WHAT WOULD YOU DO?

Dyspnea in a Diabetic Patient With Previous TAVR

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PATIENT PRESENTATION AND HISTORY

A 74-year-old woman presented to the outpatient clinic reporting severe dyspnea on exertion. She was unable to climb one flight of stairs without stopping to catch her breath and was unable to do her shopping. These symptoms had been present for years, but had become somewhat worse within the last 12 months. She tried to adjust her lifestyle but was unhappy with the results.

She had a history of breast cancer, which was treated with radiotherapy and hormone therapy years ago, and no recurrence was found at a recent checkup. Six months previously, she experienced a minor stroke with diplopia and dysarthria, presumably of cardioembolic origin. Paroxysmal atrial fibrillation was found and treated by anticoagulation with apixaban and was successfully stabilized with metoprolol.

The patient also had chronic renal insufficiency due to insulin-dependent diabetes and arterial hypertension, but her blood pressure was well controlled with an average ambulatory pressure of 120/70 mm Hg. Also, her diabetes was under control with insulin and sitagliptin. Her calculated glomerular filtration rate was 44 mL/min and her HbA1C was 6.4%.

She had been diagnosed with a von Willebrand-Jürgens syndrome, which was asymptomatic. Four years previously, she had undergone transfemoral transcatheter aortic valve replacement (TAVR; CoreValve, Medtronic) for severe arteriosclerotic aortic stenosis with mild to moderate aortic insufficiency, but she reported no improvement in her symptoms of breathlessness since the TAVR procedure.

PHYSICAL EXAMINATION AND RESULTS OF CARDIAC AND PULMONARY TESTING

The patient's height was 160 cm and her body weight was 58 kg. Her body mass index was 23 kg/m^2, blood pressure was 126/70 mm Hg, heart rate was 62 bpm and regular, pCO_2 was 5.0 kPa, and PO_2 was 9.7 kPa. The results of a physical examination revealed normal hearts sounds, no accentuated systolic murmur, no diastolic murmur, and normal pulses without bruits. Lung auscultation revealed no rales, no rhonchi, and normal movement of the diaphragm.

She had a normal sinus rhythm as determined by electrocardiography, as well as a QRS axis of 0°, an atrioventricular block I with a PQ interval of 246 ms, and a QTc interval of 395 ms with normal repolarization.

The results of pulmonary function tests revealed no major restrictive or obstructive pathology, and a transthoracic echocardiogram showed that the aortic valve prosthesis was in good condition with a Vmax of 2.1 m/s and no aortic regurgitation. She had mild mitral regurgitation and her left ventricle was of normal size (end-diastolic diameter, 42 mm; end-systolic diameter, 23 mm; volumes, 63/20 mL; ejection fraction, 69%) and there was no left ventricular hypertrophy (LVH; septum, 11 mm; posterior wall, 10 mm). Her E-wave of mitral inflow was 1.44 m/s and her E/A (ratio of e-wave and a-wave velocity at mitral inflow measured by pulsed-waved Doppler) was 1.27. The size of her right ventricle was normal, with a tricuspid annular plane systolic excursion of 22 and Vmax over a mild tricuspid regurgitation of 2.9 m/s. Her left atrial volume index was 48 mL/m^2 per body weight and her right atrial volume

index was 27. Additional laboratory workup showed a B-type natriuretic peptide (BNP) of 234 pg/mL, mild anemia (hemoglobin, 6.4 mmol/L), and otherwise normal findings.

TREATMENT

We performed cardiac catheterization. Coronary angiography showed left dominant type, slight wall irregularities on the small right coronary artery, whereas the left coronary artery was normal. The LV angiogram showed normal size and function of the left ventricle. There was no major gradient over the aortic valve. The patient's right atrial pressure was 6 mm Hg, her right ventricular pressure was 36/1-8 mm Hg (diastolic pressure from early to late diastole), pulmonary artery pressure was 37/14-23 mm Hg, pulmonary capillary wedge pressure (PCWP) was 20 mm Hg, and cardiac output was 4.8 L/min.

Her cardiovascular medication regimen was apixaban 5 mg twice daily, metoprolol 95 mg twice daily, torsemide (recently increased in two steps from 20 mg to 100 mg once daily), and valsartan 40 mg once daily. The increase in diuretic dose did not improve her breathlessness.

Overall, this patient had a technically successful TAVR, but clinical symptoms of breathlessness persisted and had slightly deteriorated since. No major pathophysiologic abnormalities could initially be found that would explain her dyspnea.

What is the most likely explanation for the patient's symptoms? Which differential diagnoses would you seriously consider?

Prof. Gustafsson: The likely explanation for the patient's symptoms is heart failure with preserved ejection fraction (HFpEF). Right heart catheterization (RHC) shows a clearly elevated PCWP at rest and, together with an echocardiogram documenting normal LV systolic function, is diagnostic. Importantly, significant coronary and lung disease were ruled out. The patient's history is significant because several factors could lead to HFpEF secondary to LV diastolic dysfunction, including hypertension, diabetes, previous aortic stenosis, and, potentially, radiotherapy (if radiation was performed to the cardiac area). Previous radiotherapy should also raise the possibility of cardiac constriction, which could lead to similar symptoms, but the low central venous pressure (CVP) on RHC, as well as the absence of echocardiographic findings suggestive of constrictive pericarditis, dispute this diagnosis.

Another potential diagnosis underlying HFpEF that must be considered is transthyretin cardiac amyloidosis (TTR-CA), especially because it was recently shown to be a frequent finding in patients undergoing TAVR.[1] However, TTR-CA is much more common in men, which makes this diagnosis less likely in this patient.

Dr. Mahfoud: The patient experienced shortness of breath on exertion. The recently implanted aortic valve was in good condition, as was her left ventricular ejection fraction. The pulmonary examinations revealed no major findings. The echocardiogram indicates impaired cardiac relaxation (pseudonormalization) with significant enlargement of the left atrium. The right heart catheterization revealed borderline mean pulmonary artery pressure with elevated PCWP.

The most likely underlying cause for the shortness of breath is HFpEF, also supported by the increased BNP levels. Hypertensive heart disease with uncontrolled (masked) hypertension during exertion may be one differential diagnosis, although her office blood pressure was normal during rest.

Are any of the diagnostic results questionable or misleading? If so, what could be the explanation?

Dr. Mahfoud: It is quite interesting that the aortic valve replacement did not result in symptom relief. This emphasizes how difficult it is diagnosing HFpEF in clinical practice, especially when concomitant valvular heart disease is present. The gold standard remains LV pressure-volume recording, which is not widely available.

Prof. Gustafsson: It is important to recognize the limitations of echocardiography in diagnosing HFpEF. In this patient, the echocardiographic criteria for LVH were not met and the E/A ratio was normal. However, this should not rule out HFpEF as the likely diagnosis. In fact, recently published studies of patients with HFpEF documented by invasive hemodynamics have shown LVH (as defined by the American Society of Echocardiography) was not present in up to 65% of patients.[2,3] A normal E/A ratio is often seen in elderly patients (pseudonormalization), and therefore, E/A ratio and LVH can never be relied on alone for determining normal from abnormal diastolic function. In contrast, this patient displayed an enlarged left atrium, which seems to be a more robust echocardiographic finding in HFpEF.

The fact that the patient's symptoms did not improve after increasing the diuretic dose should not be taken as evidence against heart failure as the underlying cause. Diuretic therapy is usually only helpful in ambulatory HFpEF if patients experience universal fluid

overload. Aggressive diuretic therapy may, in many patients, merely lead to renal dysfunction and dizziness. In the presented patient, CVP was rather low, which in my experience suggests that little effect should be expected from increased diuresis.

What kind of diagnostic procedure do you believe would be most helpful in understanding this patient´s dyspnea?

Prof. Gustafsson: The echocardiogram could be supplemented by tissue Doppler evaluation enabling measurement of early inflow velocity (E) to tissue velocity (e') ratio, which, in my opinion, is a better indicator of abnormal diastolic function than E velocity and E/A ratio (in patients with normal systolic function). Exercise-invasive hemodynamic testing can be of great value to diagnose patients with HFpEF but does not seem indicated here because an elevated PCWP was already found at rest; therefore, the diagnosis could be made without adding exercise. If there were other findings suggesting the presence of TTR-CA (ie, carpal tunnel syndrome) a cardiac MRI, technetium-99m pyrophosphate scintigraphy, or even an endomyocardial biopsy could be indicated.

Dr. Mahfoud: I would have the patient undergo RHC with exertion/volume challenge to see how hemodynamics, in particular PCWP and PAP, change during stress. Furthermore, ambulatory blood pressure monitoring and a cardiopulmonary exercise test to assess blood pressure, heart rate, and VO_2 during exercise would help to quantify the dyspnea.

Would you aim to prove and to quantify the patient's symptomatology? Which approach would you use?

Dr. Mahfoud: Diuretics may be useful to reduce symptoms. However, no drug class available has been shown to improve outcomes in patients with HFpEF. The TOPCAT study, one of the largest prospective trials in this indication, investigated the effectiveness of aldosterone antagonist use and was unable to document improved outcomes compared with placebo. Very recently, a device-based approach has developed, which intends to unload the left atrium through an interatrial septal communication with the goal of reducing pulmonary venous pressure thereby improving symptoms and, hopefully, outcomes. Our center is participating in a trial that is investigating the safety and efficacy of an interatrial shunt device (IASD) in HFpEF and I would definitely consider enrolling this particular patient.

Prof. Gustafsson: An exercise test is useful to quantify physical limitation, preferably by measuring oxygen uptake, which quantifies the cardiovascular reserve. The clinical importance of the latter, however, can be debated in this patient because it is not likely to change the therapeutic strategy. A simple stress test (without measurement of PvO_2) could uncover chronotropic incompetence, which is common in HFpEF. This could have important therapeutic implications for the drug regimen (ie, ß-blocker dose) or even indicate the need for pacemaker implantation, especially in a patient such as the one presented in whom a prolonged atrioventricular conduction is present.

APPROACH OF THE MODERATOR

After excluding the most common reasons for dsypnea on exertion, such as systolic LV and pulmonary dysfunction, and in the absence of physical signs of amyloidosis, such as marked LVH or QRS axis prolongation, or findings of pericardial constrain or chronotropic incompetence, the goal was to confirm and quantify exercise limitation. In a 6-minute walk test, the patient achieved only 240 m.

Diastolic LV dysfunction was considered the most likely explanation. A detailed echocardiographic analysis of diastolic function showed a remarkably elevated E/e' ratio of 31. Due to mild to moderate elevation of PCWPs, it was believed that exercise hemodynamics would not add important new information.

Therapeutically, the two stages of increase in diuretics did not improve her symptoms and given a right atrial pressure of 6 mm Hg, a further benefit would be unlikely and might decrease her right ventricular output.

Because a device capable of decreasing exercise rise of LV filling pressures had just been released and gained CE Mark approval (Corvia IASD, Corvia Medical, Inc.), we offered this therapy to the patient. The device is a small, stent-like, metallic prothesis ensuring a definite small atrial septal defect (ASD) of 8 mm in diameter and an approximate 25% left-to-right shunt after transseptal puncture and application.[3,4]

The IASD was implanted 1 year ago. The patient's condition has markedly improved since then, as shown by her New York Heart Association class decreasing from III to I, the 6-minute walk test improving from 240 m to 405 m, regained the ability to climb three floors of stairs, and being able to perform housework without help.

The disease severity evaluation according to the Kansas City Cardiomyopathy Questionnaire and EQ-5D-3L scores showed remarkable improvements in mobility,

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daily activities, and mood (depression and anxiety). The patient also described her general health in a visual analogue scale from 0 to 100 as improved from a baseline of 50 to 71 at 12-month follow-up.

CONCLUSION

The introduction of a small ASD in selected patients with marked diastolic heart failure can be helpful. The overlap with symptoms of aortic stenosis might be a major therapeutic challenge. In this patient, the creation of a small ASD led to considerably greater symptom relief than the aortic valve implantation. Thorough evaluation of diastolic function in patients who do not improve after TAVR is important and a consideration to treat diastolic dysfunction before or along with TAVR might become increasingly necessary. ■

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