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THE ROLE OF THE DIASTOLIC STRESS ECHOCARDIOGRAPHIC TEST IN THE DIAGNOSIS OF HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION

Abstract: We present the case of a 68-year-old female patient with exertional dyspnea, mild pretibial oedema and echocardiographically verified enlarged left atrium, but with preserved left ventricular systolic function and normal left ventricular filling pressures at rest. NT-proBNP values were within reference values. The diastolic stress echocardiographic test confirms the presence of heart failure with preserved ejection fraction (HFpEF). This case report represents the complexity of diagnosing HFpEF in everyday clinical practice.

Key words: heart failure with preserved ejection fraction, diastolic stress echocardiography

Background

Dyspnea can be caused by cardiac and non-cardiac diseases. The most common cause of dyspnea in cardiovascular patients is heart failure. Heart failure (HF) is a clinical syndrome characterized by clinical symptoms (most often dyspnea and fatigue) and clinical signs of pulmonary congestion (inspiratory crackles, elevated jugular pressure, and peripheral oedema). HF occurs as a consequence of various diseases that lead to structural and/or functional disorders of the heart which cause reduced stroke volume and/or increased filling pressure of the left ventricle (2). Almost half of the patients with HF have preserved systolic function of the left ventricle (EF) and this condition is called heart failure with preserved ejection fraction (HFpEF). The main cause of HF in these patients is diastolic dysfunction, which is manifested by increased filling pressure of the left ventricle either at rest or during exercise. However, it is very important to distinguish between HFpEF and diastolic dysfunction, because

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although diastolic dysfunction is the main pathophysiological mechanism of HFpEF, not all patients with diastolic dysfunction have clinically manifest heart failure. Despite preserved left ventricular systolic function, the prognosis of these patients is as serious as that of patients with reduced EF (2).

Diastolic dysfunction is a condition when the appropriate left ventricular (LV) volume required to maintain normal LV stroke volume at rest or during exercise requires an abnormal increase in diastolic LV filling pressure. The main pathophysiological mechanisms leading to diastolic dysfunction are: 1) impairment of myocardial relaxation due to inadequate sarcolemmal Ca^{2+} removal, 2) increased passive elastic LV stiffness due to LV remodelling, and 3) loss of diastolic suction due to attenuation of LV restoring forces (3, 4).

In clinical practice, the diagnosis of HFpEF is based on the criteria set by the EACVI, which primarily focus on transthoracic echocardiography (TTE) (2). However, a large number of these patients are asymptomatic at rest, without signs of LV hypertrophy and elevated LV filling pressure, and manifest signs and symptoms of HF only during exercise. In such patients, evaluation of hemodynamic and echocardiographic parameters during exercise can help in establishing the diagnosis (5). Diastolic stress echocardiographic test (SEHO) can be used for this purpose. Several studies have shown that the measurement of E/e' ratio at peak load as well as peak tricuspid regurgitation (TR) velocity are easily performed during the test and are invasively validated for the proportion of elevated LV diastolic filling (6, 7). The diastolic SEHO test is most often performed on an ergo bicycle with an initial load of 25W, with the load increasing by 25W every 3 minutes, until reaching the maximum frequency (220 – years of the patient) or the set echocardiographic criteria. The best candidates for this type of test are patients with stage 1 diastolic dysfunction with normal LV filling pressure at rest and signs of impaired relaxation. The diastolic SEHO test is considered positive for the diagnosis of HFpEF if 3 criteria are met: 1. E/e' ratio over 15 during peak exercise, 2. peak TR velocity > 2.8 m/s and 3. septal e' < 7 cm/s (2). A group of authors from a multicenter study also proposed the SEHO test according to the ABCDE protocol, which, in addition to the normal assessment of wall motion abnormalities during the test, also simultaneously assesses diastolic function (by measuring the peak flow over the mitral valve and peak septal and lateral e' and peak TR velocity), coronary flow reserve through the left anterior descending artery and pulmonary congestion at maximum load (by measuring B lines) (8, 9).

Case report

We present the case of a 68-year-old woman, who was referred to a cardiologist due to dyspnea on exertion. The patient has no history of coronary artery disease, no family history of coronary artery disease, former smoker (quited 20 years ago), has

been treated for hypertension for the past 8 years and has elevated LDL-cholesterol. She complains on the lack of air during exertion, which occurs when climbing to the first floor, denies chest pains, palpitations, loss of consciousness. She sleeps on a higher headboard. The patient has a body mass index (BMI) of 31.4 kg/m^2, blood pressure at rest 140/80 mmHg with mild pretibial edema. Other physical findings are normal. The value of LDL-cholesterol was 3.48 mmol/L, without deviation of other laboratory parameters, including renal function. Electrocardiographically, a sinus rhythm is registered frequency 82/min, without changes in ST segment and T wave. She is currently being treated with Ramipril 5mg 1x1, Nebivolol 2.5mg 1x1 and Atorvastatin 10mg 1x1. The patient was referred for a TTE examination, which showed that the left ventricle had normal internal dimensions (EDD 51mm, ESD 33mm), normal wall thickness (10mm), without any wall motion abnormalities. The total systolic function of the left ventricle is preserved EF 67%. The flow over the mitral valve shows impaired relaxation 0.75/0.96 m/s, septal e' 8 cm/s, lateral e' 9 cm/s, E/ e' 8.8. MR 1+ is observed in the enlarged left atrium (4.2x5.1x5.4cm, LA volume 42ml/m^2). The flows over the other valves are regular. The patient's laboratory was taken to determine the level of NT-proBNP, which was normal (98 pg/L). Coronary angiography ruled out significant epicardial coronary stenosis.

The patient then underwent a diastolic SEHO test according to the ABCDE protocol (8). The test was terminated at the 2nd minute of the second degree overload due to dyspnea after reaching target heart rate at 142/min. Subjectively without chest pain during the test. During exertion and recovery without significant ST-segment changes and without rhythm disorders. During the test, there were no wall motion abnormalities. The value of coronary flow reserve was 2.1. Peak septal e' was 6 cm/s, lateral e' 7 cm/s, the flow through the mitral valve increased to 0.98/1.12 m/s. E/e' was 15.1, the peak TR velocity was 3.1 m/s. At rest, 1 B line was recorded, while after the test there were 3 B lines, indicating mild pulmonary congestion.

Taking into account the test results, the patient was diagnosed with HFpEF. Empagliflozin 10mg 1x1 was introduced into the therapy. At the follow-up in 3 months, the patient states that she can tolerate physical exertion better, that dyspnea occurs only after greater physical exertion.

Discussion

In this paper, we presented a patient with dyspnea on exertion and normal LV filling pressure at rest, who was diagnosed with HFpEF after the diastolic SEHO test.

HFpEF is a syndrome that is quite common in the general population, especially in older population. With normal aging, end-diastolic LV volume decreases, and in apparently healthy elderly people, LV stiffness increases significantly, especially after the age of 60, which significantly contributes to LV diastolic dysfunction,

although it is not clear whether these processes contribute to HFpEF (10). Patients with HFpEF represent a very diverse population with different pathophysiological mechanisms and comorbidities. In addition, the symptoms and signs of HF can often be attributed to HFpEF, when in fact they may be caused by non-cardiac causes. Because of all this, the diagnosis of HFpEF is quite difficult, especially in patients with comorbidities that can mimic the symptoms and signs of HF, such as chronic respiratory diseases and obesity. Lung diseases are present in as many as 40% of patients with HFpEF (2).

The diagnosis of HFpEF is based on TTE. However, as in our patient, LV filling pressure in HFpEF can be normal at rest and patients have no symptoms, although they show signs of diastolic dysfunction on TTE. Using the diastolic SEHO test significantly increases the possibility of detecting HFpEF in such patients. In the study by Burgess et al. which included 37 patients who were referred for selective coronary angiography for clinically indicated reasons. All patients were in sinus rhythm, and patients with unstable angina, significant valvular disease, or previous heart valve surgery were excluded. All patients underwent TTE at rest, then diastolic SEHO test and then diagnostic coronary angiography with left heart catheterization. It was shown that in patients with elevated LV filling parameters, the E/e' ratio during exercise positively correlates very well with the increased LV filling pressure obtained invasively during left heart catheterization. It was calculated that the value E/e' > 13 corresponds to a mean filling pressure of the left ventricle of >15 mmHg. What's more, patients who had a ratio of E/e' > 10 during exercise had a functional capacity of less than 8 METs and more often exhibited dyspnea as a limiting symptom of the test (6).

In the study by Obokata et al. 74 consecutive patients who were referred for a stress test due to dyspnea were included in the examination. Patients with known coronary disease, significant valvular disease, as well as other causes of the clinical syndrome of HF (primary cardiomyopathy, constrictive pericarditis, pulmonary embolism, right heart cardiomyopathy, pulmonary hypertension) were excluded from this study. All patients underwent TTE at rest and NT-proBNP level was measured. The patients were then subjected to a diastolic SEHO test with simultaneous invasive measurement of pressure in the right heart. Also the test protocol that was used involved increasing the load by 10W for 3 minutes. Invasive measurements proved HFpEF in 50 patients, while in the other 24 a non-cardiac cause of dyspnea was confirmed. Compared to patients with a non-cardiac cause of dyspnea, patients with proven HFpEF had significantly higher values of average E/e' ratio, higher peak TR velocity, as well as increased filling pressures of both the left and right heart at lower levels of exercise. Also in this study, it was shown that the level of NT-proBNP was normal in 18% of patients with proven HFpEF. Only 34-60% of patients diagnosed with HFpEF based on resting TTE parameters also had invasively confirmed HFpEF. The addition of the diastolic SEHO test, ie the ratio E/e'>14 du-

ring exercise, increased this sensitivity to detect HFpEF to 90%, but also decreased the specificity to 71% (11).

In addition to the difficulties in establishing a diagnosis of HFpEF, there is also a big problem with therapy. Precisely because of the very wide range of cardiovascular phenotypes that lead to HFpEF, most studies dealing with the therapy of this syndrome have not shown success, because different phenotypes do not respond to the same therapy. However, certain phenotypes, such as hypertrophic cardiomyopathy, cardiac amyloidosis, and others have specific therapies, and therefore it is very important to establish the right diagnosis (2). Recent studies have shown that SGLT-2 inhibitors can help in these patients. Recently, two studies with SGLT-2 inhibitors have shown a favorable clinical effect in patients with HFpEF, as well as in patients with slightly reduced LV systolic function. Namely, the EMPEROR-PRESERVED and DELIVER studies showed a reduction in the combined primary outcome of cardiovascular mortality and hospitalization due to HF, with a significant improvement in quality of life (12, 13).

Conclusion

HFpEF can occur due to many different causes. Although these patients have a preserved ejection fraction, their prognosis is as poor as in patients with HFrEF. The diagnosis of HFpEF itself is a very big challenge. Although, according to the recommendations, TTE is the first choice in diagnosing this syndrome, it is often not enough, because many patients are asymptomatic at rest with normal LV filling pressure. The addition of the diastolic SEHO test can help us establish a diagnosis in these patients, without the need to use invasive diagnostics.

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