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OPINION

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Hypertension, diastolic stress test, and HFpEF: Does new scoring system change something?

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Heart failure with preserved ejection fraction (HFpEF) has been reported as very important risk of mortality in population of patients with heart failure (HF). Recently published study compared mortality of patients with HF with reduced, midrange, and preserved ejection fraction (HFrEF, HFmrEF, and HFpEF, respectively) and showed that there was no significant difference in 2-year all-cause mortality between HFpEF and HFmrEF patients (14% vs 12%), but it was higher among HFrEF patients (19%).[1]

Arterial hypertension represents the most prevalent risk factor in HFpEF development.[1,2] Mechanisms that connect hypertension and HFpEF are numerous, from molecular (oxidative stress, increased inflammation, endothelial dysfunction, and fibrosis), across microvascular and macrovascular dysfunction, to structural cardiac and vascular changes that include increased vascular and myocardial stiffening, increased left ventricular (LV) filling pressure, dilated left atrium (LA), and LV hypertrophy.[2,3] Even though the number of antihypertensive groups and medication within each group has never been higher, it seems that this is not enough to slow the rapid rise of prevalence of patients with HFpEF.[4] The entire medical community is making great effort to detect patients HFpEF, as it is assumed that timely diagnosis of HFpEF could significantly change the course of disease and reduce mortality in this large group of patients.

In the last few years, diastolic stress test was introduced as the new promising diagnostic tool that could reveal HFpEF before further complications occur.[5-7] The majority of the patients included in these studies were hypertensive patients. Indeed, diagnosis of LV diastolic dysfunction often could be challenging, and even the latest echocardiographic guidelines on this topic revealed large number of limitations and conditions that could make echocardiographic assessment of LV diastolic function very difficult or even impossible.[8] The authors of the guidelines claimed that diastolic exercise testing was the most appropriate in patients with grade 1 diastolic dysfunction, which involves delayed myocardial relaxation and normal LA mean pressure at rest.[8] The main limitation in the assessment of all echocardiographic parameters of LV diastolic function and most of indices describing LV filling pressure obtained by heart catheterization is load-dependence. This is why we need more techniques to assess LV filling pressure—direct (invasive) and indirect (mainly echocardiographic).

The crucial parameters to take into account during diastolic stress test are early diastolic mitral inflow measured by pulsed Doppler (E), medial mitral annular velocity measured by spectral tissue Doppler echocardiography (e'), their ratio (E/e'), and tricuspid regurgitation (TR) velocity.[8] LA pressure is increased in HFpEF patients, which induces an increase in mitral E velocity, whereas e′ velocity does not change proportionally with E due to increased myocardial stiffness in these patients. As the result, E/e' ratio significantly increases during exercise. In healthy myocardium, e' increases together with E, and overall E/e' ratio does not change. It remains unknown whether impaired LV relaxation always induces increase in LV filling pressure during exercise. Namely, it is noticed that patients with a similar level of LV diastolic dysfunction at rest could show various levels of diastolic dysfunction during exercise.[9] This might suggest that diastolic stress test have high negative predictive value and could help to rule out HFpEF, but possibly could not distinguish different grade of LV diastolic dysfunction, which would be of a great importance in hypertensive patients.

Diastolic stress testing remains technically demanding because it is conducted on supine bicycle or on treadmill when bicycle is not available. Getting all necessary data in appropriate manner

according to guidelines is not an easy task and raises the question about the feasibility of this test. Available studies reported very high feasibility (higher than 90%).[5-7] However, one has to notice that all studies were conducted in very limited group of HFpEF patients, and it is reasonable to raise the question if the results would be different in larger population of patients.

The recent consensus from the European Heart Failure Association suggested major and minor criteria and scoring system for diagnosis of HFpEF.[10] Criteria were divided into three domains: functional, morphological, and biomarker. Major functional criteria refer to echocardiographic guidelines for assessment of LV diastolic dysfunction (reduced septal e', increased E/e', and increased TR).[10] Minor functional criteria involved intermediate E/e' (9-14) and reduced LV global longitudinal strain (<−16%).[10] Major morphological criteria include dilated LA (LAVI ≥ 34 mL/m^2 in sinus rhythm and ≥40 mL/m^2 in atrial fibrillation) or LV hypertrophy defined as LV mass index ≥ 149 g/m^2 in men or ≥122 g/m^2 in women together with increased relative wall thickness ≥0.42.[10] Interestingly, minor morphological criteria were high normal values of LA volume index (29-34 mL/m^2 in sinus rhythm and ≥34-40 mL/m^2 in atrial fibrillation), increased LV mass index defined by current echocardiographic guidelines (≥115 g/m^2 in men or ≥95 g/m^2 in women) or relative wall thickness ≥0.42 or LV wall thickness ≥12 mm.[10] Major and minor biomarker criteria refer to different levels of BNP and pro-BNP with various cut-off values for patients with sinus rhythm and atrial fibrillation (values are 3 times higher in atrial fibrillation group).[10]

The proposed criteria are raising important questions that need to be resolved before clinical use of this scoring system. It is quite expected that criteria used for assessment of LV diastolic function that were already well established in the previous guidelines will be also included in this scoring system. However, this consensus introduced some new values such as intermediate LA volume index, very high LV mass indexes for both genders that are not included in any guidelines, and significantly reduced LV longitudinal strain.[10] Recent large study showed that LV global longitudinal strain inversely correlated with diastolic dysfunction and can be abnormal even in the absence of diastolic function. However, the authors suggested that LV diastolic dysfunction was uncommon in the patients with normal longitudinal strain. They proposed the cut-off of <−15% for LV longitudinal strain to discriminate between normal and abnormal diastolic function.[11] LV longitudinal strain definitely has great potential to become a useful parameter in assessment of LV diastolic dysfunction. However, it is perhaps early to use LV longitudinal strain as criterion in HFpEF scoring system. One could ask whether we should add LA global strain or LV longitudinal diastolic strain rate instead of focusing only on LV longitudinal strain that could be decreased due to many reasons and does not necessarily be associated with HFpEF. The same doubts could be raised regarding cut-off values used for LV mass index (≥149 g/m^2 in men or ≥122 g/m^2 in women) and LA volume index (both, major and minor criteria).

Why these cut-off values used in this scoring system are so important? The consensus allocates 1 or 2 points to minor or major criteria, respectively, and recommends that patients with ≥5 points have diagnosis of HFpEF, and patients with 2-4 points should undergo diastolic stress test or invasive hemodynamic measurements. The latter is a bit surprising because it equals noninvasive with invasive testing. It would be expected that noninvasive widely available technique had advantage over invasive method, which undoubtedly represents a gold standard for evaluation of LV diastolic function.

Authors explained that each domain (functional, morphological, and biomarker) could contribute with maximally 2 points, if any major criterion from this domain is positive, or 1 point if no major but any minor criterion is positive. If several major criteria within a single domain are positive, this domain still gives 2 points in the total score; and if no major but several minor criteria are positive, the contribution is still 1 point. Major and minor criteria are not additive in a single domain.

In terms of hypertensive patients, it will not be difficult to score large percentage with 2 points using this new system because they often fulfill 1 major criterion or 2 minor criteria in different echocardiographic domains (functional and morphological). In this case, one should be careful in referring all these patients to diastolic stress test or even heart catheterization for invasive hemodynamic measurements. In the literature, there are at least two suggestions that could make better filtration of those patients who should be referred to further investigation and particularly to invasive measurements. Kosmala et al[12] suggested that the implementation of a 2-step algorithm (echocardiographic evaluation of resting E/e' followed by the assessment of galectin-3) could improve the diagnosis and prognostic assessment of subjects with suspected HFpEF in patients who are not able to exercise. The investigators included patients with exertional dyspnea (90% participants were hypertensive) and showed no difference in predictive value of abnormal diastolic response to exercise (E/e'>14) and the combined strategy (resting echocardiography and galectin-3).[12] Nedeljkovic et al[13] reported that cardiopulmonary exercise test and parameters obtained with this test could accurately identify masked HFpEF in population of hypertensive patients with sensitivity of 100% and specificity of 90%.

Scoring systems in clinical medicine nowadays are more than welcome, and they significantly facilitate diagnosis and management of various groups of patients. The authors of the new scoring system for evaluation of HFpEF are introducing a set of new parameters and moreover new cut-off values. The authors stated that some thresholds that were used in consensus were based on the consensus and literature and need validation in prospective studies. Only longitudinal investigations could show if these new parameters (LV longitudinal strain), intermediate values of LA volume index and E/e', and new thresholds could help in timely diagnosis of HFpEF. Some additional techniques such as cardiopulmonary test and additional biomarker such as galactin-3 might be considered in the future scoring systems in order to avoid unnecessary invasive methods for diagnosis of HFpEF.

CONFLICT OF INTEREST

None.

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