Principles for diagnosing heart failure with preserved ejection fraction

Shirokov N. E., Yaroslavskaya E. I., Krinochkin D. V., Musikhina N. A., Gizatulina T. P., Enina T. N., Petelina T. I., Soldatova A. M., Samoilova E. P., Pogorelov N. O., Gapon L. I.

Low-grade systemic inflammation, myocardial stress, and extracellular matrix fibrosis lead to heart failure with preserved ejection fraction (HFpEF). The HFA-PEFF diagnostic algorithm and the H2FPEF score are recommended for detecting HFpEF. Their low compliance is the reason for improving the methods for diagnosing HFpEF. Modern paraclinical diagnostics of HFpEF includes an assessment of the left ventricular filling pressure during diastolic stress test. Phase analysis of left atrial strain during resting echocardiography may be promising to conclude an increase in mean left atrial pressure. Research interest is growing in relation to biomarkers involved in the regulation of collagen synthesis. Together, paraclinical diagnostics help to characterize sequential morphofunctional cardiac remodeling, increasing the possibility of HFpEF detection.

Keywords: heart failure, diastolic dysfunction, diastolic stress test, left atrium, myocardial stress.

Relationships and Activities: none.

Tyumen Cardiology Research Center, Tomsk National Research Medical Center, Tomsk, Russia

Shirokov N. E.* ORCID: 0000-0002-4325-2633, Yaroslavskaya E. I. ORCID: 0000-0003-1436-8853, Krinochkin D. V. ORCID: 0000-0003-4993-056X, Musikhina N. A. ORCID: 0000-0002-8280-2028, Gizatulina T. P. ORCID: 0000-0003-4472-8821, Enina T. N. ORCID: 0000-0002-7443-2952, Petelina T. I. ORCID: 0000-0001-6251-4179, Soldatova A. M. ORCID: 0000-0001-5389-0973, Samoilova E. P. ORCID: 0000-0002-5479-0859, Pogorelov N. O. ORCID: 0009-0003-2060-6720, Gapon L. I. ORCID: 0000-0002-3620-0659.

*Corresponding author: shirokov.ne@mail.ru

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Key messages

• When using the HFA-PEFF diagnostic algorithm and the H2FPEF score, to increase the accuracy of HFpEF detection before diastolic stress test, a phase analysis of left atrial strain and determining the concentration of myocardial fibrosis markers can be useful.

The aim of the review is to consider the role of current aspects of instrumental and laboratory diagnostics of heart failure (HF) with preserved ejection fraction (HFpEF).

Research methodology

Investigation was conducted in the PubMed database using the following keywords: “heart failure with preserved ejection fraction", "left ventricular diastolic function", "left atrial strain", “diastolic stress test", "biomarkers" for the period from January 1, 2010 to April 1, 2023. Based on results, 270 data sources were analyzed (consensus documents, meta-analyses, reviews of literature, articles, clinical case reports), 50 of which were included in the review.

Results

Epidemiology of HFpEF

Among patients with clinical manifestations of congestive HF 45% suffer from HFpEF [1]. Incidence of HFpEF has been registered since 1990 [2]. More than 30% of patients were diagnosed with decrease of ejection fraction (EF) of the left ventricle (LV) up to <50% (<10% of them suffer from myocardial infarction) [1]. 5-year mortality rate is 13%; its key causes are sudden cardiac arrest and death due to cardiac decompensation events. [3, 4].

Recommended methods for HFpEF diagnostics

First of all, on the way of HFpEF diagnostics, traditional evaluation method of contractile function — LVEF should be used [5]. Next step (with LVEF ≥50%) is a evaluation of diastolic function (DF) of LV and left atrium (LA). Due to the complexity of the diastole, there is no single recommended parameter for diastolic dysfunction (DD) indication that can be used independently - out of analysis in a comprehensive manner.

Patients with HFpEF are known to be characterized by LV hypertrophy, DD with elevated LV filling pressure (FP), dilatation of the LA, pulmonary hypertension and dysfunction of the right ventricle (RV). Thus, there is sequential functional and morphological cardiac remodeling: left parts of the heart first and then right sides [6]. Update of 2016 ASE and EACVI guidelines on DF assessment led to more precise classification of DF in comparison with the original 2009 ASE / EACVI guidelines [7, 8]. However even algorithms of current recommendations are fulfilled, DF remains doubtful in some patients (~20%), so HFpEF diagnostics is significantly complicated [7].

Table 1

DD diagnostics and impaired diastolic reserve by echocardiography

Parameter	Reference range	Interpretation	Reference source
Resting TTE			
e' lateral, cm/s	<10	Suppression of LV lateral wall relaxation	EACVI 2016
e' septal, cm/s	<7	Suppression of IVS relaxation	EACVI 2016
LA volume index, ml/m2	>34	LA cavity dilatation	EACVI 2016
TR velocity, m/s	>2.8	Pulmonary hypertension	EACVI 2016
E/e' average	>14	Increase of LV FP	EACVI 2016
LASr, %	<23	Decrease in compliance of LA to LV	Morris DA, et al. [17]
LASI	>0.26	Increase in LV diastolic stiffness	Kim D, et al. [20]
Supine bicycle stress echo			
E/e' average	≥15	Increase of LV FP	ESC 2019
TR velocity, m/s	>3.4	Increase of hemodynamic load on right sides of the heart	ESC 2019
E/e' average	>14	Increase of LV FP	EACVI/ASE 2017
E/e' septal	>15	Increase of LV FP	EACVI/ASE 2017
E/e' average (recovery period)	>13	Increase of LV FP	EACVI/ASE 2017
TR velocity, m/s	>3.1	Increase of hemodynamic load on right sides of the heart	EACVI/ASE 2017
DFRI	<13.5	Suppression of LV relaxation	Gibby C, et al. [29]

Abbreviations: FP – filling pressure, LAVI – left atrial volume index, LV – left ventricle, LA – left atrium, IVS – interventricular septum, TR – tricuspid regurgitation, TTE – transthoracic echocardiography, DFRI – diastolic functional reserve index, E/e' average – the ratio of LV early filling velocity (transmitral flow) to the average velocity of mitral valve ring movement, E/e' septal – the ratio of LV early filling velocity (transmitral flow) to velocity of movement of mitral valve annulus lateral part, e' lateral - velocity of movement of mitral valve annulus lateral part using Tissue Doppler echo, e' septal – velocity of movement of mitral valve annulus septal part using Tissue Doppler echo, LASI – left atrial stiffness index, LASr – left atrial reservoir strain.

Clinical and functional diagnostic methods of HFpEF were validated several years ago. In 2019 ESC proposed the HFA-PEFF diagnostic algorithm, which was focused on functional status of a patient. Thus, unexplained dyspnea during physical load (PhL) requires resting transthoracic echocardiography (TTE) and mandatory evaluation of natriuretic peptides (brain natriuretic peptide, BNP; N-terminal pro-brain natriuretic peptide (NT-proBNP) - markers of myocardial stress (secreted by LV during myocardial stretching due to increase of post- or preload to the left sides of the heart). Intermediary probability of HFpEF directs to diastolic stress test (DST) implementation [5]. The H2FPEF score (proposed by Mayo Clinic, USA, 2018) focuses on clinical characteristics of a patient with determination of traditional signs of DD according to TTE (Table 1) [9]. Outlined HFpEF criteria are considered obesity as predominant possible cause; and dominant consequence is atrial fibrillation (AF). However, due to low compliance of the results of HFA-PEFF and H2FPEF implementation, it is necessary to improve HFpEF diagnostic methods [10].

Focus on echocardiography: morphofunctional and hemodynamic status

Prospects for resting TTE

It is necessary to understand that the key link of HFpEF instrumental diagnostics algorithm is detection of increased mean LA pressure [11]. Phases of cardiac cycle are determined for LA function, and to a great extent, mainly, independent of the LA itself. First of all, LA (during LV contraction) serves as a reservoir for pulmonary venous flow. Then, LA becomes a channel (conduit) for the same flow, promoting LV filling (early diastole). Later, LA myocardium contracts increasing LV filling (late diastole) [12]. Quantitative analysis of each phase is available by Speckle Tracking Echo method (STE) (Fig. 1), normal range of values is obtained [13]. Taking into consideration that the phasic Left Atrial Strain (LAS) is undergone changes during DD progression, implementation of STE for HFpEF diagnostics seems to be relevant [14].

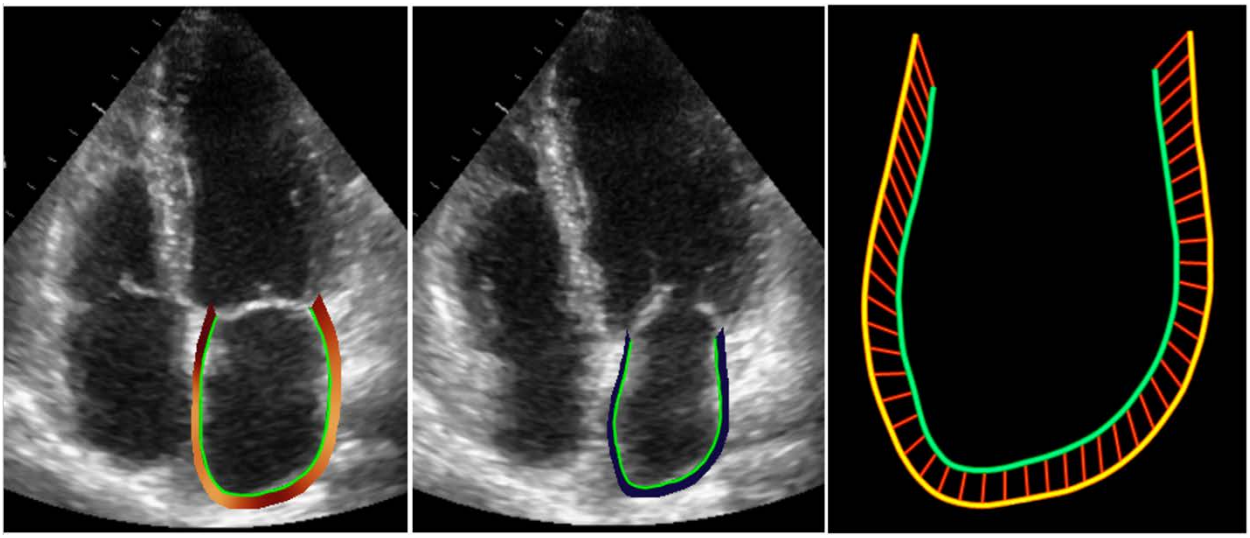

Figure 1. Distinction of LA boundaries for LAS phase analysis.

Note: apical 4-chamber view focused on the LA. The end of LV isovolumetric relaxation – on the left; the end of LA contraction – in the middle; Dynamics of LA walls movement (yellow boundary – the largest volume, green boundary - the smallest volume) – on the right.

Abbreviations: LA – left atrium, LAS – left atrial strain.

It is extremely important to mention that Left Atrial reservoir Strain (LASr) by resting TTE has strong correlation with LV FP value measured invasively, regardless of LVEF, in comparison with the E/e' ratio (a key marker of increased LV FP and HFpEF detection) [15]. Therefore, it should be underlined that LA largest part of filling is fallen to reservoir phase under conditions of normal average pressure in LA. However, increased pressure shifts LA filling to the conduit phase – LASr value decreases [11]. Therefore, this phase can be considered as determining in HFpEF diagnostics (Fig. 2). It is worth taking into account, that unlike

LV global longitudinal strain (GLS), which reflects myocardial shortening of LV and describes its contractile function, LASr represents LA myocardial lengthening. Thus, LASr can be used as conceptual measure of compliance between LA and LV [16].

Figure 2. LAS phase analysis.

Note: white line - average LA strain phase during the cardiac cycle; lines of blue, red and cyan colours – segmental LA strain (interatrial septum, roof, LA free wall, respectively - using apical 4-chamber view). Green numbers indicate LA phases that describe its function: 1 - reservoir phase (includes isovolumetric contraction, ejection, isovolumetric relaxation), 2 - conduit phase (corresponds to the opening of the mitral valve, diastasis), 3 - contraction phase (describes LA contraction, continues until the mitral valve closure). LAS phase analysis is indicated by abbreviations in yellow.

Abbreviations: LA – left atrium, LAS – left atrial strain, LASr – left atrial reservoir strain, LAScd – left atrial conduit strain, LASc – left atrial contraction strain.

Among patients with unspecified DF, more than 70% of patients have normal LA volume. In 50% of them, decrease in LASr is detected. Adding the LASr estimation to the ASE / EACVI 2016 algorithm, detection rate of DD increases by 70% [17]. Substitution of LA volume estimation for LASr assessment provides 75% reduction in unspecified DF [18]. It is extremely important to point out that decrease of LASr lower than the reference value during HFpEF diagnostics is consistent with DST results and HF functional class according to NYHA classification [17, 19]. And the left atrial stiffness index (LASI) - the ratio of E/e' to LASr - has strong correlations not only with hemodynamic parameters of the left and right parts of the heart, but also with the level of BNP [20].

Decrease in LASr lower than the value of reference range [17] marks “LA myopathy” - clinically underestimated electromechanical dysfunction of the LA, leading to AF and HFpEF decompensation (Table 1) [16, 21]. In prediction of AF onset (the predominant consequence of HFpEF using the H2FPEF score) in the presence of normal LA volume, LASr assessment is more significant; with increase of LA volume, GLS assessment is more significant [22]. Inhibition of LASr is also associated with pulmonary vascular remodeling (expressed as increase in pulmonary vascular resistance) and, as consequence, LV contractility dysfunction – decrease of right ventricle free wall strain (RV FWS) [23]. Moreover, assessing GLS, LAS and RV FWS in patients with HFpEF, specifically LASr inhibition showed the greatest association with adverse clinical outcomes (hospitalization due to HF or death) [23].

Proceeding from the above, LASr analysis can lead to timely initiation of therapeutic interventions (in addition to HFA-PEFF and H2FPEF) using STE in HFpEF diagnostics [24]. And in the chain of related phenomena acted sequentially and comprehensively, functional connection of LV and LA (LASI) might be a crucial element of left-sided heart remodeling continuum (Table 1).

Possibilities of DST within supine bicycle stress echo

Simulation of conditions for dyspnea onset is especially important to the search of its etiology. Therefore, DST is performed within the framework of supine bicycle stress echo with comprehensive assessment of the heart condition [25-27].

The cornerstone of HFpEF diagnostics is understood impaired diastolic reserve (DD with increase of LV FP by DST) [5, 26, 27]. A non-invasive sign of increased LV FP is enlarge of E/e' ratio (Fig. 3). To calculate E/e', it is necessary to determine LV hemodynamic and morphodynamic characteristics without LA participation. In the respect of these purposes, early diastolic velocities are recorded: Pulsed wave Doppler (PWD) is used to record peak E of antegrade transmitral flow (registers LV filling), PWD in association with tissue Doppler imaging (TDI) is used to record e' peak of the mitral valve annulus movement (characterizes LV distension) [26, 27].

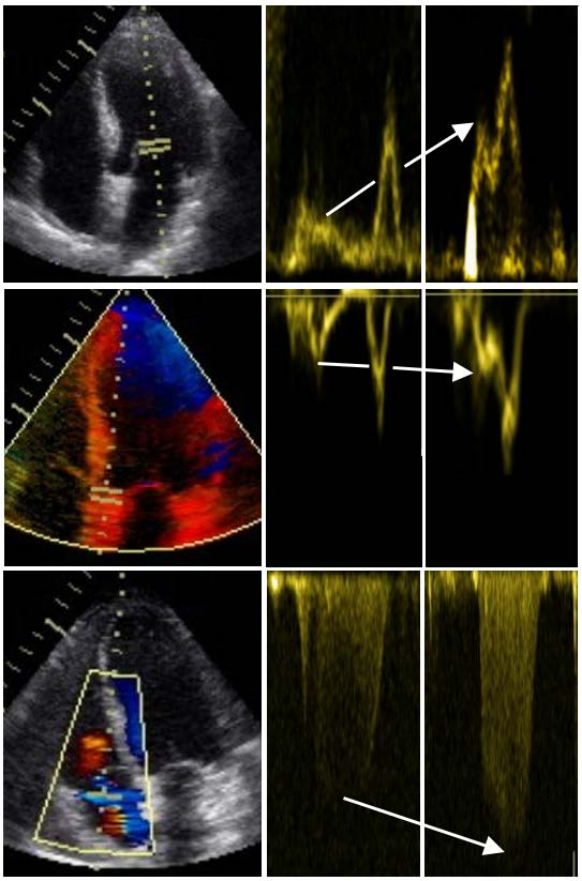

Figure 3. Detection of impaired diastolic reserve by DST in a patient with initial DD (type I - impaired relaxation).

Note: increase of transmitral peakflow E velocity, using PWD (42 cm/s to 105 cm/s) (the upper panel); the e' peak velocity changes insignificantly, the use of PWD in combination with TDI (from 5 cm/s to 6 cm/s), at base line E/e' – 8.4; E/e' at the peak of PL – 17.5 (middle panel). Increase in TP velocity was registered from 2.6 m/s to 3.4 m/s, CWD combined with color mapping (the lower panel).

Abbreviations: DST – diastolic stress test, TR – tricuspid regurgitation, PL – physical load, CWD – continuous wave Doppler, PWD – pulsed wave Doppler, TDI – tissue Doppler imaging.

During PhL, blood deposited in veins of the lower extremities rushes to the right and then to the left parts of the heart. Increase of venous return is accompanied by increase of end-diastolic volume. Implementation of the Frank-Starling mechanism maintains cardiac minute output required under new conditions. When the heart rate is above 100-120 beats/min, cardiac minute output is maintained due to hyperkinesis of LV myocardium – Bowditch-Treppe effect implementation [28]. As a result of LV myocardium

inability to stretch for LV end-diastolic volume enlargement with HFpEF (low amplitude e' by DST), LV FP increases (high amplitude E by DST). Exceedance of reference ranges for E/e' is considered reduction of diastolic reserve and HFpEF is diagnosed (Table 1) [5, 26, 27].

Suppression of diastolic functional reserve (DFRI) may serve as useful indication of LV myocardium incapability to sufficient stretch. Applying TDI (Δe' × e' rest), this additional negative sign helps in HFpEF diagnostics; its reduction is associated with low tolerance to PhL (Table 1) [29].

Significant component of HFpEF (but not necessary for positive reaction) is elevation of systolic pulmonary artery pressure (sPAP), which indicates increased hemodynamic load to the right parts of the heart (out of the physiological range), pulmonary hypertension with PhL and is responsible for dyspnea (Table 1). It is worth pointing out that elevation of sPAP without increase in E/e' is not considered a symptom of HFpEF [5].

At the final step of HFpEF detection within the framework of HFA-PEFF diagnostic algorithm is proposed (if previous steps are unsuccessful) catheterization of the right parts of the heart - invasive assessment of pulmonary artery wedge pressure (PAWP) [5]. Increase in PAWP by stress test (with its normal value at rest) is associated with greater 10-year mortality [30]. It should be paid attention that PAWP is just vicariously reflects the pressure in LA and LV end-diastolic pressure (diagnostic balloon catheter is dilated in branches of pulmonary artery – record the pressure transmitted from LA through pulmonary capillary system) [30].

Focus on biomarkers: meta-inflammation, myocardial stress, fibrosis

Principles of initiation and development of HFpEF

Immune inflammation, myocardial stress and fibrosis of extracellular matrix are closely interconnected in the context of initiation and progress of HFpEF [31].

Proinflammatory cytokines are signaling molecules stimulated migration of immunenocompetent cells. Key cytokines maintained systemic chronic low-grade inflammation (meta-inflammation) can be considered tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-1β. Excessive production of TNF-α and IL-6 is characteristic of metabolic cardiomyopathy (obesity, tissue resistance to insulin, type 2 diabetes mellitus) [32, 33], arterial hypertension and chronic kidney disease [34, 35]. For atherogenesis, high local release of IL-1β (including its autoinduction) also leads to increase in concentration of IL-6 (the latter is considered as systemic mediator of inflammation) [36].

Circulation of proinflammatory cytokines in coronary microvascular bed (in particular, TNF-α and IL-6) provokes subendothelial migration of circulating monocytes [31]. With participation of them, endothelial cells are overly produced reactive oxygen species; overall availability of nitric oxide (NO) for smooth muscle cells is reduced, that contributes to deprivation of endothelium-dependent vasodilation – develops coronary microvascular dysfunction (CMD) [31, 37].Oxidative stress also leads to deficiency NO – cGMP – PKG signaling pathway, contributing inhibition of cardiomyocytes relaxation, development of concentric LV remodeling and, what is especially important in the context of HFpEF detection, progress of DD [31, 38, 39]. Within this context we should highlight of PROMIS-HFpEF multicenter clinical study result (2018): 75% of patients with HFpEF were instrumentally confirmed CMD (decrease of coronary flow reserve <2.5). Interrelation between CMD and peripheral endothelial dysfunction was found, indicating systemic nature of meta-inflammation [40].

Among laboratory signs of immune inflammation, C-reactive protein and regulating its secretion IL-6 can become markers of HFpEF onset, probably due to relationship of their concentration with metabolic syndrome and AF [41, 42]. However, only markers of meta-inflammation are not enough to detect HFpEF.

Regarding metabolic cardiomyopathy as probable cause of HFpEF, it is important to point out "obesity paradox": with BMI increase, concentration of myocardial stress markers – BNP/NT-proBNP - becomes lower [43]. BNP/NT-proBNP is traditionally used to detect HFpEF (HFA-PEFF diagnostic algorithm), although their level is growing with decrease of LVEF [44]. This lack doesn't appear in myocardial fibrosis mediator Galektin-3 (Gal-3), concentration of which is on the contrary the highest in HFpEF patients [45, 46]. Excessive myocardial fibrosis (characterized by increase of extracellular matrix primarily due to collagen) contributes fibroblasts [47]. Their differentiation into myofibroblasts is stimulated by macrophages (monocytes, migrated

into the tissue due to immune inflammation) [48]. Perivascular fibrosis is associated with the development of CMD, interstitial fibrosis – with DD formation [31, 38]. Therefore, research interest in biomarkers involved in regulation of collagen synthesis is growing.

In the context of HFpEF development, it is extremely important to draw a parallel between instrumental and laboratory methods of its diagnostics [39]. It should be pointed out the positive correlation of E/e' ratio (a sign of increased LV FP by TTE) with concentration of fibrosis markers: Gal-3, soluble suppression of tumorigenesis-2 (sST2) and growth differentiation factor-15 (GDF-15) [44, 49]. Giving this another way, release of biomarkers, characterized excessive myocardial fibrosis, is under conditions of myocardial stress – this confirmed by instrumental and laboratory of HFpEF diagnostics.

Possibility of HFpEF phenotyping should be considered using specified biomarkers: GDF-15 concentration increases with ischemic myocardial injury, Gal-3 – with type 2 diabetes mellitus [44]. Inflammatory types are likely to be allowable to differentiate: sterile / metabolic risk-induced [50]. In turn, sST2 can be used as an indicator of HF progression – its concentration grows with increase of hemodynamic load on the right parts of the heart [44].

Conclusion

Therefore, HFpEF diagnostics should be sequential and comprehensive: based on identification of its initiation key links and development with obligatory fulfilment of instrumental (resting TTE, DST within supine bicycle stress echo) and laboratory characteristics of heart impairment (Fig. 4).

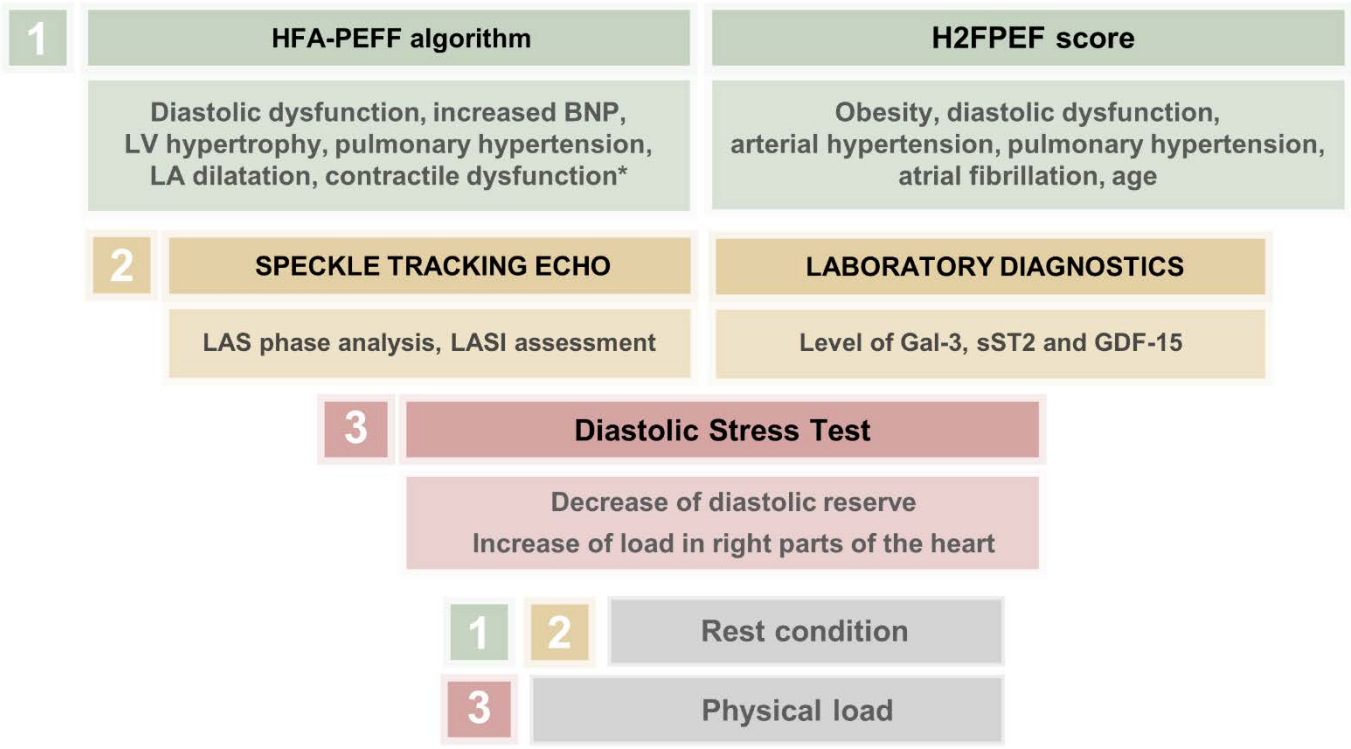

Figure 4. Proposed algorithm to diagnose HFpEF.

Note: Step 1 - fulfillment of recommended HFA-PEFF algorithm and H2FPEF score (listing signs of suspected HFpEF). Step 2 – Use of up-to-date methods of instrumental and laboratory HFpEF diagnostics at rest. Step 3 – performing DST as part of stress echocardiography with a comprehensive hemodynamic and morphodynamic assessment of the heart. * – decrease of GLS.

Abbreviations: GLS – global longitudinal strain, DST – diastolic stress test, LV – left ventricle, LA – left atrium, BNP – natriuretic peptides, HFpEF – heart failure with preserved ejection fraction, LAS – left atrial strain, LASI – Left atrial stiffness index, LASr – left atrial reservoir strain, Gal-3 – Galektin-3, GDF-15 – growth differentiation factor-15, sST2 – soluble suppression of tumorigenesis-2).

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