CHAPTER 143 ■ OTHER EMBOLIC SYNDROMES (AIR, FAT, AMNIOTIC FLUID)

MURAT SUNGUR • KÜRSAT UZUN

Pulmonary embolism usually results from the mobilization of blood clots from lower extremity or pelvis thromboses. However, embolization of other materials, including air, fat, and amniotic fluid, can also obstruct the pulmonary vessels. While these emboli are uncommon, they are generally associated with clear risk factors or precipitating events. In this chapter, the pathophysiology, clinical course, and treatment of these “other” embolic phenomena are discussed.

GAS EMBOLISM

Gas embolism is defined as the entrance of gas into the vascular compartment. Air and other gases—such as carbon dioxide and nitrogen—may result in gas emboli. The gas may reach any organ, but the most significant damage is to the organs with high oxygen consumption rates, such as brain and heart. Gas embolism can be venous or arterial and, most frequently, it is an iatrogenic problem that may be fatal (1). Hence, prevention of gas embolism is an important patient safety issue that necessitates physician awareness.

Given that, most often, gas embolism is an iatrogenic problem (Table 143.1), the highest-risk surgical procedures for venous air embolism (VAE) are sitting neurosurgical operations, posterior fossa and neck surgery, laparoscopic procedures, total hip arthroplasty, cesarean section, and central venous line procedures—both placement and removal. In addition to these factors, there are numerous case studies reporting emboli during different procedures.

During a neurosurgical procedure in the sitting position, air usually enters through the noncollapsing veins, including the dural venous sinuses and emissary veins (2). While the true incidence of VAE is unknown—because most cases are asymptomatic and the sensitivity of detection methods differs significantly—the incidence is reported to be between 7% and 50% using Doppler detection methodology (3,4). However, one study that used the transesophageal detection method reported an incidence of 76% (5).

Pathophysiology

The severity of gas embolism is related to the volume of gas entering the circulation as well as the rate of gas accumulation. In a neurologic surgery case performed in the sitting position, the volume and rate of air entry are determined by the position of the patient, venous pressure, and height of the vein above the heart. The fatal gas volume in humans is between 200 and 300 mL (7). A patient’s underlying cardiac disease may impact the volume of air necessary for lethality. For example, with underlying impaired cardiac contractility, the volume of air needed to cause cardiac arrest is less than in adults with normal cardiac function (7).

Entry of air into the pulmonary venous system acutely increases pulmonary artery pressure, degrades gas exchange, and provokes cardiac dysrhythmias (8,9). Mean arterial pressure (MAP) decreases rapidly, perhaps secondary to an immediate decrease in cardiac output or due to a reflex mechanism resulting in the release of vasoactive substances (8,9). A “paradoxical” gas embolism can occur in the presence of a right-to-left shunt, such as in a patient with a patent foramen ovale. The term paradoxical is used, as the right-sided pressures need be higher than those on the left side for passage of the gas from the right to the left heart. Right-sided heart pressures may be increased with the application of positive end-expiratory pressure (PEEP), the Valsalva maneuver, and/or a VAE, creating a right-to-left shunt (10).

The lung acts like a filter to prevent gas bubbles from moving through the circulation, but this system can be overwhelmed by a significant load of gas bubbles (11). In animals, it has been noted that at loads of less than 0.13 mL/kg, the lung can totally handle oxygen and nitrogen bubbles, but above this level, gas emboli can transverse the pulmonary bed (11). During mechanical ventilation, depending on the degree of embolization, pulmonary gas embolism impairs pulmonary gas exchange. How far a steady-state phase in gas exchange can be reached during continuous venous gas infusion depends on whether the circulation can adapt; circulation—as well as gas exchange—can become deficient with significant embolization (12). The hypoxemia and hypercapnia that may be seen with gas embolism are primarily related to significant ventilation-to-perfusion inequality (12).

Arterial gas embolism (AGE) is caused by entry of gas into the arterial system. AGE can be caused by venous gas embolism entering the arterial circulation via a right-to-left shunt or directly via the pulmonary capillary bed by overloading of the pulmonary filtering capacity. In compressed air diving, the cause of AGE is pulmonary overpressurization by failing to exhale or due to regional gas trapping during ascent, leading to alveolar rupture and entry of gas into pulmonary capillaries. Iatrogenic causes include accidental air injection during cardiopulmonary bypass or angiography. AGE can also be caused by pulmonary barotrauma during mechanical ventilation (13,14) and, although rare, may be a complication of thoracic trauma and lung surgery (15,16). Gas distribution to the organs is dependent upon their blood flow; gas entering the coronary circulation may result in a typical infarct, while gas
Section XIII: Respiratory Disorders

TABLE 143.1

ETIOLOGY OF GAS EMBOLISM

<table>
<thead>
<tr>
<th>Decompression injury</th>
<th>Vascular entrance of gas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Central line placement and removal</td>
</tr>
<tr>
<td></td>
<td>Arterial catheterization</td>
</tr>
<tr>
<td></td>
<td>Intravascular radiologic procedures</td>
</tr>
<tr>
<td></td>
<td>Intracardiac balloon rupture</td>
</tr>
<tr>
<td></td>
<td>IV fluid administration</td>
</tr>
<tr>
<td></td>
<td>Rapid IV infusion systems</td>
</tr>
<tr>
<td>Gastrointestinal procedures</td>
<td>Gastrointestinal endoscopy</td>
</tr>
<tr>
<td></td>
<td>Laparoscopic surgery</td>
</tr>
<tr>
<td></td>
<td>Endoscopic retrograde cholangiopancreatography</td>
</tr>
<tr>
<td>Neurosurgical procedures</td>
<td>Sitting-position craniotomies</td>
</tr>
<tr>
<td></td>
<td>Posterior fossa surgery</td>
</tr>
<tr>
<td></td>
<td>Cervical laminectomy</td>
</tr>
<tr>
<td></td>
<td>Spinal fusion</td>
</tr>
<tr>
<td></td>
<td>Deep brain stimulator placement</td>
</tr>
<tr>
<td></td>
<td>Lumbar puncture</td>
</tr>
<tr>
<td></td>
<td>Epidural catheter placement</td>
</tr>
<tr>
<td>Neck procedures</td>
<td>Radial neck dissection</td>
</tr>
<tr>
<td></td>
<td>Thyroidectomy</td>
</tr>
<tr>
<td></td>
<td>Nd:YAG laser surgery</td>
</tr>
<tr>
<td>Ophthalmologic procedures</td>
<td>Eye surgery</td>
</tr>
<tr>
<td>Cardiac procedures</td>
<td>Extracorporeal bypass</td>
</tr>
<tr>
<td></td>
<td>Coronary angiography</td>
</tr>
<tr>
<td>Obstetric and gynecologic procedures</td>
<td>Cesarean section</td>
</tr>
<tr>
<td>Orthopedic procedures</td>
<td>Intravaginal, intrauterine gas insufflation during pregnancy</td>
</tr>
<tr>
<td>Urologic procedures</td>
<td>Transurethral prostatectomy</td>
</tr>
<tr>
<td>Thoracic procedures</td>
<td>Liver biopsy</td>
</tr>
<tr>
<td></td>
<td>Lung trauma</td>
</tr>
<tr>
<td></td>
<td>Thoracoscopy</td>
</tr>
<tr>
<td></td>
<td>Chest tube placement</td>
</tr>
</tbody>
</table>

passing into the cerebral circulation may cause an ischemic stroke.

Diagnosis

The most important diagnostic tool is the patient history. If the patient has undergone a high-risk procedure, a high index of suspicion for gas embolism is required. Symptoms have a wide range, depending on the severity of gas embolism and presence of cerebral embolus. The most common symptoms and signs are acute dyspnea and hemodynamic instability. There are numerous nonspecific symptoms and signs including nausea, vomiting, respiratory distress, tachypnea, wheezing, chest tightness, pallor, sweating, tachycardia, bradycardia, hypotension, and sudden cardiac arrest (17–23). Neurologic symptoms may include acute dizziness, unconsciousness, paresis, paraparesis, paraplegia, and/or seizures (17–22). The so-called “mill-wheel murmur” can be auscultated in the precordial area, and is secondary to the presence of air in the cardiac chambers (23). Hemodynamic changes may be the initial signs of gas embolism. Hypotension and an acute increase in pulmonary artery pressure can be observed at early periods of gas embolism (8,9). Central venous pressure may increase, along with a right ventricular pressure increase due to elevated pulmonary artery pressure or air in the right ventricle. The differential diagnosis is very important, as the signs and symptoms of gas embolism are fairly nonspecific (Table 143.2).

Monitoring of end-tidal CO$_2$ (PetCO$_2$) is routinely used in the operating room and is increasingly available for intubated patients in the intensive care unit (ICU). There are case reports of—and animal studies have shown—a sudden and severe drop in PetCO$_2$ values in cases of gas embolism (19,24). A rapid progressive fall in PetCO$_2$ can be a sign of gas embolism in spite of a normal blood pressure. Thus, capnography should be used in both the operating room and ICU whenever air embolism is a risk (25); in our ICUs, the use of capnography is standard. However, a sudden or progressive drop in PetCO$_2$ is not necessarily a specific sign of gas embolism, even if it indicates the potential presence of an important complication, such as pulmonary thromboembolism, pneumothorax, or airway
TABLE 143.2
DIFFERENTIAL DIAGNOSIS OF GAS EMBOLISM

<table>
<thead>
<tr>
<th>Pulmonary embolism</th>
<th>Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Acute bronchospasm</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Stroke</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>Pericardial tamponade</td>
</tr>
<tr>
<td>Shock</td>
<td>Arrhythmias with hemodynamic compromise</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Cardiogenic shock</td>
</tr>
<tr>
<td></td>
<td>Septic shock</td>
</tr>
</tbody>
</table>

Prevention and Treatment

Gas embolism in the ICU is mostly iatrogenic and is preventable in most cases. The effect of patient positioning after suspected VAE is a controversial issue. It was claimed that dogs subjected to air emboli were more tolerant of air infusion, as indicated by measurement of the hemodynamic variables, while lying on their left sides (34). Investigators speculated that the left lateral recumbent (LLR) position placed the right ventricular outflow tract in a position inferior to the right ventricular cavity, allowing the air bolus to migrate superiorly and removing the obstruction to blood flow (34). The Trendelenburg position is also claimed to prevent the gas embolism from occluding the outflow tract by placing the right ventricular cavity in a more superior position (35). However, recent studies that compared different positions in canine models of VAE showed no benefit of LLR and LRR head-down over supine positions (36,37). Moreover, it was claimed that placing patients with suspected VAE in the supine position might afford physiologists a better opportunity to administer supportive therapy, including ventilatory support and oxygen, to establish access for catecholamine delivery and perform cardiopulmonary resuscitation (23). Furthermore, the Trendelenburg position may not decrease the incidence of cerebral microembolism compared to the supine position (38).

Positioning of the patients during central venous line placement and removal is also a matter of debate for the same reasons discussed above. While we recommend following local hospital policy, our practice is to place patients who will have a subclavian or internal jugular venous line inserted in the head-down position. The only situation in which this may not be appropriate is if the patient has elevated intracranial pressure or severely compromised pulmonary function. This policy is also utilized for the removal of central lines. Of course, the placement or removal of femoral venous lines would indicate that the patient be placed in reverse Trendelenburg. Placement or removal of central venous lines (CVLs) should essentially never be done while the patient is in a sitting position.

Patients should be observed when in Trendelenburg position for signs of respiratory distress and anxiety. Spontaneously breathing patients may have a higher risk of VAE compared to mechanically ventilated patients because of negative intrathoracic pressures during inspiration. If cooperative, the patient may be asked to perform a Valsalva maneuver (i.e., breath holding during expiration and humming), which can increase venous pressure (39). Air embolism after catheter removal through the residual tract has also been reported many times in the literature (40,41); thus, proper maintenance of the entrance site should be performed. VAE via a disconnected line or fractured catheter hub may also occur, and maximum attention should be paid to prevent this possibility.

Carbon dioxide (CO₂) embolism can occur during laparoscopic surgery. Most commonly, CO₂ embolism occurs when a pneumoperitoneum is created through a tear in a vessel in the abdominal wall or peritoneum (42). If CO₂ embolism is suspected, insufflation of the gas should be discontinued. The application of PEEP is not helpful in preventing air embolism during sitting-position craniotomies; furthermore, it may be harmful (2). Low central venous pressure may increase the negative pressure gradient between the atrium and wound site and, thus, the risk for VAE. Increasing central venous pressure to upper normal limits can decrease the risk for VAE (2). Aggressive resuscitation and cardiopulmonary resuscitation (CPR) should be started immediately following the collapse of the patient. Aggressive volume resuscitation is recommended to increase right atrial pressure, which can prevent further air entry into the venous circulation (23). High-concentration oxygen (100%) maximizes oxygenation of the patient and can also decrease the volume of the embolus via elimination of the obstruction. In the nonintubated patient, PetCO₂ monitoring is neither easy nor routine.

Pulse oximetry is a standard of care for procedures performed in the operating room as well as for ICU patients. A sudden drop in arterial oxygen saturation is a very common finding of gas embolism and typically indicates a severe disturbance of pulmonary function (21,26). Simple chest radiography can also show air in the vascular compartments and heart (1). Electrocardiographic (ECG) changes may be observed related to myocardial ischemia. Often, the first change noted is peaking of the P wave; S-T segment depression can follow peaking of P wave, depending on the severity of gas embolism (27). Hemoconcentration, possibly related to a shift of intravascular composition for signs of respiratory distress and anxiety. Spontaneously breathing patients may have a higher risk of VAE compared to mechanically ventilated patients because of negative intrathoracic pressures during inspiration. If cooperative, the patient may be asked to perform a Valsalva maneuver (i.e., breath holding during expiration and humming), which can increase venous pressure (39). Air embolism after catheter removal through the residual tract has also been reported many times in the literature (40,41); thus, proper maintenance of the entrance site should be performed. VAE via a disconnected line or fractured catheter hub may also occur, and maximum attention should be paid to prevent this possibility.

Carbon dioxide (CO₂) embolism can occur during laparoscopic surgery. Most commonly, CO₂ embolism occurs when a pneumoperitoneum is created through a tear in a vessel in the abdominal wall or peritoneum (42). If CO₂ embolism is suspected, insufflation of the gas should be discontinued. The application of PEEP is not helpful in preventing air embolism during sitting-position craniotomies; furthermore, it may be harmful (2). Low central venous pressure may increase the negative pressure gradient between the atrium and wound site and, thus, the risk for VAE. Increasing central venous pressure to upper normal limits can decrease the risk for VAE (2). Aggressive resuscitation and cardiopulmonary resuscitation (CPR) should be started immediately following the collapse of the patient. Aggressive volume resuscitation is recommended to increase right atrial pressure, which can prevent further air entry into the venous circulation (23). High-concentration oxygen (100%) maximizes oxygenation of the patient and can also decrease the volume of the embolus via elimination of the obstruction. In the nonintubated patient, PetCO₂ monitoring is neither easy nor routine.

Pulse oximetry is a standard of care for procedures performed in the operating room as well as for ICU patients. A sudden drop in arterial oxygen saturation is a very common finding of gas embolism and typically indicates a severe disturbance of pulmonary function (21,26). Simple chest radiography can also show air in the vascular compartments and heart (1). Electrocardiographic (ECG) changes may be observed related to myocardial ischemia. Often, the first change noted is peaking of the P wave; S-T segment depression can follow peaking of P wave, depending on the severity of gas embolism (27). Hemoconcentration, possibly related to a shift of intravascular composition for signs of respiratory distress and anxiety. Spontaneously breathing patients may have a higher risk of VAE compared to mechanically ventilated patients because of negative intrathoracic pressures during inspiration. If cooperative, the patient may be asked to perform a Valsalva maneuver (i.e., breath holding during expiration and humming), which can increase venous pressure (39). Air embolism after catheter removal through the residual tract has also been reported many times in the literature (40,41); thus, proper maintenance of the entrance site should be performed. VAE via a disconnected line or fractured catheter hub may also occur, and maximum attention should be paid to prevent this possibility.

Carbon dioxide (CO₂) embolism can occur during laparoscopic surgery. Most commonly, CO₂ embolism occurs when a pneumoperitoneum is created through a tear in a vessel in the abdominal wall or peritoneum (42). If CO₂ embolism is suspected, insufflation of the gas should be discontinued. The application of PEEP is not helpful in preventing air embolism during sitting-position craniotomies; furthermore, it may be harmful (2). Low central venous pressure may increase the negative pressure gradient between the atrium and wound site and, thus, the risk for VAE. Increasing central venous pressure to upper normal limits can decrease the risk for VAE (2). Aggressive resuscitation and cardiopulmonary resuscitation (CPR) should be started immediately following the collapse of the patient. Aggressive volume resuscitation is recommended to increase right atrial pressure, which can prevent further air entry into the venous circulation (23). High-concentration oxygen (100%) maximizes oxygenation of the patient and can also decrease the volume of the embolus via elimination of the obstruction. In the nonintubated patient, PetCO₂ monitoring is neither easy nor routine.

Pulse oximetry is a standard of care for procedures performed in the operating room as well as for ICU patients. A sudden drop in arterial oxygen saturation is a very common finding of gas embolism and typically indicates a severe disturbance of pulmonary function (21,26). Simple chest radiography can also show air in the vascular compartments and heart (1). Electrocardiographic (ECG) changes may be observed related to myocardial ischemia. Often, the first change noted is peaking of the P wave; S-T segment depression can follow peaking of P wave, depending on the severity of gas embolism (27). Hemoconcentration, possibly related to a shift of intravascular composition for signs of respiratory distress and anxiety. Spontaneously breathing patients may have a higher risk of VAE compared to mechanically ventilated patients because of negative intrathoracic pressures during inspiration. If cooperative, the patient may be asked to perform a Valsalva maneuver (i.e., breath holding during expiration and humming), which can increase venous pressure (39). Air embolism after catheter removal through the residual tract has also been reported many times in the literature (40,41); thus, proper maintenance of the entrance site should be performed. VAE via a disconnected line or fractured catheter hub may also occur, and maximum attention should be paid to prevent this possibility.

Carbon dioxide (CO₂) embolism can occur during laparoscopic surgery. Most commonly, CO₂ embolism occurs when a pneumoperitoneum is created through a tear in a vessel in the abdominal wall or peritoneum (42). If CO₂ embolism is suspected, insufflation of the gas should be discontinued. The application of PEEP is not helpful in preventing air embolism during sitting-position craniotomies; furthermore, it may be harmful (2). Low central venous pressure may increase the negative pressure gradient between the atrium and wound site and, thus, the risk for VAE. Increasing central venous pressure to upper normal limits can decrease the risk for VAE (2). Aggressive resuscitation and cardiopulmonary resuscitation (CPR) should be started immediately following the collapse of the patient. Aggressive volume resuscitation is recommended to increase right atrial pressure, which can prevent further air entry into the venous circulation (23). High-concentration oxygen (100%) maximizes oxygenation of the patient and can also decrease the volume of the embolus via elimination of the obstruction. In the nonintubated patient, PetCO₂ monitoring is neither easy nor routine.
Tachycardia \( < 120 \text{ beats/min} \) and tachypnea \( > 30 \text{ breaths/min} \) are the most common early symptoms of FES. The diagnosis of FES requires the presence of one major and four minor criteria according to Gurd’s study (58). The clinical features of FES are divided into major and minor features (Table 143.3). The diagnosis of fat embolism syndrome requires the presence of one major and four minor criteria according to Gurd and Haedinger’s study (58). A fat embolism index score has also been defined by Schoenfeld et al. for predetermined and designated clinical signs and symptoms (59) (Table 143.4). A score of 5 or more is diagnostic of FES, and negative if less than 5.

**Epidemiology**

It is difficult to estimate the true incidence of fat embolism, as there is no universal definition, and many cases with fat embolism may not develop FES. The true incidence of FES is probably higher than the reported rates—19% in patients with major trauma (60). The occurrence of fat embolism in autopsy reports in trauma patients ranges between 52% and 96% (61–63), whereas only 1% to 5% of patients develop FES (64). The incidence of FES related to femoral shaft fractures has been

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petechial rash</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Respiratory symptoms and bilateral infiltrates on chest radiograph</td>
<td>Fever</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>Retinal fat or petechia</td>
</tr>
<tr>
<td>Anuria, oliguria, fat globules in urine</td>
<td>Sudden drop in hemoglobin level</td>
</tr>
<tr>
<td>Sudden thrombocytopenia</td>
<td>High erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>Fat globules in sputum</td>
<td></td>
</tr>
</tbody>
</table>

**Fat Embolism Index Score**

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petechiae</td>
<td>5</td>
</tr>
<tr>
<td>Diffuse alveolar infiltrates</td>
<td>4</td>
</tr>
<tr>
<td>Hypoxemia (( \text{PaO}_2 &lt; 70 \text{ mm Hg} ))</td>
<td>3</td>
</tr>
<tr>
<td>Confusion</td>
<td>1</td>
</tr>
<tr>
<td>Fever ( \geq 38.5^\circ \text{C} )</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia ( \geq 120 \text{ beats/min} )</td>
<td>1</td>
</tr>
<tr>
<td>Tachypnea ( \geq 30 \text{ breaths/min} )</td>
<td>1</td>
</tr>
</tbody>
</table>

A positive fat embolism syndrome score is \( \geq 5 \) points.
Pathophysiology

The two explanations of the pathophysiologic mechanisms of FES are the mechanical and the biochemical theories; in fact, they are likely intimately related.

When bones fracture, or their medullary channel is manipulated or pressurized, fat cells are disrupted and enter the venous circulation. Large fat globules and spongosia bone fragments can obstruct the pulmonary capillaries. Smaller fat globules bypass the pulmonary circulation and enter the systemic circulation. Major systemic emboli can occur with migration of fat globules through the pulmonary capillary circuit (81,82). As previously mentioned, in the presence of an intracardiac defect—such as a PFO, seen in 20% to 30% of the population—there can be direct access of fat particles to the systemic circulation.

Bone marrow fragments have been seen in autopsy specimens of lung tissue from trauma patients (85) and in lung biopsies from similar trauma populations (86). The highest number of obstructed capillaries is seen after 24 hours of the initial injury, and vascular congestion and pulmonary edema follow the obstruction of capillaries (87,88). The amount of fat is an important indicator for the emergence of a full-blown FES because, as the number of fractures increases, the risk for FES does so as well. Mechanical obstruction of the pulmonary artery with fat may be an important reason for immediate death after trauma (82), and obstruction of the cerebral capillaries may be the cause of the altered mental status observed in FES. Petechial hemorrhages may be secondary to the presence of fat emboli in the subcutaneous capillaries.

Manipulation of the bone medulla during surgery increases intramedullary pressure, which normally ranges between 30 and 50 mm Hg. In animal models, if intramedullary pressure increases to 300 to 400 mm Hg, even when the bone is intact, venous blood shows large fat emboli (89); this effect is also observed in patients undergoing long bone surgery (90). According to the biochemical theory, increased levels of free fatty acids (FFAs) after bone fracture or manipulation have a direct toxic effect on pneumocytes. These FFAs either be freely moving in the circulation or accumulate in pulmonary capillaries. Capillary leakage, clot formation, and platelet adhesion resulting from the toxic effects of FFAs lead to organ damage. It is thought that lipase released from pneumocytes breaks down bone marrow fat to glycerol and free fatty acids, the latter in toxic concentrations. FFA damage to the pulmonary endothelium results in capillary damage and nonhydrostatic pulmonary edema (64,91,92).

The role of polyphosphonacetal neutrophils (PMNLs) in FES is not clear. Intravenous injection of fat may result in accumulation of PMNLs in the pulmonary capillaries (87). Lung tissue damage, as well as neutrophil and platelet activation, leads to the release of vasoactive substances such as histamine, serotonin, and bradykinin. The result is inflammation and edema, with resultant respiratory distress and multiorgan system failure (93). Orthopedic surgery has a greater influence on the coagulation system than does general surgery. Manipulation of bone, with resultant fat embolism, is the reason for the hypercoagulable state seen after orthopedic surgery. This includes increased platelet aggregation (94) and tissue factor release, both of which stimulate the coagulation system (94) and result in capillary clot formation in the pulmonary circulation; activation of monocytes induces pericellular fibrin deposition, which further increases the hypercoagulable state (95,96).

NO, phospholipase (PL)-A\(_2\), \(\text{O}_2^-\) free radicals, and proinflammatory cytokines such as tumor necrosis factor (TNF)-\(\alpha\), interleukin (IL)-1\(\beta\), and IL-10 play a role in the pathogenesis of FES-induced acute respiratory distress syndrome (ARDS). Alveolar macrophages are probably the major source of inducible NO synthase, producing NO in the lung (97).

Neurologic signs of FES likely occur via several mechanisms, including cerebral blood vessel occlusion by fat emboli, disruption of the blood-brain barrier due to toxic FFAs, and obstruction due to alteration in the solubility of fat in blood (98,99).

Clinical Presentation and Diagnosis

Unfortunately, there is no universal definition for FES. The diagnosis of FES requires a high index of suspicion in the proper setting, and is a diagnosis of exclusion. The severity of symptoms and signs depends on the size of the fat emboli. The classical triad for fat embolism includes respiratory insufficiency, altered mental status, and upper extremity and thoracic paresthesia; unfortunately, all three are seldom seen together. The most commonly used criteria for FES were defined by Guard et al. (58). According to these criteria, there are major and minor signs and symptoms. At least one major and four minor criteria are required for the diagnosis of FES (Table 143.3) (58). Clinical signs do not usually appear within 12 hours after the injury, and the major signs appear within 24 hours in 65% and within 48 hours in 83% of patients (56).
The most common signs and symptoms of FES are hypoxia, fever, tachycardia, anemia, and altered mental status (66). Early fever, with a fever of 38.5°C, is a common sign and may be seen at presentation to the emergency department (56). In trauma patients with fractures, early fever should provoke a suspicion of fat embolism. Petechiae are very important findings, but only present in one third of patients (66); microscopic examination of petechiae reveal fat droplets obstructing capillaries (56).

Respiratory involvement is the most common feature, with tachypnea, dyspnea, and bilateral diffuse infiltrates evident on chest radiograph (61). Cyanosis can be observed if hypoxia is significant, but anemia along with FES can prevent the occurrence of cyanosis even with significant hypoxia. The PaO2 initially decreases secondary to hyperventilation; however, if pulmonary deterioration continues, it may rise. Chest radiography shows diffuse bilateral pulmonary infiltrates; 70% of the patients demonstrate chest radiographic changes no later than 48 hours—and usually within 24 hours—after injury (100).

The early clinical signs of FES are actually the signs of SIRS. The clinical presentation of FES is also very similar to ARDS with multiple organ failure. Thus, in the presence of multiple injuries, the clinicopathologic features of FES and acute lung injury (ALI)/ARDS overlap to such an extent that absolute distinction is usually not possible (101).

With FES, cardiac output can decrease, and ventilation–perfusion mismatch will occur (102). Hemodynamic compromise secondary to fat embolism can be severe enough to cause cardiac arrest (103). Pulmonary artery pressure increases after femoral and tibial pressurization, and fat globules can be seen in the lungs, kidneys, and brain parenchyma (89). Blood drawn from the right atrium or pulmonary artery may show fat globules; however, fat droplets in plasma can be observed in more than half of trauma patients without FES (104,105). A retinal exam may reveal exudates, hemorrhages, and, rarely, fat globules (58).

High-resolution chest computed tomography (CT) scan findings of FES include ground-glass opacities, which may be associated with thickened interlobular septa. A patchy distribution resulting in a “geographic” appearance, which represents the existence of normal and abnormal lung areas with sharp borders and nodular patterns, can also be observed. Resolution of the abnormalities occurs within 2 weeks (105).

Cerebral manifestations can occur with a wide range of symptoms ranging from confusion, drowsiness, and lethargy to convulsions and coma (106–109). Pulmonary contusion along with long bone fractures may increase the risk for cerebral fat embolism (110).

Typically in FES, a cerebral CT scan reveals no abnormalities, even in patients with neurologic symptoms (111). Cerebral magnetic resonance imaging (MRI) may demonstrate hypointense lesions, disruption of the blood-brain barrier, and multiple diffuse foci of hyperintensity in the white matter of the subcortical, periventricular, and centrum semiovale regions, as well as changes related to vasogenic edema, peritumoral hemorrhages, or hemorrhagic infarcts involving gray and white matter ranging in size from a few millimeters to several centimeters (112,113). Transcranial Doppler study in trauma patients with long bone fractures can detect cerebral fat embolism (114).

Identification of fat droplets within cells recovered with bronchoalveolar lavage is another diagnostic tool that may be used. However, such findings are also frequently observed in trauma patients without FES (115,116).

### Treatment

As there is no specific treatment for FES, therapy is mostly supportive. The general goals for hypoxic respiratory failure should be instituted for presumed FES. Methyldiphenidolone given prophylactically may reduce the incidence of FES and can reduce the degree of hypoxemia associated with long bone fractures of the lower extremity (117,118). High-dose prophylactic steroids with aspirin can result in significant normalization of blood gases, coagulation proteins, and platelet numbers; however, prophylactic steroids did not improve mortality in any of the studies. Fluid loading, which dilutes the amount of free fatty acids, or increased glucose intake, which decreases free fatty acid mobilization, has not been found to be helpful (117,119).

FES may lead to cerebral edema and increased intracranial pressure (ICP) and, if there are signs of cerebral edema, intracranial pressure monitoring is recommended (120). Sedation and analgesia should be appropriately titrated to allow for frequent neurologic examinations of the patient. Ethanol with its antitilipolytic effect has also been studied, but did not show any benefit in the prevention of fat embolism (121).

Early fixation of long bone fractures can be helpful to prevent the occurrence of FES. However, it should be kept in mind that, in addition to fat embolization from the initial trauma, long bone fixation may result in additional embolizations and FES (122). Delayed stabilization of the fracture in the patient with multiple injuries increases the incidence of pulmonary complications (ARDS, fat embolism, and pneumonia), as well as the hospital and ICU stay. The cost of hospital care also significantly increases for patients who had delayed treatment of the fractures compared with those who were stabilized early (123,124). Early femur fracture fixation in patients with chest and head trauma is associated with an improved outcome (125).

Increased intramedullary pressure increases the risk of fat embolism. Reaming before nailing the femur was considered as a possible way to prevent this effect, although the reaming procedure itself increases intramedullary pressure. Reaming before femoral nail insertion did not decrease fat embolism compared to the unreamed technique (126).

### AMNIOTIC FLUID EMBOLISM

Ricardo Meyer first described the entry of amniotic fluid into the maternal circulation in 1926 (127). However, amniotic fluid embolism (AFE) was not recognized as a syndrome until Steiner and Laschbaugh's study in 1941. They reported a sudden death of a woman during labor with fetal mucin, amorphous eosinophilic material, and squamous cells in pulmonary vessels (128).

Amniotic fluid embolism is an uncommon and catastrophic syndrome that occurs during pregnancy or shortly after delivery. Although the pathophysiology was thought to involve the embolization of amniotic fluid, investigations showed that the syndrome results from biochemical mediators released after the embolization occurs (129). It has been suggested that the syndrome be renamed as the “anaphylactoid syndrome of pregnancy” because of similarities among the characteristics of AFE, septic shock, and anaphylactic shock (130).

Amniotic fluid embolism is an important cause of maternal death in developed countries, with a high morbidity and...
mortality rate. The associated mortality and morbidity has dramatically decreased to approximately 16% in recent years (131). The decline in mortality may be due to improved recognition of the disorder, so that even mild cases are included in the analysis, as well as to improvements in resuscitation.

**Epidemiology**

While the true incidence is not known because of inaccuracies in reporting maternal deaths, lack of data from mild cases, and the fact that AFE is difficult to identify and remains a diagnosis of exclusion, AFE is thought to account for up to 10% of all maternal deaths in the United States (130,132). The UK AFE registry investigated maternal and fetal morbidity and mortality rates between 1997 and 2004. In this registry, the data of 44 women with AFE were studied. The maternal death rate was 29.5% (13 patients) (133). The incidence of pulmonary emboli (PE) cases associated with pregnancy and/or delivery was 0.8% of the total PE cases in Japan. Among them, AFE was found in 73.3% (35 of 45) of the PE cases with vaginal delivery and in 21.2% (7 of 33) of PE cases with cesarean delivery (134). AFE was identified in 19 patients between 1971 and 1988 in Swedish studies (135,136). AFE occurred during labor in 70% of the women, after vaginal delivery in 11%, and during cesarean section in 19%. Kramer et al. (137) conducted an epidemiologic study evaluating the relationship between AFE and the medical induction of labor for the Maternal Health Study Group of the Canadian Perinatal Surveillance System between 1991 and 2002. In this study, the total rate of AFE was 14.8 per 100,000 deliveries and 6.0 per 100,000 singleton deliveries. The mortality rate was 0.8 per 100,000 singleton deliveries, but none was fatal in multiple deliveries (137). Gilbert and Danilens (138) investigated 1,094,248 deliveries during 5 years of pregnancy and delivery, or in the immediate postpartum period. AFE can also develop 4 to 48 hours postpartum or after cesarean delivery, and are now thought to be the most likely entry site (139). AFE was identified in 19 patients between 1971 and 1988 in Sweden (135,136). In this study, the total rate of AFE was 14.8 per 100,000 deliveries and 6.0 per 100,000 singleton deliveries. The mortality rate was 0.8 per 100,000 singleton deliveries, but none was fatal in multiple deliveries (137). Gilbert and Danilens (138) investigated 1,094,248 deliveries during a 2-year period. Fifty-three singleton pregnancies had the diagnosis of AFE, for a population frequency of 1 per 20,046 pregnancies. Burrows and Khoo (139) published a series of ten cases of AFE with a maternal mortality rate of 22%; neonatal survival rate was 95% and routine discharge was reported as 72% in this study (139).

**Pathophysiology**

The pathophysiology of AFE remains unclear. Uterine contractions during normal labor force amniotic fluid into the maternal venous circulation through small tears in the lower uterine segment or high endocardial canal (139). In order for AFE to occur, there must be a pressure gradient favoring the entry of amniotic fluid from the uterus into the maternal circulation, as well as ruptured membranes. Small tears in the lower uterine segment and endocardiac are common during labor and delivery, and are now thought to be the most likely entry site (140). Two separate life-threatening processes seem to occur either simultaneously or in sequence: cardiopulmonary collapse and coagulopathy.

**Cardiorespiratory Collapse**

The conventional explanation states that particulate matter such as fetal squamous cells, lanugo, and meconium contained in the amniotic fluid produce pulmonary vascular obstruction, leading to pulmonary hypertension, right- and left-sided heart failure, hypotension, and death. However, current evidence suggests that a mechanical origin is less likely than an immunologic reaction. In this model, pulmonary vasospasm causes physiologic pulmonary artery obstruction as a reaction to abnormal substances such as leukotrienes and metabolites of arachidonic acid in the amniotic fluid (141). Arachidonic acid metabolites have been implicated in the inflammatory response, and may in part be responsible for AFE. The presence of these metabolites in AFE suggests a possible humoral mechanism.

Humoral pathways involving a proinflammatory response with release of cytokines and arachidonic acid metabolites in AFE, anaphylaxis, and shock may be responsible for the similar clinical presentation. This complex inflammatory cascade with mediator release will lead to a systemic inflammatory response and the development of multiple organ system failure (142). Mild to moderate elevations in pulmonary artery pressures are only transiently noted in AFE (143). In an attempt to reconcile clinical and experimental findings, a biphasic model is proposed to explain the hemodynamic abnormalities that occur with amniotic fluid emboli (144). Acute pulmonary hypertension and vasospasm may be the initial hemodynamic response. The resulting right heart failure and accompanying hypoxia could account for the cases of sudden death or severe neurologic impairment. The limited hemodynamic data obtained by invasive pulmonary artery monitoring or echocardiography during the hyperacute phase of AFE demonstrated left ventricular failure as the dominant finding (144). Myocardial dysfunction may be the result of a sudden increase in maternal plasma endothelin levels that occurs with the introduction of amniotic fluid, which contains a high concentration of endothelin (145).

**Disseminated Intravascular Coagulation**

Disseminated intravascular coagulation (DIC), commonly observed as a late sequela, may be attributed to antithrombin- or thromboplastin-type effects of amniotic fluid or even complement activators. Amniotic fluid has highly potent, total thromboplastin-type effects of amniotic fluid or even complement activators. Amniotic fluid has highly potent, antifibrinolytic activity, which causes nonspecific reaction that usually occurs in DIC patients. The secondary fibrinolytic response seen in DIC patients. The secondary fibrinolytic response may predispose a patient to DIC and diffuse thrombosis by inhibiting or dampening the usual secondary fibrinolytic response seen in DIC patients. The secondary fibrinolytic response that usually occurs in DIC is responsible for hemorrhage due to plasma in digestion of numerous clotting factors; however, this secondary fibrinolytic response also serves to keep the circulation free of thrombi (146).

**Clinical Presentation**

The symptoms of AFE commonly occur during labor (80%) and delivery, or in the immediate postpartum period. AFE can also develop 4 to 48 hours postpartum or after cesarean delivery, amnioncensis, or removal of the placenta, or with first- and second-trimester abortions (147-150). The risk factors associated for AFE are older age, multiparity, marked exaggeration of uterine contraction following rupture of the uterine membranes, or markedly exaggerated uterine contraction due to the use of oxytocin or other uterine stimulatory agents, prolonged
Phase 1: Pulmonary—Respiratory distress and cyanosis
Phase 2: Hemodynamic—Pulmonary edema and hemorrhagic shock
Phase 3: Neurologic—Confusion and coma

These manifestations can occur in combination, separately, and in different magnitudes. If patients survive the initial cardiorespiratory insult, 40% to 50% progress into phase 2, which is characterized by coagulopathy, hemorrhage, and shock. In phase 2, left-sided heart failure is evident and is the most reported sign in humans. Increased pulmonary capillary wedge pressure and central venous pressure are characteristics of pulmonary edema. In phase 3, acute symptoms disappear, and injury to the brain, lung, and renal systems is noted. Phase 3 may last weeks, and patients may die as a result of severe brain and lung injury; infection and multiple organ system failure may also cause death (159).

**Diagnosis**

AFE is largely a diagnosis of exclusion. The differential diagnosis includes air or thrombotic pulmonary emboli, septic shock, acute myocardial infarction, cardiomyopathy, anaphylaxis, aspiration, placental abruptio, eclampsia, uterine rupture, transfusion reaction, and local anesthetic toxicity (161). The diagnosis of amniotic fluid embolism should be considered when a pregnant woman with one or more risk factors suddenly develops respiratory distress, bleeding, or shock. Several methods have been suggested for diagnosing amniotic fluid embolism, but none of these diagnostic tests is reliable (162).

The initial presenting signs are often seen on the ECG and the pulse oximeter. The former may show tachycardia with a right-heart strain pattern and ST–T–wave changes; pulse oximetry may reveal a sudden drop in oxygen saturation (163). The clinical diagnosis is made most frequently in 65% to 70% of cases during labor and much less frequently in 11% of cases in the postpartum period (160). Initial laboratory data should include an arterial blood gas analysis to determine the adequacy of ventilation and degree of hypoxia (160). Diagnostic markers for amniotic fluid embolism based on peripheral blood samples have also been introduced. These include sialyl Tn (STN), a mucin-associated sialylated carbohydrate antigen carried by apomucins, zinc coproporphyrin, and complement factor consumption (164,165). Significantly higher serum STN levels were found in patients with clinically apparent AFE (166). It has been demonstrated that the monoclonal antibody THK–2, an antibody directed to STN, may be a specific pathologic marker for amniotic fluid embolism (166,167). Fetal megakaryocytes and syncytiotrophoblastic cells can be found in maternal pulmonary circulation by monoclonal antibodies (CD-61—GPIIIa, β-hCG, and factor VIII–vWF antibodies) and may be diagnostic (168). Laboratory tests to evaluate the development of DIC are the anti-thrombin III level, fibrinopeptide A level, D-dimer level, prothrombin fragment 1.2 (PF 1.2); thrombin precursor protein, and platelet count. More global tests, including the prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen level, are helpful (146).
When correlated with clinical signs and symptoms, other diagnostic tools may be employed to support the presumptive diagnosis of AFE. Echocardiography may show severe pulmonary hypertension and right ventricular dilatation, with a displaced intraventricular septum pressing on the left ventricle (169). TEE may show right ventricular failure with leftward deviation of the interventricular septum and severe tricuspid regurgitation (170). Chest radiography is a helpful diagnostic tool, but it is limited by a lack of specificity. In mothers with AFI, 24% to 93% of chest radiographs show a pulmonary edema pattern (171); however, multiple patchy, nodular infiltrates and small pleural effusion may also be seen (169).

Histologic examination demonstrates foreign material in the pulmonary capillaries, arterioles, and arteries (172). Special stains such as TRH-2, a monoclonal antibody to fetal gycoprotein sulhydryl TN antigen, have been applied to pathologic specimens (172).

Treatment

Treatment is supportive. Despite the decline in mortality, no new therapies have emerged. Aggressive resuscitation may be indicated depending on the clinical presentation. Management strategies include improving oxygenation, support of circulation, and correcting coagulopathy. Arterial and pulmonary artery catheters should be placed to help guide the therapy when hemodynamic deterioration is severe (173). If the fetus is sufficiently mature and is undelivered at the time of maternal cardiac arrest, cesarean section should be instituted as soon as possible (145). Maternal oxygenation up to an arterial oxygen tension of more than 60 mm Hg should be achieved by administering oxygen via a face mask to all nonanesthetised patients. Mechanical ventilation and ventilator support should be instituted in patients with refractory hypoxemia or seizures, or in the comatose individual (174). Vasoactive drug therapy must be tailored to the clinical situation. Dopamine is suggested to enhance cardiac output and support blood pressure, although in severe shock, epinephrine or norepinephrine may be required (175).

In less than 4 hours, half of the patients who survive develop DIC, with massive hemorrhage (128). Therefore, blood products should be prepared ahead of time, and replacement with typed and crossed packed red blood cells, or with O-negative blood, is essential (176). Treatment of DIC requires the transfusion of packed red blood cells and blood products. Large-bore IV access is essential because massive transfusion may be required (177). Platelets, cryoprecipitate, and fresh frozen plasma should be administered as guided by laboratory assessment of the thromboelastogram (TEG) or international normalized ratio (INR)/PT/PTT, fibrinogen, and fibrin and fibrin degradation products. Plasma exchange, cardiopulmonary bypass, aprotinin, and recombinant activated factor VII (rVIIa) in the management of the associated coagulopathy are used to treat AFE (178–180). The successful use of uterine arterial embolization to control massive bleeding in two cases of AFE has been described (181). During cardiopulmonary resuscitation and chest compressions, and before delivery, the uterus should be displaced to the left to avoid compressing of the aorta and inferior vena cava which would compromise maternal venous return to the heart. The uterus can be displaced manually or by placing a wedge under the patient’s right hip (160).

Prognosis

AFE remains one of the most feared and lethal complications of pregnancy. The prognosis and mortality of AFE have improved significantly with early diagnosis and prompt and early resuscitative measures. A parturient with a known history of atopy or anaphylaxis is also at a high risk of AFE (182). In the National Amniotic Fluid Embolism Registry, a known history of drug allergy and atopy was found in 41% of the 46 patients with AFE (180). The mortality of a successful outcome remains the identification of high-risk patients. In some cases, death is inevitable despite early and appropriate management. Neonatal survival is reported as 70%. Although there are many new developments with respect to our knowledge of the diseases, AFE continues to be a catastrophic illness.

SUMMARY

The entry of gas into the arterial or venous system has severe clinical consequences, including death. Gas embolism is mostly an iatrogenic problem, which can be prevented most of the time. Inadvertent entry of air is the major cause of gas embolism, although medical gases such as carbon dioxide, nitrogen, and helium can be responsible. Optimal patient positioning during procedures is the mainstay of the prevention strategies for gas embolism. Hospital-wide protocols for central line placement and removal are of the utmost importance. Aggressive volume resuscitation, administration of 100% oxygen, suctioning of gas from the right side of the heart, and avoiding further entry of gas into the circulation are essential for treating and preventing venous gas embolism. Further measures include transfer of the patient to the critical care unit, vasopressor treatment, and mechanical ventilatory support. Hyperbaric oxygen administration after initial stabilization of the patient with cerebral arterial gas embolism should be performed, if available.

Fat embolism syndrome frequently occurs in trauma patients. Making the diagnosis is rather difficult, and criteria have remained unchanged for the last three decades. Fat embolism becomes clinically apparent with classic signs of respiratory failure, petechial rash, and fever. Treatment is mainly supportive. Early fracture fixation and modern critical care should help minimize the impact of fat embolism. The cornerstone of treatment is preventing hypovolemia and hypoxia, followed by operative stabilization of fractures. Further studies are required to improve our ability to diagnose and treat FES.

AFE is a catastrophic complication, which can lead to death. The etiology and pathophysiology of AFE remain unclear despite many new research developments. A high index of suspicion is required for diagnosis, which remains rare of exclusion. Right heart failure that progresses to left heart dysfunction, rapidly developing pulmonary edema, neurologic symptoms, and hematologic abnormalities are the main clinical features of AFE; aggressive supportive treatment should be performed. DIC is a very frequent complication of AFE. Blood and blood products should be prepared in advance for potential major hemorrhages. Tracheal intubation and mechanical ventilation should be instituted in patients with refractory hypoxemia or seizures.
Reference

Chapter 143: Other Embolic Syndromes (Air, Fat, Amniotic Fluid)


133. Treharre DJ, Uran’s Kingdom, a rare case of auto-immune hemolytic anemia. BJOG. 2005;112:1624–1629.


