Lesson S18: Preanesthetic Assessment of the Pregnant Patient with Pulmonary Artery Hypertension

Authored by: Elizabeth A.M. Frost, M.D., Clinical Professor, Mount Sinai School of Medicine, New York, NY

Reviewed by: Ram Roth, MD, Assistant Professor of Anesthesia, Mount Sinai Medical Center, New York, NY

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Read this article, reflect on the information presented, then go online and complete the lesson post-test and course evaluation before the termination date below. (CME credit is not valid past this date.) You must achieve a score of 80% or better to earn CME credit.

TIME TO COMPLETE ACTIVITY: 2 hours
RELEASE DATE: May 1, 2011
TERMINATION DATE: May 31, 2012

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education for physicians.

Needs statement

The presence of pulmonary hypertension in pregnant patients complicates anesthetic management and it is essential for anesthesiologists to be knowledgeable of current information regarding management of such patients. This topic is frequently reviewed in medical journals throughout the world and understanding recent trends in addressing this complication will be useful to the anesthesiologist’s clinical practice.
Learning Objectives

At the end of this activity, the participant should be able to:

1. Cite the incidence of pulmonary hypertension and pregnancy
2. List the physiologic changes of pregnancy as they relate to the cardiorespiratory system
3. Classify pulmonary hypertension
4. Diagnose and evaluate pulmonary hypertension
5. Identify the effects of pulmonary hypertension on pregnancy
6. List options for treatment of pulmonary hypertension
7. Quantify mortality rates
8. Describe the management of pulmonary hypertension during pregnancy
9. Prepare an anesthetic plan for late pregnancy termination
10. Present alternatives to termination

Case History

A 39 year old pregnant woman, primigravida at 21 weeks, presents to the emergency room complaining of excessive tiredness, dyspnea, syncope and ankle swelling. She reports no prior history of surgery and no prenatal care, and states that she was told of a heart murmur. She reports taking several multivitamin preparations and some herbal treatments.

Physical examination reveals a weight of 235 lbs and height of 64 inches. Her lips are slightly cyanotic and there is marked swelling of the feet and ankles. On auscultation, split S2 and loud P2 sounds are heard. Her BP is 155/95; heart rate 101 with frequent PVC’s; spO2 92 on room air; hct 29%; serum glucose 189 mg/dl.

A diagnosis of pulmonary artery hypertension is made and she is tentatively scheduled for termination of pregnancy.

Introduction

The first international conference on pulmonary hypertension was organized by the World Health Organization in 1973. At that time, there were no effective therapies and patients with primary or idiopathic pulmonary hypertension had a median survival of less than 3 years. Newer treatments have more than doubled the survival time leading to a greater likelihood of such patients presenting for surgery and anesthesia, including those that are pregnant. Pregnancy complicated by pulmonary hypertension poses potentially fatal risks to the mother. Two recent articles have outlined the current treatment modalities and the management of pulmonary hypertension during pregnancy.  

Classification of Pulmonary Hypertension

Pulmonary hypertension (PH) is defined by an increase in pressure in the pulmonary artery, vein or capillaries (lung vasculature), leading to dyspnea, dizziness, fainting, and other symptoms, all of which are exacerbated by exertion. Pulmonary hypertension can be a severe disease with a markedly
decreased exercise tolerance and potential heart failure. First identified by Dr. Ernst von Romberg in 1891, pulmonary hypertension was originally divided into 2 categories: primary pulmonary hypertension and secondary pulmonary hypertension, based on identifiable etiology. In 1998, the World Health Organization (WHO) proposed a clinical classification of primary and secondary pulmonary hypertension based on similarities in pathophysiology, clinical presentation, and therapeutic options, classifying, PH to one of five different types: arterial, venous, hypoxic, thromboembolic or miscellaneous. Primary PH was divided into "arterial plexiform", "veno-occlusive" and "thromboembolic" forms. At a conference in 1998 at Évian-les-Bains, the causes of secondary PH were addressed (i.e. those due to other medical conditions); and in 2003, the 3rd World Symposium on Pulmonary Arterial Hypertension was convened in Venice to modify the classification based on new understandings of disease mechanisms. The revised system developed by this group provides the current framework for understanding pulmonary hypertension. (See Table 1.) The system includes several improvements over the former 1998 Evian Classification system. Risk factor descriptions were updated, and the classification of congenital systemic-to-pulmonary shunts was revised. A new classification of genetic factors in PH was recommended but not implemented because available data were judged to be inadequate.

Table 1: The Venice 2003 Revised WHO Classification system

<table>
<thead>
<tr>
<th>Group I - Pulmonary arterial hypertension (PAH)</th>
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<tbody>
<tr>
<td>▪ Idiopathic (IPAH)</td>
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<tr>
<td>▪ Familial (FPAH)</td>
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<tr>
<td>▪ Associated with other diseases (APAH): collagen vascular disease (e.g. scleroderma), congenital shunts between the systemic and pulmonary circulation, portal hypertension, HIV infection, drugs, toxins, or other diseases or disorders</td>
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<tr>
<td>▪ Associated with venous or capillary disease</td>
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<table>
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<tr>
<th>Group II - Pulmonary hypertension associated with left heart disease</th>
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<tbody>
<tr>
<td>▪ Atrial or ventricular disease</td>
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<tr>
<td>▪ Valvular disease (e.g. mitral stenosis)</td>
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<tr>
<th>Group III - Pulmonary hypertension associated with lung diseases and/or hypoxemia</th>
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<tbody>
<tr>
<td>▪ Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD)</td>
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<tr>
<td>▪ Sleep-disordered breathing, alveolar hypoventilation</td>
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<tr>
<td>▪ Chronic exposure to high altitude</td>
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<tr>
<td>▪ Developmental lung abnormalities</td>
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<th>Group IV - Pulmonary hypertension due to chronic thrombotic and/or embolic disease</th>
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<tr>
<td>▪ Pulmonary embolism in the proximal or distal pulmonary arteries</td>
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<tr>
<td>▪ Embolization of other matter, such as tumor cells or parasites</td>
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<th>Group V Miscellaneous.</th>
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<td>Pulmonary hypertension due the direct effect on the pulmonary vasculature of inflammatory diseases such as schistosomiasis, sarcoidosis, histocytosis X, and fibrosing mediastinitis.</td>
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</table>
The classification does not include sickle cell disease, which may also cause PH. Human herpes virus 8 - also associated with Kaposi’s sarcoma - has been demonstrated in patients with PAH, suggesting that this virus may play a role in its development. An association between human herpes virus 8 and idiopathic pulmonary arterial hypertension (IPAH) remains controversial.

**Pathogenesis**

Whatever the initial cause, pulmonary arterial hypertension (WHO Group I) involves an increase in cardiac load due to the vasoconstriction of blood vessels connected to and within the lungs. Over time, the affected blood vessels fibrose, further increasing pressure within the lungs and impairing blood flow. The right ventricle hypertrophies (cor pulmonale develops), decreasing the ability of the heart to pump blood through the lungs, ultimately causing right heart failure. The decrease in blood flow through the lungs creates decreased volume of blood to the left side of the heart. This blood is also poorly oxygenated blood thereby reducing the ability to supply sufficient oxygen to the rest of the body, especially during physical activity.

Pathogenesis in pulmonary venous hypertension (WHO Group II) differs in that there is no obstruction to blood flow in the lungs. Instead, the left heart fails to pump blood efficiently, leading to pooling of blood in the lungs causing pulmonary edema and pleural effusions.

In hypoxic pulmonary hypertension (WHO Group III), the low levels of oxygen are thought to cause vasoconstriction of pulmonary arteries leading to a pathophysiology similar to pulmonary arterial hypertension.

In chronic thromboembolic pulmonary hypertension (WHO Group IV), vessels are blocked or narrowed with blood clots. Again, the pathology is similar to that seen in pulmonary arterial hypertension.

A further classification is made on functional ability. These classes are based on information adapted from the executive summary of the world symposium on Primary Pulmonary Hypertension in Evian, France in 1998.

**Class I:** These are patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

**Class II:** These are patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

**Class III:** These are patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

**Class IV:** These are patients with pulmonary hypertension with an inability to perform any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.
Epidemiology

The overall prevalence of pulmonary hypertension in the general population is unknown, owing to the heterogeneity of the disease. In specific subgroups of pulmonary hypertension patients, studies have estimated the prevalence as follows:

- In an observational study of 277 patients with HIV infection, 46% of patients had pulmonary hypertension. No change in prevalence rate was seen in patients receiving highly active antiretroviral treatment (HAART).

- A systematic review of several studies of patients with obstructive sleep apnea (OSA) estimated the prevalence of pulmonary hypertension at 15-20%.

- A systematic review of several studies among patients with chronic obstructive pulmonary disease (COPD) estimated the prevalence of pulmonary hypertension at 10-30%.

- In scleroderma patients, the incidence has been estimated to be 6-60% of all patients, with the variance based on the extent of disease.

- In patients who took the diet medication fenfluramine/phentermine, there was a 23 fold increase in the development of PH, often long after ingestion of the drug combination.

Regarding mortality and morbidity for patients with PH and based on the US Centers for Disease Control and Prevention (CDC) Pulmonary Hypertension Surveillance from 1980-2002, the following were reported:

- The age-standardized death rates for the total US population increased from 5.2 deaths to 5.4 deaths per 100,000 population.

- The main increase in death rates was seen among women, with 3.3 deaths to 5.5 deaths per 100,000 population, and blacks, with 4.6 deaths to 7.3 deaths per 100,000 population.

- The death rate in males decreased over this time, from 8.2 deaths to 5.4 deaths per 100,000 population.

Diagnosis

Because of the many etiologies of PH, a series of tests must be performed to distinguish pulmonary arterial hypertension from venous, hypoxic, thromboembolic, or miscellaneous varieties.

During physical examination, typical signs of pulmonary hypertension include altered heart sounds, such as a widely split S2; or second heart sound, a loud P2 or pulmonic valve closure sound (part of the second heart sound); (para)sternal heave, possible S3 or third heart sound, and pulmonary regurgitation. Other signs include an elevated jugular venous pressure, peripheral edema, ascites, hepatojugular reflux, and clubbing.
Further procedures are required to confirm the presence of pulmonary hypertension and exclude other possible diagnoses. These generally include pulmonary function tests; blood tests to exclude HIV, autoimmune diseases, and liver disease; electrocardiography (ECG); arterial blood gas measurements; X-rays of the chest (followed by high-resolution CT scanning if interstitial lung disease is suspected); and ventilation-perfusion or V/Q scanning to exclude chronic thromboembolic pulmonary hypertension. Trans-thoracic echocardiography (TTE) is used widely as a screening tool for PH. There is strong correlation between PA pressures and right ventricular systolic pressure. However, several factors such as severe lung disease, premature ventricular contractions, and inaccurate estimates of right atrial pressure can lead to misdiagnosis. Studies have found that TTE may overestimate PA pressures when compared with right heart catheterization (RHC). On the other hand, in about one third of patients, RHC may reveal more severe PH than is estimated from TTE.

The presence of PH does not mean PAH is present and thus assessment of PA occlusion pressures and PVR must be made. In fact, the diagnosis of PAH must be confirmed with RHC in pregnant patients, given the high morbidity and mortality associated with the combination of the two conditions. Biopsy of the lung is usually not indicated unless the pulmonary hypertension is thought to be due to an underlying interstitial lung disease. Lung biopsies carry risks of bleeding due to the high intrapulmonary blood pressure. Clinical improvement is often measured by a "six-minute walk test", i.e. the distance a patient can walk in six minutes. Stability and improvement in this measurement correlate with better survival. Brain natriuretic peptide levels (BNP) may be used to follow the progress of patients with pulmonary hypertension.

Although pulmonary arterial pressure can be estimated on the basis of echocardiography, pressure measurements with a pulmonary artery (PA) catheter provide the best assessment. PAOP and PVR cannot be measured directly by echocardiography. Therefore diagnosis of PAH requires right-sided cardiac catheterization. A PA catheter can also measure cardiac output, which is better indicator of disease severity than pulmonary arterial pressure.

A diagnosis of PAH is confirmed by presence of pulmonary hypertension with two other conditions. Pulmonary artery occlusion pressure (PAOP or PCWP) must be less than 15 mm Hg (2000 Pa) and pulmonary vascular resistance (PVR) must be greater than 3 Wood units (240 dynes•cm−5 or 2.4 mN•s•cm−5). Normal pulmonary arterial pressure in a person at sea level has a mean value of 12–16 mm Hg (1600–2100 Pa). Pulmonary hypertension is present when mean pulmonary artery pressure exceeds 25 mm Hg (3300 Pa) at rest or 30 mm Hg (4000 Pa) with exercise. Mean pulmonary artery pressure (mPAP) should not be confused with systolic pulmonary artery pressure (sPAP), which is often reported on echocardiogram reports. A systolic pressure of 40 mm Hg typically implies a mean pressure of more than 25 mm Hg. Roughly, mPAP = 0.61•sPAP + 2.

**Physiologic Changes of Pregnancy**

There are several cardiopulmonary physiologic changes with pregnancy that exacerbate PH. In the pulmonary system, minute ventilation increases by 50% at term. Arterial carbon dioxide decreases to about 34mmhg. Functional residual capacity, expiratory reserve volume and residual volume all decrease. Total lung capacity remains the same because of increase in chest circumference. The smooth muscle relaxation effects of progesterone may decrease airway resistance and improve function. Cardiac changes include a 50% increase in cardiac output, with early increases in blood volume that lead to increased stroke volume. Afterload is reduced secondary to decreased peripheral
vascular resistance. Later, cardiac output is augmented by tachycardia. Normally, pulmonary vascular resistance (PVR) decreases to allow for these changes, an accommodation that is not possible in patients with PH. As afterload increases from the higher PVR, the right ventricle cannot handle the increased cardiac output and begins to fail. Sudden death from dysrhythmia may occur. Peak plasma volumes develop about 22-24 weeks and cardiac output peaks around 32 weeks.

At the time of delivery, pain stimulates the sympathetic nervous system with sudden significant increases in heart rate, blood pressure and myocardial oxygen consumption. Vagal responses may also occur and lead to hypotension and sudden death. Valsalva maneuvers may further increase blood pressure and myocardial oxygen consumption. Also, with each uterine contraction, about 500 ml of blood is pushed into the maternal circulation. After delivery, autotransfusion from the uterine circulation and increased venous return from the relief of inferior vena cava pressure cause large fluid shifts to the maternal circulation. Right ventricular volume overload can occur easily.

Pregnancy is associated with a hypercoagulable state due to increased fibrin levels, reduced fibrinolytic activity, increased procoagulant activity with higher resistance to activated protein C, lower protein S, and increased clotting factor activity. Any degree of thromboembolism contributes to a poor outcome in pregnant patients with PH.

**Pulmonary Hypertension and Pregnancy**

Pulmonary hypertension affects a relatively small number of pregnancies (approximately 0.0003%). Older studies report mortality rates as high as 60%. More recent studies indicate a decline in mortality to approximately 25%, with patients in the IPAH group showing the most improvement (17%), perhaps due to the PAH specific therapy that is typically used for patients with IPAH.

Previously undiagnosed PH may initially manifest with the stress of pregnancy. It can also develop acutely during pregnancy. Sudden onset of dyspnea, syncope or chest pain should be immediately investigated. Differential diagnoses include sleep apnea, asthma, arteriovenous malformations, atrial myxoma, amniotic fluid embolism, atrial septal defect, cardiomyopathy (dilated, hypertrophic or restrictive), chronic obstructive pulmonary disease, emphysema, mitral regurgitation and stenosis, restrictive and interstitial lung disease and systemic lupus erythematosus.

As soon as a diagnosis of PH is made, patients require regular assessment of RV function with TTE. Should dysfunction be detected, early delivery is recommended. While no anesthetic technique has proven superior, the few available studies report that most patients were delivered under spinal or epidural anesthesia. Of note is that during delivery, hypotension may develop from the several medications used to treat PH including oxytocin, pulmonary vasodilator drugs, inotropes (dobutamine) and analgesics. Vasopressin preferentially increases systemic vascular resistance without increasing PVR and is a viable option to support blood pressure without compromising RV function. Maternal death is most likely to occur in the postpartum period when maximum fluid shifts occur.

**Treatment**

While there is no curative therapy (short of lung transplantation), several treatments have shown promise in improving outcome for patients with PH. Therapy is dictated in part by the cause, whether it be arterial, venous, hypoxic, thromboembolic, or other. Since pulmonary venous hypertension is
synonymous with congestive heart failure, the treatment is to optimize left ventricular function by the use of diuretics, beta blockers, ACE inhibitors, etc., or to repair/replace the mitral valve or aortic valve. Digoxin, diuretics, and oxygen have been advocated but results are inconsistent. High dose calcium channel blockers are useful in only 5% of IPAH patients who are vasoreactive by pulmonary artery catheter measurements. Unfortunately, calcium channel blockers have been largely misused, being prescribed to many patients with non-vasoreactive PAH, leading to excess morbidity and mortality. The criteria for vasoreactivity have changed. Only those patients whose mean pulmonary artery pressure falls by more than 10 mm Hg to less than 40 mm Hg with an unchanged or increased cardiac output when challenged with adenosine, epoprostenol, or nitric oxide are considered vasoreactive. Of these, only half are responsive to calcium channel blockers in the long term. Several agents have recently been introduced for primary and secondary PAH. The trials supporting the use of these agents have been relatively small, and the only measure consistently used to compare their effectiveness is the "6 minute walking test". Many have no data on mortality, benefit or time to progression.

RV failure is the most common cause of death in pregnant patients with PH. Thus therapy targets reducing PVR. Three of the many vasoactive pathways involved in the abnormal proliferation and contraction of the smooth muscle cells of the pulmonary arteries have been targeted with drugs — endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives. Prostacyclin (prostaglandin I2) is commonly considered the most effective treatment for PAH. Epoprostenol (synthetic prostacyclin, marketed as Flolan®) is given via continuous infusion that requires a semi-permanent central venous catheter. This delivery system can cause sepsis and thrombosis. Flolan® is unstable, and has to be kept cold during administration. Since it has a half-life of 3 to 5 minutes, the infusion has to be continuous (24/7), and interruption can be fatal.

Other prostanoids have been developed. Treprostinil (Remodulin®) can be given intravenously or subcutaneously, but the subcutaneous injection can be very painful. An increased risk of sepsis with intravenous Remodulin has been reported by the CDC. Iloprost (Ilomedin®) is also used in Europe intravenously and has a longer half life. Iloprost (marketed as Ventavis®) was the only inhaled form of prostacyclin approved for use in the US and Europe, until the inhaled form of treprostinil was approved by the FDA in July 2009, marketed under the trade name Tyvaso®. The inhaled form of administration has the advantage of selective deposition in the lungs with less systemic side effects; however coughing and throat irritation commonly occur. Oral and inhaled forms of Remodulin® are under development. Beraprost is an oral prostanoid available in South Korea and Japan.

The dual endothelin receptor antagonist bosentan (ETA and ETB), marketed as Tracleer®, was approved in 2001. Sitaxentan, a selective endothelin receptor antagonist that blocks only the action of ETA, has been approved for use in Canada, Australia, and the European Union, marketed under the name Thelin®. It has not been approved for marketing by the U.S. Food and Drug Administration (FDA). In 2010, Thelin® was withdrawn by Pfizer due to severe side effects. A new trial to address the FDA’s concerns began in 2008. A similar drug, ambrisentan, is marketed as Letairis® in U.S.(Gilead Sciences). In addition, another dual/nonselective endothelin antagonist, Actelion-1, from the makers of Tracleer®, entered clinical trials in 2008.

Sildenafil, a selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), was approved for the treatment of PAH in 2005, marketed as Revatio®. In 2009, tadalafil, another PDE5 inhibitor, marketed under the name Adcirca® or Cialis® was also approved.
The nitric oxide (NO) signaling pathway is important for many physiological functions including vascular smooth muscle relaxation, neuronal signal transduction and inhibition of platelet aggregation. The source of NO in vivo is the enzyme nitric oxide synthase. The principal receptor for NO is soluble guanylate cyclase (sGC). Several sGC activators, including cinaciguat and riociguat, are undergoing clinical trials for the treatment of PAH.

There is conflicting data as to the fetal effects of these medications. However, at least anecdotal reports indicate safe usage with most of them.\(^2\)

Several surgical procedures have been described for the treatment of PH. Atrial septostomy creates a communication between the right and left atria and relieves pressure on the right side of the heart, but at the cost of relative hypoxia. Lung transplantation cures pulmonary arterial hypertension, but leaves the patient with the complications of transplantation, and a post-surgical median survival of just over five years.\(^18\) Pulmonary thromboendarterectomy (PTE) is a difficult, major procedure that is currently performed in a few select centers but with apparent good success in select patients.

**Management of the case**

Right heart catheterization indicated that the patient had severe pulmonary hypertension (WHO Group IV). Further evaluation determined that she had severe mitral stenosis. She was counseled as to continuation of the pregnancy. Given her obesity, gestational diabetes, and the established right heart dysfunction, it was agreed that late termination would be the safest choice with mitral valve replacement in the near future. The patient was reluctant to agree as this was her first and perhaps only, pregnancy. She was given further opportunity to discuss the situation and to review the available data with a team of obstetricians, cardiologists, and anesthesiologists with input from psychologists and social workers. She acknowledged that the chances of her survival and that of the baby were less than 50% and she agreed to proceed with termination. A course of high dose calcium channel blockers was started.

Decision was made to perform the termination in an operating room prepared for open heart surgery. A cardiac surgeon was placed on stand by as was the entire team. Anxiolysis was achieved with midazolam 4 mg. The radial artery was cannulated and a pulmonary artery catheter placed. After antacid prophylaxis, epidural analgesia was achieved to a T8 level. Vasopressin was prepared but was not required. Evacuation was completed in 12 minutes. Oxytocin was withheld because of the theoretical risk of increase of PVR. The patient was transferred to the ICU and carefully observed for 24 hours. She was then discharged and scheduled for further evaluation prior to mitral valve replacement.

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*Dr. Elizabeth A.M. Frost, who is the editor of this continuing medical education series, is clinical professor of anesthesiology at The Mount Sinai School of Medicine in New York City. She is the author of Clinical Anesthesia in Neurosurgery (Butterworth-Heinemann, Boston) and numerous articles. Dr. Frost is past president of the Anesthesia History Association and former editor of the journal of the New York State Society of Anesthesiologists, Sphere. She is also editor of the book series based on this CME program, Preanesthetic Assessment, Volumes 1 through 3 (Birkhäuser, Boston) and 4 through 6 (McMahon Publishing, New York City).*
REFERENCES

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Post-test

1. Pulmonary hypertension is characterized by:
   a. Dizziness and decreased exercise tolerance
   b. Fainting and palpitations
   c. Systemic hypotension and ankle swelling
   d. Hypoglycemia and dyspnea

2. According to the revised WHO classification of PH:
   a. Group 1 refers only to venous abnormalities
   b. Group 2 considers PH associated with left heart disease
   c. Group 3 includes congenital shunts
   d. Group 4 applies to genetic factors

3. Hypoxic pulmonary hypertension:
   a. Exerts a pathophysiology similar to PAH
   b. Causes vasodilation of pulmonary arteries
   c. Usually shows normal paO2
   d. Is classified as WHO Group IV

4. Classification on functional ability in patients with PH:
   a. Stems from the first international conference on PH in 1973
   b. Is divided into 7 classes
   c. Was adapted from a summary of the conference on PH at Evian in 1998
   d. Indicates that class I patients are unable to perform any physical activity without symptoms

5. The human herpes virus 8:
   a. Has been demonstrated in patients with PAH
   b. Is associated with Kaposi’s sarcoma
   c. Has not been definitively linked to IPAH
   d. All of the above
6. **Pulmonary venous hypertension:**
   a. Is classified as WHO Group III
   b. Causes significant obstruction to blood flow through the lungs
   c. Results in pulmonary edema and pleural effusions
   d. Does not involve the left ventricle

7. **Which of the following statements regarding the prevalence of PH is not true?**
   a. Prevalence rates of PH and HIV are significantly decreased with highly active antiretroviral treatment
   b. PH occurs in about 20% of patients with OSA
   c. About 10-30% of patients with COPD have PH
   d. The variance of PH in scleroderma is wide and varies with the extent of the disease

8. **Diagnosis of PH can be made on the following findings:**
   a. Widely split S2 and loud P2 heart sounds
   b. Pulmonary artery pressure > 25mm Hg at rest and PVR >3 Wood units
   c. Hepatojugular reflux
   d. All of the above

9. **Physiologic changes in pregnancy are least likely to include:**
   a. 50% increase in minute ventilation
   b. An increase in paCO2 due to inactivity
   c. Unchanged total lung capacity
   d. Significant increase in cardiac output

10. **Factors that increase the risk of PH during pregnancy include:**
    a. Autotransfusion at the time of delivery
    b. Pain of contractions during labor
    c. Hypercoagulable state
    d. All of the above