much of the patient's anxiety as possible. Patients with ES are aware of their precarious physiology and are cognizant of the extra demands their disease process places on the anesthetist. A poised, calm, unhurried professional is the first step toward achieving the goal of anxiolysis. Every move will be more closely scrutinized, begin-

Table 4. Complications associated with Eisenmenger syndrome⁴

Hyperviscosity
Cerebrovascular accident
Cholelithiasis
Renal dysfunction
Hemostatic abnormalities
Hemoptysis
Hypertrophic osteoarthropathy
Hyperuricemia and gout

ning with the manner in which the anesthetist presents himself or herself to the act of obtaining IV access. For IV access, it is critically important to flush *all* air from the administration tubing, similar to the care one takes with IV access for a neonate. Even the smallest air bubbles introduced via the IV catheter can translate to a significant air embolism within the pulmonary microvasculature of a patient with ES.

Administration of a small dose of benzodiazepine will aid in attaining some measure of anxiety relief; however, a smaller than calculated dose would be recommended due to the potential adverse effect on the respiratory drive. The anesthetist must take great care to make the transfer of control, from self to anesthetist, a logical and methodical process with the greatest degree of patient understanding and cooperation possible. Detailed explanations and patiently, actively listening to the patient and family are *absolute prerequisites* in fostering this most critical relationship.

The chief consideration must be to make every attempt possible to avoid worsening the degree of right-to-left shunting that is already present. This translates to minimizing or avoiding decreases in the patient's SVR. Any significant decrease in the SVR directly translates into the enhancement of the degree (volume) of the patient's right-to-left shunting. Whether regional anesthesia or general anesthesia is the technique selected, nearly every anesthetic medication—from inhaled volatiles, to IV, to epidural or subarachnoid—produces a decrease in SVR. As a result, the right-to-left cardiac shunt is effectively worsened.

Induction with most of the “usual” medications, such as thiopental, propofol, and etomidate, should not be undertaken. Each of these medications is known to produce unacceptable decreases in SVR when administered in doses adequate to produce a totally obtunded patient. Ketamine is the only medication to actually support SVR and would be the appropriate choice for induction of general anesthesia in a patient with ES. Intubation can be facilitated with

a nondepolarizing muscle relaxant (NDMR), preferably one without significant associated histamine response. The steroidal-based NDMRs are metabolized predominantly in the liver. If the patient is receiving a continuous infusion of epoprostenol or receiving the oral agent, bosentan, metabolism of the steroidal-based NDMRs may be prolonged. As with the induction agents, the inhaled volatile agents currently available produce large decreases in the SVR. The newest agents, desflurane and sevoflurane, are better choices than isoflurane because of the rapidity with which the depth of anesthesia can be changed. Between desflurane and sevoflurane, desflurane can, at times, be more supportive with regard to the patient's SVR because of the mild sympathetic stimulation that it can produce. A viable inhalational alternative to the volatile agents is xenon. The superiority of xenon in cardiac and hemodynamic stability has been reported and documented numerous times.^{20,21} Xenon is not available in the United States but continues to be studied extensively in Europe.

The goal of mechanical ventilation throughout the surgical procedure is aimed more toward a lower carbon dioxide level than a higher level of oxygen saturation. Patients with ES have adapted to the reduced oxygen saturation and hypoxemia produced by the disease process. Hyperoxemia can be beneficial because it helps dilate the pulmonary vessels and lower the PVR; however, an elevated carbon dioxide level results in acidosis and increased PVR, which worsens the degree of right-to-left cardiac shunting. Adequate analgesia also is extremely important throughout the hospital experience. Pain produces increases in PVR, SVR, and cardiac oxygen requirements. Changes in any one of these parameters can be greatly magnified in patients with ES.

The pneumoperitoneum required for the laparoscopic procedure can be beneficial to patients with ES. Establishment of the pneumoperitoneum produces an increase in the SVR while maintaining venous return and cardiac output.²² This benefit is rather limited in scope; the procedure should, if at all possible, be accomplished within 40 minutes or less. After 40 minutes of carbon dioxide insufflation, retention of carbon dioxide begins to become problematic for patients with ES because it can contribute to acidosis and increased PVR.

As an alternative to general anesthesia maintained with volatile agents, total IV anesthesia has been reported as safe and effective.²² Induction achieved with ketamine still would be the better choice, accompanied by an infusion of remifentanyl. Direct laryngoscopy should be facilitated by using NDMRs as delineated earlier. On intubation, a low-dose infusion of propofol can be initiated.²² The infusion rate for the

propofol should be based on and adjusted using the patient's blood pressure and some method of awareness monitoring as guidelines.

Regional anesthesia use in patients with ES has been reported in several cases.²³⁻²⁵ Subarachnoid and epidural blockades have been used in treating patients with ES, most commonly to facilitate cesarean section delivery of a fetus. In one recent report, incremental, continuous subarachnoid blockade was used safely.²³ Epidural blockade also has been reported as a successful alternative to general anesthesia.^{24,25} The key for using regional anesthesia is maintaining the SVR as close to the preanesthetic level as possible. Adequate fluid loading before initiation of the regional technique selected is vitally important. In addition, the regional technique best suited for patients with ES would allow for minimizing the sympathectomy induced by the regional anesthetic. For these reasons, epidural blockade or continuous subarachnoid infusion techniques can be considered almost equally but are both superior to a single-injection subarachnoid blockade. Epidural and continuous subarachnoid infusion allow the patient and the anesthetist to adjust to the onset of the blockade, physiologically by the patient and mechanically by the anesthetist using fluids and/or vasoactive medications if necessary.

Monitoring

When the anesthetist encounters a patient with ES in the operating room, the patient has the appearance of a sick, infirm patient. Because one of the goals is maintaining the patient's SVR as close to the preoperative level as possible, physiologic monitoring will necessarily be more elaborate or involved than typical for the same procedure in a healthier patient. Central venous pressure and radial arterial pressure monitoring are necessary for estimating the patient's SVR. Pulmonary artery balloon floatation catheter use is somewhat controversial because achieving the proper terminal position of the catheter tip can be challenging as a result of the size of the patent congenital heart defect. Also, the readings obtained within the pulmonary vasculature may be inconsistent because of the damage it has sustained over time. Transesophageal echocardiography is particularly pertinent when larger surgical procedures, longer duration, and greater fluid shifts and administration are anticipated.

Therapeutic phlebotomy has been discussed earlier. Blood loss during surgery is virtually inevitable. Because of the effects of blood loss on SVR, any blood lost must be replaced in a volume-for-volume manner. The rationale is to avoid hypotension, relative or absolute, so as not to cause or allow a significant SVR reduction and, thus, degradation of the shunting that already exists.

Conclusion

A patient with ES presents a daunting anesthetic challenge. Already in a debilitated state, physically and emotionally, even the slightest degradations in cardiac and circulatory parameters are greatly magnified. Because of the tremendous advances in medical understanding, care, and management, patients with ES are surviving 20, 30, or more years after receiving the diagnosis. As a result, the likelihood of caring for such a patient, although still somewhat rare, continues to increase. Caring for a patient with ES requires the anesthetist to perform an even more tedious and tenuous balancing act to preserve the SVR and lower or maintain the PVR so as not to exacerbate the right-to-left shunting that already exists. It can be accomplished safely but requires the anesthetist to be even more deliberate, patient, and tolerant than may usually be the case.

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