# 39-Year-Old Woman With Dyspnea and Chest Pain

Scott A. Helgeson, MD; Asha U. Nookala, MD; and Joseph L. Blackshear, MD

A 39-year-old woman was admitted to the hospital with a 7-month history of dyspnea that had worsened over the preceding 2 days, along with several months of pleuritic chest pain that radiated from the left side of the chest to the back. Her medical history was notable for atrial fibrillation (AF) treated with catheter ablation 10 months earlier and nonischemic congestive heart failure diagnosed at age 30 years at an outside institution. The patient did not have orthopnea, edema, cough, or weight gain. She had been treated previously with warfarin prophylaxis for AF, but this treatment was discontinued 2 months before presentation. Her family history was notable for pulmonary embolism in her father at age 40 years.

The patient had been hospitalized twice at other facilities in the preceding 2 months, the first hospitalization for hypoxemic respiratory failure. Work-up included chest radiography and computed tomography (CT), which revealed patchy areas of ground-glass opacities and bilateral consolidations. Echocardiography documented an ejection fraction of 63%, normal diastolic function, and an estimated mean pulmonary artery pressure of 24 mm Hg. A video-assisted thoracopic lung biopsy identified nonspecific interstitial pneumonitis. The patient received a 7-day course of meropenem and linezolid. During the second hospitalization, pulmonary infiltrates were treated with cefepime and levofloxacin.

On presentation to our facility, the patient's vital signs were normal, and physical examination findings were remarkable for an increased pulmonic second heart sound on cardiac auscultation and diffuse chest wall tenderness. No jugular venous distention was noted, nor were cardiac murmurs, right ventricular lift, peripheral edema, or stigmata of chronic liver disease or venous congestion.

Electrocardiography revealed sinus tachycardia (heart rate, 106 beats/min) with no other abnormalities. Chest radiography identified diffuse bilateral interstitial opacities with Kerley B lines suggestive of pulmonary edema. Echocardiography confirmed the findings of the outside study but revealed a prominent color jet emanating from the right superior pulmonary vein and accelerated diastolic flow velocity of greater than 1 m/s (reference range,[1] 0.47-0.54 ms) by Doppler. Laboratory testing revealed the following notable results (reference ranges provided in parentheses): hemoglobin, 11.2 g/dL (12.0-15.5 g/dL); white blood cell count, 20.4 × $10^9$/L (3.5-10.5 × $10^9$/L); segmented neutrophils, 92.5% (44.4%-70.9%); immature granulocytes, 1.1% (0.0%-3.0%); lymphocytes, 4.1% (17.8%-41.5%); quantitative D-dimer, 1.7 μg/mL (≤0.5 μg/mL); arterial pH, 7.43 (7.35-7.45); partial pressure of arterial carbon dioxide, 33.7 mm Hg (35-45 mm Hg); partial pressure of arterial oxygen, 63.3 mm Hg (80-100 mm Hg); glucose, 295 mg/dL (70-140 mg/dL); lactate, 2.2 mmol/L; B-type natriuretic peptide, 82 pg/mL (≤64 pg/mL); troponin T, <0.01 ng/mL (<0.01 ng/mL); and serum procalcitonin, <0.05 ng/mL (≤0.15 ng/mL).

**1. Which *one* of the following is the *most likely* explanation for this patient's dyspnea?**

a. Acute coronary syndrome
b. Constrictive pericarditis
c. Pulmonary vein stenosis (PVS)
d. Heart failure with preserved ejection fraction
e. Pulmonary artery hypertension (PAH)

Acute coronary syndromes typically occur with angina that is substernal, lasts a few minutes, occurs with exertion, and is relieved with rest or nitroglycerin. Acute coronary syndrome is diagnosed on the basis of clinical presentation, electrocardiographic findings, and troponin levels. Constrictive pericarditis is one cause of heart failure with a normal left ventricular ejection

**See end of article for correct answers to questions.**

Resident in Internal Medicine, Mayo School of Graduate Medical Education, Jacksonville, FL (S.A.H.); Resident in Internal Medicine, Mayo School of Graduate Medical Education, Rochester, MN (A.U.N.); Advisor to residents and Consultant in Cardiovascular Diseases, Mayo Clinic, Jacksonville, FL (J.L.B.).

fraction. Most cases are idiopathic, and AF is commonly associated. However, jugular venous distention, peripheral edema, and possibly ascites would be expected, as well as left atrial enlargement.

Pulmonary vein stenosis has been described as a complication arising after catheter ablation for AF,[2] with onset of clinical findings typically 3 to 6 months after ablation. Pulmonary vein stenosis may cause a pulmonary edema pattern on chest radiography, consolidation-like findings over the affected lung such as dullness to percussion, increased fremitus, whisper pectoriloquy, bronchial breath sounds, and crackles. Recurrent pneumonias are common with PVS, and hemoptysis may occur. Pulmonary artery hypertension may or may not develop secondary to the stenosis. There are no laboratory findings consistent with PVS.

The patient had normal echocardiographic findings including normal left ventricular diastolic function. Although she had a history of AF, which is often associated with heart failure with preserved ejection fraction, there was no evidence of underlying diastolic dysfunction on echocardiography. Pulmonary artery hypertension presents nonspecifically with exertional dyspnea, fatigue, and occasionally syncope that develop over the course of years. Once PAH becomes severe, right ventricular failure develops and exertional chest pain, syncope, edema, ascites, and pleural effusion may start to appear. Physical examination usually elicits an increased intensity of the pulmonic second heart sound. Echocardiography will identify a mean pulmonary artery pressure of more than 25 mm Hg.

Echocardiography confirmed the findings of the outside study but also revealed a prominent color jet emanating from the right superior pulmonary vein and accelerated diastolic flow velocity of more than 1 ms by Doppler, which is seen in PVS. This finding, in conjunction with knowledge of the potential complications from the prior ablation procedure, suggested a diagnosis of PVS.

**2. At this time, which *one* of the following is the *most appropriate* test to establish a diagnosis of PVS?**

a. Transesophageal echocardiography
b. Bronchoscopy
c. Ventilation-perfusion scan and venous phase–gated CT angiography
d. Oxygen consumption exercise study
e. Right-sided heart catheterization with nitric oxide challenge

Transesophageal echocardiography is able to visualize all the pulmonary veins in 96% of patients and may reveal evidence supporting a diagnosis of PVS, but image interpretation is highly dependent on the experience of the physician, and precise anatomic detail such as lumen diameter and length of stenosis are not definable by transesophageal echocardiography.[3] Bronchoscopy is unlikely to establish a tissue diagnosis in a patient with pulmonary infiltrates who already had an open lung biopsy.

Venous phase–gated CT angiography is the test most likely to define the precise anatomy of the junction of the 4 pulmonary veins to the left atrium. The venous phase detail is important because standard pulmonary embolism protocol–gated CT angiography or nongated CT scanning would lack sufficient spatial resolution in the pulmonary veins for this purpose. The physiologic consequences of PVS would best be appreciated with radionuclide ventilation-perfusion lung scanning for evidence of perfusion defects that match the PVS.

An exercise test with measured oxygen consumption is an excellent means of assessing maximum cardiac output in patients with known cardiac disorders. Although this test has value in distinguishing cardiogenic dyspnea from dyspnea due to lung disease, it would not aid in making a precise diagnosis in this instance. Right-sided heart catheterization accurately measures pulmonary artery pressures, pulmonary vascular resistance, and pulmonary capillary wedge pressure, and nitric oxide inhalation assesses pulmonary vascular responsiveness, which aids in choosing treatment in patients with PAH. This test allows detailed visualization of the pulmonary veins but is an invasive test. This test should be performed but is not the best test at this time.

Our patient underwent venous phase CT angiography, which revealed occlusion of the left superior pulmonary vein and high-grade stenosis of the left inferior pulmonary vein and both right pulmonary veins. Ventilation-perfusion scanning documented absent perfusion to the left lung. On the basis of the clinical presentation and the imaging results, symptomatic PVS


Mayo Clin Proc. ■ July 2016;91(7):e87-e91 ■ http://dx.doi.org/10.1016/j.mayocp.2015.12.020
www.mayoclinicproceedings.org

as a complication of AF catheter ablation was diagnosed. Our patient had had an ablation of the 4 pulmonary veins performed within the atrium, but a review of the procedure note from the outside institution revealed that a persistent focus of ectopic activity remained in the left superior pulmonary vein, and ablation was later performed within that vein.

**3. Which *one* of the following is the *best* predictor of development of PVS in this patient?**

a. In-vein ablation
b. Pulmonary artery hypertension
c. Hypertension
d. History of pulmonary emboli
e. Paroxysmal AF

In the early days of catheter ablation for AF, focal ablation was performed within the vein itself. Because it was associated with PVS in more than 5% of patients, ablation within the vein has largely been abandoned in favor of circumferential ablation of the left atrial surface surrounding the 4 pulmonary veins, with 2 studies documenting a reduction in incidence from 7.9% and 11% to 1% and 1.4%, respectively.[4,5] Our patient does not have PAH, and having PAH is not in itself a risk factor for development of PVS, nor is hypertension. Our patient has a history of pulmonary emboli, but pulmonary emboli do not cause or increase the risk for PVS. Atrial fibrillation does not increase the risk for development of PVS.

Our patient underwent an in-vein ablation and has since had development of PVS. She continued to require increasing amounts of oxygen during the initial laboratory and imaging assessment.

**4. In view of the diagnosis of PVS, which *one* of the following is the *most appropriate* treatment option for this patient?**

a. Monitor the patient
b. Balloon angioplasty without stenting
c. Balloon angioplasty with stenting
d. Pulmonary vein bypass
e. Anticoagulation

This patient has symptomatic occlusion of 1 pulmonary vein and stenosis of the remaining 3 pulmonary veins. Because the pathophysiology of PVS is intimal thickening in response to prior injury, increasing stenosis is suggested by the progression of her symptoms, and thus monitoring without intervention is inappropriate. Watchful waiting may be an option for asymptomatic patients, but success with catheter intervention is markedly improved if performed before occlusion develops.[3] Balloon angioplasty without stenting was the treatment of choice in the past because there were no available stents large enough to fit the pulmonary veins. Although the cumulative experience is relatively small, balloon angioplasty with stenting appears to be associated with lower rates of restenosis compared with angioplasty alone.[4,6] There have been no published data showing the use of pulmonary vein bypass for the treatment of PVS. Anticoagulation for patients with PVS is important, but it is used to prevent thrombosis after stenting.

Our patient underwent angioplasty with stenting. The left superior vein was confirmed to be occluded. After placement of 2 stents, the left inferior pulmonary vein stenosis was reduced from 90% to 0%, and the pulmonary vein to left atrial pressure gradient was reduced from 25 mm Hg to 3 mm Hg. The right superior pulmonary vein stenosis of 80% was reduced to 10%, and the pressure gradient declined from 12 mm Hg to 3 mm Hg. The right inferior pulmonary vein stenosis was reduced from 90% to 10%, and the pressure gradient was 3 mm Hg after placement of 2 stents. The first day after stent placement, the patient reported subjective feelings of decreased dyspnea, required no oxygen supplementation at rest, and required only minimal oxygen supplementation with exertion. Repeated ventilation-perfusion scanning and CT with and without gating revealed no immediate improvement in results, which is expected.

**5. Which *one* of the following is the *best* way to manage PVS long-term after treatment?**

a. Blood pressure control
b. Routine magnetic resonance imaging
c. Routine chest radiography
d. Anticoagulation
e. Cholesterol control

After treatment with angioplasty and stenting, patients will require long-term management because of a high risk for restenosis. Blood pressure control has not been found to decrease mortality or morbidity after treatment. Routine

magnetic resonance imaging is an option, but because of imaging artifacts, CT angiography remains the preferred imaging modality for long-term follow-up. Chest radiography can only identify the consequences of PVS, so it is not a sufficient option for follow-up. Anticoagulation should be initiated in patients who undergo angioplasty with stenting to prevent thrombosis. No trial data have been published that suggest the required duration of anticoagulant therapy; currently, anticoagulation is most commonly recommended for an indefinite period. The most common complication of pulmonary vein angioplasty with or without stenting is restenosis, and it may occur in up to 50% of veins treated.[6] In one study, recurrent symptoms occurred early, at a mean of 3.2±2.8 months, with a greater rate in those who had stent placement than in those who did not.[6] Other complications included strokes (in 0.28% of patients) and transient ischemic attacks (in 0.66%).[6] Cholesterol control, like blood pressure control, has not been documented to improve outcomes in these patients.

The patient was discharged with warfarin and clopidogrel treatment and scheduled follow-up appointments. She underwent CT angiography at 1-month follow-up. The CT angiography revealed that the 3 pulmonary veins treated with stents were widely patent. The left superior pulmonary vein remained occluded. The patient's previous imaging findings of patchy areas of ground-glass opacities and septal thickening have substantially improved except in the left upper lobe, which is the area drained by the occluded left superior pulmonary vein. The patient is scheduled for 3- and 6-month follow-up.

## DISCUSSION

Catheter ablation for AF using pulmonary vein isolation developed after it was discovered that "focal" AF could be traced to nests of cardiac cells within the walls of pulmonary veins proximal to their pulmonary venous-left atrial connection. Focal ablation within the vein often cured the arrhythmia but was associated with a 5% to 11% incidence of pulmonary vein stenosis, which plummeted to less than 1% when ablation within the pulmonary veins was abandoned in favor of ablation outside the orifice.[4] The learning curve is important, with low-volume centers and centers with less experience having unacceptably high rates of this complication, which appears to be rare if ablation is done outside the vein orifice with intracardiac echocardiographic monitoring and careful monitoring of temperature and energy delivery.[5]

Pulmonary vein stenosis typically presents 3 to 6 months after an ablation and is often missed. The true incidence of PVS is highly dependent on procedural factors and patient sex, but it has been estimated that the rate may persist at 1% to 3%. If the true overall rate is 2%, then with 50,000 to 100,000 ablations being performed currently in the United States, as many as 2000 cases could be seen annually nationwide.[7] Many factors have been studied for their independent predictive value for development of PVS, and odds ratios for the most predictive factors are age, 1.00; female sex, 2.23; structural heart disease, 0.74; pulmonary vein diameter, 1.11; and paroxysmal atrial fibrillation, 0.82.[8] The diagnosis should be suspected in the aftermath of AF ablation in any patient with vague or overt pulmonary symptoms such as shortness of breath and fatigue and pulmonary findings including fibrotic changes, recurrent pneumonia, congestion, or hemoptysis. Older and female patients experience this complication more often than younger and male patients following an ablation.[8] There is also an increased risk with smaller-diameter pulmonary veins.[8]

Computed tomographic angiography is necessary to diagnosis PVS and may be used for screening and monitoring the patient after stent placement. Echocardiography may be used to aid in diagnosis, chiefly through the detection of increased pulmonary vein velocities or right ventricular enlargement or dysfunction, but because of its inability to document stenosis severity and occlusion of individual veins, it is not sufficient. When restenosis after pulmonary vein angioplasty or stenting occurs, it also typically presents symptomatically about 3 months after the procedure. Computed tomography is the preferred diagnostic modality for restenosis. At some centers, routine follow-up imaging studies are obtained 1, 3, and 6 months postoperatively.

Currently, angioplasty with stenting to correct the stenotic lesion is the preferred treatment option. However, restenosis occurs in approximately 47% of patients, and it seems likely that future investigation of drug-eluting stents will


Mayo Clin Proc. ■ July 2016;91(7):e87-e91 ■ http://dx.doi.org/10.1016/j.mayocp.2015.12.020
www.mayoclinicproceedings.org

be undertaken,[6] Because drug-eluting stents retard the formation of a neointima, the need for effective anticoagulant or antiplatelet therapy or combinations thereof will need further clarification. Watching and waiting should not be used in symptomatic patients because of the risk of pulmonary damage already occurring before symptoms present. Patients should be screened after stenting for the development of symptoms of restenosis, usually for up to 2 years after the procedure for restenosis.

Untreated PVS has a poor prognosis with a high likelihood of pulmonary fibrosis, pulmonary necrosis due to lack of blood flow, and/or death. The optimal duration of anticoagulation therapy after angioplasty with stenting is unknown.

A patient's time course of symptoms is important for the diagnosis of disease. For patients who undergo a procedure and became symptomatic soon after, the clinician should maintain a broader differential diagnosis that includes postoperative complications. In our patient, recognition of the association of the patient's symptoms with the previous procedure would have allowed for earlier diagnosis and would have resulted in earlier treatment and possibly salvaged patency of the left superior pulmonary vein and reduction of subsequent hospitalizations.

**Correspondence:** Address to Joseph L. Blackshear, MD, Division of Cardiovascular Diseases, Mayo Clinic, 4500 San Pablo Rd S, Jacksonville, FL 32224 (blackshear.joseph@mayo.edu).

## REFERENCES

1. Gentile F, Mantero A, Lippolis A, et al. Pulmonary venous flow velocity patterns in 143 normal subjects aged 20 to 80 years old: an echo 2D colour Doppler cooperative study. *Eur Heart J*. 1997;18(1):148-164.
2. Packer DL, Keelan P, Munger TM, et al. Clinical presentation, investigation, and management of pulmonary vein stenosis complicating ablation for atrial fibrillation. *Circulation*. 2005; 111(5):546-554.
3. Barrett CD, Di Biase L, Natale A. How to identify and treat patient with pulmonary vein stenosis post atrial fibrillation ablation. *Curr Opin Cardiol*. 2009;24(1):42-49.
4. Packer DL. Strategies on how to diagnose, prevent, and treat pulmonary vein stenosis. In: Natale A, Jalife J, eds. *Atrial Fibrillation: From Bench to Bedside*. Totowa, NJ: Humana Press; 2008:291-306.
5. Saad EB, Rossillo A, Saad CP, et al. Pulmonary vein stenosis after radiofrequency ablation of atrial fibrillation: functional characterization, evolution, and influence of the ablation strategy. *Circulation*. 2003;108(25):3102-3107.
6. Prieto LR, Schoenhagen P, Arruda MJ, Natale A, Worley SE. Comparison of stent versus balloon angioplasty for pulmonary vein stenosis complicating pulmonary vein isolation. *J Cardiovasc Electrophysiol*. 2008;19(7):673-678.
7. Cappato R, Calkins H, Chen S, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circulation*. 2005;111(9):1100-1105.
8. Dong J, Vasamreddy CR, Jayam V, et al. Incidence and predictors of pulmonary vein stenosis following catheter ablation of atrial fibrillation using the anatomic pulmonary vein ablation approach: results from paired magnetic resonance imaging. *J Cardiovasc Electrophysiol*. 2005;16(8):845-852.

**CORRECT ANSWERS: 1. c. 2. c. 3. a. 4. c. 5. d**