A Perfect Storm

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows.

A 21-year-old male college student presented to the student health center after two days of extreme fatigue. Over the course of the previous two months, frequent headaches, difficulty concentrating, and a decrease in his capacity for exercise had developed. He recently had had several days of nasal congestion and sore throat, but these symptoms had improved. A cursory physical examination showed no abnormalities, but his oxygen saturation on pulse oximetry was only 55 percent.

The patient presents with recent upper respiratory tract symptoms superimposed on a background of chronic nonspecific illness. The combination of long-standing headaches and difficulty concentrating suggests that there may be a problem affecting the central nervous system, but symptoms of fatigue and decreased exercise tolerance raise additional concerns. The finding of an oxygen saturation of 55 percent on pulse oximetry is most unexpected. Assuming that the measurement is not in error, my initial suspicion would be that there is either severe pulmonary disease or a right-to-left shunt (either intracardiac or intrapulmonary). Since pulse oximetry provides no information about arterial carbon dioxide tension, it is also possible that the primary problem is marked hypercapnia, and that the hypoxemia is secondary to hypoventilation.

The patient had no clinically significant medical history. He took no medications, drank alcohol rarely, and did not smoke or use illicit drugs. His parents were healthy, and there was no history of heritable disease. The patient was transferred to a local emergency department, where supplemental oxygen was administered. A measurement of arterial blood obtained while 50 percent oxygen was delivered by face mask revealed a pH of 7.22, a partial pressure of arterial carbon dioxide (PaCO₂) of 78 mm Hg, and a partial pressure of arterial oxygen (PaO₂) of 43 mm Hg. He rapidly became obtunded and required endotracheal intubation.

The blood gas values represent a respiratory acidosis. The pH for this level of PaCO₂ indicates that the acidosis is partially compensated (acute worsening of chronic respiratory failure). The elevated level of PaCO₂ also indicates that hypoventilation is present. In cases of pure hypoventilation, the alveolar–arterial oxygen difference should be normal (although frequently there is accompanying atelectasis that leads to a mild increase). A substantive increase would indicate an additional process such as a shunt, ventilation–perfusion mismatch, or a diffusion abnormality. Because the patient is breathing ambient air in addition to oxygen through the face mask, it is impossible to know the true percentage of oxygen he is inhaling. The alveolar–arterial oxygen difference is likely to be elevated, but the marked hypercapnia indicates that hypoventilation is an important — if not the chief — mechanism for the hypoxemia.
The underlying cause of hypoventilation can be at the level of the central nervous system (diminished drive to breathe), the respiratory “pump” (disease affecting the chest wall or inspiratory muscles), or the lungs (typically associated with increased dead space or severe ventilation-perfusion mismatch). Given this patient’s age and the absence of a history of drug use, I would be most concerned about an acute or subacute process affecting the respiratory drive (such as encephalitis) or the respiratory pump (such as the Guillain–Barré syndrome or a myopathy). Parenchymal lung disease with hypercapnia in someone of the age of this patient and with this tempo of onset would be unusual.

The patient was 187 cm tall and weighed 68 kg. He was sedated and mechanically ventilated with an inspiratory oxygen concentration of 60 percent. He was afebrile, his pulse was 110 beats per minute, and his blood pressure was 130/75 mm Hg. His oxygen saturation was 100 percent. A cardiac examination was notable for a right ventricular heave and accentuation of the pulmonic component of the second heart sound. An examination of the lungs was normal. The liver was palpable 1 cm below the right costal margin. There was no peripheral edema.

The physical examination is notable for a normal lung examination and for the clinically significant abnormalities revealed on the cardiac examination, suggesting pulmonary hypertension. Although data from the physical examination often help narrow the differential diagnosis, in this case the finding of pulmonary hypertension necessitates expanding the diagnostic possibilities. One scenario is that the pulmonary hypertension is secondary to chronic disturbances in gas exchange (primarily alveolar hypoxia and, to a lesser extent, hypercapnia), as might be seen with a variety of disorders affecting the respiratory drive or pump. Alternatively, diseases with structural involvement of the pulmonary vasculature, such as pulmonary emboli or primary pulmonary hypertension, could be responsible, and certainly are compatible with a normal lung examination.

The white cell count was 9500 per cubic millimeter, the hematocrit was 63 percent, and the platelet count was 172,000 per cubic millimeter. The aspartate aminotransferase level was 788 U per liter (normal range, 6 to 30) and the alanine aminotransferase level 1396 U per liter (normal range, 10 to 40). The level of blood urea nitrogen was 19 mg per deciliter and the level of creatinine was 1.1 mg per deciliter. The serum creatine kinase level was measured at 135 U per liter (normal range, 24 to 195). Anteroposterior chest radiography showed clear lung fields. The pulmonary arteries appeared enlarged, and there was mild scoliosis (Fig. 1).

The combination of erythrocytosis and pulmonary hypertension, along with the previous finding of hypoxemia, suggests a chronic process. One possibility is that chronic hypoxia (from an as-yet-undefined cause) may have led to pulmonary hypertension. Alternatively, elevated pulmonary artery pressures with a right-to-left intracardiac shunt might underlie the chronic hypoxemia. The latter scenario could occur either with pulmonary hypertension causing flow through a patent foramen ovale or with Eisenmenger’s syndrome complicating a long-standing left-to-right shunt. Elevated levels of serum aminotransferases may reflect either liver disease or muscle disease. However, in the presence of a normal level of creatine kinase, the most likely explanation is hepatic congestion due to pulmonary hypertension and right heart failure. At this point, I would obtain a transthoracic echocardiogram to evaluate the patient’s cardiac function. I am also interested in a more detailed neurologic examination when he is able to comply, particularly to assess muscle strength and the possibility...
of an underlying neuromuscular disease associated with respiratory muscle weakness. Significant kyphoscoliosis can lead to chronic hypoventilation and respiratory failure, but mild scoliosis alone could not explain his gas-exchange problems.

A spiral computed tomographic (CT) scan was negative for pulmonary embolism. No parenchymal abnormalities were present. Transthoracic echocardiography revealed normal left ventricular size and function, moderate right ventricular hypertrophy, and mild right ventricular hypokinesis (Fig. 2). The systolic pressure in the pulmonary artery was estimated to be 80 mm Hg. A “saline bubble” study (contrast echocardiography) performed to evaluate for a right-to-left intracardiac shunt was negative. After a period of mechanical ventilation, right heart catheterization was performed. The pulmonary artery pressure was 62/24 mm Hg, with a mean pressure of 44 mm Hg. The pulmonary artery occlusion pressure was 13 mm Hg. There was no evidence of an intracardiac shunt.

The negative result on the spiral CT scan is quite helpful in ruling out clinically significant thromboemboli in the proximal pulmonary arteries. The catheterization results confirm the presence of pulmonary arterial hypertension and rule out an intracardiac shunt. It is important to determine whether the patient’s pulmonary hypertension is due to a primary disorder of the pulmonary vasculature or whether it is secondary to vasoconstriction induced by hypoxia (and perhaps hypercapnia), as could be caused by disorders affecting ventilatory control and the respiratory pump. Such disorders are still of primary concern.

With the correction of hypoxemia, the patient’s pulmonary artery pressures improved substantially. He did well on a spontaneous breathing trial and was extubated and given supplemental oxygen. Following extubation, he was initially alert, cooperative, and comfortable. However, over the next hour, his oxygen requirement increased and he became somnolent. An arterial blood gas measurement revealed a pH of 7.17, a PaCO$_2$ of 70 mm Hg, and a PaO$_2$ of 219 mm Hg. The patient was reintubated.

We are again faced with deteriorating gas exchange and mental status. My presumption is that his PaCO$_2$ was maintained in a much lower (probably normal) range while he was intubated, and that he is now having an acute rise in the PaCO$_2$. We still have no evidence of pulmonary parenchymal disease or airway disease that might be associated with hypercapnia, and I suspect that the increasing oxygen requirement is due to hypoventilation rather than to a primary problem with oxygenation. Although primary pulmonary vascular disease (a concern raised by the presence of pulmonary hypertension) can produce significant ventilation–perfusion mismatch, patients generally increase their overall ventilation accordingly and thereby avoid hypercapnia. I still consider it most likely that the primary problem is with either ventilatory control or the neuromuscular apparatus affecting the muscles of respiration, resulting in abnormal gas exchange and pulmonary hypertension.

The patient quickly recovered to his preextubation status and was alert and oriented. He was placed on a T-piece weaning trial, and while in the semirecumbent position showed paradoxical abdominal movement with an inward motion of the abdomen during inspiration. On evaluation, his negative inspiratory force at functional residual capacity was 25 cm of water (normal, >40). The results of both motor and sensory examination of his arms and legs showed no abnormalities.

Paradoxical abdominal movement indicates clinically significant bilateral diaphragmatic weakness
or paralysis, which now appears to be the mechanism underlying the patient’s hypoventilation and hypercapnia. The abnormal value for negative inspiratory force further demonstrates the presence of inspiratory muscle weakness. These findings raise new questions, including whether or not the poor diaphragmatic function is due to a problem with innervation or whether it represents primary muscle disease. I would also like to know whether the problem is systemic or limited to the diaphragm. At this point, I would consult with a neurologist to help distinguish between causes that might involve the peripheral nerves and those that primarily involve the muscles.

The patient was successfully extubated with the use of intermittent, noninvasive positive pressure ventilation and careful oxygen titration. A neuromuscular specialist was consulted, who noted that the patient had bilateral winging of the scapulae, decreased muscle mass in the trapezius and paraspinal region, and an extremely rigid spine. The anteroposterior diameter of the chest was quite narrow. Fluoroscopy showed impaired diaphragmatic motion. The loss of normal spine curvature and atrophy of the paraspinal muscles were evident on magnetic resonance imaging of the cervical and thoracic spine (Fig. 3).

The examination provides information about two seemingly unrelated findings that probably worked in concert to produce respiratory failure — a rigid spine and muscle weakness, including impairment of the diaphragm. Does the patient have a primary muscle disease or neurologic disease? I find it difficult to pinpoint a specific cause, given the physical examination and information presented so far.

Regardless of the underlying reasons, the combination of respiratory-muscle weakness and a rigid chest wall sets the stage for the development of hypoventilation and respiratory failure. The patient’s right ventricular hypertrophy and polycythemia indicate that his hypoxemia had been chronic. What then tipped him over the edge and caused his acute presentation? Perhaps it was the preceding illness. Fever is known to increase carbon dioxide production, and the illness may have also exacerbated his underlying respiratory-muscle weakness.

The rigid spine syndrome was diagnosed in this patient. He was discharged to home and provided with nocturnal noninvasive ventilation to facilitate gas exchange and reduce respiratory-muscle fatigue during sleep. With this strategy, he has had normalization of his arterial blood gas values and resolution of his pulmonary hypertension. The patient was offered genetic testing but declined. He is physically active and doing well.

**Figure 3. Magnetic Resonance Imaging of the Cervical and Thoracic Spine.**

Sagittal imaging (Panel A) shows the loss of normal spinal curvature. Axial imaging (Panel B) reveals mild atrophy of the paraspinal muscles and early replacement with fat.

The rigid spine syndrome describes a complex that includes proximal muscle weakness, joint contrac-
Hypoventilation in a young adult is rare and should raise concern for congenital diseases. Congenital central hypoventilation is characterized by normal ventilation when the patient is awake but hypoventilation with shallow breathing when the patient is asleep. The disease is often diagnosed during infancy; however, recent discovery of the genetic abnormality has enabled identification of less severe disease in adults.\(^{11,12}\) Congenital neuromuscular disease has already been mentioned, and should be considered in all patients, but particularly those with severe scoliosis. Other diseases that should be considered in young adults include myasthenia gravis, multiple sclerosis, Guillain–Barré syndrome, and viral encephalitides such as the West Nile virus.

During sleep, physiologic reductions in alveolar ventilation and respiratory drive magnify hypoxemia and hypercapnia. As a result, the initial manifestations of hypoventilation often include disturbed sleep, daytime somnolence, and morning headaches. With long-standing disease, polycythemia, pulmonary hypertension, and right heart failure may develop. Early diagnosis and treatment can prevent or delay these complications.
Because the initial manifestations of hypoventilation are common and nonspecific, the key to the diagnosis is maintaining a high clinical suspicion, particularly in patients with known neuromuscular or chest wall disorders. A careful history and physical examination, chest radiography, and arterial blood gas measurement will identify the diagnosis in most cases. Pulmonary-function testing can be helpful in distinguishing between the chief causes of hypoventilation and in documenting the degree of physiological impairment. The total lung capacity and forced vital capacity are reduced in patients with muscle weakness and chest wall disorders, but normal in patients with respiratory-drive problems. The maximum inspiratory pressure is decreased in patients with neuromuscular disease but normal in those with chest wall disorders and respiratory-drive abnormalities. Diaphragmatic dysfunc-
tion can be diagnosed by demonstrating a significant reduction in forced vital capacity between the upright position and the supine position. Fluoroscopy is reasonably sensitive for detecting unilateral diaphragmatic paralysis, but has a high false negative rate in patients with bilateral disease. Measurement of transdiaphragmatic pressure with use of esophageal and gastric balloons provides the most accurate assessment of diaphragmatic muscle strength.

The ideal treatment of alveolar hypoventilation involves correction of the underlying disease state. Unfortunately, in many patients this is not possible. Treatment is often supportive and consists primarily of supplemental oxygen and noninvasive positive pressure ventilation. The goals of therapy are to relieve hypoxemia-related fatigue, dyspnea, confusion, and hypercapnia-related headache and somnolence and to prevent long-term sequelae such as the development of pulmonary hypertension and right heart failure. When administered properly, nocturnal noninvasive ventilation can have profound benefits, as in the case described here.

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