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A REVIEW ON EISENMENGER'S SYNDROME

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ABSTRACT
Eisenmenger syndrome(ES) is a constellation of symptoms that arise from congenital heart defect and result in large anatomic shunts. Physical findings vary depending upon the underlying defect and the stage of the pathophysiological abnormalities. Diagnosis is based on the echocardiography or advanced imaging and cardiac catheterization. Cardiac arrhythmias and sudden cardiac death are important late complications of this syndrome. Conservative management with medications and/or lung and cardiac transplantation are therapeutic approaches that can offer quality of life improvement. Recently advanced therapies of pulmonary arterial hypertension(PAH) have been become available, and have been effective in reducing mortality.

KEYWORDS: Congenital Heart Disease, Shunts, PAH.

INTRODUCTION

Eisenmenger (I-sun-meng-uhr) syndrome is a long term complication of an paired heart defect that someone was born with (congenital).

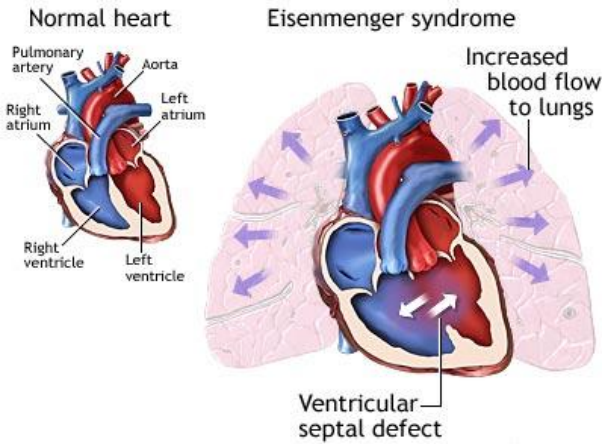
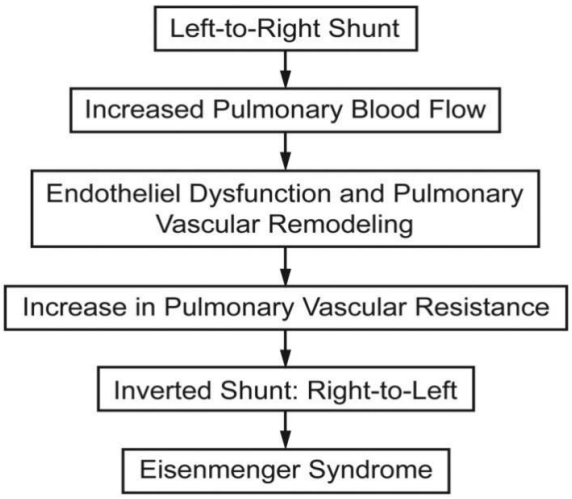


Figure 2: Normal heart Vs Typical Eisenmenger heart.

Eisenmenger syndrome (ES) is a constellation of symptoms that arise from a congenital heart defect and result in large anatomic shunts. Due to anatomic variations present at birth, hemodynamic forces initially result in a left-right shunt, which develops into severe pulmonary arterial hypertension (PAH) and elevated vascular resistance. Ultimately, due to increased pulmonary vascular resistance, the left-to-right shunt will become a right-to-left shunt, resulting in significant hypoxemia and cyanosis.



Flow chart 1: Pathogenesis.

PAH is a mean pulmonary arterial pressure greater than 25 mmHg while resting or 30 mmHg when exercising. This may occur in large shunts , unrepaired congenital heart disease as early as the first decade of life.

Over a many years, increased blood flow can damage the small blood vessels in the lungs. This cause high blood pressure in lungs. As a result, the blood flow goes backwards through a whole between the two pumping chambers. This allows oxygen-poor blood to travel to the rest of the body.

Eisenmenger syndrome may being to develop before a child puberty. However, it also can develop in young

adulthood, and may progress throughout young adulthood.

Symptoms

In most cases, the symptoms of Eisenmenger syndrome show up before puberty. Sometimes, they can be spotted during infancy or early childhood.

These symptoms are easiest to spot.

- A bluish or grayish color skin, lips, fingers, and toes because of lack of oxygen (cyanosis).
- Large, rounded fingernails and toenails (clubbing).
- Numbness and tingling of fingers and toes
- Easily tiring and shortness of breath with activity
- Shortness of breath while at rest
- Coughing up blood
- Fainting
- Fluid buildup in parts of the body (edema)
- An abnormal heart rhythm
- Dizziness or headaches
- Chest pain and tightness
- Swelling in the joints caused by too much uric acid(gout)
- Skipped or racing heartbeats (palpitations)
- Stroke

Epidemiology

Eisenmenger syndrome usually develops before puberty, but it may also start manifesting in adolescence and early adulthood. Approximately 8% of patients with congenital heart disease develop Eisenmenger syndrome. Quality of life is limited by symptoms, but patients can survive until the third and fourth decades of life.

The prevalence of Eisenmenger syndrome if difficult to quantify, but it is declining in the developed world with the identification and surgical correction of congenital heart conditions. Patients from underdeveloped countries are more likely to have late presentations of Eisenmengers syndrome due to uncorrected congenital cardiac lesions.

The frequency of pulmonary hypertension and the subsequent development of reversed shunting vary depending on the heart defect and operative intervention. Such variations include the following.

- Large, nonrestrictive ventricular septal defect (VSD) or patent ductus arteriosus (PDA): Approximately 50% of infants with one of these defects develop pulmonary hypertension by early childhood
- VSD or PDA and transposition of the great arteries: About 40% of patients develop pulmonary hypertension with in the first year of life.
- Large secundum atrial septal defect (ASD): The history of a large secundum ASD differs in that the 10% of cases that progress to pulmonary hypertension do so more slowly and usually not until after the third decade of life
- Persistent truncus arteriosus and unrestricted pulmonary blood flow: All patients develop severe pulmonary hypertension by the second year of life
- Common artrio ventricular canal: Almost all patients develop severe pulmonary hypertension by the second year of life
- Surgically-created systemic-to-pulmonary shunt: The frequency of pulmonary hypertension varies depending on size and anatomy
- Blalock-Taussig anastomosis (surgical procedure communicating the subclavian artery to the pulmonary artery): About 10% of patients develop pulmonary hypertension
- Waterston (another palliative procedure to communicate the ascending aorta to pulmonary artery) or Potts (descending aorta to pulmonary artery) shunt: About 30% of patients develop pulmonary hypertension

Etiology

Eisenmenger syndrome is a condition that results from abnormal blood circulation from the heart to lungs. It occurs due to an unpaired hole (shunt) between the chambers or blood vessels of your heart. This shunt is known has congenital heart failure which majorly occurs at neonatal state.

Specific genes that cause Eisenmenger syndrome have not been identified and the condition is not thought to be inherited.

Heart defects includes

Atrioventricular canal defect: There will be a large hole at the center of the heart where the walls between the atria and ventricles meet. It leads malfunction.

Atrial septal defect: Which infuses the shunt in the walls of tissue that separates the right and left of the upper chambers of your heart.

Patent ductus arteriosus: Pulmonary artery carries the oxygen between the poor blood to the lungs and rich blood to the rest of your body.

Ventricular septal defect: This shunt mainly divides the pumping chambers of your heart which is the most common cause of Eisenmenger syndrome.

Other Complications

Cyanosis
High red blood cell count
Irregular heart rhythm
Pregnancy risks
Increased risk of infection
Cardiac failure
Kidney diseases
Coughing up blood
Stroke

Pathophysiology

When a significant anatomic defect which exists between the two sides of the heart then a shunt will be present which leads blood to flow down the normal pressure gradient from the left side to the right side. The size of the defect is directly proportional to the amount of blood shunt, and beat to beat volume of blood pumped through a left to right breach is a percentage of anticipated cardiac output of the left ventricle. It is harmless when it shows clinically a low index or percentage of cardiac output ejected through shunt.

A high index or percentage of CO ejected through a left-to-right shunt heralds Eisenmenger physiology. The left to right shunting of blood results in increasing blood pressure which leads to maladaptive changes that finally results in pulmonary hypertension. Increased right sided blood volume and pressure causes a cascade of pathologic damage to the delicate pulmonary capillaries, causing them to be incrementally replaced with scar tissue.

Scar which is known has dead lung tissue does not contribute to oxygen transfer, therefore decreasing the useful volume of the pulmonary vasculature. This scars have the features of less flexibility and compliance than normal lung tissue, causing further increases in pulmonary blood pressure which leads to damage of more blood capillaries.It is because of this maladaptive response that at the onset of Eisenmenger syndrome,this damage will be in irreversible state.

Persistently increased resistance and decreased compliance of the pulmonary vessels which causes myocardium of the right heart to hypertrophy(RVH).The onset ofEisenmenger syndrome begins when right ventricular hypertrophy causes right side heart pressure to exceed that of the left side heart pressure, leading to reversal of blood flow through the shunt. As a consequence,deoxygenated blood returning from the body bypasses the lungs through the reversed shunt and proceeds directly to systemic circulation, leading to cyanosis and resultant organ damage.

Right to left side shunt causes reduced oxygen saturated in the arterial blood due to mixing of oxygenated blood returning from the lungs with the deoxygenated blood returning from the systemic circulation.This decreased saturated is sensed by the kidneys, resulting in a compensatory increase in erythropoietin production and an increased production of red blood cells in an attempt to increase oxygen delivery. As the bone marrow increase erythropoiesis, the systemic reticulocyte count and risk for hyperviscosity syndrome increases.

A person who is suffering with Eisenmenger syndrome is paradoxically subject to the possibility of both uncontrolled bleeding due to damaged capillaries and high pressure, as well as spontaneous clots due to hyperviscosity and stasis of blood.

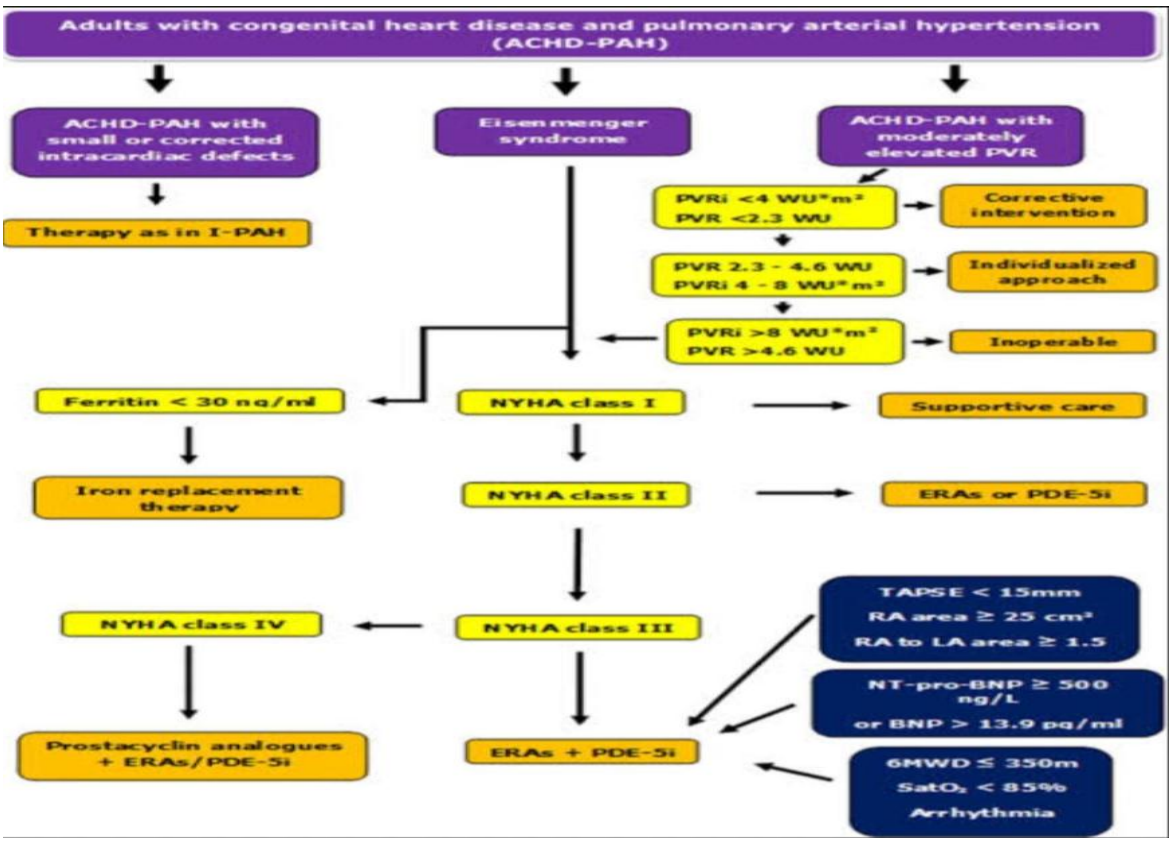


Figure 2: Algorithm of ES.

Eisenmenger syndrome mostly defected by ASD, VSD and PDA.

The following three main processes result in the ultimate reversal of a left- to- right into a right-to-left shunt.

1.Vasoconstriction: There will be a imbalance in pulmonary vascular tone,followed by
2.Vascularremodeling: It is due to the proliferation of pulmonary vascular smooth muscle, and finally
3.Thrombosis: It is caused by the increased resistance of blood flow.

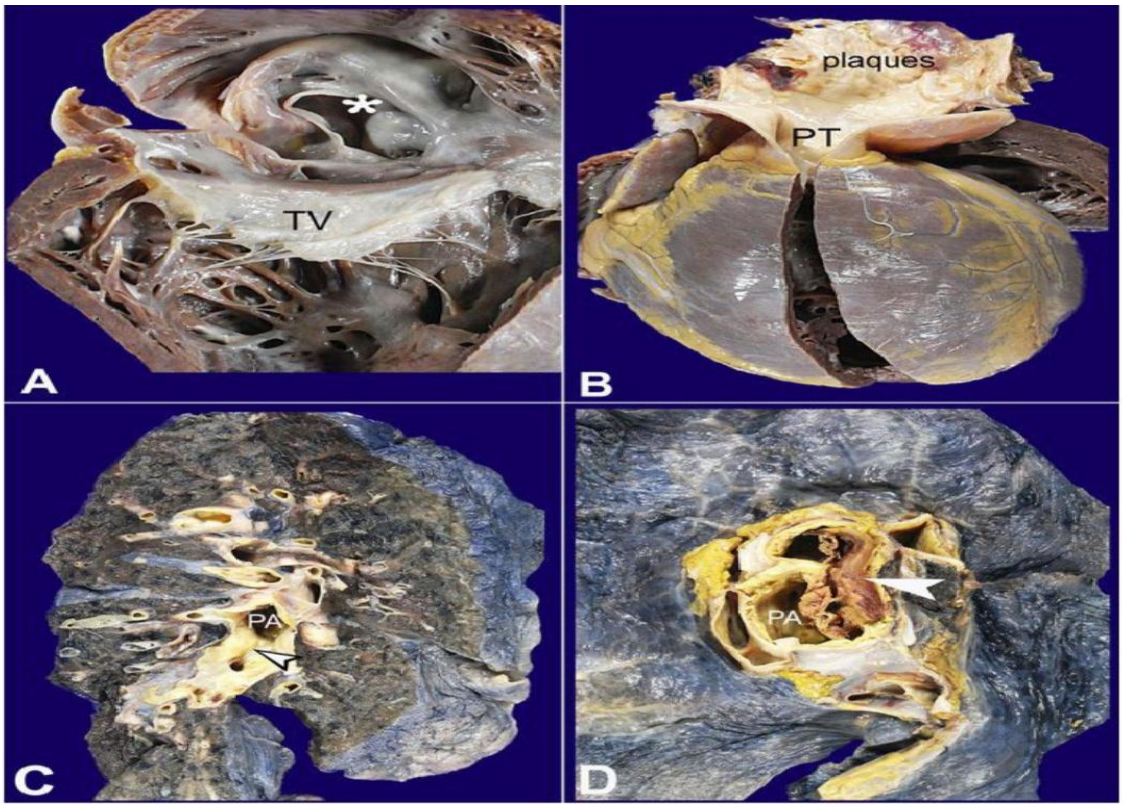


Figure 3:-A and B – Gross examination of the heart A-Opened right cardiac chambers.The asterisk marks the atrial septal defect located at the fossa ovalis(so called secundum defect);B-The right ventricle hypertrophy and pulmonary artery trunk (PT) dilation with atherosclerotic plaques; C and D – Macroscopic findings of the lungs; C – The dilation and atherosclerosis of the pulmonary artery(PA) (arrowhead points to a plaque) and its branches; D – PA thrombosis (white arrowhead).TV=tricuspid valve.

Diagnosis

Eisenmenger syndrome diagnosis is not apparent but it requires cardiac catheterization for assessment of the pulmonary artery pressure. It is an invasive procedure to measure pressures in the heart and lungs.

It also consists of medical history, physical examination and relevant diagnosis tests. These tests may include.

- **Bloodtests**:It checks blood cell counts, which are gradually increases in Eisenmenger syndrome. It also measures the kidney functions, liver function and iron levels.
- **Electrocardiogram(ECG)**: It diagnosis the heart defects by recording the electrical signals of the heart through electrodes attached to the skin.
- **Computerizedtomographyscan (CTscan)**:It takes out the images of the lungs which visualize the cross section of them. To observe the images more clearly dyes have been used.

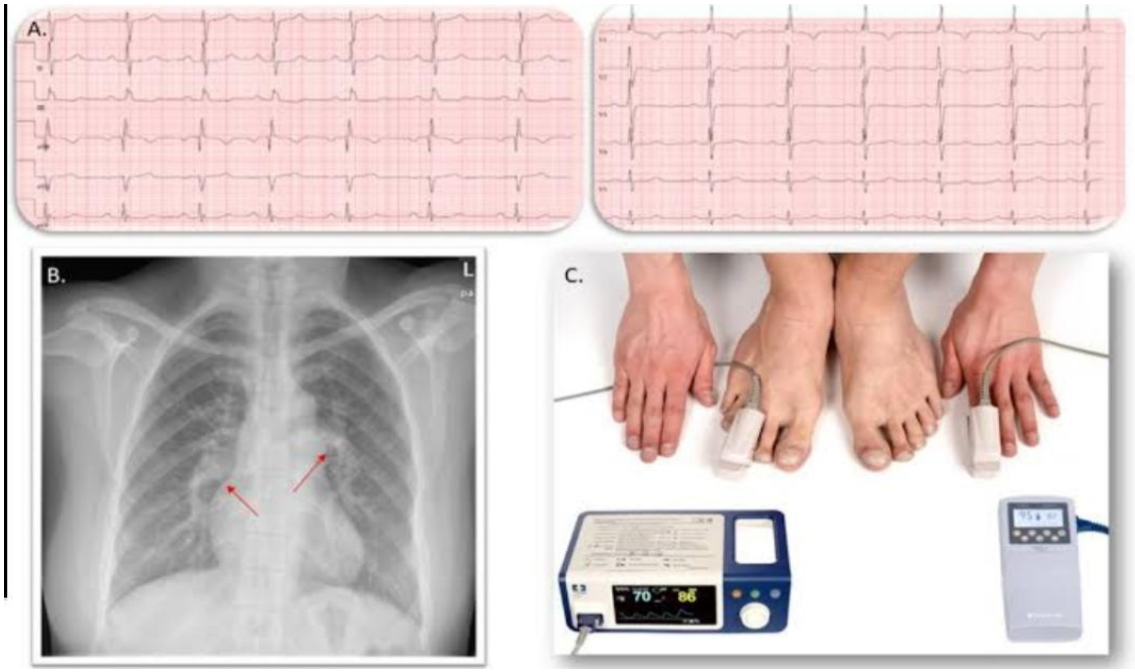


Figure 4: Typical ECG, Chest X-ray of ES patients.

- **Magneticresonanceimaging** (**MRI**): It shows images by using magnetic field and radio waves of the blood vessels in your lungs.
- Chest X-ray: Thisis used to look at cardiac and pulmonary artery enlargement.
- **Echocardiogram**:It is also known has ultrasound of the heart. This test is used for the sound waves to create detailed images of the heart.It helps to look at the structure of the heart and blood flow to identify the heart disfunctions.
- **Cardiaccatheterization**: In this test doctor inserts a thin,flexible tube(catheter) into an artery in groin to measure blood pressure ,the size of any sepataldefect,and the pressures and flow across the defect.
- **Walkingtest**: It is a six minutes walking test to check your tolerance.
- **Labtest**: Ferritin
- **Clinicalcalculator**: Transferrin saturation.

Treatment

General management of Eisenmenger syndrome.

Although the patients with ES, can survive the fourth and fifth decades of life, their condition is associated with high morbidity, reduced functional status and frequent hospitalizations. In ES, the chronic hypoxemia, together with low cardiac output and PAH, has significant multisystem effects, resulting in a vast spectrum of complications.

Some includes Cardiac arrhythmia, hemoptysis, right heart failure are important late complications and are frequent cause of death. Other complications such as pulmonary artery dilation and in situ thrombosis, cyanosis due to secondary erythrocytosis, increased blood viscosity, iron deficiency anemia are frequent in this cohort.

The rarity of this condition, combined with its complex pathophysiology, lead to the insufficient understanding of the principles underlying its proper treatment, introduction of some new drugs like

Prostacycline analogs: [Epoprostinol, Treprostinil, Beraprost, Illoprost],

Phosphodiesterase inhibitors: [Sildenafil, Tadalafil],

Endothelin receptor antagonist: [Bosentan, Sitaxanthan, Ambrisentan] and

Nitric oxide.

These drugs should be administered to the patients, in Ⅲ-Ⅳ class studied by NYHA (New York Heart Association), for the PAH.

Other Managements

A. Medical

Use of calcium blockers is still a controversy as they worsen the condition but also have minor beneficial effects (The mainstay of medical therapy is to avoid medications that have not proven to be beneficial).

Long-term home oxygen therapy was reported to improve survival in children with CHD and concomitant pulmonary vascular disease in a small group of certain studies, but there is no data regarding adults with this syndrome. Although home oxygen therapy is not recommended in general but may be helpful in patients with profound hypoxemia and dyspnea at rest or with limited activity. Patients with lesions considered at high risk for many unwanted conditions, so they should be given instructions regarding antibiotic prophylaxis before undergoing a procedure that may cause bacteremia.

Drugs which are potentially harmful to Eisenmenger patients.

Nonsteroid anti-inflammatory drugs, Danazol, Systemic vasodilators, Diuretics, Estrogens (including contraceptive pills), Anesthetic induction agents, Fertility hormones(used for In-Vivo method).

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; hemocrit) increases, the blood viscosity increases commensurately, and eventually blood flow and oxygen transport decline. In adults with ES and associated with hyperviscosity, phlebotomy can be performed safely, blood pressure should be monitored frequently throughout the phlebotomy, with careful avoidance of hypotension. Phlebotomy should be performed in the erythocytic patients with symptomatic hyperviscosity; *it is not indicated in those with an elevated hematocrit without symptoms of hyperviscosity.*

C. Transplantation

Once the ES has developed, closure of the systemic-to-pulmonary connection is no longer possible. The only definitive treatment is lung transplantation and repair of the congenital heart defects or heart-lung transplantation. Lung transplantation or heart-lung transplantation will only be considered in cases with irreversible pulmonary hypertension; if the pulmonary vascular resistance is more than 5 wood units or when the transpulmonary gradient is 12mmHg or more. In other cases, cardiac repair or isolated heart transplantation can be considered. Hence, lung transplantation is only an option for patient who have markers of a poor prognosis (syncope, refractory right-sided heart failure, NYHA functional class Ⅳ, or severe hypoxemia). Because of the reasonably good survival among patients treated medically, careful selection of patients for transplantation is imperative.

D. Anticoagulation

Patients with ES are at higher risk of PA thrombosis, also at an increased risk of bleeding, including potentially life-threatening pulmonary hemorrhage. It is not routine to anticoaglate patients with ES, unless there are coexisting conditions such as atrial fibrillation, pulmonary thromboemboli, chf or embolic events in absence of significant hemoptysis or other bleeding risks. OACs are associated with an increased risk of iron deficiency anemia and patients should be routinely investigated for this.

Endothelin receptor antagonists (ERAs) can reduce the efficacy of anticoagulants such as Warfarin; therefore, necessitate close monitoring of the international normalized ratio (INR) is needed to maintain an adequate therapeutic index. Novel OACs have not been tested in large groups though. But with the recent Food and Drug Administration (FDA) approval of IARUCIZUMAB for reversal of Dabigatran, this may become an option in the future.

E. Iron deficiency

While inappropriate phlebotomy is the primary cause of microcytic hypo chromic anemia, other causes include recurrent hemoptysis or epistsxes and menorrhagia in females. A good nutritional status with sufficient iron intake in patients with microcytic iron deficiency.

Iron replacement in patients with microcytic iron deficiency (low Hb, ferritin and MCV) must be carefully administered beginning with a small daily dose of ferrous sulfate (325mg which is 65mg of elemental iron) given orally.

F. Noncardiac surgery

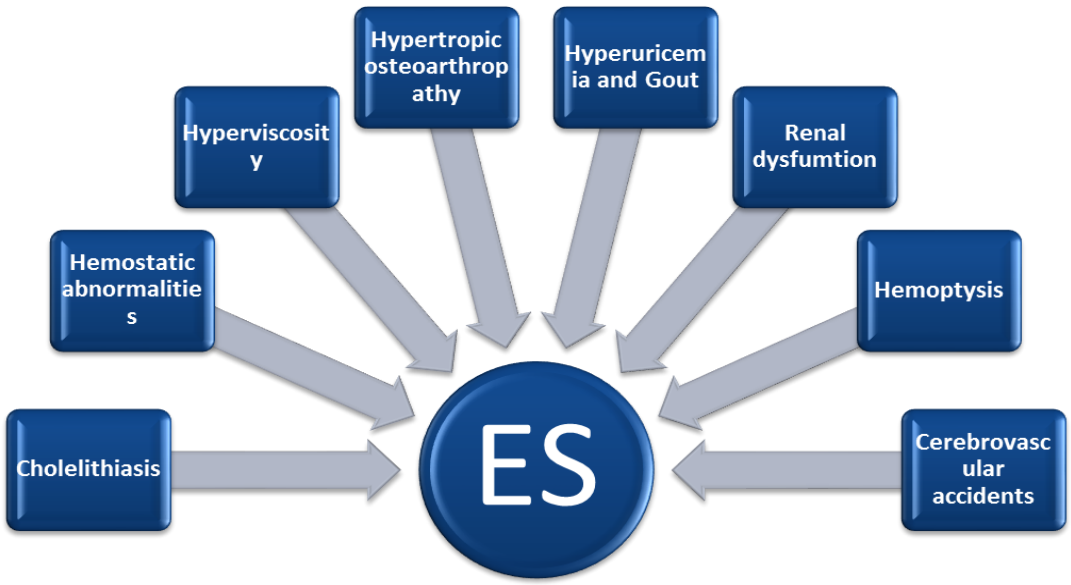
PAH, CHD and ES are known risk factors for perioperative complications. Patients with PAH are often counseled against elective surgery because of the risk of early and sudden postoperative deaths. Some studies state that in PAH, the RV cannot accommodate large alterations in preload or after load induced by fluid shift, anesthetic medication, insufflations of gas in the abdomen during laparoscopic procedures or autonomic changes precipitated by hypoxia or hypercapnia, resulting in worsening RV function, can be precipitated by systemic hypotension and arrhythmias during surgery.

Therefore, the choice of anesthetic is crucial for patients with PAH. The same principles of risk management apply to ES. The two main principles of perioperative risk management are the prevention of systemic hypotension and avoidance of an increase in PVR(PH crisis).Close monitoring, optimization of systemic blood pressure, pain, oxygenation and ventilation, avoidance of exacerbation factors and use of vasopressors and pulmonary therapies as necessary are essential elements of perioperative management.

Special considerations

A. During travelling to, or at, High altitude.
B. Pregnancy.
C. Contraception (Other gynecologic issues).
D. Physical activity.
E. Smoking & Alcoholism.

Complications associated with Eisenmenger syndrome



Patient education

Consider the following points in patient education.

1. Emphasize that diet and weight control are essential.
2. Educate patients to avoid smoking.
3. Provide an exercise prescription.
4. Advise abstinence from or only moderate intake of alcohol.
5. Stress the importance of bacterial endocarditis prophylaxis before surgical procedures.
6. Educate patients about contraception options and pregnancy risk (there is about a 50% mortality in pregnant patients with Eisenmenger syndrome).
7. Consider recommending contraception by means of tubal ligation.
8. Note that oral or implantable contraceptives may promote pulmonary infarction through activation of the coagulation cascade.
9. Educate patients about the signs and symptoms of polycythemia and hyperviscosity.
10. Inform patients about the importance of dental hygiene.

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