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34-Year-Old Man With Exertional Syncope, Dyspnea, and Chest Pain

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See end of article for correct answers to questions.

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A 34-year-old man presented for evaluation of recurrent syncope, chest pain, and shortness of breath on exertion. His medical history included localized testicular cancer, which was treated with orchiectomy and radiation 2 years before presentation.

Symptoms started 7 years before this presentation with light-headedness and exertional syncope with walking 2 blocks. He denied postsyncopal confusion and urinary incontinence. Initial evaluation at an outside institution included an electrocardiographic (ECG) stress test, a Holter monitor, and a tilt-table test, the results of which were reportedly normal. Neurologic evaluation was negative for seizure disorder. The patient was diagnosed as having vasovagal syncope and was treated with midodrine and fludrocortisone for 1 year without improvement. Syncopal episodes progressed and became daily occurrences.

Nine months before presentation, the patient experienced exertional chest pain and dyspnea. The pain was pressurelike and burning in the anterior chest, without radiation, and was relieved with rest. On presentation to Mayo Clinic, his physical examination was remarkable for a body mass index of 31 (calculated as weight in kilograms divided by height in meters squared), negative orthostatics, a slight right ventricular (RV) lift, a split second heart sound with an accentuated pulmonary component, and a soft systolic murmur at the left sternal border that varied with breathing. His family history was unremarkable for sudden death, premature coronary artery disease (CAD), or other heart or lung disease. The patient never smoked and rarely consumed small amounts of alcohol. He denied the use of herbal and dietary supplements and was not taking long-term medications. A chest radiograph showed a prominent right atrium. An ECG demonstrated a sinus mechanism with right axis deviation and findings of RV hypertrophy.

1. Which *one* of the following is the *most* likely diagnosis?

a. Vasovagal syncope
b. Heart failure with preserved ejection fraction
c. Pulmonary hypertension (PH)
d. Hypertrophic obstructive cardiomyopathy (HOCM)
e. Coronary artery vasospasm

Vasovagal syncope can be considered in patients with exertional dyspnea once other cardiac causes are ruled out.[1] Although dyspnea on exertion can suggest heart failure with preserved ejection fraction, there are no other symptoms or examination findings to suggest heart failure in this relatively younger patient. However, in this patient's case, symptoms, physical examination findings, and ECG findings are most suggestive of PH. Physical examination findings in PH are due to RV enlargement, tricuspid regurgitation, and RV failure. These findings include increased intensity of the pulmonary component in the second heart sound and splitting of the second heart sound as the RV fails or right bundle branch block develops. Murmurs associated with PH include a holosystolic tricuspid regurgitation murmur and a diastolic pulmonary valve regurgitation murmur. Other physical examination findings in PH may include elevated jugular venous pressure, RV third heart sound, and findings consistent with severe tricuspid regurgitation (a prominent V wave in the jugular venous pulse, which is most useful; hepatomegaly; peripheral edema; and a pulsatile liver). The ECG findings in PH may include right axis deviation and RV hypertrophy.[2]

With exertional syncope or dyspnea, HOCM is possible. However, physical examination often demonstrates a systolic murmur at the left lower sternal border that accentuates with release of the Valsalva maneuver and a left ventricular gradient with or without systolic anterior motion of the mitral valve on an echocardiogram. Common ECG findings in HOCM include left

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axis deviation and left ventricular hypertrophy.[3] Coronary artery vasospasm can cause chest pain but not necessarily related to exertion, and an ECG may show ischemia. Additional diagnostic testing was ordered to evaluate this patient's exertional syncope.

2. Which *one* of the following would be the *best* next diagnostic test?

a. Coronary artery angiography
b. Transthoracic echocardiography
c. Repeated tilt-table testing
d. 30-day event monitoring
e. Exercise (treadmill) stress test

Although a coronary angiogram would be useful to rule out CAD, the pretest probability of CAD was low in this patient, and, therefore, coronary artery angiography is not an appropriate next step. In this patient's case, a cardiac cause of syncope is suggested by his exertional symptoms, and the best next step is to evaluate with an echocardiogram. A repeated tilt-table test is not indicated because the patient's symptoms are not consistent with vasovagal syncope or autonomic dysfunction, and he had normal study results in the past. Although an arrhythmia should still be considered, a 24-hour Holter monitor is sufficient because symptoms occur daily. An exercise stress test may be useful to evaluate for abnormal arrhythmia with exertion; however, this test result was also previously normal.

An echocardiogram in this patient demonstrated a normal ejection fraction of 60%, normal valves, RV enlargement with mild decreased systolic function, and estimated RV systolic blood pressure of 45 mm Hg.

3. At this time, which *one* of the following tests is *most* useful to confirm the suspected diagnosis and guide treatment?

a. Cardiac magnetic resonance imaging (MRI)
b. Coronary computed tomographic (CT) angiography
c. Right-sided heart catheterization with vasodilator challenge
d. No further tests needed
e. Myocardial biopsy

Cardiac MRI and coronary CT angiography can help evaluate RV and pulmonary artery anatomy; MRI can also help estimate pulmonary arterial pressure (PAP).[4] However, right-sided heart catheterization with hemodynamic assessment and vasodilator challenge is the criterion standard for confirming the diagnosis of PH and guiding treatment. Right-sided heart catheterization directly measures PAP and pulmonary capillary wedge pressure (PCWP). Elevated PCWP indicates a secondary cause of PH due to left-sided heart disease. Pulmonary arterial hypertension (PAH) is defined as a mean PAP (mPAP) greater than 25 mm Hg, pulmonary vascular resistance of at least 3 Wood units, and PCWP less than 15 mm Hg. After obtaining baseline hemodynamic measurements, nitric oxide is infused to assess for a vasodilator response. A positive response is defined as a decrease in mPAP of 10 mm Hg or more to a value of 40 mm Hg or less without concomitant worsening in the cardiac index.[5] A small proportion of patients with a positive vasodilator challenge response have a survival benefit from treatment with calcium channel blockers (CCBs).[6] Further testing is needed to confirm the diagnosis in this case. Cardiac biopsies have no diagnostic role in PH.

The patient in this case had an mPAP of 62 mm Hg (97/40 mm Hg), pulmonary vascular resistance of 9.5 Wood units, normal PCWP, and a normal cardiac index. With nitric oxide therapy, the mPAP decreased dramatically to 29 mm Hg without a decrease in the cardiac index, indicating a positive response. The difference in RV systolic blood pressure on the initial echocardiogram and right-sided heart catheterization was likely due to a combination of time-dependent variability in pulmonary arterial hemodynamic measurements and imperfect correlation in the calculated RV systolic blood pressure from echocardiography to that measured using a catheter.[2]

4. Which *one* of the following *is not* an appropriate screening test for secondary causes of this patient's newly diagnosed disorder?

a. Overnight oximetry for sleep apnea
b. Serologic testing for connective tissue disease (CTD)
c. Ventilation-perfusion scanning for chronic thromboembolic disease
d. Pulmonary function testing for chronic lung disease
e. Cardiac MRI for the presence of atrial septal defect

Screening for secondary causes is indicated in patients with newly diagnosed PH. Nocturnal hypoxia with or without obstructive sleep apnea must be considered, so overnight oximetry should be performed. Connective tissue diseases, for example, systemic sclerosis, lupus, Sjögren syndrome, and mixed CTD, can be secondary causes, and appropriate serologic testing should be performed. Chronic thromboembolic disease and chronic lung disease are also secondary causes of PH; ventilation-perfusion scanning and pulmonary function studies, respectively, will help rule out these causes. Echocardiography, rather than MRI, is the test of choice for diagnosis of atrial septal defects because it defines the location of the defect and can illustrate the functional effect of shunting.[7]

In this patient, results of serologic testing for CTD and CT angiography for pulmonary embolism were negative. However, overnight oximetry demonstrated notable nocturnal hypoxemia and mild obstructive sleep apnea with 13 drops in saturation and a low normal baseline oxygen saturation of 91%. Although sleep apnea may partially contribute to elevated pulmonary pressures in this patient, obstructive sleep apnea does not typically cause severe PH. Owing to the severely elevated mPAP and response to vasodilator challenge, type 1 PAH was still believed to be the more important contributor to the patient's condition.

5. What is the *most appropriate* treatment for this patient?

a. Amlodipine
b. Verapamil
c. A phosphodiesterase-5 (PDE5) inhibitor
d. An endothelin receptor antagonist
e. Prostacyclin

Amlodipine or other dihydropyridine CCBs (nifedipine) are the initial drugs of choice for PH in patients with a positive vasodilator challenge response during invasive testing. These drugs provide a vasodilatory effect in the pulmonary vasculature without seriously reducing cardiac function. Verapamil, a nondihydropyridine CCB, is contraindicated in the treatment of PH as its negative inotropic effect can further decrease the function of a diseased RV.[8] A PDE5 inhibitor and an endothelin receptor antagonist would be used in initial treatment if the vasodilator challenge response was negative. A CCB combined with another drug can be considered if there is a positive vasodilator challenge response and severe disease at presentation. Prostacyclin therapy is initiated in patients with severe disease and poor functional class.[5]

The patient in this case was initially treated with amlodipine. After 8 months of treatment, the patient's symptoms resolved. Six-minute walk improved from 151 m with 90% saturation to 657 m with 93% saturation. Eight months after treatment, an echocardiogram showed a moderately enlarged RV with a borderline decrease in systolic function. Repeated right-sided heart catheterization showed an improvement in mPAP to 44 mm Hg from 62 mm Hg. However, owing to elevated pulmonary pressures and an enlarged RV, the patient was administered a PDE5 inhibitor in addition to amlodipine.

DISCUSSION

Pulmonary hypertension is divided into 5 categories.[5] Pulmonary arterial hypertension represents type 1 PH and is a progressive disease involving the pulmonary vasculature that can lead to RV failure and death. It can occur as an idiopathic process or as part of another underlying systemic disease. Type 1 PH includes idiopathic PAH, familial PAH, and PAH associated with CTD, drugs/toxins, congenital heart disease, human immunodeficiency virus, and portal hypertension, among other diseases. Type 2 PH involves PH secondary to left-sided heart disease (eg, systolic or diastolic heart failure and valvular disease). Type 3 PH refers to PH associated with lung diseases or hypoxemia (eg, interstitial lung disease and sleep apnea). Type 4 PH includes chronic thromboembolic PH. Type 5 PH is associated with miscellaneous disease processes, such as sarcoidosis and compression of pulmonary vessels by tumor.[5]

The most common presenting symptom of PH is dyspnea on exertion. However, one-third of patients experience exertional chest pain and one-third experience exertional syncope. With a syncopal presentation, several clues in the history and on the ECG should prompt a cardiac evaluation with an echocardiogram. These findings include exertional triggers, supine syncope, ECG changes

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(bundle branch blocks, second- or third-degree atrioventricular block, Brugada syndrome, an abnormal QT interval, and arrhythmias), sudden onset of palpitations after syncope, and a family history of unexplained sudden death.[1,3] In PH, syncope may be explained by arrhythmias, systemic vasodilation, or extreme transient elevation of PAP with exertion.[5]

Physical examination will likely reveal increased intensity of the pulmonic component of the second heart sound, which is evident if heard at the apex. Other examination findings in PH include persistent splitting of the second heart sound with RV failure or development of right bundle branch block. Murmurs associated with PH include a holosystolic tricuspid regurgitation murmur and a diastolic pulmonary valve regurgitation murmur. The right-sided murmurs are augmented with inspiration. The ECG findings in PH may include right axis deviation and RV hypertrophy in 79% and 87% of patients, respectively.[9]

Initial workup for PH should include screening in high-risk patients, such as those with a family history of PAH or CTD and those with exposures to known causative toxins, such as fenfluramine (a dietary supplement), other anorexigens, L-tryptophan, methamphetamine, and cocaine. Further diagnostic approach should characterize the hemodynamic profile and evaluate for secondary causes to optimally tailor the therapeutic regimen. If the initial echocardiogram is suggestive of PH (elevated RV systolic blood pressure, RV enlargement, and reduced RV function), the findings should be confirmed by right-sided heart catheterization to characterize the hemodynamic properties and allow assessment of the vasodilator challenge response.[5] Vasodilator challenge response is infrequent and occurs in only approximately 13% of patients with PH.[6] Of patients who have a response, only approximately half will benefit from therapy with a CCB. A more dramatic response to vasodilation suggests that the patient is more likely to benefit from CCB therapy.[6] Once PH is confirmed, secondary causes should be considered.[5]

Treatment of PAH includes prevention, supportive treatment of secondary causes, and targeted treatment with vasodilators. Repair of left-to-right shunts (eg, atrial septal defect) prevents long-term complications, including PH. Supportive treatment of secondary causes includes diuretics in left-sided heart failure, treatment of hypoxemia in sleep disorders, and anticoagulation in chronic thromboembolic disease.[5] Thrombotic arteriopathy has also been found to be associated with idiopathic PH, and systemic anticoagulation is recommended in patients with PH.[10]

Targeted PH treatment improves hemodynamic variables, functional class, and quality of life. Four major classes of PH medications include (1) CCBs, (2) prostacyclin analogues, (3) endothelin receptor antagonists, and (4) PDE5 inhibitors. Calcium channel blockers are used in some patients who demonstrate a vasodilation response during invasive testing. Response is defined as a decline in mPAP of at least 10 mm Hg to an absolute value of 40 mm Hg or less while maintaining cardiac output. However, response to vasodilator challenge is infrequent, occurring in approximately 13% of patients, and only approximately half of those patients benefit from CCB therapy. Use of dihydropyridine CCBs in patients with a negative vasodilator challenge response can result in marked clinical worsening, with decreased cardiac output and no change in PAP. Nifedipine, diltiazem, and amlodipine can be used without detrimental effects on cardiac output. Long-term response to CCB therapy is rare, and, for this reason, patients treated with CCBs alone should be monitored carefully for disease progression. Additional therapy with other pulmonary vasodilators may eventually be required.[5,6]

Endothelin-1 receptor antagonists (bosentan and ambrisentan) counteract the effects of endothelin-1, a potent pulmonary vasoconstrictor. In PAH, elevated endothelin-1 levels correlate with disease severity.[5] Prostacyclin analogues are metabolic derivatives of arachidonic acid and potent pulmonary vasodilators that improve exercise capacity, quality of life, hemodynamic variables, and survival. Sudden interruption of epoprostenol infusion may cause rebound severe PAH and death. The PDE5 inhibitors and endothelin receptor antagonists are good initial therapies for mild to moderate PAH when CCBs are contraindicated. Prostacyclin should be considered as first-line therapy in patients with severe symptoms.[5,11] Multidrug therapy is also often required. Two or more drugs from different classes may be used to augment the effects of

vasodilation or to allow use of lower doses of both medications.[5]

Last, surgical treatment of PH includes lung transplant or palliative balloon atrial septostomy. Lung transplant is considered in patients who are severely impaired despite treatment with intravenous prostanoids. Transplant candidacy should be addressed at the start of intravenous prostacyclin analogue therapy. Balloon atrial septostomy may be helpful in appropriately selected patients, such as those with RV failure and relatively normal arterial oxygenation. Septostomy works by creating a right-to-left shunt resulting in decompression of the RV with improvement in RV hemodynamic measurements.[5,12]

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