Lesson 247: PreAnesthetic Assessment of the Patient With α₁-Antitrypsin Deficiency

**Written by:**
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**Disclosure Statement:**
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**Needs Statement:**
Deficiency of α₁-antitrypsin (AAT), an autosomal-recessive disorder, is an underdiagnosed and misdiagnosed condition that presents in a variety of ways, including progressive alveolar destruction ultimately leading to emphysema. AAT is also associated with an increased risk for liver disease. Type AAT not managed properly, renal failure, further liver damage, serious side effects of pharmacotherapy, and pulmonary complications such as tension pneumothorax may develop. Proper preoperative optimization, drug selection, and intraoperative monitoring will all be considered because the pulmonary and hepatic manifestations of AAT present a challenge to the anesthesiologist. A knowledge of AAT and its consequences have recently been identified as important for anesthesiologists.

**Learning Objectives:**
At the end of this activity, the participant should be able to:
1. Summarize the physiologic role of the protein AAT.
2. Discuss the epidemiology of AAT deficiency.
3. Recognize the phenotypes associated with AAT deficiency.
4. Identify important risk factors for the disease.
5. List features that should increase the clinician’s suspicion of AAT deficiency.
6. Review the pathophysiology of lung and liver diseases associated with AAT deficiency.
7. Describe the clinical manifestations of the disease.
8. Summarize the criteria used in the diagnosis of AAT deficiency.
9. Discuss standard and emerging treatments for patients with the disease.
10. Present an anesthetic plan for the patient with AAT deficiency.

**Target Audience:**
Anesthesiologists

**Case History:**
A 36-year-old woman was scheduled for elective surgery to treat carpal tunnel syndrome. A review of systems revealed that the patient had a family history of emphysema and had experienced chronic progressive dyspnea on exertion during the last 3 years. The dyspnea was associated with intermittent wheezing without cough or mucus production. Her family physician had given her bronchodilators for exertional dyspnea, but they were not effective. The patient admitted that she had smoked approximately half a pack of cigarettes per day for the past 14 years. Otherwise, her medical history was not significant, except for a tendency to bruise easily. The anesthesiologist asked for a pulmonary evaluation of the patient.

**Call for Writers:**
If you would like to write a CME lesson in Anesthesiology News, please e-mail Elizabeth A.M. Frost, MD, at Efrostf@com.

**Efficiency of α₁-antitrypsin (AAT):**
AAT is an autosomal-recessive disorder that is commonly underdiagnosed and misdiagnosed.1 It has been postulated that fewer than 10% of individuals with this disorder have received a correct diagnosis.1 AAT is a member of the serine protease inhibitor superfamily. It protects the lungs from neutrophil elastase, which normally digests damaged or aging cells and bacteria. A deficiency of AAT predisposes lung tissue to uncontrolled proteolytic attack by the enzyme. Mutations to the AAT gene can result in reduced serum levels of AAT, causing progressive alveolar destruction.4 In addition, individuals with AAT deficiency are at risk for the early-onset of severe emphysema.4 The deficiency is also associated with an increased risk for juvenile hepatitis, cirrhosis, and hepatocellular carcinoma.4,5

**Genetics:**
AAT deficiency is inherited in an autosomal pattern, with a codominant expression of alleles. Variants of the AAT gene are classified according to the protease inhibitor (Pi) system based on rate of migration during starch gel electrophoresis: slow (S), medium (M), fast (F), and very slow (Z).7 The normal genotype, PMM, results in serum levels of AAT between 20 and 53 mcromol/L. PIZZ is the genotype most frequently associated with severe AAT deficiency, resulting in serum levels of AAT between 3.4 and 7.0 mcromol/L—16% of the level found in individuals with the PMM genotype. A variety of other genotypes are associated with AAT deficiency, including PIMZ, PMS, PI3, PI2, PI2Z(null), PI(2-nul)(null), in addition to several rare Pi genotypes.8

**Epidemiology:**
Although AAT deficiency is generally regarded as a disease of northern European Caucasians, recent evidence indicates that it is much more widespread than once believed, affecting populations worldwide. The disease has been found to occur in African blacks, Arabs and Jews in the Middle East, Caucasians in Australia, New Zealand, Europe, and North America; and natives of the central, eastern, and southeastern regions of Asia.2 In populations of sub-Saharan Africa, 13 novel variants of the gene, in addition to 9 known variants, have been discovered.9 The prevalence of the PIZZ phenotype is highest in North America, southern Europe, and central Asia.1 It has been estimated that there are at least 116 million of the

**Preanesthetic Assessment:**
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Table 1. Risk Factors for Increased Lung Damage

<table>
<thead>
<tr>
<th>Possible risk factors</th>
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<tbody>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Increasing age</td>
</tr>
<tr>
<td>Male gender</td>
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<tr>
<td>Previous asthmatic symptoms</td>
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<tr>
<td>Occupational exposure to airway irritants</td>
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<td>Exposure to environmental tobacco smoke</td>
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Table 2. Conditions That Should Increase Suspicion of AAT Deficiency

<table>
<thead>
<tr>
<th>Early-onset emphysema (patient ≤ 45 years old)</th>
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<tbody>
<tr>
<td>Emphysema presenting without recognized risk factors</td>
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<tr>
<td>Emphysema associated with prominent basilar hyperlucency</td>
</tr>
<tr>
<td>Unexplained/idiopathic liver disease</td>
</tr>
<tr>
<td>Necrotizing panniculitis C-ANCA-positive vasculitis</td>
</tr>
<tr>
<td>(antineutrophil cytoplasmic antibody)</td>
</tr>
<tr>
<td>Family history of emphysema, bronchiectasis, liver disease, or panniculitis</td>
</tr>
<tr>
<td>Idiopathic bronchiectasis</td>
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</tbody>
</table>

AAT: α1-antitrypsin; C-ANCA: cytoplasmic antineutrophil cytoplasmic antibody

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PIMS or PIMZ phenotype and 3.4 million of the PiSS, PiSZ, or PIZZ phenotype in a total of 58 countries surveyed. These recent statistics suggest that AAT deficiency is not a rare disease, as once believed; rather, it possibly deserves recognition as one of the most common single-locus genetic disorders in the world.1,2

Risk Factors

Serum levels of AAT are determined on a hereditary basis; however, several additional factors predispose individuals to a greater decline in lung function. The most significant risk factor for the development of emphysema in individuals with AAT deficiency is smoking. Smoking leads to an infiltration of neutrophils and macrophages into the lungs, with the subsequent secretion of proteases. The increased number of proteases and the reduced levels of AAT antiproteases produce an additive proteolytic effect, leading to the development of emphysema.4 Individuals with the PIZZ deficiency allele who smoke cigarettes tend to develop more severe pulmonary impairment at an earlier age and have a significantly lower life expectancy than nonsmoking individuals with the PIZZ allele.5 Several additional risk factors have been associated with a premature decline in lung function, including male gender, increasing age, previous asthmatic symptoms, and exposure to airway irritants in individuals older than 50 years (Table 1).1,11

The underrecognition of AAT deficiency may be the result of several factors. Patients with deficiency phenotypes present clinically with nonexclusive respiratory and hepatic syndromes, such as emphysema, chronic bronchitis, and chronic liver disease. Therefore, a wide differential may lead to misdiagnosis. In addition, the PYZ allele exhibits incomplete penetrance, and the severity of the disease is affected by many factors, such as smoking and respiratory tract infections. As a result, individuals with severe AAT deficiency can exhibit a wide range of symptoms, and clinically significant lung impairment is absent in many individuals.15

Because AAT deficiency is frequently underdiagnosed and misdiagnosed, several features should encourage further investigation, if present (Table 2).13

Progression of Disease

Lungs

Symptoms associated with AAT deficiency may include dyspnea at rest or during exercise, wheezing, coughing, recurring lung infections, and sputum production, in addition to a history of suspected allergies and/or asthma.1 Low serum levels of AAT are associated with a high risk for emphysema; 96% of those who exhibit lung disease in conjunction with AAT deficiency are homozygous for the Z allele.12 A deficiency of AAT throughout the acinus results in increased susceptibility to proteolysis as the consequence of a chronic, low-grade influx of neutrophils into the lung and the subsequent release of elastase. The slow degradation of the lung secondary to the imbalance of elastase and AAT throughout the acinus results in panacinar emphysema. In addition, destruction is greatest in the lower lobes of the lungs as a result of a higher perfusion rate and increased numbers of neutrophils.4 Chest radiographs of patients with AAT-associated emphysema show hyperinflation of the lungs, a flattened diaphragm, an increased anteroposterior diameter of the chest, and widening of the retrosternal air space. Increased lung compliance because of a reduction in elastic recoil leads to an increase in the work of breathing.14

The pulmonary functional residual capacity and residual volume are increased as a result of airway collapse and the trapping of air. The total lung capacity may be normal to increased. Hyperinflation of the lungs leads to a physiologic dead space in zone 1, and impaired gas exchange results from proteolytic destruction of the alveoli. Therefore, the ratio of dead space to tidal volume (V/DVT) is increased. These patients show ventilation-perfusion (V/Q) abnormalities because of altered air distribution and impaired gas exchange. The V/Q mismatch is greater at the base of the lungs, and may result in hypoxemia.4 The ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC) is typically decreased, with abnormal flow-volume curves indicating a decrease in flow with decreased lung volumes. The development of pulmonary hypertension as a result of the loss of alveolar capillary beds and pulmonary vasconstriction may lead to right heart strain and cor pulmonale—further complications of the deficiency.14

Liver

Associated variants of AAT deficiency exhibit a migratory defect between the endoplasmic reticulum and the Golgi apparatus of the hepatocyte.6 The rough endoplasmic reticulum of the hepatocytes of individuals homozygous for the Z allele (PiZZ) contains an abnormal accumulation of AAT. Loop-sheet polymers have been shown to form from mutant AAT, and during episodes of inflammation, the polymers form faster than they can be degraded, leading to the development of hepatic inclusions and hepatocellular damage.11 Such accumulations have been associated with mitochondrial autophagy and caspase activation.16 AAT deficiency is the most commonly diagnosed form of hereditary liver disease. Approximately 10% to 15% of individuals homozygous for the Z allele present with some degree of liver disease within the first 20 years of life.5 In children with liver disease caused by AAT deficiency, symptoms may include—but are not restricted to—jaundice at birth, pruritus, cirrhosis, portal hypertension, nausea, vomiting, problems with nursing, pale stools, cholestasis, enlarged spleen, enlarged abdomen, esophageal varices, and difficulty gaining weight.17 In young adults, liver disease may manifest as hepatitis and fibrosis, which can progress to cirrhosis and hepatic failure with portal hypertension. These patients are also at increased risk for the development of hepatocellular carcinoma.4

Panniculitis

Inflammation of subcutaneous fat lobules or the connective tissue that separates the lobules is known as panniculitis.4 Several cases of panniculitis, presenting as painful red nodules on the thighs that can ulcerate spontaneously and drain, have been associated with AAT deficiency. The panniculitis of AAT deficiency is characterized by a massive influx of neutrophils, necrosis, macrophage proliferation, and frequent and widespread destruction of elastic tissue.18,19 Panniculitis can be exacerbated by cryotherapy, surgical debridement, and extravasation of intravenous (IV) medications such as clarithromycin.20,21

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Screening and Diagnosis

Currently, AAT deficiency is diagnosed by analysis of the serum levels of AAT and the AAT isoelectric focusing pattern. The concentration of AAT in the serum can be determined by radial immunodiffusion, nephelometry, or rocket immunoelectrophoresis, and the values compared with the established ranges for the common phenotypes. The ranges for the common phenotypes include the following: PMM, 20 to 53 mcmol/L; PMZ, 15 to 42 mcmol/L; PZZ, 3.4 to 7.0 mcmol/L; and PSZ, 10 to 23 mcmol/L. Relative plasma concentrations of AAT are as follows: PMM, 100%; PMZ, 83%; and PZZ, 16% (Table 3).8

The sensitivity and specificity of the serum AAT levels are 100% and 99%, respectively, with a positive predictive value of 94% and a negative predictive value of 100%. Therefore, in the initial evaluation of a patient for AAT deficiency, the serum AAT level alone may be sufficient to predict the PiZZ phenotype.23

Because isoelectric focusing requires extensive labor and is usually performed in reference laboratories, there has been interest in developing a faster, less expensive method of AAT genotyping. A novel method has been developed that uses the restriction enzymes Hpy99I and SexAI. It is quick and 75% less expensive than amplification–reverse hybridization commercial kits, and it shows complete agreement with the standard methods for detecting S and Z variants.24

The Alpha-1 Antitrypsin Deficiency Task Force of the American Thoracic Society and European Respiratory Society has developed recommendations for genetic testing that are classified as types A through D (Table 4). The 4 types were determined by evaluating issues favorable or unfavorable to testing and then weighing the issues according to the amount of evidence supporting each one.

According to the AAT Deficiency Task Force, patients for whom the type A recommendation for diagnostic testing is appropriate include the following:

- asymptomatic adults who have emphysema, chronic obstructive pulmonary disease, or asthma with airflow obstruction that is incompletely reversed after aggressive treatment with bronchodilators
- those with unexplained/idiopathic liver disease, including neonates, children, adults, and especially the elderly
- asymptomatic individuals who exhibit continuous obstruction on pulmonary function tests and who have identifiable risk factors, such as smoking and occupational exposure
- adults with a diagnosis of necrotizing panniculitis. (Note that in populations with a prevalence of AAT deficiency lower than that in the general North American and northern European population, the type B recommendation for diagnostic testing is available.)

A type B recommendation for diagnostic testing applies in the following cases:

- adults with idiopathic bronchiectasis
- adolescents with persistent airflow obstruction
- asymptomatic individuals with persistent airflow obstruction and no risk factors
- adults with cytoplasmic antineutrophil cytoplasmic antibody (C-ANCA)–positive vasculitis (antineutrophilic 3–positive vasculitis)

According to the type C recommendation, genetic testing is not appropriate for asthmatic adults whose airflow obstruction is completely reversible. For population screening of neonates, adolescents, or adults, the type D recommendation was developed—although exceptions may be made in countries where: 1) the prevalence of AAT deficiency is high (1 in 1,500), 2) smoking is prevalent, and 3) adequate counseling services are available.25

At present, there is no definite cure for AAT deficiency. Although an early diagnosis may be beneficial (eg, affected individuals can be advised not to smoke to improve their prognosis), it is important for clinicians to consider the ethical ramifications of diagnosing AAT in asymptomatic individuals; the consequences may include emotional distress, anxiety, discrimination, and difficulties with obtaining insurance and employment.

Table 3. AAT Levels in Adults by Pi Type

<table>
<thead>
<tr>
<th>Pi Type</th>
<th>Serum Level, mcmol/L</th>
<th>Relative Circulating Concentration, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM (normal)</td>
<td>20-53</td>
<td>100</td>
</tr>
<tr>
<td>MZ</td>
<td>15-42</td>
<td>83</td>
</tr>
<tr>
<td>ZZ</td>
<td>3.4-7.0</td>
<td>16</td>
</tr>
<tr>
<td>SZ</td>
<td>10-23</td>
<td>16</td>
</tr>
<tr>
<td>SS</td>
<td>20-28</td>
<td>16</td>
</tr>
<tr>
<td>MS</td>
<td>18-62</td>
<td>16</td>
</tr>
</tbody>
</table>

AAT, α1-antitrypsin; Pi, protease inhibitor

Table 4. Testing Recommendations for 4 Types Of AAT Deficiency

<table>
<thead>
<tr>
<th>Type</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Genetic testing should be recommended</td>
</tr>
<tr>
<td>B</td>
<td>Genetic testing should be discussed; patient could reasonably accept or decline</td>
</tr>
<tr>
<td>C</td>
<td>Genetic testing is not recommended (ie, testing should not be encouraged)</td>
</tr>
<tr>
<td>D</td>
<td>Genetic testing should not be performed and is discouraged</td>
</tr>
</tbody>
</table>

AAT, α1-antitrypsin

Adapted from Am J Respir Crit Care Med. 2003;168:818-900.1

Treatment

Pulmonary Manifestations

I.V. augmentation therapy with purified α1-protease inhibitor (α1-Pi) has been shown to slow the rapid decline in FEV1, that occurs in some patients with AAT deficiency. Early detection of the disorder and the initiation of augmentation therapy at an earlier stage of the disease may thus delay the decline in functional lung tissue.26 In addition, augmentation therapy has been correlated with a decrease in elastase and leukotriene B4, a chemoattractant involved in airway inflammation.27 α1-Pi has been shown to reduce the severity and frequency of lung infections, decrease the rate of deterioration in lung function, and reduce the mortality associated with AAT deficiency.27 However, α1-Pi is exceptionally costly, and after I.V. administration, only 2% to 3% concentrates in the lungs. To address this problem, the administration of α1-Pi in aerosol form has been investigated and found to be effective in depositing adequate amounts in the lung periphery, with a greater effect in patients with low-grade disease.28

Additional therapies for patients with AAT deficiency and related emphysema are directed at controlling the associated symptoms. These include bronchodilators, inhaled corticosteroids, long-term oxygen therapy, lung volume reduction surgery, and lung transplantation.28

New treatments are based on the observation that the manifestations of AAT deficiency–associated emphysema generally develop relatively early; furthermore, the emphysema tends to occur without other pulmonary diseases—so-called “pure” emphysema. Emerging treatments include all-trans-retinoic acid, which stimulates alveolar growth, and aerosolized hyaluronic acid, which reduces the destruction of alveoli.29-32

Hepatic Manifestations

If AAT deficiency manifests as liver disease, the only currently available treatment is liver transplantation. In children, liver transplantation results in a 5-year survival rate of >70%; in adults, the long-term survival rate is 60%.33,34 Relatively new therapies have been directed at the release of trapped AAT to decrease congestion of the hepatocytes and thus see Lesson 247 page 38

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Perioperative Anesthetic Considerations

Emphysema

Preoperative efforts for patients presenting with emphysema are directed toward optimizing pulmonary function. Intraoperative and postoperative management is designed to minimize the residual depressant effects of anesthetics and decrease pain that may impair oxygenation and ventilation after surgery.

Preoperatively, patients are encouraged to stop smoking; reversible pathologies (eg, bronchospasm) are treated. Furthermore, any bacterial infections should be eradicated. Although pulmonary function testing does not help predict postoperative pulmonary complications, it can be used to assess the response to therapy. In smokers undergoing abdominal surgery, pulmonary function tests revealing airway obstruction have predicted bronchospasm, but not the need for prolonged endotracheal intubation.

A cessation of smoking for even brief periods can change the hemodynamics of the lungs. This enhancement can be achieved because the effects of carbon monoxide on oxygenation and of nicotine on the cardiovascular system are transient. Carbon monoxide has a half-life of 4 to 6 hours, and thus smoke-free intervals of 12 to 18 hours can substantially decrease the level of carboxyhemoglobin. In fact, the PAO₂ at 50% hemoglobin saturation increases from 22.9 to 26.4 mm Hg within 12 hours after smoking cessation. The plasma levels of carboxyhemoglobin decrease from 6.5% to 11% in the same time interval. The transient sympathomimetic effects of nicotine are also avoided with smoking cessation. A decrease in postoperative pulmonary complications, however, has not been demonstrated after a short-term abstinence from smoking.

Conversely, hypersecretion of mucus, impairment of mucociliary transport, and narrowing of the small airways, all of which result from cigarette smoking, are not relieved by short-term abstinence. Such processes occur over the course of weeks. Studies have demonstrated that more than 2 months of abstinence from smoking is required to decrease postoperative pulmonary complications after coronary artery surgery.

Patients who smoke and patients with chronic obstructive pulmonary disease experience a higher rate of pulmonary complications. No specific drugs or techniques are mandated for the management of patients with emphysema associated with AAT deficiency; however, regional anesthesia is preferred for these patients whenever possible. No specific sedation protocol seems to affect the rate of postoperative pulmonary complications. A recent study demonstrated that regional anesthesia alone for various abdominal surgeries was used successfully and safely in selected high-risk patients, indicating that regional techniques may be a safe alternative to general anesthesia in that population.

The anesthesiologist must also be aware that acute respiratory failure may develop postoperatively in patients who have emphysema associated with AAT deficiency. For this reason, continued tracheal intubation and mechanical ventilation may be necessary, especially after intrathoracic or upper abdominal surgery. The postoperative use of neaural opioids—which aid in pain-free breathing—may promote early tracheal extubation and reduce requirements for systemic analgesics. However, careful observation of the patient (especially in ward settings) is essential to ensure adequate respiration. Routine orders should be modified to include continuous monitoring of oxygenation.

When general anesthesia is required, volatile anesthetics with humidification and mechanical ventilation are generally used. The drugs are rapidly eliminated by the lungs, so that residual ventilatory depression during the early postoperative period is minimized. If nitrous oxide is combined with volatile anesthetics, the anesthesiologist must consider the potential passage of the anesthetic gas into pulmonary bullae related to emphysema. The enlargement and rupture of bullae can be a possible sequela, ultimately resulting in the development of a tension pneumothorax during anesthesia.

For the maintenance of anesthesia, opioids, although acceptable, may be less useful than inhaled anesthetics. Prolonged depression of ventilation results from a slower rate of elimination by the liver or kidneys. Remifentanil is rapidly metabolized in an organ-independent manner. Other classes of agents must be carefully considered, particularly if there is significant damage to the lungs or liver. Studies have suggested that even thiopental and midazolam can prolong ventilatory depression in patients with respiratory pathology. In addition, multiple regression analysis has demonstrated that long-acting neuromuscular blockers may be associated with a higher risk for pulmonary complications than are the short-acting versions. It should be eradicated.

To optimize arterial oxygenation in patients with emphysema, controlled ventilation should be used. Turbulent airflow can be minimized and optimal ventilation-perfusion matching maintained with large tidal volumes (10-15 mL/kg) along with slow inspiratory flow rates (6-10 breaths/min). This type of controlled ventilation provides sufficient time for complete exhalation, thereby minimizing air trapping in obstructive cases. Finally, regardless of the selected ventilation protocol, the anesthesiologist should make objective adjustments based on pH, arterial blood gas status, oxygen saturation, and capnography.

Cirrhosis

Coagulation studies should be conducted preoperatively. If the prothrombin time is prolonged, parenteral vitamin K...
should be administered. If vitamin K supplementation fails to improve prothrombin synthesis, severe liver disease is likely. Such patients often present with thrombocytopenia, which may require platelet transfusion. In addition, hypoglycemia may be present, and the anesthesiologist must consider the intraoperative administration of glucose. Proper hydration is essential because the hepatic blood flow is usually decreased in cirrhotic patients. Furthermore, decreases are a result of the anesthetic-induced depression of cardiac output, which may jeopardize the oxygen supply to the liver.

The choice of muscle relaxant is also important. Succinylcholine or mivacurium may be used, although a decreased production of plasma cholinesterase proportionally related to damage of the liver prolongs the effect. Patients with cirrhosis may require larger initial doses of nondepolarizing muscle relaxants because the hepatic blood flow is usually decreased in cirrhotic patients. Hydration is essential because the hepatic blood flow is usually decreased in cirrhotic patients. Furthermore, decreases are a result of the anesthetic-induced depression of cardiac output, which may jeopardize the oxygen supply to the liver. Studies reveal that perfusion and oxygenation of the hepatocytes seem to be well maintained when isoflurane, desflurane (the least metabolized of the inhalation agents), and sevoflurane are used, but not halothane. A recent study in which pulsed Doppler probes were implanted in anesthetized patients demonstrated that halothane acts mainly as a vasoconstrictor in the liver vascular bed. Isoflurane, however, acted as a vasodilator, confirming the advantage of isoflurane for oxygen supply and cardiac output.

The management of the case

The patient was a 54-year-old woman with a history of biopsy proven esophageal varices. She had undergone a spontaneous rupture of the varices 6 months later when her carpal tunnel symptoms increased. Her medical history included chronic obstructive pulmonary disease (COPD) and asthma. She was taking prednisone, inhaled albuterol, and albuterol nebulizer treatments. Her family history was significant for hepatocellular carcinoma.

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Lesson 247: PreAnesthetic Assessment of the Patient With $\alpha_1$-Antitrypsin Deficiency

Post-test

1. The main role of $\alpha_1$-antitrypsin (AAT) is to:
   a. digest damaged and aging cells in lung parenchyma
   b. increase chemotaxis of neutrophils and macrophages into the lung parenchyma
   c. protect the lung tissue from degradation by neutrophil elastase
   d. protect hepatocytes from proteolysis

2. Patients with lung disease related to AAT deficiency exhibit all of the following except:
   a. decreased lung compliance
   b. increased anteroposterior diameter of the chest
   c. hyperinflation of the lungs
   d. ventilation–perfusion abnormalities

3. In the treatment of patients with lung disease related to AAT deficiency, $\alpha_1$-protease inhibitor has been shown to:
   a. reduce the severity and frequency of lung infections
   b. decrease the rate of deterioration of lung function
   c. reduce the mortality associated with AAT deficiency
   d. all of the above

4. The symptoms of children with liver disease related to AAT deficiency may include:
   a. jaundice at birth
   b. nausea and vomiting
   c. problems with nursing
   d. all of the above

5. Which of the following statements is a correct description of the progression of disease in the lungs of patients with AAT deficiency?
   a. The functional residual capacity (FRC) and residual volume (RV) are decreased because of airway collapse and trapping of air, and the total lung capacity (TLC) may be normal to increased.
   b. The FRC and RV are increased because of airway collapse and trapping of air, and the TLC may be normal to increased.
   c. The FRC and RV are increased because of airway collapse and trapping of air, and the TLC may be decreased.
   d. The FRC and RV remain the same, and the TLC may be normal to increased.

6. During preoperative management of the patient:
   a. Pulmonary function tests do not help predict postoperative pulmonary complications, but they can be used to assess the patient’s response to therapy.
   b. Fluid restriction is advised to preserve hepatic function.
   c. Pulmonary function tests are recommended for all patients with chronic obstructive pulmonary disease.
   d. all patients with unexplained lung disease and their families should undergo genetic testing

7. Classic severe deficiency of AAT is associated with which of the following phenotypes?
   a. PiMM
   b. PiZZ
   c. all that exhibit slow migration during starch gel electrophoresis
   d. PiMZ

8. Which of the following statements regarding the epidemiology of AAT deficiency is (are) correct?
   a. The prevalence of the PiZZ phenotype is highest in North America, southern Europe, and central Asia.
   b. Recent evidence has demonstrated that AAT deficiency is much more widespread than previously believed, affecting populations worldwide.
   c. AAT deficiency has been discovered in a variety of populations, including African blacks, Arabs and Jews in the Middle East; Caucasians in Australia, New Zealand, Europe, and North America; and natives of central, eastern, and southeastern Asia.
   d. All of the preceding statements are correct.

9. The most significant risk factor for the development of emphysema in individuals with AAT deficiency is:
   a. male gender
   b. increasing age
   c. previous asthmatic symptoms
   d. smoking

10. In the patient with AAT deficiency, brief periods of smoking cessation:
    a. are of no value
    b. should not be encouraged because the effects of carbon monoxide on oxygenation are transient
    c. indicate that smoke-free intervals of 12 to 18 hours significantly decrease carboxyhemoglobin levels
    d. increase sympatmic activity as the anxiety of the patient increases