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Possibility of using European (HFA-PEFF) and American (H2FPEF) algorithms for diagnosing heart failure with preserved ejection fraction in Russian clinical practice

This article focuses on the significance of a unified approach to diagnosing heart failure with preserved left ventricular ejection fraction (HFpEF). The key hemodynamic index of HFpEF is increased left ventricular filling pressure (LVFP) and its noninvasive marker, the E/e' value obtained by tissue Doppler echocardiography (EchoCG). The modern verified algorithms for HFpEF diagnosis, HFA–PEFF and H2FPEF, mandatorily take into account the E/e' value. However, the routing use of these algorithms in the Russian practice may be complicated since even among "advanced" specialists who are interested in heart failure, 38% of the interviewed do not use or do not know how to use tissue Doppler EchoCG or the algorithm for diagnosing HFpEF with E/e'. In addition to the obvious way of overcoming this problem by equipping respective medical facilities with ultrasonic apparatuses with tissue Doppler EchoCG software and educating physicians, a possibility of using simplified HFA algorithm without the E/e' value is being considered. However, such approach will inevitably lead to erroneous estimation of the probability of HFpEF and, at the best, to underestimation of this probability with ensuing mistakes in diagnosis and treatment. Simplifying the HFA–PEFF and H2FPEF algorithms by omitting one or more parameters is possible but this requires a special investigation to develop a new rating scale and actually a new algorithm, which, in turn, will require a new validation.

Keywords HFpEF; left ventricular filling pressure; E/e'; stress test

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Heart failure with preserved ejection fraction (HFpEF) is a special focus due to imperfect knowledge of this syndrome and the lack of reliable methods of diagnosis and treatment. The lack of a clear understanding of the nature of HFpEF caused an inevitable disagreement among experts in assessment of basic indicators, such as the prevalence of HFpEF, life expectancy, and individual indicators, such as patient selection criteria, the interpretation of trial results, etc. For example, the prevalence of HFpEF in all patients with HF is about 50% according to foreign experts [1] and almost 80% according to the Russian experts [2]; according to the TOPCAT trial, mortality of HFpEF patients is 21.8% in the United States and Canada, and 8.4% in Russia and Georgia, and the same drugs are administered [3].

There is an obvious need for a harmonization of the HFpEF criteria. This became possible with the development of a model integrating etiological origins, pathogenetic mechanisms, and hemodynamic consequences of the syndrome [4].

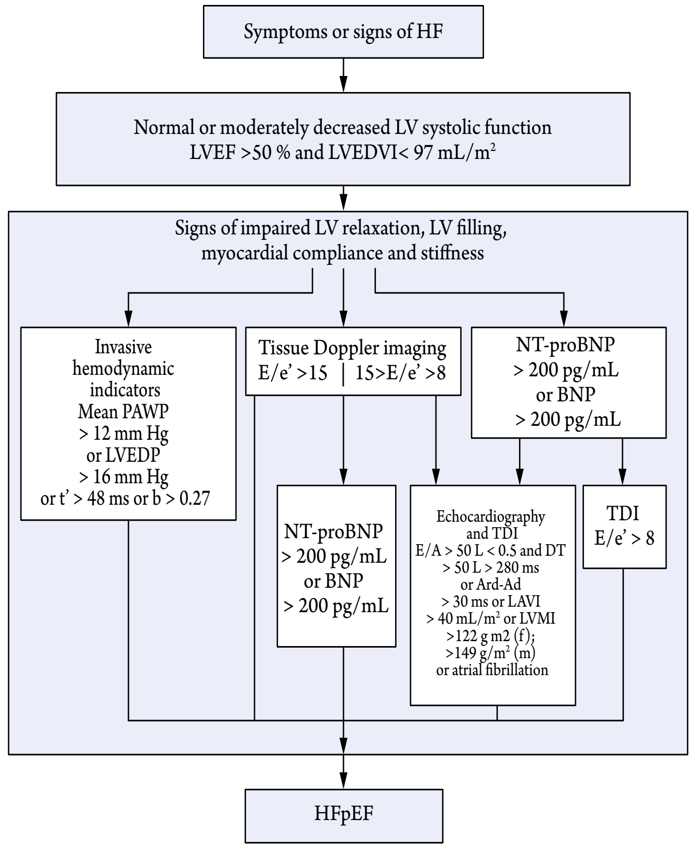
An increase in the left ventricular (LV) filling pressure due to diastolic dysfunction (DD) is the main hemodynamic constant that determines the presence of HFpEF [5]. Increased LV filling pressure that is the main cause of cardiac dyspnea and low exercise tolerance in patients with HF, and it is high LV filling pressure that can play a key role in the diagnosis of HFpEF, as it is a kind of analogue of reduced LVEF for systolic HF.

All more or less objectified algorithms using LV filling pressure for the diagnosis of HFpEF are based on the identification of its threshold value. LV filling pressure can be directly measured by cardiac catheterization, which is still the gold standard for the diagnosis of HFpEF [6], but it is not suitable for routine clinical practice due to its complexity and invasive nature. Echocardiography and tissue Doppler imaging (TDI) is backbone of the diagnosis of HFpEF, and involves the estimation of the E/e' ratio, a key non-invasive parameter that allows quickly and accurately assessing LV filling pressure and, thus, the presence or absence of DD [7].

In 2007, Paulus et al. were first to propose a diagnostic algorithm [8], which offered to determine LV filling pressure both invasively by catheterization and noninvasively using the E/e' ratio in patients with suspected HFpEF (clinical picture of HF + LVEF>50%) (Figure 1). The E/e' ratio of>15 clearly indicated the presence of HFpEF; at 15>E/e'>8 (gray zone), additional clarification of elevated LV filling pressure was required using indirect signs, such as NT-proBNP>220 pg/mL, LV hypertrophy, left atrial dilation, or atrial fibrillation. The E/e' ratio<8 clearly indicated the absence of high LV filling pressure and ruled out the presence of HFpEF. The lack of a stepwise approach and the presence of several parallel diagnostic routes (hemodynamic measurements, echocardiography, or NT-proBNP) were the main drawback of this algorithm, which resulted in a possibility of ambiguous judgment on the presence or absence of HFpEF in one and the same patient. Moreover, very high percentage of patients with suspected HFpEF was not clearly verified.

Subsequent changes in the diagnostic algorithms of HFpEF had mainly clarifying nature and did not affect mandatory proving of increased LV filling pressure (i.e., E/e') at rest and, importantly, during exercise. The current algorithm for the diagnosis of HFpEF, which was developed and approved by the Expert Council of the European Society of Cardiology (HFA-ESC) in 2019, provides for a procedure for a cumulative scoring of functional, morphological, and biochemical parameters at rest (Figure 2), which, if is ≥5, becomes a marker of abnormally increased LV filling pressure and the basis for the diagnosis of HFpEF (the HFA-PEFF diagnostic algorithm) [9]. The advantage of this algorithm is the ability to identify patients with initial HFpEF with LV filling pressure that do not yet exceed the critical limit at rest (total score of 2–4 – gray zone) but abnormally increased during exercise: if E/e' at peak exercise is ≥15, then this gives another 2–3

Figure 1. Diagnostic algorithm for HFpEF proposed by Paulus et al. (2007)



LV, left ventricle; LVEF, left ventricular ejection fraction; PAWP, pulmonary artery wedge pressure; LVEDP, left ventricular end-diastolic pressure; TDI, tissue Doppler imaging; E, early diastolic filling velocity; e', early diastolic mitral velocity; Ard-Ad, difference of the duration of retrograde pulmonary blood flow Ar and mitral blood flow A; DT, deceleration time of early diastolic flow E; NT-proBNP, N-terminal pro-brain natriuretic peptide; BNP, brain natriuretic peptide; LAVI, left atrial volume index; LVMI, left ventricular mass index; HFpEF, heart failure with preserved ejection fraction.

Figure 2. Diagnostic algorithm for HFpEF proposed by the Expert Council of the European Society of Cardiology (HFA-ESC; 2019)

	Functional	Morphological	Biomarkers, sinus rhythm	Biomarkers, atrial fibrillation
Major	Septal e' < 7 cm/s or lateral e' < 7 cm/s or mean E/e' > 15 or TR velocity > 2.8 m/s (PASP > 35 mm Hg)	LAVI > 34 mL/m² or LVMI ≥ 149/122 g/m² (m/f) and RWT > 0.42	NT-proBNP > 220 pg/mL or BNP > 80 pg/mL	NT-proBNP > 660 pg/mL or BNP > 240 pg/mL
Minor	Mean E/e' 9–14 or GLS < 16 %	LAVI 29–34 mL/m² or LVMI ≥ 115/95 g/m² (m/f) or RWT > 0.42 or LVPWT ≥ 12 mm	NT-proBNP 125–220 pg/mL or BNP 35–80 pg/mL	NT-proBNP 365–660 pg/mL or BNP 105–240 pg/mL

Major criteria: 2 points	≥ 5 points: HFpEF
Minor criteria: 1 point	2–4 points: diastolic stress test or invasive assessment of hemodynamics

TR, tricuspid regurgitation; PASP, pulmonary artery systolic pressure; GLS, global longitudinal strain; e', early diastolic mitral velocity; E, early diastolic filling velocity; LAVI, left atrial volume index; LVMI, left ventricular mass index; RWT, relative wall thickness (LV posterior wall thickness x 2/ LVEDD); LVPWT, left ventricular posterior wall thickness; BNP, brain natriuretic peptide; NT-proBNP, N=terminal pro-brain natriuretic peptide; HFpEF, heart failure with preserved ejection fraction.

Table 1. Score of the probability of HFpEF in the H2FPEF algorithm taking into account all 6 signs and excluding the value of filling pressure (F=0)

#	Obesity	Hyper-tension	Atrial fibrillation	Pulmo-nary hyper-tension	Advanced age	LV filling pressure (F)	Score	Score with F=0	Area	Proba-bility
1	0	0	0	0	0	0	0	0	-	–
2	0	1	0	0	0	0	1	1	-	–
3	0	0	0	1	0	0	1	1	-	–
4	0	0	0	0	1	0	1	1	-	–
5	2	0	0	0	0	0	2	2	-	–
6	0	1	0	1	0	0	2	2	-	–
7	0	1	0	0	1	0	2	2	-	–
8	0	0	0	1	1	0	2	2	-	–
9	0	0	3	0	0	0	3	3	-	–
10	2	1	0	0	0	0	3	3	-	–
11	2	0	0	1	0	0	3	3	-	–
12	2	0	0	0	1	0	3	3	-	–
13	0	1	0	1	1	0	3	3	-	–
14	0	1	3	0	0	0	4	4	-	–
15	0	0	3	1	0	0	4	4	-	–
16	0	0	3	0	1	0	4	4	-	–
17	2	1	0	1	0	0	4	4	-	–
18	2	0	0	1	1	0	4	4	-	–
19	2	1	0	0	1	0	4	4	-	–
20	2	0	3	0	0	0	5	5	-	–
21	0	1	3	1	0	0	5	5	-	–
22	0	0	3	1	1	0	5	5	-	–
23	0	1	3	0	1	0	5	5	-	–
24	2	1	0	1	1	0	5	5	-	–
25	2	1	3	0	0	0	6	6	-	–
26	2	0	3	1	0	0	6	6	-	–
27	2	0	3	0	1	0	6	6	-	–
28	0	1	3	1	1	0	6	6	-	–
29	2	1	3	1	0	0	7	7	-	–
30	2	0	3	1	1	0	7	7	-	–
31	2	1	3	0	1	0	7	7	-	–
32	2	1	3	1	1	0	8	8	-	–
33	0	0	0	0	0	1	1	0	altered	decreased
34	0	1	0	0	0	1	2	1	altered	decreased
35	0	0	0	1	0	1	2	1	altered	decreased
36	0	0	0	0	1	1	2	1	altered	decreased
37	2	0	0	0	0	1	3	2	-	decreased
38	0	1	0	1	0	1	3	2	-	decreased
39	0	1	0	0	1	1	3	2	-	decreased
40	0	0	0	1	1	1	3	2	-	decreased
41	0	0	3	0	0	1	4	3	-	decreased
42	2	1	0	0	0	1	4	3	-	decreased
43	2	0	0	1	0	1	4	3	-	decreased
44	2	0	0	0	1	1	4	3	-	decreased
45	0	1	0	1	1	1	4	3	-	decreased
46	0	1	3	0	0	1	5	4	altered	decreased
47	0	0	3	1	0	1	5	4	altered	decreased
48	0	0	3	0	1	1	5	4	altered	decreased
49	2	1	0	1	0	1	5	4	altered	decreased
50	2	0	0	1	1	1	5	4	altered	decreased
51	2	1	0	0	1	1	5	4	altered	decreased
52	2	0	3	0	0	1	6	5	-	decreased
53	0	1	3	1	0	1	6	5	-	decreased
54	0	0	3	1	1	1	6	5	-	decreased
55	0	1	3	0	1	1	6	5	-	decreased
56	2	1	0	1	1	1	6	5	-	decreased
57	2	1	3	0	0	1	7	6	altered	decreased
58	2	0	3	1	0	1	7	6	altered	decreased
59	2	0	3	0	1	1	7	6	altered	decreased
60	0	1	3	1	1	1	7	6	altered	decreased
61	2	1	3	1	0	1	8	7	-	decreased
62	2	0	3	1	1	1	8	7	-	decreased
63	2	1	3	0	1	1	8	7	-	decreased
64	2	1	3	1	1	1	9	8	-	decreased

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points to the total score, which in addition to the initial 2–4 points at rest determines the 100% probability of the presence of HFpEF. The target stress testing was called «diastolic stress test» (Figure 3) and is described in detail in our article [7]. Moreover, the fundamental importance of stress testing in the diagnosis and differential diagnosis of HFpEF was once again emphasized in the latest ESC consensus statement [10].

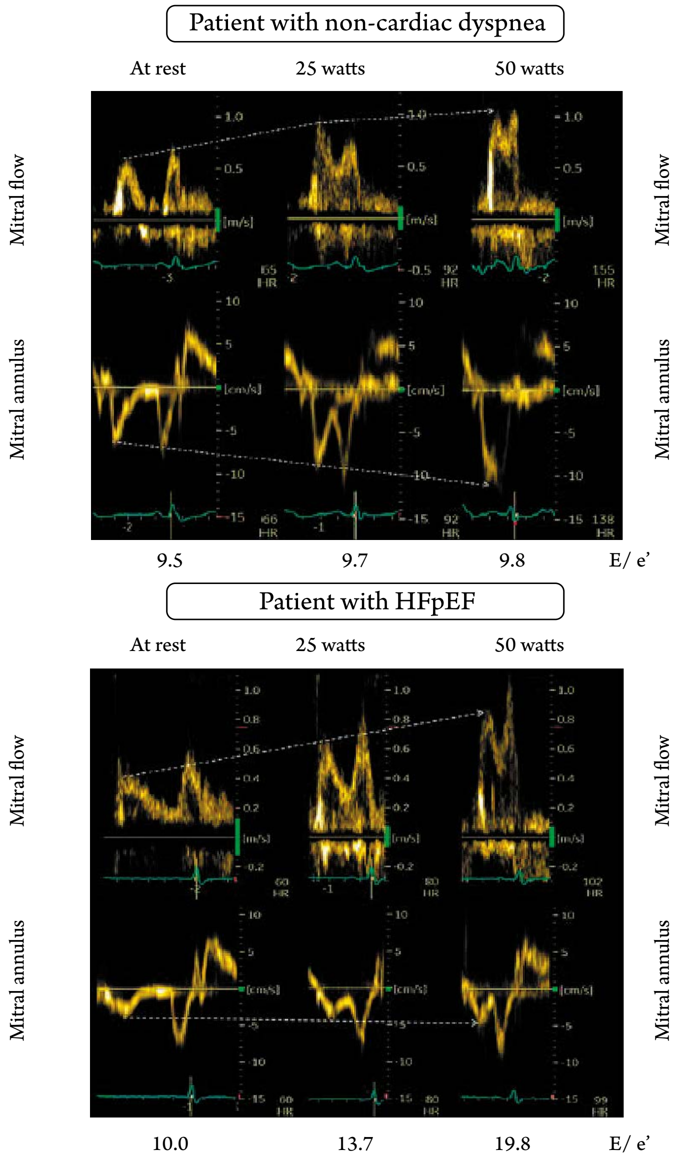
Thus, the high consumer quality of the HFA-PEFF diagnostic algorithm is determined by the ability to directly measure LV filling pressure using a non-invasive ultrasound indicator E/e'. If an echocardiograph with the TDI mode is available, this algorithm can be used in general clinical practice.

An interesting approach was proposed by the American experts, the so-called H2FPEF algorithm (Figure 4) [11]. The advantage of this algorithm is that simple and available clinical and echocardiographic characteristics allow assessing the probability that a patient with unexplained dyspnea at rest or during exercise has HFpEF. This algorithm also uses a scoring system and a total score of≥6 corresponds to the 90–95% probability of the presence of HFpEF. It is noteworthy that all six indicators used are directly (E/e' and pulmonary artery systolic pressure (PASP)) or indirectly (obesity, advanced hypertension, elderly age and atrial fibrillation (AF)) associated with abnormally high LV filling pressure. The H2FPEF algorithm is particularly attractive for general practice, including outpatient practice, since it does not require a clarifying stress test.

Both algorithms, HFA-PEFF and H2FPEF, were tested in the RELAX (type-5 CGMP phosphodiesterase inhibitor sildenafil) and TOPCAT (aldosterone antagonist spironolactone) trials, in which the diagnosis of HFpEF was as accurate as possible; the ARIC (a cohort of adult Americans with long-term prospective follow-up) trial was used the control. Both algorithms had exceptionally high diagnostic accuracy in ruling out HFpEF at low scores (≤ 1) and high diagnostic accuracy in confirming HFpEF at high scores (≥ 5–6). At the same time, when the European HFA-PEFF algorithm was used, the prognostic curves diverged significantly for patients with different scores (low/medium/high), and in case of the American H2FPEF algorithm, only for patients with high and low scores [12]. Another comparative study confirmed that both the American H2FPEF and the European HFA-PEFF algorithms had high specificity in detecting HFpEF, but the H2FPEF algorithm provided higher sensitivity and overall diagnostic accuracy than HFA-PEFF, and it requires fewer input variables [13].

However, despite the apparent simplicity, both algorithms (especially H2FPEF) provide for the use of an in-depth echocardiographic protocol with TDI. Thus, the question arises whether this protocol with the determination of E/e' using TDI is available in the general clinical practice, especially outpatient practice, in Russia.

Figure 3. Diastolic stress test in asymptotic patient with diastolic dysfunction grade 1 and patient with HFpEF



The E and e' velocities increased during exercise in the asymptomatic patient approximately equally leaving the E/e' ratio unchanged. The E velocity increased in the patient with HFpEF much more than e' resulting in a significant increase in the E/e' ratio. The images were received using a General Electrics Vivid E-95 device.

The results of an anonymous survey conducted by us in the OSSN Telegram channel on June 17, 2022 answered this question to some extent (Figure 5). The question was worded as follows: Do you use tissue Doppler imaging with the calculation of E/e' for the diagnosis of heart failure with preserved ejection fraction (HFpEF) in your real practice?. Five answer options were offered, one being «positive» and the other four

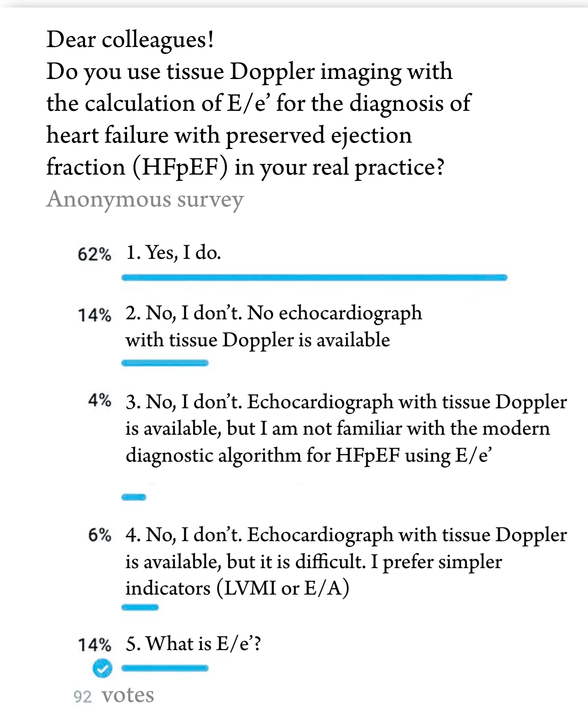
Figure 4. Algorithm for determining the probability of HFpEF proposed by the American experts (2018)

Clinical characteristics		Value	Score
H2	Heavy	Body mass index > 30 kg/m²	2
	Hypertensive	Two or more antihypertensive drugs	1
F	Atrial Fibrillation	Persistent or paroxysmal	3
P	Pulmonary Hypertension	Pulmonary artery systolic pressure according to TDI >35 mm Hg	1
E	Elder	Age > 60 years	1
F	Filling Pressure	TDI E/e' > 3	1
Cumulative H2FPEF score			(0–9)

Score	0	1	2	3	4	5	6	7	8	9
Probability of HFpEF	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	0.95	

LV, left ventricle; TDI, tissue Doppler imaging; e', early diastolic mitral velocity;
E, early diastolic filling velocity; HFpEF, heart failure with preserved ejection fraction.

Figure 5. Anonymous survey of the OSSN Telegram followers (June 17, 2022)



«negative» with different reasons. It should also be noted that the respondents who took part in this survey are not a representative sample of physicians directly involved in the treatment and diagnosis of patients with HF. At the same time, the 92 physicians who answered our question, of course, are active practitioners.

However, their answers clearly showed that 38% of our respondents being specialists this medical area do not use or do not know how to use TDI or the diagnostic algorithm for HFpEF using E/e'. The objective reason, i.e., the absence of an echocardiograph with the function of TDI, was mentioned by only 14% of respondents, and 24% of negative answers were associated with the lack of knowledge of modern diagnostic algorithms for HFpEF (!). Needless to say, how much worse the results of such a survey on the problem of HFpEF verification can be in community hospitals and outpatient clinics.

Given the current situation, the experts suggest two ways to cope with this problem. The first and most obvious way is the full equipment of hospitals and outpatient clinics with modern ultrasound devices and training of physicians in current diagnostic algorithms for HFpEF. The second and less obvious way is to simplify the diagnostic algorithm of HFpEF to abandon TDI and the determination of E/e'. The first option seems mandatory, but will take a long time and require government involvement, and the second option allows solving the problem relatively quickly with the involvement of only the expert community.

The discussed methods of simplification in order to increase the availability of the HFpEF diagnostic algorithm include the HFA-PEFF and H2FPEF algorithms but without taking into account the TDI indicator E/e'. Shallow logic of such reasoning can be explained by the example of H2FPEF: if E/e' weighing 1 point is excluded from this algorithm, then the maximum total score of the remaining indicators can still be 8, which is enough to prove high probability of the presence of HFpEF.

The question is whether it is eligible to use the score of the probability of the presence of HFpEF presented in the H2FPEF algorithm taking into account one (or more) parameters?

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Analysis of the possibility of modifying statistical methods for developing algorithms

Both algorithms (H2FPEF and HFA-PEFF) involve the use of scores to assess the probability of the presence of HFpEF. Reducing the score (excluding or replacing any parameter (s) from the score) will distort the probability of the presence of HFpEF and underestimate the accuracy of the probability assessment in the best case. This can be especially true if an excluded parameter makes a statistically significant contribution in a univariate analysis. A reclassification in such a situation should be performed based on the sample, using which the score was developed, and it should be shown how much the probability of the presence of HFpEF decreases if this parameter is excluded. Exclusion of a parameter from the score developed based on the analysis of the contribution of all parameters can lead to wrong conclusions and neglect of patients in need of treatment. For example, if E/e' is excluded from the H2FPEF score (F in Figure 4), that is F=0 in calculating the score for all patients, then 32 combinations will be automatically removed from consideration of 64=26 possible combinations of indicators. Thus, if F=1 in reality, and the calculation is made for F=0, then the score will be underestimated in half of the possible combinations of parameters (Table 1). Moreover, a score area changes for 14 relatively frequent combinations described in the structure of the H2FPEF algorithm [11], which affects the thresholds of zone divisions, and the corresponding probability of the presence of HFpEF is underestimated.

Indeed, due to complex measurement of certain indicators, such as E/e', their number can be reduced, but with this approach, scoring of each sign will change, which will require additional statistical analysis of the data obtained or a new study as a matter of fact. Moreover, a new HFpEF probability score will be obviously less accurate than the existing one, and it is not a fact that it will be able to meet the diagnostic needs.

E/e' can be theoretically abandoned in the European HFA-PEFF algorithm but only in one condition – if an in-depth echocardiographic examination (without TDI) high PASP (>35 mm Hg) is detected and the total score for the diagnosis of HFpEF is≥5. However, any score of less than 5 will require a diastolic stress test with a mandatory assessment of changes in E/e'. That is, the determination of E/e' will still be mandatory for a significant part of patients with suspected HFpEF, and a complete abandonment of this parameter will inevitably decrease the diagnostic potential of this algorithm.

Thus, it turns out that the implementation of a full diagnostic potential inherent to the HFA-PEFF and H2FPEF algorithms is only possible if all the parameters are taken into account; abandonment of any of them (especially E/e') is unacceptable, because this will distort of the obtained result.

In conclusion, returning to the issue of coping with the problem of verifying the diagnosis of HFpEF in the real-world clinical practice in Russia, it should be recognized that there is currently no alternative for complete equipment of hospitals and outpatient clinics with modern ultrasound devices and training of physicians in modern diagnostic algorithms for HFpEF.

The second way to overcome this problem, i.e., cutting the existing HFA-PEFF and H2FPEF algorithms, primarily by abandoning the use of E/e', is possible but will require conducting a special study to develop a new evaluation score and, in fact, a new algorithm, which in turn will require new evidence of its validity.

No conflict of interest is reported.

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