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Continuing Medical Education

Advanced pulmonary vascular disease: the Eisenmenger syndrome

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FOLLOWING THE INITIAL DESCRIPTION GIVEN BY Victor Eisenmenger, in 1897,[1] of a 32 year-old man with cyanosis and haemoptysis, who was found after death to have a large ventricular septal defect, it was Paul Wood, in 1958,[2] who coined the term Eisenmenger syndrome to describe situations where high flow of blood to the lungs due to a left-to-right shunt results in pulmonary vascular occlusive disease, and reversal of the shunt across the defect. In this review, we provide a broad outline of the disease, and attempt to answer some of the questions that relate to diagnosis and management of this syndrome, recognizing that there is considerable paucity of studies that have been specifically designed to address them.

Definition

The Eisenmenger syndrome represents an advanced stage of a spectrum of structural and functional changes in the pulmonary vasculature in patients with congenitally malformed hearts, which lead to a progressive increase in pulmonary vascular resistance. To most clinicians, the term also includes patients who never presented with increased flow of blood to the lungs, such as those suffering advanced pulmonary vascular disease early in life, and those with cyanotic congenital cardiac defects, such as transposition, associated with exceedingly high pulmonary vascular resistance. An updated definition that represents a consensus among experts needs to be developed.

While now seldom seen in industrialized nations, patients with the Eisenmenger syndrome continue to be common in most developing countries, where infant cardiac surgery is largely unavailable to the average child with a congenitally malformed heart. In these parts of the world, those with the syndrome make up a sizable fraction of a large population of unoperated patients with congenital cardiac defects. Until recently, the absence of specific options for treatment for pulmonary vascular disease associated with congenital cardiac defects resulted in varying degrees of therapeutic nihilism, and little structured management was offered, particularly in developing countries. Fortunately, the prognosis is far better than in most other forms of pulmonary arterial hypertension, including the idiopathic form. Apart from newer medications, a number of measures can be undertaken to allow patients with pulmonary hypertension associated with congenital cardiac disease to lead reasonably productive lives, with perhaps improved longevity.

Current knowledge

All congenital cardiac defects producing an increased flow of blood to the lungs have a propensity to develop pulmonary vascular disease.[3] The likelihood, and rate, of development of vascular abnormalities is determined by a number of variables, which include the quantum of left-to-right shunting, the nature of the underlying defect, and the duration of exposure of the pulmonary vascular bed to increased flow. Patients

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with left-to-right shunts at the level of ventricles or great arteries, so-called post-tricuspid shunts, have a greater chance of developing pulmonary vasculopathy as compared to those with shunts at atrial level, obviously pre-tricuspid. Cyanotic cardiac defects with increased pulmonary blood flow, such as transposition with ventricular septal defect or patent arterial duct, or common arterial trunk, are particularly likely to develop early vasculopathy, often during infancy.

A number of additional variables appear to operate, but are poorly understood. The response of the pulmonary vasculature to the high pulmonary flow is not uniform from patient to patient, and does not occur in a predictable fashion. There is a spectrum in the development of pulmonary vascular disease, with a subset of patients with a high pulmonary vascular resistance and advanced pulmonary vascular occlusive lesions in early infancy at one side, and adults who remain operable with large left-to-right shunts at the other. Conditions such as Trisomy 21, thoracic and spinal skeletal deformities, and lung parenchymal disease, are often associated with a higher likelihood of developing pulmonary vascular disease.

Exposure of the lungs to high flows of blood results in impaired endothelially mediated relaxation and increased vasomotor tone, accompanied by histological changes in the arterial walls.[3–5] The histological changes include extension of smooth muscles into peripheral pulmonary arteries, medial hypertrophy, reduction of total cross-sectional area of the peripheral pulmonary arterial tree, and formation of dilated lesions, as for example, the so-called plexiform lesions. Loss of endothelial barrier function resulting from high flow and pressure, activation of the endothelin system, decreased production of prostacyclin, decreased production of nitric oxide, increased turnover of serotonin, and altered expression of potassium channels, have all been implicated in the pathobiology of vascular remodeling in pulmonary arterial hypertension in general, and are likely to occur in congenital cardiac disease.[3–5]

Clinical evaluation

The Eisenmenger syndrome should be viewed as a multisystem disease.[6] Multiple systems of organs are affected as a result of chronic hypoxia, erythrocytosis, and cardiac failure (Table 1). Infectious complications, such as endocarditis and brain abscess, are common. Diagnostic evaluation should therefore be comprehensive.

The commonest symptom is exercise intolerance. Other common symptoms include dyspnoea, syncope, chest pain, cyanosis, and haemoptysis. Pulmonary hypertension is readily evident on physical examination in the form of a loud pulmonary component of the second heart sound, prominent pulmonary arterial pulsations, a right ventricular heave, and in many instances, an early diastolic murmur of pulmonary regurgitation. Additional murmurs of tricuspid regurgitation may be present, but the murmur across the primary cardiac defect disappears.

Central cyanosis is usually readily identifiable, and is often accompanied by clubbing. It may be limited to the legs in patient with reversal of the shunt through a patent arterial duct, or only apparent through measurement of saturations of oxygen. This can happen in presence of significant anaemia, or if the nail beds are pigmented.

Diagnosis and testing

The investigations that need to be ordered are dictated to some degree by the presenting manifestations and available resources. For the average uncomplicated patients presenting at a tertiary care center, the purpose of investigations includes the following:

- To confirm the diagnosis of severe pulmonary hypertension
- Correctly to characterize the underlying cardiac lesions
- To exclude any potentially reversible cause for elevation of pulmonary vascular resistance and other causes of hypoxia
- To evaluate the extent of multi-organ dysfunction
- To obtain an objective estimate of the baseline functional state.

Table 1. Clinical features in the Eisenmenger syndrome.

Abnormalities	Clinical manifestations
Elevated and fixed pulmonary vascular resistance	Exercise intolerance, dyspnoea, syncope, sudden death
Secondary erythrocytosis	Hyperviscosity, relative iron, folic acid and vitamin B_{12} deficiency
Bleeding diathesis	Hemoptysis, cerebral hemorrhage, menorrhagia, epistaxis
Right ventricular failure	Liver enlargement, oedema
Arrhythmias	Syncope, sudden cardiac death
Altered red cell rheology and thrombotic diathesis	Cerebrovascular events, such as stroke or transient ischaemic attacks, intrapulmonary thrombosis
Renal dysfunction	Incresased blood urea nitrogen, hyperuricaemia and gout
Hepatobiliary dysfunction	Calcium bilirubinate gall stones, cholecystitis
Infections	Endocarditis, cerebral abscess
Skeletal disease	Scoliosis and hypertrophic osteoarthropathy

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Investigations need to be chosen judiciously in those environments in which resources are limited. Although most of the investigations (Table 2) provide useful information, they sometimes have only a limited impact on choices of treatment, and the well-being of the patient.

Treatment

Recognizing the fact that multiple systems are deranged in most patients with the syndrome, these patients should be managed in a facility where a multidisciplinary approach is feasible. Specialized clinics conducted by cardiologists with expertise in adult congenital cardiac disease are ideally suited for them. Consultations with cardiac electrophysiology, obstetrics and gynecology, nephrology, pulmonology, haematology, neurology, orthopaedics, and gastroenterology are required in many patients. For female patients, advice about contraception is essential. The clinic should be supported by a comprehensive laboratory for haematologic and biochemical tests, and imaging services. Dedicated paramedical staff, including medical social workers and specialized nursing staff, are necessary to provide support, and counsel them on a number of specific issues. Appropriate educational material, with information on common questions relating to the disease, should be prepared and made available to all patients.

Lifestyle

Limitation in exercise tolerance is invariable, and risk of dehydration is substantial, especially in tropical climates. Occupations that require frequent traveling, or long commutes, are perhaps best avoided. Many patients are able to lead reasonably productive and independent lives, pursuing occupations that involve minimal physical stress. Activities and occupation are largely directed by the

Table 2. Suggested diagnostic approach to patients with suspected Eisenmenger syndrome.

Investigation	Rationale	Recommendations
Measurement of saturation of oxygen	Assessment of severity of hypoxaemia	At initial evaluation and on follow-up
Arterial blood gas	An elevated level of carbon dioxide may suggest underlying lung disease	When impaired lung function is suspected, as in patients with spinal skeletal deformities and obstruction of the upper airways
Chest X-ray	Analysis of the cardiac size and chambers as well as the lung fields is crucial for a preliminary understanding of cardiac remodeling and associated disorders	At initial evaluation and on follow-up if clinically indicated
Pulmonary function tests	Impaired lung function can substantially elevate pulmonary vascular resistance and contribute to hypoxia	Clinical suspicion of lung disease, spinal skeletal deformities, or obstructed airways merit thorough evaluation of lung function
Electrocardiogram	Allows identification of chamber enlargement and underlying rhythm. Atrial flutter is common in these patients	At initial evaluation and on follow-up
Trans-thoracic echocardiography	Complete diagnosis of the underlying congenital cardiac defect, assessment of pulmonary arterial systolic pressure, assessment of ventricular function and competence of valves	At initial evaluation and follow-up when indicated
Trans-esophageal echocardiography	Provides a consistently better quality of imaging, and is of particular value in patients with poor transthoracic windows	Patients with unsatisfactory trans-thoracic images because of limited windows
Six-minute walk test	Simple, inexpensive and reproducible measure of functional capacity. Demonstrated prognostic value in idiopathic pulmonary arterial hypertension	At baseline and during follow-up
Formal exercise testing with measurement of oxygen consumption	Oxygen consumption of less than 10.4 ml/min/m^2 is associated with poor prognosis in idiopathic pulmonary arterial hypertension	Not routinely recommended. May be warranted as clinical trial end point
Cardiac catheterization and angiography	Measurement of pulmonary arterial pressures and vascular resistance; assessment of response to vasodilators. Analysis of the capillary network and proximal arteries and veins to identify thrombotic lesions and stenoses	Routine catheterization may be unnecessary in advanced Eisenmenger syndrome if noninvasive evaluation provides adequate information for therapeutic decisions

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patients themselves, and therefore education and counselling is particularly important. Air travel can be undertaken, but dehydration associated with long flights should be prevented through generous intake of fluids.[7] Acute exposures to altitudes in excess of 2,500 meters should be avoided.[8] Prophlaxis against endocarditis, and meticulous attention to oral and dental hygiene, is mandatory. Annual immunization against influenza and pneumococcal infections may be considered in regions where these infections are prevalent.

Pregnancy and contraception

Pregnancy is associated with a substantial risk of maternal and fetal mortality.[5,9] The risks of pregnancy should be explained to women with the syndrome as soon as the diagnosis is confirmed. The options for contraception include progestogen impregnated intrauterine coils, and subdermal implants of progesterone. Standard oral oestrogen contraceptive pills are associated with risk of thrombosis, and laparoscopic sterilization carries the risk of general anaesthesia. In the event the patient becomes pregnant, and does not wish to terminate the pregnancy, an obstetrician and anaesthesiologist should be consulted, and the patient should be carefully monitored during pregnancy, at the time of delivery, and 1 to 2 weeks post-partum, when the risk of death is at its highest.

Non cardiac surgery

Non-cardiac surgery carries a substantial additional risk. There are no specific protocols for anaesthesia recommended for patients with the Eisenmenger syndrome. Careful attention to detail, and close monitoring throughout the surgery, and in the early postoperative period, is necessary. The anaesthesiologist should be involved whenever surgery is planned, and the specific physiologic derangements associated with the underlying cardiac condition should be explained. Inhalational agents produce a reduction in systemic vascular resistance, and therefore an increase in right-to-left shunting, so further declines in saturation can be expected.[10] Additional issues include the risk of bleeding, and rapid changes in intravascular volume.

Secondary erythrocytosis: phlebotomy

Routine phlebotomy often worsens iron deficiency, and is associated with an increased risk of stroke,[11,12] along with further reduction in exercise tolerance.[13] Compensated secondary erythrocytosis is often well tolerated.[12] Even levels of the haematocrit around 65% are well tolerated in many patients. For reasons that are not clear, it is often difficult to stop doing serial phlebotomies once they are started. Haemodilution, therefore, should be strictly limited to relieving hyperviscosity-related symptoms, such as blurry vision, headaches, dizziness, arthralgia, and worsening of dyspnoea. In all instances, maintaining an iron-replete state is crucial.

Anticoagulant therapy

Although there is no clear evidence supporting the benefit of chronic anticoagulation in the specific setting of the syndrome, previous studies point toward a tendency to the development of extensive pulmonary arterial thrombosis.[14,15] On the other hand, most specialists would agree that these patients are at risk for bleeding episodes. Anticoagulation, therefore, should not be considered if serious monitoring is not possible for any reasons. In this way, special blood tubes are needed to measure the prothrombin time in the presence of an elevated haematocrit.

Oxygen therapy

The long-term effects of supplementation of oxygen still need to be confirmed. Improved survival has been reported in a small group of children with pulmonary vascular disease receiving long-term therapy.[16] Long-term nocturnal therapy, however, does not improve symptoms, exercise capacity, nor outcomes in adult patients with the syndrome.[17]

Emerging pharmacologic interventions

A number of newer agents promise to change the outlook of patients with the Eisenmenger syndrome. These agents target the pulmonary vasculature with a relatively high degree of selectivity. Data on their use in congenital cardiac disease with advanced pulmonary vasculopathy is still quite preliminary, and large trials are awaited. In terms of drugs that can be administered orally, agents have been specifically developed for endothelin receptor antagonism, and phosphodiesterase-5 inhibition.[18–21] Details regarding the mechanism of action, published evidence, and recommendations for the use of these drugs, as well as the prostanoids, are beyond the scope of this review. Most importantly, patients with the Eisenmenger syndrome have a relatively favorable natural history as compared, for example, to those with idiopathic pulmonary hypertension, with much better survival curves.[22,23] Thus, the short-term benefits that have been observed in terms of exercise endurance and haemodynamics may not be predictive of long-term improvement of outcomes. In this way, years of follow-up are needed before benefits can be demonstrated in terms of survival.

In the only prospective and controlled study published so far in the specific setting of the Eisenmenger syndrome, bosentan improved exercise endurance at 16 weeks, without any deleterious effects on gas exchange.[18] Studies that enroll patients with class III and IV symptoms are likely to yield results over a relatively shorter duration of follow-up in view of the substantially poor prognosis in this group. In a retrospective analysis of 43 patients in an institutional registry, many in Class II, no survival advantage could be demonstrated among those who received the newer therapies in comparison with those who remained on standard care.[24]

The availability of the so called new therapies for pulmonary hypertension led many physicians to become more aggressive in terms of assigning patients to closure of the defects. It should be emphasized, however, that there are no long-term studies on the efficacy of these drugs, and patients may deteriorate more rapidly than if they had never been operated on. Thus, in terms of operation, benign neglect is often preferable.

Conclusions

Several areas may be worth pursuing potentially to improve the outlook for patients with pulmonary hypertension associated with congenital cardiac disease. The basis of extraordinary individual variability in the tendency to develop severe pulmonary vasculopathy needs to be thoroughly investigated. Likewise, the remarkable performance of the right ventricle deserves further research. These investigations would improve our understanding, and may allow development of additional specific strategies for treatment. Besides, large randomized controlled trials are needed in the specific setting of the Eisenmenger syndrome for a better understanding of the impact of newer therapies, either alone or in combination, on the long-term outcomes. Ideally, these trials should consider the inclusion of hard endpoints such as long-term survival, and compare conventional and new treatments in patients with the same type of intracardiac abnormality.

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