62-Year-Old Woman With Acute Hypotension and Hypoxia After Surgical Repair of Hip

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A 62-year-old woman presented to the emergency department after a mechanical fall onto her left hip. She had been in her usual state of health earlier that day, but after the fall she experienced intractable leg pain and was unable to bear weight on her left hip. She reported no chest pain, dyspnea, palpitations, light-headedness, or dizziness before the event. Her medical history was notable for hypertension and nicotine and alcohol dependence. Her initial physical examination revealed evidence of severe left hip tenderness and pain with motion. The remainder of her examination findings were unremarkable. Radiography of the left hip revealed a left intertrochanteric hip fracture with minimal displacement. She underwent prompt surgical repair with internal fixation using a cephalomedullary nail. The patient tolerated the procedure well with no complications and minimal blood loss. Postoperatively, she received deep venous thrombosis prophylaxis with subcutaneous heparin. Her pain subsided considerably after the operation.

At 36 hours postoperatively, the patient experienced sudden shortness of breath with severe respiratory distress. On examination, she was somnolent and had a blood pressure of 90/54 mm Hg and a heart rate of 131 beats/min. She was tachypneic (respiratory rate, 20 breaths/min) and hypoxic (oxygen saturation, 90% with a face mask delivering 40% fraction of inspired oxygen). The patient was afebrile and drowsy but was able to follow commands. Cardiac examination revealed a right ventricular (RV) precordial heave, elevated jugular venous pressure, and cool extremities with a weakly palpable pulse. Auscultation identified a right-sided third heart sound but no murmurs. Lung examination revealed diffuse bilateral crackles but no decreased breath sounds at the base or dullness to percussion suggestive of a pleural effusion. She had bilateral mild pitting edema on the lower extremities, with slightly more on the left than on the right.

Laboratory results included the following (reference ranges provided parenthetically): hemoglobin, 7.8 g/dL (12.0-15.5 g/dL) with a mean corpuscular volume of 116.6 fL (81.6-98.3 fL); leukocyte count, 8.5 $\times$ 10^9/L (3.5-10.5 $\times$ 10^9/L); and creatinine, 0.5 mg/dL (0.6-1.1 mg/dL). The troponin T level was mildly elevated at 0.02 ng/mL (<0.01 ng/mL), without a notable change on repeated measurement. Extensive bilateral infiltrates and decreased lung volumes were noted on chest radiography. Electrocardiography revealed sinus tachycardia with low voltage and nonspecific ST-T wave changes.

1. On the basis of the information obtained thus far, which *one* of the following would the *most appropriate* next step?

a. Flexible bronchoscopy
b. Coronary angiography
c. Computed tomographic (CT) angiography of the chest
d. Noncontrast head CT
e. Transthoracic echocardiography

Bronchoscopy could potentially detect features such as superimposed infection, lipid-laden macrophages in bronchoalveolar lavage (BAL) fluid, or intrinsic lung disease. However, its diagnostic utility is limited in evaluating for pulmonary embolism, which is the top differential diagnosis in this patient. Additionally, the patient's relatively high risk of pulmonary and cardiovascular decompensation make the procedure unfavorable at this time. Acute coronary syndrome is a diagnosis that could be considered given the patient's elevated troponin T level. However, the patient did not have chest pain and had no electrocardiographic findings suggestive of acute infarct, so coronary angiography would not be indicated at this time. The patient's tachycardia,

See end of article for correct answers to questions.

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hypotension, and hypoxia in the setting of a recent surgical procedure are highly suggestive of a pulmonary embolism, and this diagnosis must be evaluated with CT angiography of the chest. Noncontrast head CT should be considered if other potential etiologies of the patient's somnolence and altered mental status are ruled out. However, at this time the patient clearly has evidence of hypoxia and circulatory compromise that would be contributing to her neurologic changes. Transthoracic echocardiography cannot definitively diagnose pulmonary embolism and is most useful in cases in which pulmonary embolism is strongly suspected but unable to be confirmed by CT angiography.

Computed tomographic angiography of the chest revealed bilateral ill-defined ground-glass opacities with scattered areas of interlobular septal thickening and no evidence of pulmonary embolism. The ground-glass pattern appeared consistent with pulmonary edema, but there were no pleural effusions. The patient's respiratory failure and altered mental status worsened, and intubation was required. She remained hypotensive, and echocardiography revealed severe RV dilation and dysfunction and severe tricuspid regurgitation from annular dilation. The left ventricle (LV) was underfilled and hyperdynamic with an ejection fraction of 70% and normal E/e′ ratio (noninvasive estimate of LV filling pressure). An echocardiogram obtained a few months previously had documented an ejection fraction of 58%, grade 1 diastolic dysfunction, a normal RV, and no evidence of valvular disease.

Given the patient's persistent shock with acute RV dysfunction and pulmonary infiltrates of unclear etiology, a Swan-Ganz catheter was placed. The following parameters were obtained: cardiac index, 2.2 L/min per m^2 (2.6-4.2 L/min per m^2) with an initial pulmonary artery or mixed venous oxygen saturation of 46% (60%-80%); systemic vascular resistance (SVR), 2800 dynes · s/cm^5 (800-1200 dynes · s/cm^5); right atrial pressure, 12 mm Hg (2-6 mm Hg); pulmonary capillary wedge pressure, 10 mm Hg (6-12 mm Hg); pulmonary artery pressure, 30/22 mm Hg (15-25/8-15 mm Hg) with a mean pulmonary artery pressure of 25 mm Hg (<25 mm Hg); and pulmonary vascular resistance, 408.2 dynes · s/cm^5 (<250 dynes · s/cm^5).

2. On the basis of the hemodynamic findings, which *one* of the following types of shock does the patient have?

a. Hypovolemic shock
b. Cardiogenic shock
c. Distributive shock
d. Neurogenic shock
e. Anaphylactic shock

Hypovolemic shock would be associated with a low (not high) right atrial pressure, and the patient's history and examination findings do not suggest any source of rapid exsanguination. The patient's low cardiac index and low mixed venous oxygen saturation suggest the presence of low cardiac output and cardiogenic shock. In this scenario, the SVR is high as a compensatory vasoconstrictor response to the low cardiac output in an effort to maintain blood pressure and organ perfusion. The presence of increased pulmonary vascular resistance, increased mean pulmonary artery pressures, and a normal pulmonary capillary wedge pressure suggests RV failure as the etiology of cardiogenic shock (as opposed to LV failure). The increase in pulmonary vascular resistance suggests an increase in afterload as the etiology of her RV failure. In acute RV failure, the increase in mean pulmonary artery pressure is typically not severe because of the acute nature of the event and lack of time for ventricular remodeling.[1]

Distributive shock is not consistent with this patient's clinical picture, given the increased systemic vascular resistance, decreased cardiac output, and low mixed venous oxygen saturation, effectively ruling out sepsis as the primary contributor to the patient's hemodynamic presentation. Neurogenic shock results from disruption of the sympathetic nervous system secondary to brain or spinal cord injury. Typical findings include hypotension and bradycardia in the setting of brain or spinal cord injury. Our patient's tachycardia and increased SVR document the presence of a compensatory physiologic sympathetic response. Our patient does not have findings consistent with anaphylactic shock, such as wheezing, stridor, angioedema, or urticaria.

Milrinone and vasopressin were initiated to support the hemodynamics, and the patient continued to require mechanical ventilation with low tidal volume and positive

Mayo Clin Proc. ■ August 2016;91(8):e111-e116 ■ http://dx.doi.org/10.1016/j.mayocp.2016.03.011
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end-expiratory pressure. Broad-spectrum antibiotics were administered because of concern for pulmonary infection.

3. Which *one* of the following is the *most likely* etiology of the ground-glass changes in the lungs bilaterally on CT?

a. Cardiogenic pulmonary edema
b. Noncardiogenic pulmonary edema
c. Diffuse alveolar hemorrhage
d. Pulmonary infarct
e. Aspiration pneumonia

Ground-glass changes and infiltrates on pulmonary CT are nonspecific. The term *ground glass* refers to partial filling of the lung spaces with transudate or exudate, interstitial thickening, or partial alveolar collapse. This condition is in contrast to consolidation, which completely obscures the underlying pulmonary vasculature. The differential diagnosis is broad and includes pulmonary edema and hemorrhage, interstitial pneumonia, atypical pneumonia, and hypersensitivity pneumonitis.[2] In our patient, the presence of interlobular septal thickening suggests pulmonary edema, but in the context of a normal pulmonary capillary wedge pressure, cardiogenic pulmonary edema is extremely unlikely. Noncardiogenic pulmonary edema is caused by a capillary leak, which occurs in many disorders that cause acute respiratory distress syndrome (ARDS). It is a diagnosis of exclusion but in our case seemed most likely on the basis of the clinical setting and the exclusion of other potential diagnoses. Our patient did not have any predisposing factors for diffuse alveolar hemorrhage (vasculitis, connective tissue disorder, or coagulopathy), making this diagnosis less likely. A pulmonary infarct would produce a wedge-shaped, pleural-based opacification on CT, which was not present in our patient. Aspiration pneumonia generally causes opacification of the affected lobes, with the posterior segments of the upper lobes and superior segments of the lower lobes being most commonly affected when aspiration occurs in the supine position.

Bronchoalveolar lavage performed at the time of intubation revealed no blood and no evidence of purulent secretions suggestive of infection. Oil Red O staining revealed 100% lipid-laden macrophages.

4. Given the patient's presentation, which *one* of the following is the *most likely* diagnosis?

a. Fat embolism syndrome
b. Acute aspiration pneumonitis
c. Severe pneumonia resulting in ARDS
d. Acute myocardial infarction
e. Diffuse alveolar hemorrhage

The findings of hypoxemia, neurologic changes, and acute right-sided heart failure in the setting of a recent hip operation and the absence of pulmonary embolism suggest fat embolism syndrome. This diagnosis is further supported by the finding of 100% lipid-laden macrophages in the BAL specimen. Other potential causes of lipid-laden macrophages on BAL include aspiration, lipid infusions, and cystic fibrosis.[3] Our patient does not have a history of lipid infusion, and her age and lack of relevant family history make cystic fibrosis unlikely. Aspiration pneumonitis is possible given the patient's history of alcoholism and recent anesthesia and is difficult to differentiate in this case. However, the magnitude of lipid involvement in the alveolar cells is more consistent with fat embolism syndrome because more than 70% of lavage cells containing lipid droplets is not typically seen in trauma cases without fat embolism syndrome.[4] A severe pneumonia with hypoxia and ARDS would not typically present with such a severe increase in RV afterload and RV failure from merely hypoxic vasoconstriction. Moreover, the BAL fluid specimen was negative for purulent secretions and did not suggest infection, and the patient was afebrile with a normal white blood cell count. Acute myocardial infarction would present with electrocardiographic changes as well as a persistent elevation in cardiac enzymes, rather than the very mild, stable elevation seen in our patient. Regional wall motion abnormalities are often seen on echocardiography. A diffuse alveolar hemorrhage syndrome would be reflected by greater than 20% of the macrophages staining positive for hemosiderin because of chronic intra-alveolar bleeding, which is not consistent with our patient's presentation.

The patient was diagnosed as having fat embolism syndrome. Antibiotics were discontinued, but she continued to require mechanical ventilation and inotropic support.

5. **Which *one* of the following is the *most appropriate* initial treatment for this patient?**
   a. Discussion to initiate comfort care measures
   b. Therapeutic low-molecular-weight heparin
   c. Mechanical embolectomy
   d. High-dose corticosteroids
   e. Supportive care

The overall mortality from fat embolism syndrome is 5% to 15%, most commonly from the development of ARDS and acute right-sided heart failure. However, even severe symptoms are typically transient and improve with time. In our patient, moving toward comfort care measures would be premature because the body has not yet had time to resorb the embolism. Heparin and mechanical embolectomy are not indicated for treatment of fat embolism syndrome because thrombus is not present. Although there is limited evidence that corticosteroids may be beneficial in the treatment of fat embolism syndrome, the evidence is not currently sufficient to recommend their routine usage. Supportive care is the mainstay of fat embolism syndrome treatment. High flow rate oxygen should be given to maintain arterial oxygen saturation, and maintaining adequate volume status and electrolyte balance should be considered. In patients requiring mechanical ventilation, lung protective strategies should be employed. With adequate supportive care, most patients recover.[5]

Our patient recovered with conservative therapy and supportive care. She was weaned off mechanical ventilation and milrinone. Her compensatory tachycardia resolved as her RV function recovered, and she was ultimately discharged home.

DISCUSSION

Our patient presented with hypotension, hypoxia, and altered mental status in the acute postoperative period after internal fixation of a left intertrochanteric hip fracture. With the presence of RV failure, the initial concern was for pulmonary embolism, which was promptly ruled out. Some initial features did suggest that pulmonary embolism was less likely. The bilateral pulmonary edema from ARDS is not a usual occurrence with a pulmonary embolism. Nonetheless, pulmonary embolism is a common diagnosis that should remain high on the differential after trauma, regardless of timing or atypical features. Ultimately, our patient was diagnosed as having fat embolism syndrome, with acute lung injury as a driving force resulting in acute RV failure and cardiogenic shock.

Although small fat emboli occur in many patients with long bone fractures, they are usually asymptomatic. Rarely, these emboli cause multisystem dysfunction, referred to as fat embolism syndrome. The exact incidence of fat embolism syndrome is unknown but has been reported to range from 0.12% to 29%, likely because of variability in diagnostic criteria.[6-8] One study found that the 3-year incidence of fat embolism syndrome in patients surgically treated for a pelvis, femur, or tibia fracture was 7.86%, with a modest decrease in incidence in patients pretreated with methylprednisolone.[9] Risk factors for the development of fat embolism syndrome include multiple fractures of the femur, male sex, and age between 10 and 39 years.[7] Conventional cementing of the femoral stem in femoral fractures is associated with an 85% incidence of fat embolism, which was reduced to 25% with the use of a venting hole to reduce interosseous pressure.[10] Fat embolism syndrome is very uncommon outside of orthopedic conditions but has been reported in association with massive soft tissue injury or burns as well as acute pancreatitis, fatty liver, and corticosteroid therapy.

The pathogenesis of fat embolism syndrome remains in contention. The mechanical theory claims that fat droplets themselves enter the venous circulation, which deposit into pulmonary capillaries and through arteriovenous shunts to the cerebral circulation, producing local inflammation and ischemia. If the embolism is massive enough, occlusion of the pulmonary capillary meshwork can occur, resulting in acute right-sided heart failure and resultant cardiogenic shock.[5] Alternatively, the biochemical theory states that hormonal changes triggered by trauma or sepsis trigger the release of free fatty acids into the circulation, which then migrate and can cause multiorgan dysfunction and neurologic abnormalities.[11]

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The clinical presentation of fat embolism syndrome can be highly variable. Classically, the triad of presenting symptoms is hypoxemia, neurologic abnormality, and petechial rash in the setting of recent trauma or surgical treatment. However, this triad is not present in all patients, with neurologic dysfunction present in 86% of patients, pulmonary dysfunction (tachypnea, dyspnea, hypoxemia) in 75%, and a petechial rash on the conjunctiva, axilla, chest, or neck in 60%.[8] Neurologic abnormalities are usually nonfocal and highly variable in presentation and can range from mild confusion to lethargy and seizure. Other symptoms such as anemia, thrombocytopenia, fever, and oliguria may develop in concordance with the clinical triad. Half of patients with fat embolism syndrome have development of hypoxemia that warrants mechanical ventilation, with 5% to 8% of patients having progression to ARDS.[8]

The diagnosis of fat embolism syndrome is based primarily on clinical features and the exclusion of other causes of the symptoms; pulmonary embolism and infection such as pneumonia or meningitis are high on the differential diagnosis. Aspiration pneumonitis should be considered and in the absence of the characteristic rash may not be clinically distinguishable from fat embolism syndrome. The original clinical diagnostic criteria proposed by Gurd and Wilson[12] required 1 major criteria (petechial rash, respiratory insufficiency, cerebral involvement), and 4 minor criteria (tachycardia, fever, retinal changes, jaundice, renal signs, thrombocytopenia, anemia, elevated erythrocyte sedimentation rate, fat macroglobinemia). The utility of these criteria, however, is not well established, and other diagnostic schemes have been proposed.[13] Arterial blood gas studies typically reveal hypoxia, with PO_2 of less than 60 mm Hg and respiratory alkalosis.[8] Imaging findings are nonspecific: CT of the chest usually reveals changes in the lung parenchyma in 3 predominant patterns—ground-glass changes with a geographic distribution, ground-glass opacities with interlobular septal thickening, and nonspecific nodular opacities—but may sometimes be normal.[14] Head CT is performed primarily to rule out other causes of neurologic dysfunction and may yield normal results or findings consistent with diffuse microvascular injury.

Hemodynamic monitoring may reveal evidence of pulmonary hypertension and acute right-sided heart failure, typically with a normal pulmonary capillary wedge pressure and LV ejection fraction. The RV tolerates acute increases in afterload poorly, and a massive embolism obstructing 80% of the pulmonary capillary meshwork may result in RV systolic dysfunction and resultant cardiogenic shock. In such a case, the mean pulmonary artery pressure is not a reliable indicator of afterload. There may only be a modest increase in pulmonary artery pressure because of insufficient time for ventricular remodeling to occur. This feature is in contrast to chronic increases in afterload, such as with chronic pulmonary arterial hypertension in which the RV will hypertrophy in response with RV failure occurring only in end-stage disease. Staining of alveolar macrophages from BAL fluid for lipids may assist in the diagnosis of fat embolism syndrome. Normal values for lipid-laden macrophages are typically below 5%, and greater than 70% of lavage cells containing lipid inclusions is consistent with the diagnosis.[3,4] However, such a finding is also present in patients with sepsis and severe hyperlipidemia, which must first be ruled out. Urine, blood, and sputum cytological investigation for fat globules may support the diagnosis, but the sensitivity of these investigations is low.[5]

Treatment of fat embolism syndrome is supportive. The most common cause of mortality is acute right-sided heart failure. The use of corticosteroids and albumin therapy is controversial, and their benefit is not well established. In cases of fulminant fat embolism syndrome, extracorporeal membrane oxygenation may be used as a temporizing measure until clinical improvement occurs.[15] The overall mortality in fat embolism syndrome is between 5% and 15% in patients who receive supportive care, with most deficits resolving within a year.[5,8]

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REFERENCES

1. Matthews JC, McLaughlin V. Acute right ventricular failure in the setting of acute pulmonary embolism or chronic pulmonary hypertension: a detailed review of the pathophysiology, diagnosis, and management. *Curr Cardiol Rev*. 2008; 4(1):49-59.

2. Leung A, Miller RR, Müller NL. Parenchymal opacification in chronic infiltrative lung diseases: CT-pathologic correlation. *Radiology*. 1993;188(1):209-214.
3. Gratadour P, Védrinne JM, Guillaume C, Gagnieu MC, Motin J. Intra-macrophage lipid particles collected by bronchoalveolar lavage: incidence and diagnostic value [in French]. *Ann Fr Anesth Reanim*. 1993;12(5):462-468.
4. Mimoz O, Edouard A, Beydon L, et al. Contribution of bronchoalveolar lavage to the diagnosis of posttraumatic pulmonary fat embolism. *Intensive Care Med*. 1995;21(12): 973-980.
5. Gupta A, Reilly CS. Fat Embolism. *Contin Educ Anaesth Crit Care Pain*. 2007;7(5):148-151.
6. Bulger EM, Smith DG, Maier RV, Jurkovich GJ. Fat embolism syndrome: a 10-year review. *Arch Surg*. 1997;132(4):435-439.
7. Fabian TC, Hoots AV, Stanford DS, Patterson CR, Mangiante EC. Fat embolism syndrome, prospective evaluation in 92 fractured patients. *Crit Care Med*. 1990;18(1):42-46.
8. Shaikh N. Emergency management of fat embolism syndrome. *J Emerg Trauma Shock*. 2009;2(1):29-33.
9. Hysa E. Fat embolism among patients with hip and long bone fractures in Albania. *Mater Sociomed*. 2012;24(4):248-250.
10. Pitto RP, Koessler M, Kuehle JW. Comparison of fixation of the femoral component without cement and fixation with use of a bone-vacuum cementing technique for the prevention of fat embolism during total hip arthroplasty: a prospective, randomized clinical trial. *J Bone Joint Surg Am*. 1999;81(6):831-843.
11. Gossling HR, Pellegrini VD Jr. Fat embolism syndrome: a review of the pathophysiology and physiological basis of treatment. *Clin Orthop Relat Res*. 1982;165:68-82.
12. Gurd AR, Wilson RI. The fat embolism syndrome. *J Bone Joint Surg Br*. 1974;56B(3):408-416.
13. Lindeque BG, Schoeman HS, Dommisse GF, Boeyens MC, Vlok AL. Fat embolism and the fat embolism syndrome: a double-blind therapeutic study. *J Bone Joint Surg Br*. 1987;69(1):128-131.
14. Malagari K, Economopoulos N, Stoupis C, et al. High-resolution CT findings in mild pulmonary fat embolism. *Chest*. 2003; 123(4):1196-1201.
15. Webb DP, Mckamie WA, Pietsch JB. Resuscitation of fat embolism syndrome with extracorporeal membrane oxygenation. *J Extra Corpor Technol*. 2004;36(4):368-370.

CORRECT ANSWERS: 1. c. 2. b. 3. b. 4. a. 5. e

Mayo Clin Proc. ■ August 2016;91(8):e111-e116 ■ http://dx.doi.org/10.1016/j.mayocp.2016.03.011
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