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A young woman with severe hypoxemia, electrocardiographic changes, and altered mental status

A 44-YEAR-OLD WOMAN with hypertension and a history of previous cigarette smoking presents to a community hospital with dyspnea of a few hours' duration.

On arrival in the emergency department, the patient is afebrile; her heart rate is 105 beats per minute, respiratory rate 60 per minute, blood pressure 144/100 mm Hg (she has prescriptions for hydrochlorothiazide and amlodipine [Norvasc], though she has not taken them for 3 or 4 weeks), and oxygen saturation 75% while receiving oxygen at 4 L/minute by nasal cannula.

On physical examination, she is thin and disoriented. Her heart rate is fast but the rhythm is regular, without murmurs, gallops, or rubs. Her distal pulses are weak. Her lungs have crackles in all fields bilaterally; her abdomen is normal; her extremities are warm and well perfused without edema. She knows who she is and who her mother is, but otherwise she is disoriented; her pupils are equal and reactive to light, and she can spontaneously move her eyes and all four limbs when asked.

A chest roentgenogram is obtained and reveals diffuse bilateral pulmonary edema with a normal-sized cardiac silhouette. Blood samples are obtained and sent to the laboratory.

Before the laboratory values and the roentgenogram are available, however, the patient's respiratory status deteriorates. She cannot maintain an adequate level of oxygenation even while breathing 100% supplemental oxygen by non-rebreather face mask. Concerned, her physicians insert an endotracheal tube, begin mechanical ventilation,

and then obtain an arterial blood gas sample, which reveals the following:

- pH 7.24 (normal range 7.35–7.45)
- Partial pressure of carbon dioxide, arterial (PaCO_2) 38 mm Hg (34–46)
- Partial pressure of oxygen, arterial (PaO_2) 71 mm Hg (85–95)
- Alveolar-arterial oxygen gradient 604 mm Hg (see below).

■ WHAT IS CAUSING HER HYPOXEMIA?

1 Which of the following causes of hypoxemia are not applicable in this patient?

- ☐ Hypoventilation
- ☐ Low inspired oxygen fraction (FiO_2)
- ☐ Diffusion defect
- ☐ Ventilation-perfusion mismatch
- ☐ Shunt

The normal gradient in the partial pressure of oxygen between the alveoli and the arterial blood (the A-a gradient) is negligible: in a woman of 44 years, it would be approximately 15 mm Hg. In this patient, however, the calculated gradient is 604 mm Hg, indicating marked hypoxemic respiratory failure. What could be causing it?

Hypoventilation raises the PaCO_2 and decreases the PaO_2 ; however, this patient's PaCO_2 is normal. Furthermore, hypoventilation would not cause an increased A-a gradient.

A low FiO_2 can occur at high altitudes. It cannot be the cause of this patient's hypoxemia, since she continues to have marked hypoxemia even while breathing 100% oxygen.

Her vital signs:

Pulse 105

Respirations 69

BP 144/100

O₂ saturation

**75% on O₂ 4 L/m
per nasal
cannula**

What is the diagnosis?

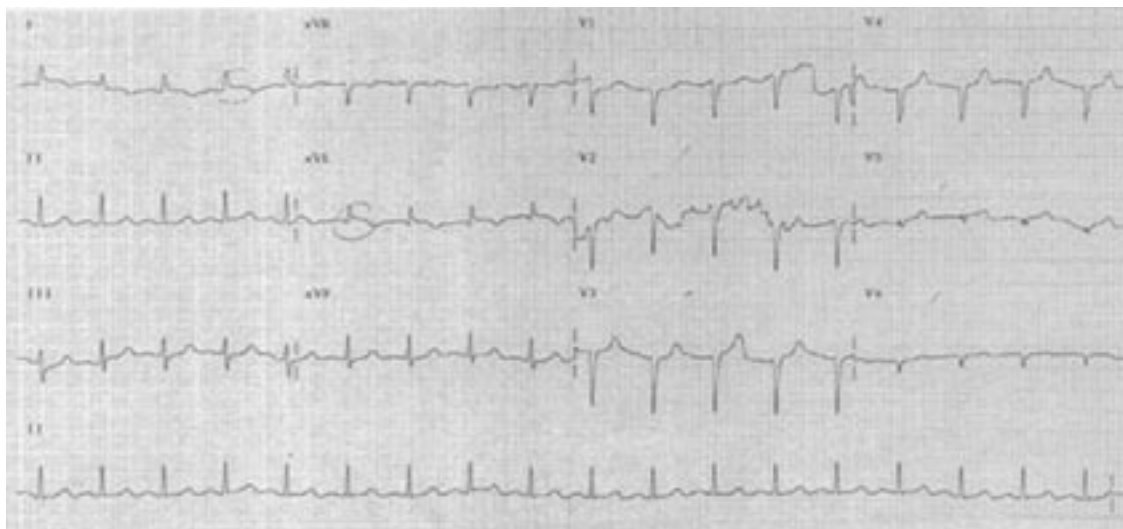


FIGURE 1. The patient's electrocardiogram on presentation.

Diffusion defects, ventilation-perfusion (V/Q) mismatch, and shunts are among the possible causes of hypoxemia with an increased A-a gradient.

Diffusion defects. Some of the lung disorders that cause diffusion defects (impairment in the lung's oxygen delivery to the bloodstream) are chronic obstructive lung disease, interstitial fibrosis and other interstitial lung diseases, and interstitial edema. The hypoxemia caused by diffusion defects is usually more profound during exertion or increased demand and often improves somewhat with supplemental oxygen.

Given the findings on chest radiography in our patient, a diffusion defect is a possibility in this case.

Ventilation-perfusion mismatch occurs along a spectrum, from an extreme impairment in ventilation (in which V/Q approaches zero; also known as "shunt" physiology) to an extreme impairment in perfusion (in which V/Q approaches infinity; also known as "dead space" physiology). The dead space can increase with pulmonary embolism or other abnormalities in the pulmonary vascular bed. Depending on the cause and degree of the V/Q mismatch, the hypoxemia may improve somewhat with supplemental oxygen.

As this patient's chest roentgenogram does reveal another potential diagnosis, and since there is no obvious historical clue point-

ing to a perfusion defect, this is a less likely diagnosis.

Shunt, as mentioned above, is an extreme form of V/Q mismatch in which perfusion is not associated with any ventilation, and is usually the result of a direct connection between the right and left heart circulation (arteriovenous malformation, cardiac septal defect, the normal bronchial circulation). If hypoxemia is due to shunting, it does not usually improve with supplemental oxygen, and this refractory hypoxia without explanation is often the clue to pursue a workup of this pathologic mechanism. Less extreme forms of decreased ventilation in perfused lung tissue may be the result of varying degrees of air-space disease (eg, pneumonia, pulmonary edema, atelectasis).

The presentation in this case is an acute one, which would make a chronic shunting process less likely as the diagnosis.

■ CASE CONTINUED: AN ABNORMAL ELECTROCARDIOGRAM

2 While the physicians are considering the patient's hypoxia and its possible causes, they obtain an electrocardiogram (**FIGURE 1**). All of the following could account for the findings on this patient's electrocardiogram except which one?

- ☐ Acute myocardial infarction
- ☐ Subarachnoid hemorrhage

Her arterial
blood gases:
pH 7.24
Paco₂ 38
Pao₂ 71 on
100% Fio₂
via mechanical
ventilation

Pulmonary embolism

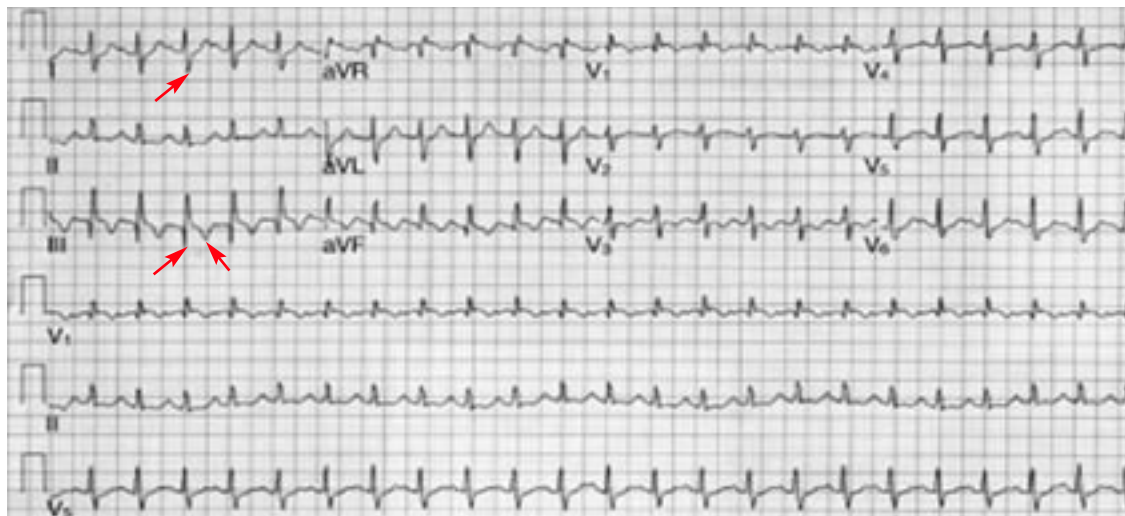


FIGURE 2. Twelve-lead electrocardiogram showing sinus tachycardia, right-axis deviation, and incomplete right bundle-branch block. Note the deep S wave in lead I, Q wave in lead III, and the T-wave inversion in lead III (S1Q3T3 pattern) with ST-segment and T-wave deviations in V₁–V₃. These changes suggest pulmonary embolism.

DELIARGYRIS EN, FALSON JM, WILLIS PW 4TH. PULMONARY EMBOLUS IN TRANSIT. CLIN CARDIOL 1999; 22:673–674.

- ☐ Pulmonary embolism
- ☐ Acute pericarditis
- ☐ Hyperkalemia

This patient has sinus tachycardia, ST-segment elevation in leads I and aVL, and abnormal R-wave progression in leads V₁ through V₆.

Acute myocardial infarction is a possibility, given the ST-segment elevation in limb leads I and aVL and the Q waves throughout the precordial leads. Furthermore, the combination of diffuse pulmonary edema and ST-segment elevation may indicate severe multi-vessel or left main coronary artery disease and resultant cardiogenic shock due to myocardial infarction. In addition, her altered mental state could be the result of poor cerebral blood flow due to myocardial infarction or of general decompensation due to a large myocardial infarction.

Subarachnoid hemorrhage can cause QT-interval prolongation (noted in 61% of cases), ST-segment elevation or depression (29%), and T-wave inversion (24%).¹ These changes usually resolve after the acute phase, and their pathogenesis is not well understood. The cerebrovascular insult of a subarachnoid hemorrhage would also explain our patient's altered mental state.

Pulmonary embolism. First described in 1935, the oft-quoted “S1Q3T3” pattern on electrocardiography seen with pulmonary embolism (**FIGURE 2**)² may be apparent in only 20% of cases.³ T-wave inversion in leads V₁ through V₃ is probably the most sensitive change, seen in 43% of patients with acute pulmonary embolism and in 75% of patients with acute pulmonary embolism complicated by right ventricular dysfunction.⁴ Sinus tachycardia, ST-segment elevation, right bundle branch block, and right axis deviation may also be seen. The utility of electrocardiography in diagnosing pulmonary embolism is highly variable, and the use of scoring systems to improve its sensitivity and specificity is under investigation.⁵

Our patient's electrocardiographic findings are not typical of pulmonary embolism, the alveolar filling pattern on her chest roentgenogram suggests another cause of her hypoxia, and she has no obvious risk factors or historical evidence for this diagnosis.

Acute pericarditis most often causes diffuse ST-segment elevation and PR-segment depression. In addition, the ST segment is often depressed and the PR segment is elevated in lead aVR (**FIGURE 3**).

Hypoxemia due to shunting usually does not improve with supplemental O₂

Acute pericarditis

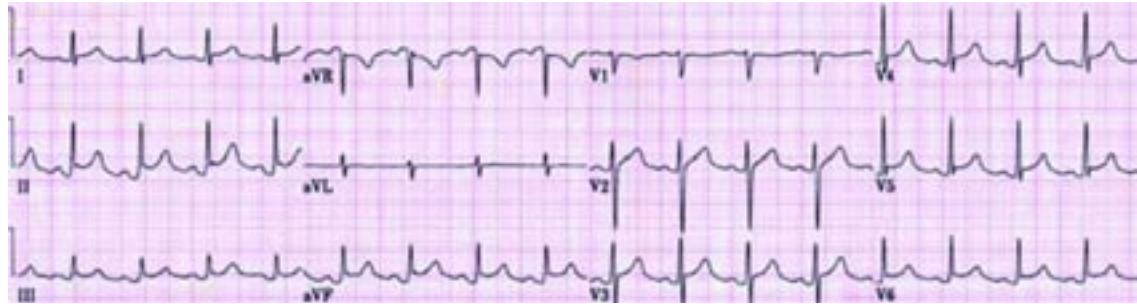


FIGURE 3. Electrocardiogram demonstrating acute pericarditis. Note the diffuse ST-segment elevation as well as PR-segment depression.

Although focal pericarditis can result in localized ST-segment elevation as seen in this patient, her pulmonary edema, severe hypoxemia, and altered sensorium make this diagnosis less likely.

Hyperkalemia is usually associated with other electrocardiographic changes, including peaking of the T waves, widened QRS complex, and loss of P waves (**FIGURE 4**), none of which are present on this patient's electrocardiogram.

Case continued: More information

The patient's blood tests return:

- White blood cell count $50.0 \times 10^9/L$ (normal range 4.0–11.0)
- Polymorphonuclear cells 84%
- Hematocrit 50% (37–47)
- Platelet count $250 \times 10^9/L$ (150–400)
- Serum creatinine 1.0 mg/dL (0.7–1.4)
- Creatine kinase (CK) 616 U/L (30–220)
- CK-MB fraction 38 ng/mL (0.0–8.8)
- Troponin-I 10.71 $\mu g/L$ (0–0.4).

Bedside transthoracic echocardiography reveals a globally hypokinetic left ventricle with an estimated left ventricular ejection fraction of 10%.

WHAT IS CAUSING HER SYSTOLIC DYSFUNCTION?

3 What is the most likely cause of the patient's systolic dysfunction?

- ☐ Acute myocardial infarction
- ☐ Myocarditis
- ☐ Subarachnoid hemorrhage

Acute myocardial infarction is complicated by cardiogenic shock (discussed below)

in approximately 10% of cases, most often with ST-segment elevation, and carries a 56% to 74% mortality rate.⁶ The prognosis is much better when emergency revascularization can be performed.⁷

Our patient has acute decompensation, positive biomarkers of myocardial necrosis, and a markedly diminished ejection fraction, all of which make the diagnosis of acute myocardial infarction likely.

Acute myocarditis is a rarer, inflammatory condition that can be the result of infection (viral, bacterial, or fungal), autoimmune disorders (eg, giant cell arteritis, Wegener granulomatosis), or drug toxicity (eg, from cocaine, alcohol, or anthracyclines). Its clinical presentation can range from mild chest discomfort to cardiogenic shock. Left ventricular dysfunction is most often global, and the prognosis varies, depending on its cause.

Subarachnoid hemorrhage remains a diagnostic possibility in our patient, as approximately one third of patients with subarachnoid hemorrhage have concomitant systolic cardiac dysfunction. Half of these patients have global left ventricular failure, and the other half have regional wall motion abnormalities.⁸ Invariably, the systolic dysfunction resolves within a matter of weeks. Up to 50% of patients with subarachnoid hemorrhage also have elevations in biomarkers of myocardial necrosis.⁹

Although the pathogenic cascade of this condition is not completely understood, current evidence suggests that catecholamines released during the cerebral insult play a role in mediating the cardiac dysfunction. Therefore, it is similar to stress-induced cardiomyopathy, or “broken heart” syndrome.¹⁰

Acute myocardial infarction is complicated by cardiogenic shock in about 10% of cases

Hyperkalemia

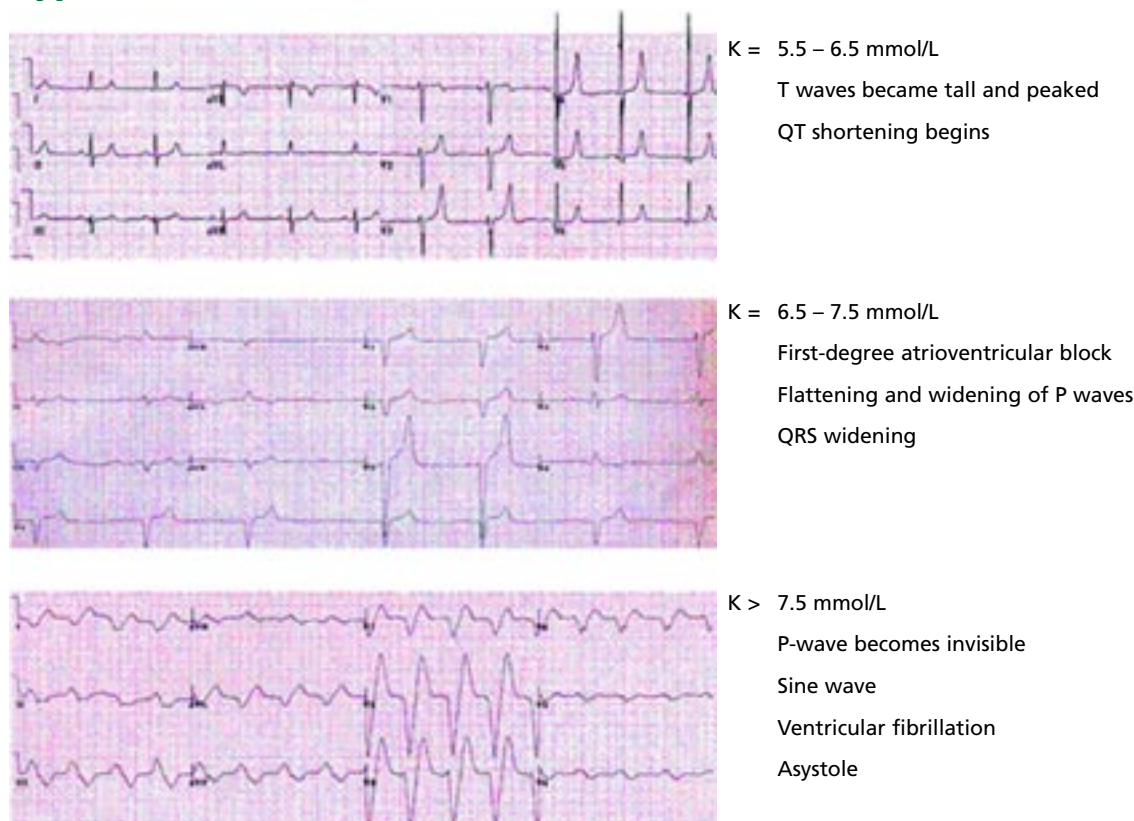


FIGURE 4. Electrocardiographic changes of progressive hyperkalemia.

Case continued:

The patient undergoes angiography

Given the findings on electrocardiography, blood testing, and transthoracic echocardiography, the physicians entertain a diagnosis of ST-segment elevation myocardial infarction. They therefore prepare to transfer the patient to a tertiary care hospital for emergency coronary angiography and possibly primary percutaneous coronary intervention. Before she is transferred, treatment is begun with aspirin, clopidogrel (Plavix), and continuous intravenous infusion of unfractionated heparin and eptifibatide (Integrilin). Additionally, because she has significant hypertension (at times reaching 212/145 mm Hg), the patient receives intravenous boluses of labetalol (Normodyne).

At the tertiary care hospital, angiography reveals a normal right-dominant coronary system that is angiographically free of disease. The unfractionated heparin, epti-

batide, aspirin, and clopidogrel are therefore discontinued.

While in the catheterization laboratory, the patient becomes hypotensive, and because she is known to have global systolic dysfunction, her physicians insert an intraaortic balloon counterpulsation device and begin an intravenous norepinephrine infusion. She is then transferred to the cardiac intensive care unit.

Pulmonary artery catheterization in the intensive care unit reveals the following hemodynamic variables:

- Pulmonary artery pressure 35/14 mm Hg (normal range 15–30/5–13)
- Mean pulmonary artery pressure 26 mm Hg (10–18)
- Pulmonary capillary wedge pressure 12 mm Hg (2–12)
- Cardiac index 1.34 L/min/m² (2.8–4.2)
- Systemic vascular resistance 3,029 dyne • sec • cm⁻⁵ (1,600–2,400).

About 1/3 of patients with subarachnoid hemorrhage also have systolic dysfunction

A remarkable recovery

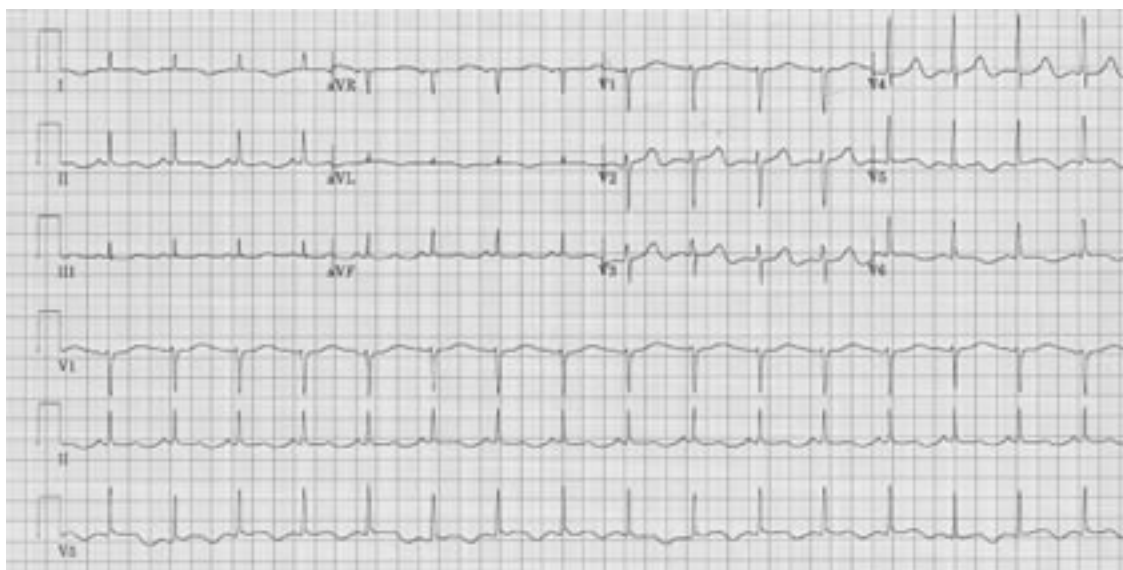


FIGURE 5. Electrocardiogram on the second day of the patient's hospitalization.

■ WHAT CAN CAUSE THIS HEMODYNAMIC PATTERN?

4 What is the interpretation of the pulmonary artery catheterization findings?

- ☐ Cardiogenic shock
- ☐ Septic shock
- ☐ Hypovolemic shock

Cardiogenic shock is a state in which tissue perfusion is compromised due to decreased heart function. It can occur in many clinical situations, such as after myocardial infarction or in valvular cardiomyopathies, myocarditis, or other conditions that compromise the function of the heart. Hemodynamically, it is usually manifests as a low cardiac index, high pulmonary capillary wedge pressure, and high systemic vascular resistance. In some cases, however, the systemic vascular resistance may in fact be low, mimicking a picture of distributive, or septic, shock.¹¹

This patient's cardiac index is markedly low and her systemic vascular resistance is markedly high; however, her pulmonary capillary wedge pressure is normal, providing incongruent data for a diagnosis of cardiogenic shock.

Septic shock, which is due to the body's inflammatory response to infection, is clinically characterized by fever or hypothermia,

tachycardia, tachypnea, and hypotension in a patient with infection. The hemodynamic characteristics are an increased cardiac index, low pulmonary capillary wedge pressure, and low systemic vascular resistance.

This patient's low cardiac index and high systemic vascular resistance do not support a diagnosis of septic shock.

Hypovolemic shock is the result of profound volume depletion leading to tissue hypoperfusion. It can be due either to fluid loss or to bleeding. As a result, cardiac preload is reduced and the cardiac index falls. Additionally, the pulmonary capillary wedge pressure is low and the systemic vascular resistance is high.

Our patient has each of these findings. Though we know that her systolic function is markedly reduced, the numbers obtained by pulmonary artery catheterization provide evidence that volume resuscitation is needed.

Case continued: New information from the family

At this point, detailed discussion with the patient's family provides a more lucid history of her present illness than that obtained earlier. They note that the patient had complained of myalgias, diarrhea, and cough in the week before admission. In the hours leading up to her presentation to the hospital, she had

By day 20 in the hospital, the patient is feeling well and has had a remarkable neurologic recovery

begun acting “out of it,” had difficulty walking, complained of headache, and then became dyspneic. They became worried by these symptoms and contacted emergency medical services.

Given this new information about the patient’s neurologic problems, her physicians order immediate computed tomography of the head, which reveals subarachnoid hemorrhage, likely originating from an aneurysm at the superior aspect of the basilar artery.

A neurosurgeon performs an emergency ventriculostomy at the bedside to relieve her hydrocephalus. Within hours, the patient is weaned from vasopressors, intraaortic balloon counterpulsation is discontinued, her supplemental oxygen requirements decrease, and her cardiac index increases to 3.0.

On the second hospital day, the patient undergoes coil embolization of the basilar artery aneurysm. A new electrocardiogram done on that day shows that the initial changes have resolved (FIGURE 5), and transthoracic echocardiography reveals a nearly normal left ventricular ejection fraction. By the 20th day of her hospital stay, the patient is feeling well and has undergone a remarkable neurologic recovery without focal physical weakness and with only mild memory deficits surrounding the sentinel event.

■ FINAL POINTS

This patient’s case highlights the neurocardiac axis. Subarachnoid hemorrhage and other cerebral insults can be associated with electrocardiographic changes, systolic dysfunction, and release of biomarkers of myocardial necrosis. While not completely elucidated, the pathophysiology of this relationship seems to be the result of catecholamine effects on the myocardium, and is manifest histologically as contraction band necrosis. Research is

ongoing at the basic and clinical levels to further delineate the non-catecholamine-mediated mechanisms in this disorder.

The patient’s marked hypoxemia at the time of admission was likely due to another well-characterized but poorly understood systemic manifestation of cerebrovascular insult, ie, neurogenic pulmonary edema. Pulmonary artery catheterization shortly after admission revealed a normal pulmonary capillary wedge pressure. As a result, the diffuse bilateral alveolar filling pattern on chest radiography was not consistent with cardiogenic pulmonary edema. Similarly, the rapidity with which her hypoxemia resolved is not consistent with the acute respiratory distress syndrome. Neurogenic pulmonary edema can be seen in various types of cerebral insult, and pathophysiologic hypotheses include a neurally mediated increase in pulmonary capillary permeability resulting in pulmonary edema.

Also, our patient’s pulmonary artery catheterization revealed a component of hypovolemia. Patients with subarachnoid hemorrhage may have profound hypovolemia that is the result of central salt wasting and natriuresis, often accompanied by hyponatremia.¹² Some have suggested that aggressive volume repletion in the setting of subarachnoid hemorrhage may help mitigate the risk of secondary ischemic injury, but the data are controversial.¹³ Nevertheless, our patient required aggressive fluid resuscitation due to her hemodynamic compromise.

This interesting case highlights the importance of thorough history-taking in establishing a diagnosis, as well as the need to maintain a broad differential diagnosis, even if the findings on electrocardiography, transthoracic echocardiography, and laboratory testing seem definitive. Thankfully, this patient recovered almost completely with minimal residual deficiencies. ■

Keep the differential diagnosis broad, even when testing seems definitive

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