

# Post-Tussive Syncope in a 39-Year-Old Intravenous Drug User

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**A** 39-year-old man with a medical history of Human Immunodeficiency Virus (HIV) infection for 4 years presented to the emergency department with a chief complaint of fainting after vigorous coughing. The patient was functionally normal until 2 months prior to admission when he developed dyspnea on exertion and a slowly progressive cough productive of white sputum. These symptoms worsened, and one day before admission the patient had a severe coughing spell followed by the abrupt loss of consciousness. The loss of consciousness lasted approximately 1 minute, after which he became fully alert and oriented. The patient had no light-headedness, chest pain, palpitations, nausea, vomiting, or diaphoresis prior to this syncopal episode. No seizure activity or urinary/fecal incontinence was described. There was no prior history of syncope or seizures. On the day of admission he had a second similar episode of syncope after coughing and sought medical attention.

The patient had a past medical history of HIV infection and hepatitis C. A CD<sub>4</sub> count measured 7 months

before admit was 360/mm<sup>3</sup>. Three years prior to admission he had a short period of antiretroviral treatment that he discontinued due to nausea. His social history included a ten-pack-year history of smoking, daily intravenous heroin use, occasional intranasal cocaine use, and alcohol intake of one case of beer a week. He had been incarcerated for the 3 months prior to admission, during which time he had no access to alcohol or drugs. He had no past surgical history or allergies and was taking no medications at the time of his syncope. Family history was unremarkable. Review of systems was negative for paroxysmal nocturnal dyspnea, orthopnea, or peripheral edema.

Physical exam showed a well nourished, healthy appearing man in no apparent distress. Vital signs on admission were a blood pressure of 137/85 mm Hg, heart rate of 91 beats per minute, temperature of 36°C, and a respiratory rate of 24 breaths per minute. Oxyhemoglobin saturation while he breathed air was 98%. Cardiovascular exam demonstrated a regular rate and rhythm with a loud P<sub>2</sub>, a left parasternal heave, and a

## CME INFORMATION

### TARGET AUDIENCE

The January/February Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, emergency medicine physicians, pediatricians, dermatologists, radiologists, and neurologists.

### EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to identify and understand the pathophysiology, clinical presentation, diagnosis, and treatment of pulmonary hypertension.

### CREDIT

The LSMS Educational and Research Foundation designates

this educational activity for a maximum of one (1) hour of category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

### DISCLOSURE

Dr. McElveen has nothing to disclose.  
Dr. Walters has nothing to disclose.  
Dr. Amoss has nothing to disclose.  
Dr. Lopez discloses that he is a member of the LSMS *Journal* Board and the LSMS *Journal* Editorial Board.  
Dr. deBoisblanc has nothing to disclose.

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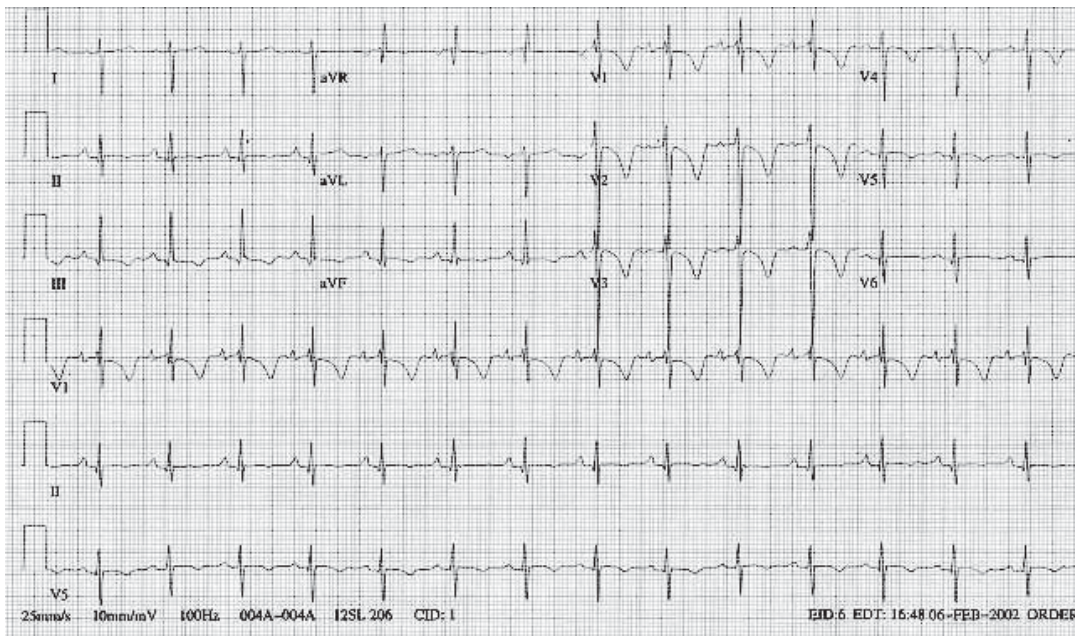


**Figure 1.** Anterior-posterior radiograph of the chest demonstrating enlargement of proximal pulmonary arteries.

I/VI holosystolic murmur along the left sternal border that increased in intensity with inspiration. His jugular venous pressure was estimated at 15 cm H<sub>2</sub>O, and prominent *v* waves were noted. His lungs were clear to auscultation, and his abdominal exam was unremarkable. Blood chemistry values, including liver function tests, were normal. The patient's peripheral white blood cell count was 4,900/mm<sup>3</sup> with a normal hemoglobin and a platelet count of 103,000/mm<sup>3</sup>. Serum and urine toxicology screens were negative. Arterial blood gases in the emergency department were a pH of 7.47, pCO<sub>2</sub> of 32.4mmHg, pO<sub>2</sub> of

102mmHg, and HCO<sub>3</sub> 23mEQ/L on an FIO<sub>2</sub> of 0.28. The admission anterior-posterior chest radiograph is shown in Figure 1, and the initial electrocardiogram is shown in Figure 2.

The patient was admitted to the hospital with a diagnosis of syncope due to pulmonary arterial hypertension and was begun on enoxaparin 1 mg/kg subcutaneously every 12 hours while a work-up for venous thromboembolism was pursued. Following a low-probability, ventilation/perfusion lung scan and a negative bilateral lower extremity Doppler ultrasound, enoxaparin was discontinued. A transthoracic contrast echocardiogram revealed markedly dilated right-sided chambers, severe tricuspid regurgitation, a pulmonary arterial systolic pressure estimate of 90 mmHg, and no intracardiac shunt. There were no clinical findings consistent with obstructive sleep apnea, chronic obstructive pulmonary disease, or connective tissue disease; and his ventilatory function tests were normal. Antinuclear antibody titer and rheumatoid factor were negative. A right heart catheterization demonstrated a pulmonary arterial pressure of 95/56mmHg, a mean right atrial pressure of 13 mm Hg, and a normal pulmonary arterial occlusion pressure. There was no intracardiac shunt. Pulmonary vasoreactivity was tested with epoprostenol, to which there was no significant vasodilator response. The patient was diagnosed with HIV-related pulmonary hypertension (HRPH) and was discharged on highly active antiretroviral therapy (HAART), warfarin, digoxin, and a cough suppressant pending approval of domiciliary, continuous, intravenous epoprostenol.



**Figure 2.** Electrocardiogram demonstrating right axis deviation and right ventricular hypertrophy.

## DISCUSSION

### Clinical Evaluation of Pulmonary Hypertension

Pulmonary hypertension most commonly presents with symptoms of insidious dyspnea on exertion. Other presenting symptoms may be chest pain, cough, or syncope. Abnormal physical exam findings characteristic of right ventricular pressure overload include a left parasternal heave, loud  $P_2$ , elevated central venous pressure, and the murmurs of tricuspid regurgitation and pulmonic regurgitation. ECG findings may include P pulmonale, right axis deviation, R/S ratio greater than one in  $V_1$ , complete or incomplete right bundle branch block, and secondary ST-T changes over the anterior precordial leads. Chest radiography often shows prominent proximal pulmonary arteries with peripheral tapering and enlargement of the right ventricle on the lateral projection. Because the signs and symptoms of pulmonary hypertension can mimic other cardiopulmonary diseases, the diagnosis of pulmonary hypertension is often first suspected after performing two-dimensional echocardiography, which estimates pulmonary arterial systolic pressure by measuring the peak velocity of the jet of tricuspid regurgitation.

Once the diagnosis of pulmonary hypertension is suspected, the work-up should focus on identifying potential secondary causes. An international consensus panel has classified pulmonary hypertension into 1) diseases of the respiratory system and/or hypoxemia, 2) thromboembolic pulmonary hypertension, 3) pulmonary venous hypertension, 4) pulmonary arterial hypertension, and 5) disorders directly affecting the pulmonary vasculature (eg, sarcoidosis). Because our patient had normal ventilatory function tests, nearly normal arterial blood gases, no sleep-disordered breathing, a normal ventilation/perfusion lung scan, and no evidence of pulmonary venous hypertension by echocardiography or right heart catheterization, he fit the diagnostic category of primary pulmonary arterial hypertension. Pulmonary arterial hypertension has been associated with congenital intracardiac shunts, several systemic connective tissue diseases, diet pill use, liver disease, and HIV infection. When no identifiable secondary cause can be found for a case of pulmonary arterial hypertension, the patient is given a diagnosis of primary pulmonary hypertension (PPH).

Pulmonary function testing with arterial blood gas measurement is the major diagnostic test used to identify patients with pulmonary parenchymal or airways diseases. Nocturnal polysomnography is used when sleep apnea is suspected. Because 50% of patients eventually demonstrated to have chronic thromboemboli do not have a documented history of pulmonary embolism, a ventilation perfusion lung scan is always indicated.

Left ventricular systolic or diastolic dysfunction, valvular heart disease, and pericardial diseases are the

most common causes of pulmonary venous hypertension. These disorders are best evaluated with 2-D echocardiography and cardiac catheterization, which also can be used to exclude most cases of congenital intracardiac shunts.

Many diseases or disorders have been associated with pulmonary arterial hypertension. Among the collagen vascular diseases, limited scleroderma (formerly known as the CREST syndrome) is the most common. Other causes include HIV infection, cirrhosis due to hepatitis C or alcohol abuse, and use of sympathomimetic or anorectic drugs, such as cocaine, amphetamines, or fenfluramine. The clinical features, and histopathology, and treatment approach to most cases of secondary pulmonary arterial hypertension resemble those of primary pulmonary hypertension.

### HIV-Related Pulmonary Hypertension

The most likely diagnosis in our patient was HIV-related pulmonary hypertension. As noted above, hepatitis C and chronic cocaine use also are causes of pulmonary hypertension. Although our patient had hepatitis C and had abused cocaine, these were thought to be unlikely causes of his pulmonary hypertension because 1) he had no evidence of liver dysfunction, and 2) his cocaine use had been infrequent. Furthermore, the relative rarity of cocaine as a cause of severe pulmonary arterial hypertension makes this even less likely.

First described by Kim and Factor in 1987, pulmonary hypertension as a complication of HIV infection is now well-recognized.<sup>1</sup> The estimated incidence of symptomatic pulmonary hypertension in HIV infection is approximately 0.5%. Although the exact etiology is still unclear, it is believed that the virus plays an indirect, rather than direct, role in the pathogenesis of the vasculopathy. Support for this concept include data from Mette et al<sup>2</sup> who were unable to isolate the virus from lung tissue of HIV-infected individuals with pulmonary hypertension. The correlation between the level of CD<sub>4</sub> cells and the prevalence or severity of pulmonary hypertension is poor; data on viral load are lacking.<sup>3</sup>

Several investigators have suggested that mediator release triggered by the virus may be the mechanism underlying HRP. Endothelin-1 (ET-1), a potent endogenous vasoconstrictor, is produced by macrophages and vascular endothelial cells. Several studies have demonstrated increased concentrations of ET-1 in lung specimens from patients with primary pulmonary hypertension as compared to patients without pulmonary hypertension. This increase was correlated with the increase in pulmonary vascular resistance.<sup>4</sup> Ehrenreich *et al* demonstrated that HIV-1 glycoprotein 120 stimulates the secretion of ET-1 from macrophages, supporting the theory that ET-1 plays a role in HRP.<sup>5</sup> Other cytokines,

such as IL-1B, IL-6, TNF-a, and PDGF, also have been proposed to play a role in the etiology. A genetic predisposition to pulmonary arterial hypertension may also exist in some patients with HIV infection. Morse et al showed an increased frequency of certain HLA subclasses in patients with HRPB as compared to controls.<sup>6</sup>

The treatment options for HRPB are limited. In a case-controlled study involving 19 patients, Opravil *et al* observed a mean decrease in pulmonary artery pressure of 3.2 mm Hg in patients receiving antiretroviral therapy versus an increase of 19 mm Hg in those untreated; the median survival was unchanged between the two groups.<sup>7</sup>

Continuous intravenous epoprostenol infusion (prostacyclin, PGI<sub>2</sub>) has been shown to improve survival in patients with PPH. Aguilar and Farber studied the effects of long-term epoprostenol infusion in six patients with HRPB.<sup>8</sup> They found a decrease in mean pulmonary artery pressure of 21.7mm Hg. Both cardiac output and New York Heart Association functional class improved in all patients. A long-acting analog of epoprostenol, treprostenil, is an effective alternative that can be administered subcutaneously although injection-site pain may limit its acceptance.

Bosentan, an oral, endothelin-1, dual-receptor antagonist, has recently been approved by the FDA. Because it is currently the only oral treatment indicated for pulmonary arterial hypertension, it has great appeal in patients with HRPB. The potential for serious hepatotoxicity and drug interactions with anti-retroviral therapies should restrict its use to specialists. Finally, retrospective studies suggest that patient survival is improved with warfarin therapy to an INR 2.0–3.0.

In summary, HIV-related pulmonary hypertension is an occasional complication of HIV infection. The pathogenesis of pulmonary hypertension in this disorder remains unknown. Treatment options are limited, but antiretroviral therapy, epoprostenol infusion or oral bosentan, and warfarin may be beneficial.

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## CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 63. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to February 29, 2004. Participants must attain a minimum score of 75% to receive credit.

**For each question, choose the one answer that is most correct.**

1. All of the following physical exam findings are characteristic of pulmonary hypertension except:
  - a) Split S<sub>2</sub> with a loud P<sub>2</sub> component
  - b) Holosystolic murmur at the left sternal border that increases with inspiration
  - c) Holosystolic murmur at the apex that radiates to the axilla
  - d) Elevated central venous pressure
2. True or False. Use of diet pills including amphetamines and fenfluramine is associated with an increased incidence of pulmonary arterial hypertension.
3. Pulmonary arterial hypertension has been associated with all of the following except :
  - a) Congenital intracardiac shunts
  - b) Scleroderma
  - c) Cirrhosis
  - d) HIV infection
  - e) Iron deficiency anemia
4. Beneficial treatment options for patients with HIV-related pulmonary hypertension include all of the following except:
  - a) Steroids
  - b) Antiretroviral therapy
  - c) Epoprostenol infusion
  - d) Oral bosentan
  - e) Warfarin

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