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EISENMENGER SYNDROME: PULMONARY HYPERTENSION RESULTING IN A RIGHT-TO-LEFT CARDIAC SHUNT

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ABSTRACT

Eisenmenger syndrome is a complication of uncorrected congenital heart defects that cause left-to-right shunting. Increased pulmonary vascular resistance develops over time, leading to pulmonary vascular injury and pulmonary hypertension, and reversing the shunting to right-to-left. This cardiac shunt reversal allows deoxygenated blood into the systemic circulation, resulting in symptoms of chronic hypoxemia. Signs of chronic hypoxemia, such as cyanosis and digital clubbing, are present, and heart sounds and electrocardiogram findings are variable, depending on the underlying structural defect. Diagnosis of Eisenmenger syndrome is suggested by chest radiography and electrocardiography, and confirmed by echocardiography and cardiac catheterization. Once pulmonary hypertension has developed, surgical repair of the underlying defect is no longer possible. Treatment is limited to supportive measures, with transplant the only curative option.

INTRODUCTION

Congenital heart defects are among the most common birth defects, affecting approximately 1% of live births.[1] A congenital heart defect that causes left-to-right shunting of blood, resulting in changes to the endothelial lining and muscle tissue, hence increases the pressure in the pulmonary circulation. If left untreated, the defect may result in severe pulmonary vascular obstruction, eventually leading to a bidirectional cardiac shunt, and even complete reversal of left-to-right shunting to right-to-left. This cardiac shunt reversal is known as Eisenmenger syndrome (ES), and an estimated 8% of patients with congenital heart defects are at risk of developing the condition.[1] The structural anomalies that, if untreated, lead to ES include ventricular septal defect (VSD), persistent truncus arteriosus, transposition of the great arteries, and, to a lesser extent, atrial septal defect and patent ductus arteriosus.

ES represents the most severe form of pulmonary hypertension, and development of the condition is dependent on several factors, including the site and size of the defect, and the presence of any coexisting cardiac anomalies. Development of ES can be prevented by early closure of the underlying structural anomaly, but once the condition develops, surgical repair is contraindicated.[2] The incidence of ES has markedly decreased in developed countries, due to the early diagnosis and repair of causative anomalies. This review outlines the underlying pathophysiology of ES, and describes the clinical presentation, diagnosis, and management of the condition.

HISTORY

In 1897, the German physician Victor Eisenmenger first described the condition after the autopsy of a 32-year-old man who had dyspnea and progressive cyanosis, and who subsequently died of massive hemoptysis.[3] The autopsy revealed a large VSD and severe pulmonary vascular disease. In 1958, Paul Wood determined that ES resulted from systemic pulmonary hypertension as a consequence of elevated pulmonary vascular resistance (PVR), leading to reversed cardiac shunting through a VSD.[4] Since then, the definition of ES has been expanded to include reversed cardiac shunting through any communication between the pulmonary and systemic circulations.

PATHOPHYSIOLOGY

In the normal heart, the systemic circulation is the higher pressure circuit, with systemic vascular resistance (SVR) at 700 to 1400 dyn•sec•cm^{-5}, and the pulmonary circulation is the lower pressure circuit, with PVR at 20 to 130 dyn•sec•cm^{-5}.[5] Therefore, in the instance of one or more structural defects resulting in communication between the pulmonary and systemic circulations, a volume of blood flows down the pressure gradient from left-to-right (ie, from the high-pressure systemic circulation to the low-pressure pulmonary circulation). As a result of the volume of this shunt entering the right side of the heart, the stroke volume of the right ventricle is increased. A combination of the chronic increased right-sided blood pressure and increased blood volume results in mechanical injury of the pulmonary capillaries.[5]

According to current thinking, endothelial cell dysfunction results from the shear and mechanical injury caused by the increased right-sided blood pressure.[5] Endothelial cell dysfunction leads to increased production of vasoconstrictive agents, such as endothelin, as well as decreased production of vasodilatory agents, such as prostacyclin. In addition to the endothelial cell dysfunction, there is an increased synthesis of growth factors and cytokines that result in the migration and replication of vascular smooth muscle. These vascular alterations involve the entire arterial tree, where proliferation of myointimal cells and smooth muscle cells promotes thickening of the vascular intima and media, and a subsequent reduction in luminal diameter, as well as a thickening of the internal and external elastic membranes.

A combination of the narrowed pulmonary vascular lumen and the decreased compliance of the vessels due to medial hypertrophy increases the PVR, and results in compensatory right ventricular hypertrophy (RVH). Eventually, this combination of elevated PVR and RVH leads to an increase in right heart pressure that is sufficient to reverse the left-to-right cardiac shunt. As such, blood now flows through the structural defect from right-to-left, causing deoxygenated blood to enter the left side of the heart and flow out through the aorta, leading to hypoxemia and cyanosis (**Figure**). The resulting decrease in oxygen saturation culminates in the secondary polycythemia commonly seen in ES.

SIGNS AND SYMPTOMS

The symptoms associated with ES do not usually present until age 20 to 40 years,[7] except in the case of pregnancy. The hemodynamic changes corresponding to pregnancy serve to further the deterioration of the intracardiac shunt, increasing the risk to both mother and child.[8]

Many of the symptoms of ES are specifically related to either the pulmonary hypertension or the resulting chronic hypoxemia that are typical of the disease. Thus, patients with ES frequently present with dyspnea on exertion, cyanosis, fatigue, syncope, atrial and ventricular arrhythmias, and digital clubbing. Angina is also often present, due to decreased myocardial oxygenation and increased right ventricular strain.

Hemoptysis is a late symptom, and may be caused by either hypoxemia or pulmonary vascular injury (PVI). Rarely, symptoms of right heart failure may be present, such as peripheral edema, hepatomegaly, and jugular venous distention.

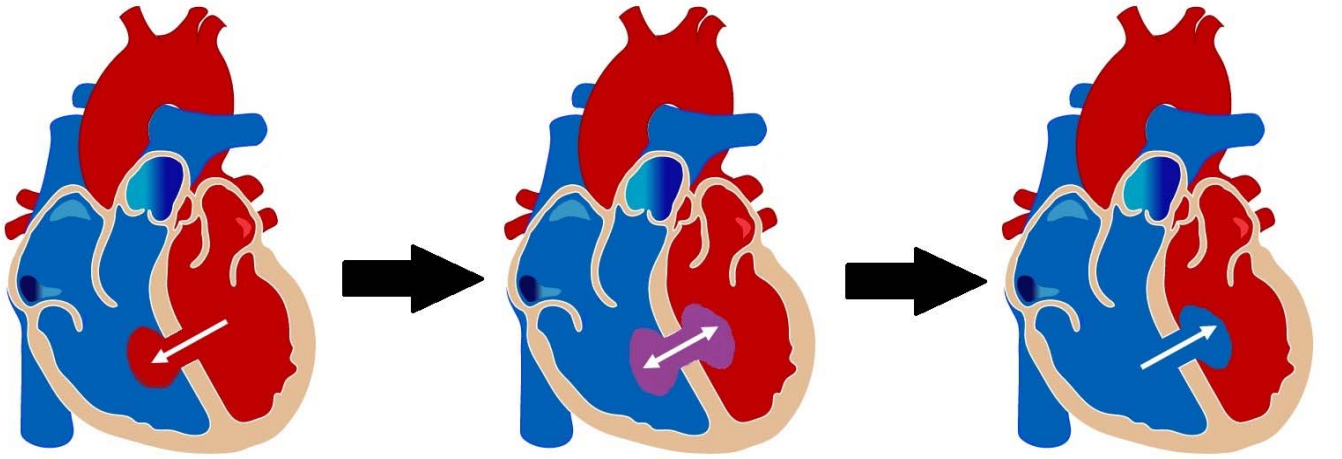

Figure 1: The development of Eisenmenger syndrome

On examination, central cyanosis is evident, and a holosystolic murmur of tricuspid regurgitation may be heard at the lower left sternal border. A loud, single, second heart sound is a frequent finding.

Laboratory findings of ES are consistent with chronic hypoxemia. As such, elevated hematocrit (>55 %), increased hemoglobin levels (commonly in excess of 20 $g \bullet dL^{-1}$), prolonged bleeding times, and decreased oxygen saturation are almost always seen.[9] Increased turnover of erythrocytes may also be seen as microcythemia, hyperuricemia, and hyperbilirubinemia.

DIAGNOSIS

A diagnosis of ES may be suggested by chest radiography. In the early stages of the disease, chest radiography resembles the typical appearance of increased pulmonary flow, namely right ventricular or biventricular enlargement, right atrial or biatrial enlargement, and a dilated pulmonary trunk. With more advanced PVI, a normal cardiac shadow is seen, with a dilated pulmonary trunk and pulmonary arteries. Diminished peripheral pulmonary vasculature may also be seen in severe disease.

Electrocardiography will resemble that found in RVH, such as frontal plane QRS right axis deviation, tall monophasic R-waves in RV leads (V3R and V4R), deep S-waves in LV leads (V3-V9), and ST-segment and T-wave changes directed opposite to QRS direction.[10] There also will be specific electrocardiograph changes associated with the causative structural heart defect.

Confirmation of the diagnosis is made by either echocardiography or cardiac catheterization. Echocardiography with Doppler studies is useful for revealing the underlying structural defect, as well as any coexisting abnormalities, and for determining the direction of intracardiac blood flow.[11] Cardiac catheterization allows for examination of the internal cardiac structure, measurement of pulmonary arterial pressures, and calculation of PVR. Cardiac catheterization also permits the exclusion of other causes of pulmonary hypertension.[2]

COMPLICATIONS

As well as being one of the presenting symptoms, one of the most frequently seen complications associated with ES is hemoptysis, arising from either hypoxemia or PVI. Although the hemoptysis is usually mild and self-limiting, on rare occasions it can be massive and the cause of sudden death among this patient population, as observed in the case with which Eisenmenger first described the condition.[3]

As well as chronic hypoxemia resulting from pulmonary hypertension, patients also have an underlying congenital structural abnormality, and thus are vulnerable to several bleeding disorders commonly associated with congenital heart defects, such as thrombocytopenia, abnormal fibrinolysis, and acquired type II von Willebrand factor abnormalities.[12] As a result, abnormal or prolonged bleeding is of great concern, especially as any loss in blood volume will lower the SVR, and further the severity of the right-to-left shunt. Patients are also at risk of developing brain abscess or endocarditis.

Another frequently seen complication of ES is renal dysfunction as a direct result of cyanosis, hypoxemia, and polycythemia. Hence, the extent of renal dysfunction is directly related to the severity of these factors, and ranges from decreased glomerular filtration rate (from reduced blood flow) to nephrotic syndrome.

The secondary polycythemia commonly seen in this condition often results in hyperviscosity, and thus there is a serious danger of thrombotic events, such as pulmonary embolism or cerebrovascular accident, from the altered hemodynamic state. Polycythemia may also result in hyperuricemia, gout, cholelithiasis, or hypertrophic osteoarthropathy, and the severity of these complications is correlated with the extent of erythrocytosis.[13]

TREATMENT

Ideally, corrective surgery to repair the underlying defect should have been performed earlier to prevent ES. Surgical repair of the underlying structural defect is not possible once pulmonary hypertension has developed.[2] Closure of the defect, and hence fixation of the shunt, causes increased right ventricular pressure, and thus furthers right heart failure. Surgical repair can only be considered if significant left-to-right shunt flow remains, and if the pulmonary circulation is shown to be responsive to vasodilator therapy. Drugs that may lower pulmonary arterial pressure, such as prostacyclin antagonists,[14] endothelin anatagonists,[6] and nitric oxide enhancers,[15] are being studied for use in patients with pulmonary hypertension. Other treatment may also include aspirin to reduce the risk of thrombosis, allopurinol to treat associated gout, and digitalis to reduce the symptoms of right heart failure. Current

National Institute for Health and Care Excellence guidelines state that all patients be given endocarditis prophylaxis prior to any surgical procedure likely to cause bacteremia.[16]

In addition to medical therapy, supportive treatment including the avoidance of factors that may worsen the condition (such as volume depletion, high altitudes,[17] and pregnancy[7]) and the use of supplemental oxygen may be beneficial.[18] Phlebotomy may also be necessary to maintain the hemoglobin level at <20 $g \bullet dL^{-1}$, to minimize the complications associated with hyperviscosity.[2]

Transplant is the only specific treatment option for patients with ES, but due to the associated risks, it is reserved for those with severe symptoms and an unacceptable quality of life. There are 2 options for transplant; either a bilateral lung transplant or a heart-lung transplant. If the cardiac defect is simple and fixable, and the PVI has been shown to be irreversible, then a bilateral lung transplant with surgical repair of the cardiac defect is possible. However, if the cardiac defect is complex, then a heart-lung transplant is necessary. A good prognosis can be obtained with a transplant, with 5-year and 10-year survival rates for those receiving both heart and lungs estimated to range from 30% and 50%, to 50% and 70%, respectively.[19,20] As with any transplant procedure, the main complications are infection and rejection, and there is the possibility of obliterative bronchiolitis.[20]

CONCLUSIONS

Eisenmenger syndrome, as the end result of numerous untreated congenital heart defects, represents a unique and challenging pathophysiology. Patients do not usually present until the third decade of life, and the main symptoms are those of chronic hypoxemia; thus, ES presents as a multisystem disease. Although advances in medical understanding, and early diagnosis and repair of congenital heart defects, have decreased the incidence of the condition, treatment options for patients with ES remain severely limited. Further research into the treatment of pulmonary hypertension is necessary, to enable safe repair and an effective cure of the cardiac anomaly present in patients with ES.

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