REVIEW ARTICLE

Echocardiography in patients with heart failure: recent advances and future perspectives

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ABSTRACT
Echocardiography is a relatively inexpensive and widely available technique that has a pivotal role in the assessment and management of patients with heart failure (HF). Advancements in cardiac ultrasound, especially the advent of myocardial deformation imaging, have provided a comprehensive insight into the complexity of cardiac derangements underlying HF, contributing to the better understanding of the disease process. The essential issues that echocardiography can help address include: establishing / confirming diagnosis, categorizing and phenotyping patients, prognosticating, guiding therapeutic decision-making, and monitoring responses to treatment. Novel echocardiographic technologies permit early recognition of preclinical myocardial abnormalities, as well as further tracking of pathologic alterations and therapeutic responses. The predictive utility of a large number of echocardiographic indices, offering an abundance of prognostic information independent of and incremental to clinical data, underpins their use in risk stratification strategies. The evolution of existing modalities, as well as the wider implementation of automation and artificial intelligence, provides the basis for the future development and expanded clinical application of echocardiography.

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Introduction Heart failure (HF), a complex clinical syndrome involving a wide range of circulatory derangements, accounts for a substantial proportion of cardiovascular morbidity and mortality worldwide. It is characterized by patient symptoms and physical examination findings caused by a structural and / or functional cardiac abnormality, resulting in a reduced cardiac output and / or elevated intracardiac pressures at rest or during stress.[1] The prevalence of HF increases in parallel with the growing population burden of aging and comorbidities, thus posing a significant challenge to healthcare systems.[2] Available data indicate that the number of individuals with HF in Poland exceeds 750 000 and will soon increase by one-fourth.[3] Accordingly, effective strategies to prevent HF and improve management of affected patients are a matter of ongoing interest. An example of a targeted policy in this context is the system of coordinated care for HF patients, including outpatient care, pharmacotherapy, as well as interventional treatment and rehabilitation, which has been recently proposed in Poland.[3]

Echocardiography provides a great amount of detailed information on cardiac structure, function, and hemodynamics in a readily available and cost-effective way. Moreover, it is performed virtually in all patients with a clinical suspicion of HF, especially in those with signs and/or symptoms of HF such as breathlessness, fatigue, elevated jugular venous pressure, pulmonary crackles, and peripheral edema. The essential issues that echocardiography can help address include: establishing or confirming diagnosis, categorizing and phenotyping patients, prognosticating, guiding therapeutic decision-making, and monitoring responses to treatment.

Echocardiography and classification of heart failure The 2 principal mechanisms responsible for HF symptoms (ie, impairment of left ventricular [LV] contractility and LV filling) are not mutually exclusive and frequently coexist.[4] However,

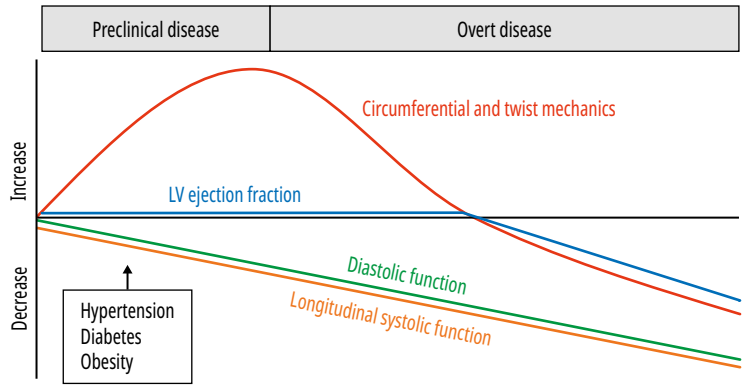

FIGURE 1 Changes in left ventricular (LV) functional profile in the progression from asymptomatic to symptomatic heart failure. Modified from Cikes and Solomon.[10]

despite the complexity of an underlying pathophysiologic background, the main clinical classification of chronic HF is based on LV ejection fraction (LVEF), a measure of systolic performance. The advantage of LVEF is its widespread use, which allows easy communication about cardiac status. However, the parameter also has some important limitations that compromise its ability to satisfactorily characterize individuals with HF. The major reasons for the inaccuracy of LVEF measured by echocardiography are significant test-retest variability (which may be as high as ±14%),[5] preload and afterload dependence, susceptibility to insufficient image quality, intraventricular conduction disturbances (especially left bundle branch block when regional systole and diastole are not simultaneous) and heart rhythm irregularities, and, in case of 2-dimensional echocardiography, geometric assumptions on LV shape to estimate LV volumes.[6] The use of 3-dimensional echocardiography in the assessment of LVEF mitigates the problem of geometric assumptions; however, this modality has its own drawbacks such as low spatial and temporal resolution.

Clinically, no clear relationship between LVEF and New York Heart Association functional class can be found.[7] The distinction of 3 HF categories within the spectrum of LVEF, specifically separating out HF with mid-range ejection fraction (ie, the "grey zone" group), has narrowed down the ranges of both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF), thus improving the homogeneity of their phenotyping profiles.[1]

The need for revisiting the cutoff values of LVEF in the context of the therapeutic decision-making was reinforced by a subgroup analysis of the PARAGON-HF trial (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction), which revealed a dual response to sacubitril/valsartan in patients with HFpEF, with a clear benefit from this treatment in the subset of patients with LVEF lower than 57%.[8]

Approaches to left ventricular mechanics

The intricacy of LV mechanics is one reason why the information provided by LVEF is insufficient. The limited value of LVEF in describing LV contractile phenomena is irrespective of the method used for its assessment. Left ventricular ejection is governed by longitudinal and circumferential shortening, radial thickening, and rotational motion. This multidimensional pattern is possible due to the complex LV architecture including circumferential fibers in the midmyocardium and longitudinal fibers in the subendocardium and subepicardium, forming a right-handed and left-handed helix, respectively. The rotation of the LV base and apex in opposite directions, attributable to differences in the helical geometry of the subendocardial and subepicardial layers, precipitates twisting of the LV, which is an important contributor to LV volume reduction during systole and untwisting and suction during diastole.

The subendocardial fibers responsible for LV longitudinal contraction are most vulnerable to wall stress and damage.[9] Accordingly, the selective involvement of the inner layer of the LV wall in the early phase of the disease results in LV longitudinal dysfunction. In these circumstances, when the contractility of subepicardial and midmyocardial fibers remains preserved, it is quite common to identify increased circumferential and twist mechanics, both of which balance a decrement in the long-axis performance and permit the maintenance of LVEF within the normal range.[4] The early decrease in LV longitudinal systolic function parallels or, in some cases, even precedes the development of diastolic abnormalities.[10] This pattern of LV functional changes can be found in the preclinical stage of HFpEF. Moreover, it is associated with aging and the presence of some comorbidities, such as hypertension, diabetes, and obesity.[4] Mechanistically, the progressive loss of compensatory support from the nonlongitudinal components of LV mechanics, occurring in the natural history of the disease, may result in the deterioration of overall LV performance and the advent of HF symptoms (FIGURES 1 and 2).

In contrast to the above scenario, the concurrent involvement of all myocardial layers (eg, during an acute myocardial infarction) or the expansion of the pathologic process over the midmyocardium and subepicardium leads to a reduction in all components of LV mechanics and decrease in LVEF, usually with concomitant LV dilation.[4] All of these features are consistent with the morphological and functional profile of HFrEF.

Myocardial deformation imaging has emerged as an option that can provide a comprehensive insight into the physiology and pathophysiology of cardiac function. The currently recommended technique for the evaluation of myocardial

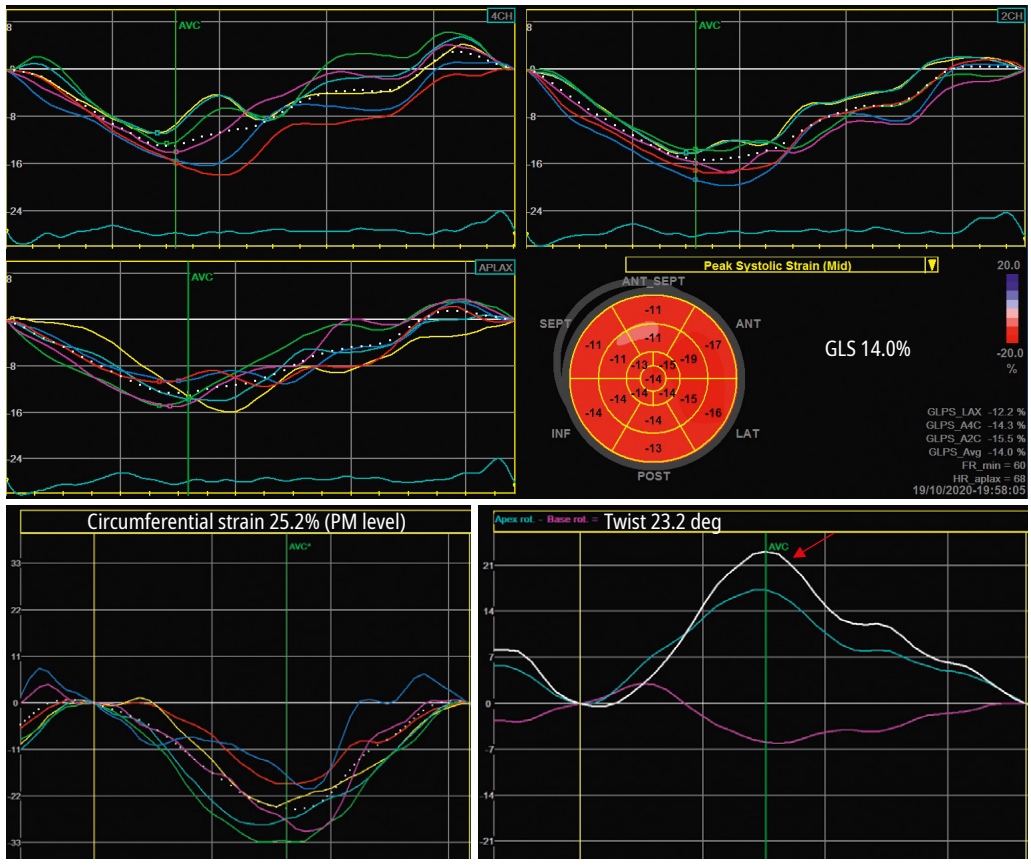

FIGURE 2 Example of left ventricular mechanics in the preclinical stage of heart failure. Decreased magnitude of global longitudinal strain accompanied by a compensatory increase in circumferential strain and twist (red arrow; calculated as a net difference between basal and apical short-axis planes).
Abbreviations: AVC, aortic valve closure; GLS, global longitudinal strain; PM, papillary muscle

deformation is speckle-tracking echocardiography. Despite some apparent limitations, such as the relatively low temporal resolution, this technique is more feasible and more likely to be implemented in daily clinical practice than the previously used modality based on tissue Doppler imaging. The measurements of deformation indices derived from speckle-tracking echocardiography can be carried out both in the ventricles and atria. For the LV, the highest feasibility is noted for longitudinal strain; intermediate, for circumferential strain; and lowest, for radial strain.

The assessment of myocardial deformation allows the identification of dysfunction that would otherwise be missed. The most common deformation parameters include strain, strain rate, twist, as well as twisting and untwisting rate. Of these, longitudinal strain has been most extensively employed as a clinical tool. Both the amplitude and timing of deformation indices can be quantified. This, in addition to assessing the overall potential of the individual components of myocardial function, can give insight into electromechanical coupling.

The presence of normal LVEF may not be synonymous with normal LV systolic function. This apparent paradox, best seen in HFpEF, can be explained by the dependence of LVEF on a variety of geometric factors. In the presence of increased LV wall thickness and/or decreased end-diastolic volume, LVEF may remain normal despite the reductions in both LV longitudinal and circumferential shortening.[11] The contribution of circumferential shortening to LVEF is greater than longitudinal shortening; therefore, LVEF is less prone to a decline in the context of impaired longitudinal function.[11] These findings strongly support the use of LV deformation indices in addition to LVEF for the assessment of LV systolic function.

Apart from the ability to reflect global myocardial performance, deformation parameters can reveal segmental differences in cardiac mechanics. These measurements provide an incremental value to the diagnosis of diseases characterized by the regional heterogeneity of LV function, such as amyloidosis (relative preservation of apical strain) or Fabry disease (functional impairment mainly in the mid or basal posterolateral segments).[12]

Myocardial deformation parameters are primarily dedicated to the assessment of cardiac contraction; however, some indices, such as

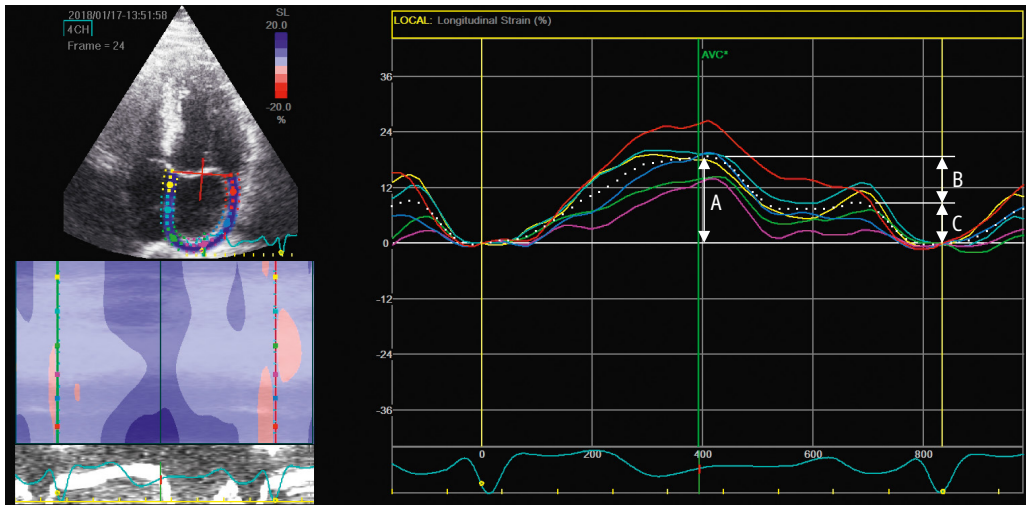

FIGURE 3 Reduced left atrial strain in a patient with heart failure: A represents left atrial reservoir strain (18.6%), B represents left atrial conduit strain (10.4%), and C represents left atrial contractile strain (8.2%)
Abbreviations: see FIGURE 2

strain rate during isovolumic relaxation, strain rate during early filling, and LV untwisting rate, can be used to describe diastolic function. As the measurement of deformation parameters is affected by loading conditions (probably more for strain than strain rate)[4], it may not adequately reflect myocardial contractility. This interplay between myocardial deformation and changing cardiac load can lead to misleading clinical conclusions, especially in the disease states characterized by high LV afterload and in serial assessments, when visit-to-visit fluctuations in blood pressure may affect the magnitude of LV deformation. To diminish this problem, the estimation of myocardial work correcting longitudinal deformation for systolic blood pressure on the basis of noninvasive load-strain loops has been proposed. This approach provides additional information on LV function by calculating constructive and wasted work, as well as myocardial efficiency, but further validation is warranted.[13]

Identification of preclinical cardiac impairment The detection of preclinical myocardial abnormalities is of crucial importance to prevent the progression to overt disease. Depending on the underlying burden of comorbidities, the hallmarks of subclinical HF include a constellation of cardiac functional and structural disorders, with the most frequent being LV diastolic and longitudinal systolic dysfunction, LV hypertrophy, and left atrial (LA) derangements.[14] Recent guidelines[15] proposed a diagnostic process for diastolic dysfunction that is based on an integrated assessment of mitral inflow, annular velocities, LA volume, and tricuspid regurgitant velocity, with the auxiliary role of other diastolic parameters and clinical judgment. Among novel markers, LA strain and LV untwisting rate may prove particularly useful for the detection of abnormal LV diastolic performance (FIGURES 3 and 4). It has been found that the aberrations of LA strain may precede atrial volumetric changes.[16-18] The multi-aspect information provided by LA strain, including LV filling, LA relaxation, and LA contractility (reflected by reservoir, conduit, and booster pump components, respectively), underpins its potential to identify early cardiac disease.

Left ventricular ejection fraction is usually too insensitive to detect minor systolic derangements in the preclinical phase of HF. A vast body of research demonstrated that the identification of early longitudinal systolic impairment can be accomplished with the use of myocardial deformation or systolic myocardial velocities,[16,19] although the latter is supported by less extensive evidence. Left ventricular functional abnormalities detected by echocardiography were shown to correlate with reduced exercise capacity even in the asymptomatic stage.[20]

In its natural history, the preclinical phase of HF may deteriorate and progress to HFpEF or even to HFrEF. A meta-analysis of several studies of asymptomatic patients showed that diastolic dysfunction is associated with a 70% increased risk of overt HF.[21] From a pathophysiologic standpoint, the transition to symptomatic HF is related to the progression of hemodynamic disturbances in LV filling and contractility, which can be monitored and identified by echocardiography.

Echocardiographic evaluation of left ventricular filling pressure Elevated LV filling pressure represents the hemodynamic consequence of LV diastolic dysfunction. There are a number of definitions of LV filling pressure elevation (including heightened pulmonary capillary wedge pressure [PCWP], mean LA pressure, LV pre-A

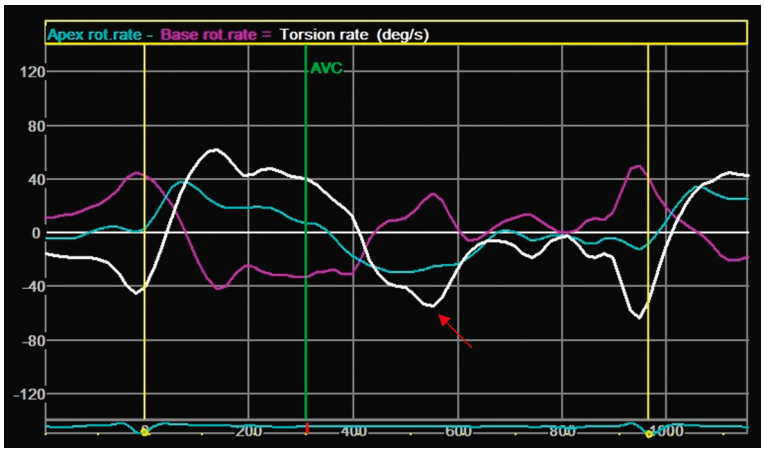

FIGURE 4 Reduced left ventricular untwisting rate in a patient with heart failure with preserved ejection fraction; early diastolic untwisting rate (calculated as a net difference between basal and apical short-axis planes), 55 deg/s (red arrow)
Abbreviations: see FIGURE 2

pressure, mean LV diastolic pressure, and LV end-diastolic pressure [LVEDP]), as well as echocardiographic parameters used for the estimation of filling pressure. The diagnostic accuracy of the most commonly used echocardiographic marker, early diastolic transmitral flow velocity to early diastolic mitral annular tissue velocity ratio (E/e'), has been questioned, given its variable and frequently modest correlations with invasive measurements.[22] A recent meta-analysis reported a pooled *r* coefficient to be only 0.56.[23] In the 2016 guidelines for the evaluation of diastolic function, the American Society of Echocardiography and European Association of Echocardiography (ASE / EACVI) proposed an algorithm for LV filling pressure approximation based on the combination of variables reflecting both a long-term elevation of LV filling pressure and LV filling pressure during echocardiographic imaging (early diastolic transmitral flow velocity [E], early to late diastolic transmitral flow velocity ratio [E/A], E/e', and tricuspid regurgitation velocity [TRV]). The validation of this approach against cardiac catheterization was carried out in 2 multicenter studies, which confirmed the feasibility but demonstrated some differences in the diagnostic accuracy of this new noninvasive strategy (sensitivity and specificity of 87% and 88% in the first study and 75% and 74% in the second study).[24,25] The reason for this discrepancy might be the different clinical profiles of the studied cohorts and, more importantly, the different metrics of LV filling pressure used as the frame of reference (PCWP vs LVEDP). The better correlation of the 2016 algorithm with PCWP than with LVEDP is consistent with previous findings on the associations of individual Doppler indices used in this approach with invasive hemodynamic data.[26] The robustness of the current recommendations is higher for the identification of elevated than nonelevated LV filling pressure.[24]

Another significant limitation of the current guidelines is the relatively large number of patients with indeterminate or uncertain LV filling pressure. In this setting, other echocardiographic parameters correlating with invasive hemodynamic measurements might be helpful, including LA strain, pulmonary venous flow indices, and Valsalva maneuver–induced changes in the mitral inflow pattern.[27]

Role of exercise echocardiography A significant proportion of patients complaining of exertional dyspnea (and therefore suspected of HFpEF) may not show elevation of LV filling pressure at rest. In these individuals, exercise stress test can unmask advanced LV filling abnormalities as well as other derangements associated with reduced functional capacity. From a pathophysiologic perspective, impaired LV relaxation and compliance, abnormal increment in LV early diastolic suction, and reduced myocardial contractility reserve result in an inadequate exercise-associated increase in stroke volume and cardiac output in patients with HFpEF, together with an elevation of LV filling pressure, both of which underlie limitations in exercise capacity.[22,28] Both bicycle (preferably supine) and treadmill exercise protocols are useful for this purpose.[15] Passive leg lifting and isometric exercise with handgrip may be potential alternatives to dynamic exertion but need to be more extensively validated to be recommended for clinical use.[29-31]

The mitral E/e' ratio is the most commonly used parameter to evaluate the LV diastolic response to exercise. However, the ability of this marker to track exertional alterations in LV filling pressure has been inconsistent across an array of studies including HFpEF and non-HFpEF populations.[32-34] Therefore, to improve the diagnostic accuracy of the approach based on a single parameter, the 2016 guidelines recommend the use of an extended algorithm including exercise E/e', exercise TRV, and baseline e'.[15] To consider the test positive, all the 3 criteria have to be met (TABLE 1, FIGURE 5). However, the major problem with the practical application of this multimarker strategy is the inability to obtain a reliable TRV Doppler signal during exercise in 30% to 50% of patients, which affects sensitivity and negative predictive value of this approach.[28,32] Some data suggest that the reliance in such circumstances on exercise E/e' alone might be an option to improve sensitivity at the cost of an acceptable drop in specificity.[32] Ultimately, it should be highlighted that the false-positive result rate of exercise echocardiography has been reported to be about 20%.[28,32] Therefore, the complete ascertainment of LV filling pressure response to exertion can be provided only by invasive hemodynamic stress testing.

Apart from examining the LV diastolic domain, exercise stress allows an assessment of

TABLE 1 Interpretation of diastolic exercise echocardiography according to the current position papers

2016 ASE / EACVI guidelines[a]		2019 HFA-PEFF algorithm[b,c]
Positive	Definitely negative	Positive
Exercise E/e' >14 (average) or >15 (septal)	Exercise E/e' (average or septal) <10	Exercise E/e' (average) ≥15
Exercise TR velocity >2.8 m/s	Exercise TR velocity <2.8 m/s	Exercise TR velocity >3.4 m/s
Septal e' <7 cm/s (lateral e' <10) at baseline	–	–

a All criteria need to be fulfilled

b When only E/e' is positive: +2 points to the HFA–PEFF score; when both criteria are positive: +3 points to the HFA–PEFF score

c The algorithm consists of: pretest assessment (P), diagnostic workup with echocardiogram and natriuretic peptide score (E), advanced workup with functional testing in case of uncertainty (F), and final etiological workup (F).

Abbreviations: ASE, American Society of Echocardiography; E, peak early diastolic mitral flow velocity; e', peak early diastolic mitral annular velocity; EACVI, European Association of Cardiovascular Imaging; HFA, Heart Failure Association of the European Society of Cardiology; TR, tricuspid regurgitation

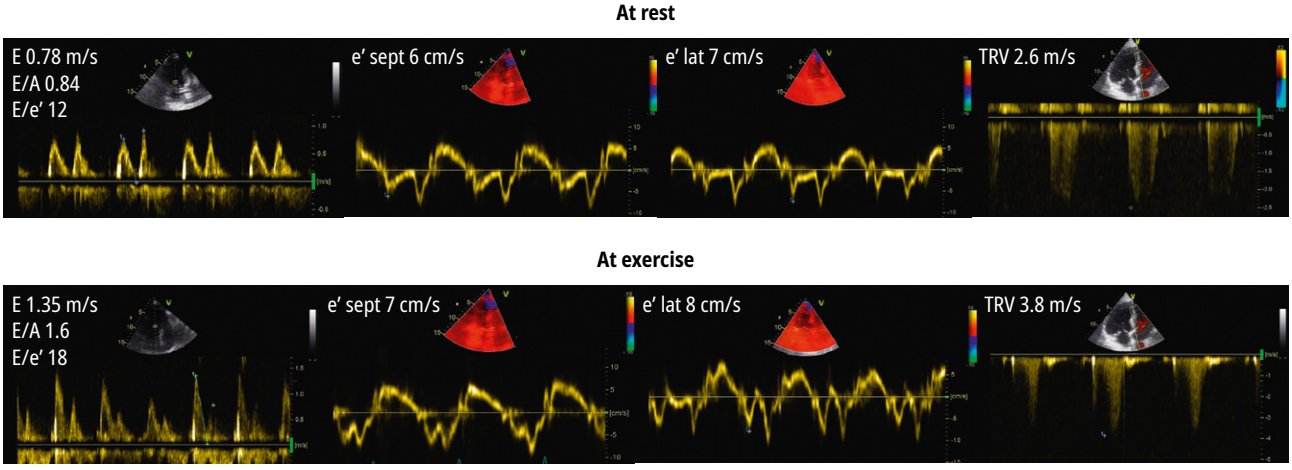

FIGURE 5 Positive result of diastolic exercise echocardiography; exercise E/e', 18; exercise TRV, 3.8 m/s. Note the change in mitral inflow pattern at exercise. Abbreviations: TRV, tricuspid regurgitation velocity; others, see TABLE 1

other aspects of exercise physiology, including LV systolic and chronotropic reserve, as well as other potential reasons for exercise intolerance, such as myocardial ischemia, dynamic mitral regurgitation, LV outflow tract obstruction, or exaggerated increase in blood pressure. Special attention in the context of reduced functional capacity in HFpEF should be paid to the abnormal LV contractile response to exertion, demonstrated both by using deformation imaging (global longitudinal strain [GLS] and global longitudinal strain rate) and volumetric measurements.[35-37] Blunted LV deformation reserve may be an essential cardiac functional abnormality in some patients with HFpEF, as revealed by machine-learning algorithms.[38] Left ventricular systolic behavior under an exercise load might be evaluated in greater detail by myocardial work.[39] Left ventricular systolic reserve can also be assessed in HFrEF with dobutamine or exercise echocardiography for prognostic and clinical decision-making purposes, including the prediction of response to β-blockers or cardiac resynchronization therapy (CRT).[31] A promising option is the calculation of force-based contractile reserve (the stress-to-rest ratio of force expressed as systolic arterial pressure measured by cuff sphygmomanometer to end-systolic volume determined by 2-dimensional echocardiography), which is load independent. It appears to be more effective in identifying abnormal contractile potential and may improve diagnostic and risk stratification protocols in HF.[40]

Irrespective of the LVEF status, the detection of B-lines during stress testing by lung ultrasound, reflecting the acute increase in extravascular lung water resulting from LV filling pressure elevation, provides evidence that exertional dyspnea is related to pulmonary congestion.[41,42]

Use of echocardiography in the diagnosis of heart failure with preserved ejection fraction There is an increasing role of echocardiography in the diagnosis of HFpEF. The 2016 European Society of Cardiology guidelines on HF endorsed at least one of the following: LV hypertrophy, LA enlargement, or mitral inflow/tissue Doppler abnormalities as an obligatory criterion defining this HF category.[1] A recently developed score to predict HFpEF in unexplained

dyspnea on the basis of a combination of clinical (age, body mass index, antihypertensive treatment, and history of atrial fibrillation) and echocardiographic variables (resting E/e' and right ventricular systolic pressure) demonstrated superb discriminatory power (area under the curve, 0.886) (TABLE 1).[43]

The latest algorithm for the recognition of HFpEF developed by the Heart Failure Association (HFA) of the European Society of Cardiology strengthens the position of echocardiography in the diagnostic workup.[28] Along with natriuretic peptides, several cardiac functional and structural echocardiographic indices (e', E/e', TRV, GLS, LV mass, relative wall thickness, and LA volume) serve as the mainstay of this scoring system (referred to as HFA-PEFF) for estimating the likelihood of HFpEF. Obtaining a low or high probability of diagnosis concludes the evaluation, but in the case of an intermediate score, further assessment is needed, with diastolic exercise echocardiography as an option. Compared with the 2016 ASE / EACVI position paper, the HFA recommends higher threshold values of resting and exercise E/e' ratio as well as TRV to improve diagnostic specificity (TABLE 1).

Role of echocardiography in patients with functional mitral regurgitation Functional mitral regurgitation (FMR) resulting from LV remodeling is a common finding in patients with HFrEF. It was shown to have an adverse effect on both symptom status and prognosis.[44,45] Echocardiography allows an extensive evaluation of the underlying mechanism and severity of FMR, as well as mitral valve and LV geometry, specifically the measurements of tenting height, tenting area, posterior leaflet angle, mitral annulus diameter, and interpapillary muscle distance, all of which are necessary to determine patient eligibility for surgical and percutaneous interventions on the valve. Three-dimensional echocardiography has the potential to provide more information on the morphologic and functional derangements of the mitral valve than the 2-dimensional approach. Moreover, it may be helpful in establishing FMR severity by direct planimetric measurements of the vena contracta.[46] Importantly, the ratio between quantified FMR severity and LV remodeling may be the key to the appropriate selection of HFrEF patients with "disproportionate" FMR for mitral clip insertion. For example, at an LV end-diastolic volume of 200 ml, an effective regurgitant orifice area of more than 0.3 cm^2 is disproportionate to the LV size and a clip would be beneficial, whereas an effective regurgitant orifice area of 0.2 cm^2 is proportionate and a clip may offer less benefit (FIGURE 6).[47]

In patients with a disproportion between symptoms and FMR severity quantified at rest, exercise echocardiography allows better clinical and prognostic assessment.[48] Intraprocedural echocardiographic guidance is essential for the successful transcatheter implementation of devices for FMR repair.

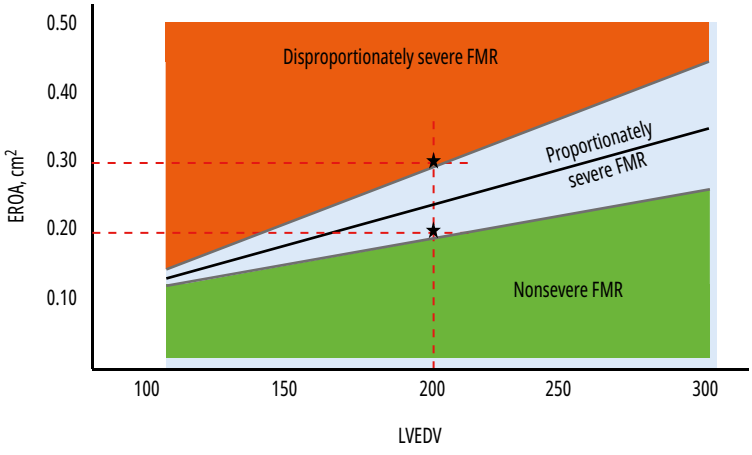

FIGURE 6 Relationship between effective regurgitant orifice area (EROA) and left ventricular end-diastolic volume (LVEDV) in functional mitral regurgitation (FMR). At an LVEDV of 200 ml, an effective regurgitant orifice area of more than 0.3 cm^2 is disproportionate, whereas an EROA of 0.2 cm^2 is proportionate to the left ventricular size (asterisks). Modified from Grayburn et al.[47]

Role of echocardiography in prognosis and risk prediction in patients with heart failure Echocardiography offers a wealth of prognostic information that can improve patient management. For a long time, LVEF has been recognized as an important predictor of HF and adverse clinical outcomes. However, its prognostic ability is not equipotential across the entire range of its values. Importantly, LVEF does not adequately assess clinical risk when relatively preserved (eg, >45%)[49-51] and is of limited value for determining eligibility for device therapies in primary prevention of sudden cardiac death.[52,53]

Global longitudinal strain was shown to provide additional prognostic information independent of LVEF.[51] In a meta-analysis including a wide spectrum of cardiovascular diseases, GLS was on average 1.5-fold better prognosticator of major adverse cardiac events than LVEF, with the superiority of GLS being most discernible in the normal or near-normal ranges of LVEF.[51] Accordingly, GLS adds incremental prognostic value both in HFpEF and HFrEF; however, its role as a prognosticator is more critical in the former category.[54,55] The associations of global LV deformation with increased cardiovascular risk were also demonstrated in post-infarct patients developing HF, both for GLS[56-58] and global circumferential strain.[56]

A number of echocardiographic parameters have been tested in the assessment of mechanical dyssynchrony to improve patient selection for CRT. Yet, despite considerable efforts, none of them has gained enough support to justify routine use,[59,60] although septal flash and apical

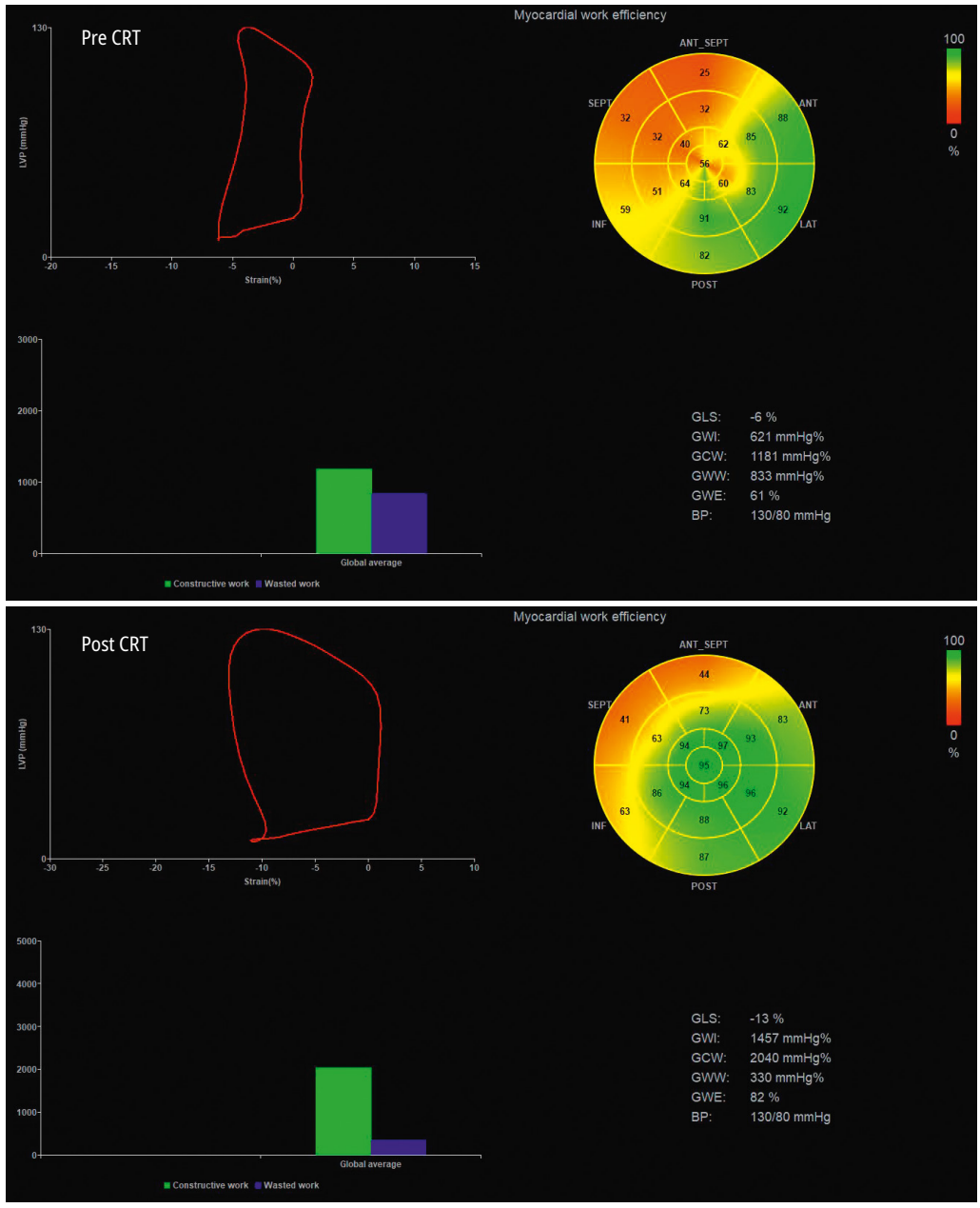

FIGURE 7 Beneficial effect of cardiac resynchronization therapy (CRT) on myocardial work and deformation in a patient with heart failure with reduced ejection fraction. Note an increase in global longitudinal deformation, work index, constructive work, and work efficiency with a concomitant decrease in global wasted work in response to CRT.
Abbreviations: GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency; others, see TABLE 2

rocking offer some promise. However, myocardial deformation can be useful in determining the optimal location of the LV lead, defined as the myocardial segment with preserved viability (radial strain >10%) and the most delayed radial contraction.[61,62] Preliminary data indicate that quantification of wasted myocardial work can help identify a substrate for improvement with CRT (FIGURE 7).[63,64] Global longitudinal strain was helpful in predicting reverse remodeling and 1-year mortality after CRT implantation.[65] Moreover, longitudinal deformation–based measures of LV dyssynchrony proved to be strong prognosticators of ventricular arrhythmias in HFrEF.[66,67] The incremental value in predicting ventricular tachycardia or fibrillation was demonstrated for reduced longitudinal strain in the inferior wall,[68] which underpins the importance of LV regional function assessment in the diagnostic workup of patients with HF.

The predictive utility of a large number of diastolic indices was shown in multiple clinical conditions.[15] Notably, the estimation of LV filling pressure has prognostic significance in HF regardless of EF category. A restrictive mitral inflow pattern as well as increased E/e' ratio are

TABLE 2 Echocardiographic prognostic markers in heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, and preclinical disease evaluated in selected studies (continued on the next page)

Study	Patients, n	Echocardiographic parameter	Outcome	Major findings
HFrEF				
Curtis et al[50]	7788	LVEF	Mortality	Higher LVEF associated with a linear decrease in mortality up to an LVEF of 45%; no association above the value of 45%
Solomon et al[49]	7599	LVEF	Mortality, HF hospitalization	As above
Sengelov et al[54]	1065	GLS	Mortality	GLS was superior to other echocardiographic parameters including LVEF, especially in male patients with atrial fibrillation.
Biering-Sorensen et al[68]	1064	LV longitudinal strain in the inferior wall	VF or VT	Assessment of regional longitudinal deformation in the inferior wall provided incremental prognostic information over clinical and other echocardiographic predictors.
Modin et al[96]	151	RR interval–corrected GLS	Mortality	Only corrected GLS, but not uncorrected GLS or LVEF, was associated with outcome in patients with atrial fibrillation.
Nahum et al[97]	125	GLS	Mortality, HF hospitalization, cardiac transplant, mechanical ventilation	GLS superior to LVEF and other echocardiographic parameters
Acil et al[70]	132	E/e'	Cardiac death, transplantation, HF hospitalization	E/e' superior to other diastolic as well systolic parameters
Meris et al[85]	610	LAVI	Mortality and HF hospitalization	LAVI: an independent predictor after adjustment for clinical variables in patients with myocardial infarction complicated by HF and/or LV dysfunction
Rossi et al[87]	1157	LA area	Mortality and HF hospitalization	LA area: a powerful predictor providing additional prognostic information beyond LV systolic and diastolic parameters (individual patient meta--analysis)
HFpEF				
Shah et al[55]	447	GLS	CV mortality, HF hospitalization, aborted cardiac arrest	GLS was the strongest echocardiographic prognosticator. The highest risk at GLS ≤15.8%.
Wang et al[77]	80	GLS at exercise	Mortality and HF hospitalization	Exercise GLS was the strongest predictor of adverse outcome, superior to other echocardiographic indices including exercise E/e'.
Kosmala et al[76]	205	LV longitudinal deformation and E/e' at exercise	Mortality and HF hospitalization	Both abnormal systolic and diastolic responses to exercise were predictive of adverse outcome, independent of and incremental to clinical data and BNP levels. Measurements of myocardial deformation and E/e' at exercise prognostically outperformed those acquired at rest.
Okura et al[71]	50	E/e'	Mortality and HF hospitalization	Prognostic value of E/e' incremental to other echocardiographic parameters including e' and LVEF
Santos et al[86]	357	LA reservoir strain	CV mortality, HF hospitalization, aborted cardiac arrest	LA strain was a predictor of adverse outcome independent of clinical factors but of LV strain and LV filling pressure.
Melenovsky et al[98]	101	LA emptying fraction	Mortality	LA dysfunction was a significant risk predictor in HFpEF.
Lam et al[91]	244	TRV	Mortality	TRV: the only echocardiographic parameter predicting outcome, superior to E/e', LAVI, RWT, and LVMI
Melenowski et al[99]	96	RV FAC	Mortality	RV dysfunction was associated with adverse outcome independent of PA pressure.

TABLE 2 Echocardiographic prognostic markers in heart failure with reduced ejection fraction, heart failure with preserved ejection fraction, and preclinical disease evaluated in selected studies (continued from the previous page)

Study	Patients, n	Echocardiographic parameter	Outcome	Major findings
Mohammed et al[94]	562	TAPSE	Mortality and HF hospitalization	RV dysfunction was predictive of poor outcome independent of PASP, age, sex, and comorbidities.
Jasic-Szpak et al[90]	170	LA reservoir and contractile strain	Incident atrial fibrillation	LA strain provided predictive information about atrial fibrillation in HFpEF, independent of and incremental to clinical data, LAVI, and LV diastolic and systolic indices.
Preclinical disease				
Yang et al[100]	410	GLS, LVMI, LAVI, and diastolic function indices	CV mortality and new-onset HF	LA enlargement, LV hypertrophy, abnormal GLS, and E/e' were independent predictors of adverse outcome. GLS was the most sensitive marker.
Przewlocka-Kosmala et al[74]	465	LV untwisting rate	CV mortality and new-onset HF	The prognostic value of apical untwisting rate was independent of and incremental to clinical data, LAVI, and GLS.

Abbreviations: BNP, brain natriuretic peptide; CV, cardiovascular; FAC, fractional area change; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrial; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; RV, right ventricular; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion; VF, ventricular fibrillation; VT, ventricular tachycardia; others, see TABLE 1, FIGURE 2, and FIGURE 5

highly predictive of adverse clinical outcomes, both in HFpEF and HFrEF.[69-72] Among the parameters reflecting myocardial relaxation, reduced LV untwisting rate has emerged as a prognostic indicator both in the preclinical and overt stage of HFpEF.[73-75]

The importance of exercise echocardiography in the evaluation of patients with suspected or confirmed HFpEF has been further reinforced by the findings that the reductions of both LV diastolic and systolic reserves can add an incremental value to risk stratification in this condition, and that exertional measurements of E/e' and longitudinal myocardial deformation are prognostically superior to those attained at rest.[76,77]

In addition to the measures of LV function, also LV structural markers, such as hypertrophy, mass index, and type of remodeling and geometry, are independently associated with increased cardiovascular risk in HF.[78-81]

The evaluation of LA size and function holds prognostic significance both in HFpEF and HFrEF. Left atrial enlargement and dysfunction, accounting for HF atriopathy, can be predictive of atrial fibrillation, HF hospitalization, stroke, and cardiovascular mortality.[80,82-88] The most robust echocardiographic atrial prognosticators are LA volume for structural as well as LA strain and phasic volumetric measurements for functional remodeling. Left atrial dysfunction, assessed mainly by LA strain, was shown to provide information independent of and incremental to LA size for predicting clinical outcomes in HF.[89,90]

Pulmonary hypertension and right ventricular (RV) dysfunction are common findings in HF, both of which independently contribute to increased clinical risk.[91-94] Classic RV functional parameters (including tricuspid annular plane systolic excursion, fractional area change, and tricuspid annular systolic velocity) have prognostic value but also limitations related to translational movement that is avoided by the measurement of RV strain.[95] The predictive independence of RV function from RV afterload may mark the progression to more advanced disease, with a lower likelihood of meaningful recovery.

In view of the abundance of predictors and their synergism in providing prognostic information, the current risk stratification strategies cannot be based upon single echocardiographic parameters but have to incorporate multiple markers reflecting different cardiac domains.[54,75,90] Accordingly, LV and LA longitudinal strain, LA volume, E/e' ratio, TRV, and RV function indices might be postulated for inclusion in prognostic algorithms in all HF categories. Such an integrated approach can be expected to optimize the extraction of prognostic data from the echocardiogram.

Selected studies that demonstrated the prognostic significance of echocardiographic parameters in HF are presented in TABLE 2.

Perspectives It is hard to conceive of how modern HF management might be delivered in the absence of echocardiography. This inexpensive and widely-available technique has roles in the detection of HF, phenotyping subgroups, risk assessment, and in informing management. Three perspectives seem to be particularly germane. First, echocardiography is a reliable non-invasive technique for the assessment of hemodynamics and physiology. Despite wishes to the contrary, no combination of biomarkers has yet been able to provide the depth of knowledge

provided by this imaging tool. Second, the potential of echocardiography in HF has been fulfilled by the incorporation of new science and technologies, especially quantitative approaches to the assessment of diastolic function and myocardial deformation. The implication of this observation is that a simple qualitative echocardiography protocol, based on subjective evaluation of the 2-dimensional images by a nonexpert is likely to underdeliver. Third, notwithstanding the impact of new technology in echocardiography, it is viewed as an "old" test that is less visually striking (and much less expensive) than new imaging techniques, such as cardiac magnetic resonance imaging. The consequence is that relatively few cardiologists are trained to use this technique to its full potential. We see automation and artificial intelligence as the solution to this practice gap and expect that within years, handheld devices will automatically acquire and process images to provide parameters relevant to HF at bedside.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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REFERENCES

1 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Kardiol Pol. 2016; 74: 1037-1147.

2 Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med. 2002; 347: 1397-1402.

3 Nessler J, Kozierkiewicz A, Gackowski A, et al. Comprehensive Heart Failure Care pilot study: starting point and expected developments. Kardiol Pol. 2019; 77: 994-999.

4 Omar AM, Bansal M, Sengupta PP. Advances in echocardiographic imaging in heart failure with reduced and preserved ejection fraction. Circ Res. 2016; 119: 357-374.

5 Thavendiranathan P, Poulin F, Lim KD, et al. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol. 2014; 63: 2751-2768.

6 Nesbitt GC, Mankad S, Oh JK. Strain imaging in echocardiography: methods and clinical applications. Int J Cardiovasc Imaging. 2009; 25 (suppl. 1): 9-22.

7 Mele D, Andrade A, Bettencourt P, et al. From left ventricular ejection fraction to cardiac hemodynamics: role of echocardiography in evaluating patients with heart failure. Heart Fail Rev. 2020; 25: 217-230.

8 Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019; 381: 1609-1620.

9 Januzzi JL, Chandrashekhar Y. Strain echocardiography: the new gold standard for imaging ventricular function? J Am Coll Cardiol. 2017; 70: 955-957.

10 Cikes M, Solomon SD. Beyond ejection fraction: an integrative approach for assessment of cardiac structure and function in heart failure. Eur Heart J. 2016; 37: 1642-1650.

11 Stokke TM, Hasselberg NE, Smedsrud MK, et al. Geometry as a confounder when assessing ventricular systolic function: comparison between ejection fraction and strain. J Am Coll Cardiol. 2017; 70: 942-954.

12 Perry R, Selvanayagam JB. Echocardiography in infiltrative cardiomyopathy. Heart Lung Circ. 2019; 28: 1365-1375.

13 Harbo MB, Nordén ES, Narula J, et al. Quantifying left ventricular function in heart failure: what makes a clinically valuable parameter? Prog Cardiovasc Dis. 2020; 63: 552-560.

14 Kosmala W, Jellis CL, Marwick TH. Exercise limitation associated with asymptomatic left ventricular impairment: analogy with stage B heart failure. J Am Coll Cardiol. 2015; 65: 257-266.

15 Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016; 17: 1321-1360.

16 Ernande L, Bergerot C, Rietzschel ER, et al. Diastolic dysfunction in patients with type 2 diabetes mellitus: is it really the first marker of diabetic cardiomyopathy? J Am Soc Echocardiogr. 2011; 24: 1268-1275.e1.

17 Sharman JE, Laurent S. Central blood pressure in the management of hypertension: soon reaching the goal? J Hum Hypertens. 2013; 27: 405-411.

18 Sharman JE, Marwick TH, Abhayaratna WP, Stowasser M. Rationale and design of a randomized study to determine the value of central Blood Pressure for GUIDing managEment of hypertension: the BP GUIDE study. Am Heart J. 2012; 163: 761-767.

19 Fang ZY, Schull-Meade R, Downey M, et al. Determinants of subclinical diabetic heart disease. Diabetologia. 2005; 48: 394-402.

20 Wong CY, O'Moore-Sullivan T, Leano R, et al. Alterations of left ventricular myocardial characteristics associated with obesity. Circulation. 2004; 110: 3081-3087.

21 Echouffo-Tcheugui JB, Erqou S, Butler J, et al. Assessing the risk of progression from asymptomatic left ventricular dysfunction to overt heart failure: a systematic overview and meta-analysis. JACC Heart Fail. 2016; 4: 237-248.

22 Obokata M, Reddy YNV, Borlaug BA. The role of echocardiography in heart failure with preserved ejection fraction: what do we want from imaging? Heart Fail Clin. 2019; 15: 241-256.

23 Nauta JF, Hummel YM, van der Meer P, et al. Correlation with invasive left ventricular filling pressures and prognostic relevance of the echocardiographic diastolic parameters used in the 2016 ESC heart failure guidelines and in the 2016 ASE/EACVI recommendations: a systematic review in patients with heart failure with preserved ejection fraction. Eur J Heart Fail. 2018; 20: 1303-1311.

24 Lancellotti P, Galderisi M, Edvardsen T, et al. Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. Eur Heart J Cardiovasc Imaging. 2017; 18: 961-968.

25 Andersen OS, Smiseth OA, Dokainish H, et al. Estimating left ventricular filling pressure by echocardiography. J Am Coll Cardiol. 2017; 69: 1937-1948.

26 Nishimura RA, Appleton CP, Redfield MM, et al. Noninvasive doppler echocardiographic evaluation of left ventricular filling pressures in patients with cardiomyopathies: a simultaneous Doppler echocardiographic and cardiac catheterization study. J Am Coll Cardiol. 1996; 28: 1226-1233.

27 Oh JK, Miranda WR, Bird JG, et al. The 2016 diastolic function guideline: is it already time to revisit or revise them? JACC Cardiovasc Imaging. 2020; 13: 327-335.

28 Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020; 22: 391-412.

29 Choi EY, Shim CY, Kim SA, et al. Passive leg-raise is helpful to identify impaired diastolic functional reserve during exercise in patients with abnormal myocardial relaxation. J Am Soc Echocardiogr. 2010; 23: 523-530.

30 Jake Samuel T, Beaudry R, Haykowsky MJ, et al. Isometric handgrip echocardiography: a noninvasive stress test to assess left ventricular diastolic function. Clin Cardiol. 2017; 40: 1247-1255.

31 Lancellotti P, Pellikka PA, Budts W, et al. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr. 2017; 30: 101-138.

32 Obokata M, Kane GC, Reddy YN, et al. Role of diastolic stress testing in the evaluation for heart failure with preserved ejection fraction: a simultaneous invasive-echocardiographic study. Circulation. 2017; 135: 825-838.

33 Burgess MI, Jenkins C, Sharman JE, Marwick TH. Diastolic stress echocardiography: hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. J Am Coll Cardiol. 2006; 47: 1891-1900.

34 Talreja DR, Nishimura RA, Oh JK. Estimation of left ventricular filling pressure with exercise by Doppler echocardiography in patients with normal systolic function: a simultaneous echocardiographic-cardiac catheterization study. J Am Soc Echocardiogr. 2007; 20: 477-479.

35 Donal E, Thebault C, Lund LH, et al. Heart failure with a preserved ejection fraction additive value of an exercise stress echocardiography. Eur Heart J Cardiovasc Imaging. 2012; 13: 656-665.

36 Haykowsky MJ, Brubaker PH, John JM, Set al. Determinants of exercise intolerance in elderly heart failure patients with preserved ejection fraction. J Am Coll Cardiol. 2011; 58: 265-274.

37 Kosmala W, Rojek A, Przewlocka-Kosmala M, et al. Contributions of nondiastolic factors to exercise intolerance in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2016; 67: 659-670.

38 Przewlocka-Kosmala M, Marwick TH, Dabrowski A, Kosmala W. Contribution of cardiovascular reserve to prognostic categories of heart failure with preserved ejection fraction: a classification based on machine learning. J Am Soc Echocardiogr. 2019; 32: 604-615.e6.

39 Przewlocka-Kosmala M, Marwick TH, Mysiak A, et al. Usefulness of myocardial work measurement in the assessment of left ventricular systolic reserve response to spironolactone in heart failure with preserved ejection fraction. Eur Heart J Cardiovasc Imaging. 2019; 20: 1138-1146.

40 Picano E, Bombardini T, Kovačević Preradović T, et al. Left ventricular contractile reserve in stress echocardiography: the bright side of the force. Kardiol Pol. 2019; 77: 164-172.

41 Agricola E, Picano E, Oppizzi M, et al. Assessment of stress-induced pulmonary interstitial edema by chest ultrasound during exercise echocardiography and its correlation with left ventricular function. J Am Soc Echocardiogr. 2006; 19: 457-463.

42 Miglioranza MH, Gargani L, Sant'Anna RT, et al. Lung ultrasound for the evaluation of pulmonary congestion in outpatients: a comparison with clinical assessment, natriuretic peptides, and echocardiography. JACC Cardiovasc Imaging. 2013; 6: 1141-1151.

43 Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation. 2018; 138: 861-870.

44 Robbins JD, Maniar PB, Cotts W, et al. Prevalence and severity of mitral regurgitation in chronic systolic heart failure. Am J Cardiol. 2003; 91: 360-362.

45 Trichon BH, Felker GM, Shaw LK, et al. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol. 2003; 91: 538-543.

46 Thavendiranathan P, Liu S, Datta S, et al. Quantification of chronic functional mitral regurgitation by automated 3-dimensional peak and integrated proximal isovelocity surface area and stroke volume techniques using real-time 3-dimensional volume color Doppler echocardiography: in vitro and clinical validation. Circ Cardiovasc Imaging. 2013; 6: 125-133.

47 Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. JACC Cardiovasc Imaging. 2019; 12: 353-362.

48 Asgar AW, Mack MJ, Stone GW. Secondary mitral regurgitation in heart failure: pathophysiology, prognosis, and therapeutic considerations. J Am Coll Cardiol. 2015; 65: 1231-1248.

49 Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation. 2005; 112: 3738-3744.

50 Curtis JP, Sokol SI, Wang Y, et al. The association of left ventricular ejection fraction, mortality, and cause of death in stable outpatients with heart failure. J Am Coll Cardiol. 2003; 42: 736-742.

51 Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart. 2014; 100: 1673-1680.

52 Dagres N, Hindricks G. Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death? Eur Heart J. 2013; 34: 1964-1971.

53 Narayanan K, Reinier K, Uy-Evanado A, et al. Frequency and determinants of implantable cardioverter defibrillator deployment among primary prevention candidates with subsequent sudden cardiac arrest in the community. Circulation. 2013; 128: 1733-1738.

54 Sengeløv M, Jørgensen PG, Jensen JS, B et al. Global longitudinal strain is a superior predictor of all-cause mortality in heart failure with reduced ejection fraction. JACC Cardiovasc Imaging. 2015; 8: 1351-1359.

55 Shah AM, Claggett B, Sweitzer NK, et al. Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone. Circulation. 2015; 132: 402-414.

56 Hung CL, Verma A, Uno H, et al. Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction. J Am Coll Cardiol. 2010; 56: 1812-1822.

57 Munk K, Andersen NH, Terkelsen CJ, et al. Global left ventricular longitudinal systolic strain for early risk assessment in patients with acute myocardial infarction treated with primary percutaneous intervention. J Am Soc Echocardiogr. 2012; 25: 644-651.

58 Ersbøll M, Valeur N, Mogensen UM, A et al. Relationship between left ventricular longitudinal deformation and clinical heart failure during admission for acute myocardial infarction: a two-dimensional speckle-tracking study. J Am Soc Echocardiogr. 2012; 25: 1280-1289.

59 Gorcsan J, Abraham T, Agler DA, et al. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting-a report from the American Society of Echocardiography Dyssynchrony Writing Group endorsed by the Heart Rhythm Society. J Am Soc Echocardiogr. 2008; 21: 191-213.

60 Chung ES, Leon AR, Tavazzi L, et al. Results of the predictors of response to CRT (PROSPECT) trial. Circulation. 2008; 117: 2608-2616.

61 Saba S, Marek J, Schwartzman D, et al. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. Circ Heart Fail. 2013; 6: 427-434.

62 Khan FZ, Virdee MS, Palmer CR, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. J Am Coll Cardiol. 2012; 59: 1509-1518.

63 Vecera J, Penicka M, Eriksen M, et al. Wasted septal work in left ventricular dyssynchrony: a novel principle to predict response to cardiac resynchronization therapy. Eur Heart J Cardiovasc Imaging. 2016; 17: 624-632.

64 Galli E, Leclercq C, Fournet M, et al. Value of myocardial work estimation in the prediction of response to cardiac resynchronization therapy. J Am Soc Echocardiogr. 2018; 31: 220-230.

65 Park JH, Negishi K, Grimm RA, et al. Echocardiographic predictors of reverse remodeling after cardiac resynchronization therapy and subsequent events. Circ Cardiovasc Imaging. 2013; 6: 864-872.

66 Kosiuk J, Dinov B, Bollmann A, et al. Association between ventricular arrhythmias and myocardial mechanical dispersion assessed by strain analysis in patients with nonischemic cardiomyopathy. Clin Res Cardiol. 2015; 104: 1072-1077.

67 Haugaa KH, Goebel B, Dahlslett T, et al. Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. J Am Soc Echocardiogr. 2012; 25: 667-673.

68 Biering-Sørensen T, Knappe D, Pouleur AC, et al. Regional longitudinal deformation improves prediction of ventricular tachyarrhythmias in patients with heart failure with reduced ejection fraction: a MADIT-CRT substudy (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). Circ Cardiovasc Imaging. 2017; 10: e005 096.

69 Hamdan A, Shapira Y, Bengal T, et al. Tissue Doppler imaging in patients with advanced heart failure: relation to functional class and prognosis. J Heart Lung Transplant. 2006; 25: 214-218.

70 Acil T, Wichter T, Stypmann J, et al. Prognostic value of tissue Doppler imaging in patients with chronic congestive heart failure. Int J Cardiol. 2005; 103: 175-181.

71 Okura H, Kubo T, Asawa K, et al. Elevated E/E' predicts prognosis in congestive heart failure patients with preserved systolic function. Circ J. 2009; 73: 86-91.

72 Somaratne JB, Whalley GA, Gamble GD, Doughty RN. Restrictive filling pattern is a powerful predictor of heart failure events postacute myocardial infarction and in established heart failure: a literature-based meta-analysis. J Card Fail. 2007; 13: 346-352.

73 Kosmala W, Przewlocka-Kosmala M, Marwick TH. Association of active and passive components of LV diastolic filling with exercise intolerance in heart failure with preserved ejection fraction: mechanistic insights from spironolactone response. JACC Cardiovasc Imaging. 2019; 12: 784-794.

74 Przewlocka-Kosmala M, Marwick TH, Yang H, et al. Association of reduced apical untwisting with incident HF in asymptomatic patients with HF risk factors. JACC Cardiovasc Imaging. 2020; 13: 187-194.

75 Kosmala W, Przewlocka-Kosmala M, Rojek A, Marwick TH. Comparison of the diastolic stress test with a combined resting echocardiography and biomarker approach to patients with exertional dyspnea: diagnostic and prognostic implications. JACC Cardiovasc Imaging. 2019; 12: 771-780.

76 Kosmala W, Przewlocka-Kosmala M, Rojek A, et al. Association of abnormal left ventricular functional reserve with outcome in heart failure with preserved ejection fraction. JACC Cardiovasc Imaging. 2018; 11: 1737-1746.

77 Wang J, Fang F, Wai-Kwok Yip G, et al. Left ventricular long-axis performance during exercise is an important prognosticator in patients with heart failure and preserved ejection fraction. Int J Cardiol. 2015; 178: 131-135.

78 Tischler MD, Niggel J, Borowski DT, LeWinter MM. Relation between left ventricular shape and exercise capacity in patients with left ventricular dysfunction. J Am Coll Cardiol. 1993; 22: 751-757.

79 Mannaerts HF, van der Heide JA, Kamp O, et al. Early identification of left ventricular remodelling after myocardial infarction, assessed by transthoracic 3D echocardiography. Eur Heart J. 2004; 25: 680-687.

80 Zile MR, Gottdiener JS, Hetzel SJ, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. Circulation. 2011; 124: 2491-2501.

81 Katz DH, Beussink L, Sauer AJ, et al. Prevalence, clinical characteristics, and outcomes associated with eccentric versus concentric left ventricular hypertrophy in heart failure with preserved ejection fraction. Am J Cardiol. 2013; 112: 1158-1164.

82 Tsang TS, Abhayaratna WP, Barnes ME, M et al. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol. 2006; 47: 1018-1023.

83 Benjamin EJ, D'Agostino RB, Belanger AJ, et al. Left atrial size and the risk of stroke and death. The Framingham Heart Study. Circulation. 1995; 92: 835-841.

84 Moller JE, Hillis GS, Oh JK, et al. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. Circulation. 2003; 107: 2207-2212.

85 Meris A, Amigoni M, Uno H, et al. Left atrial remodelling in patients with myocardial infarction complicated by heart failure, left ventricular dysfunction, or both: the VALIANT Echo study. Eur Heart J. 2009; 30: 56-65.

86 Santos AB, Roca GQ, Claggett B, et al. Prognostic relevance of left atrial dysfunction in heart failure with preserved ejection fraction. Circ Heart Fail. 2016; 9: e002 763.

87 Rossi A, Temporelli PL, Quintana M, et al. Independent relationship of left atrial size and mortality in patients with heart failure: an individual patient meta-analysis of longitudinal data (MeRGE Heart Failure). Eur J Heart Fail. 2009; 11: 929-936.

88 Hsiao SH, Chiou KR. Left atrial expansion index predicts all-cause mortality and heart failure admissions in dyspnoea. Eur J Heart Fail. 2013; 15: 1245-1252.

89 Santos AB, Kraigher-Krainer E, Gupta DK, et al. Impaired left atrial function in heart failure with preserved ejection fraction. Eur J Heart Fail. 2014; 16: 1096-1103.

90 Jasic-Szpak E, Marwick TH, Donal E, et al. Prediction of AF in heart failure with preserved ejection fraction: incremental value of left atrial strain. J Am Coll Cardiol Cardiovasc Imaging. 2021; 14: 131-144.

91 Lam CS, Roger VL, Rodeheffer RJ, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. J Am Coll Cardiol. 2009; 53: 1119-1126.

92 Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol. 2001; 37: 183-188.

93 Leung CC, Moondra V, Catherwood E, Andrus BW. Prevalence and risk factors of pulmonary hypertension in patients with elevated pulmonary venous pressure and preserved ejection fraction. Am J Cardiol. 2010; 106: 284-286.

94 Mohammed SF, Hussain I, AbouEzzeddine OF, et al. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. Circulation. 2014; 130: 2310-2320.

95 Lejeune S, Roy C, Ciocea V, et al. Right ventricular global longitudinal strain and outcomes in heart failure with preserved ejection fraction. J Am Soc Echocardiogr. 2020; 33: 973-984.e2.

96 Modin D, Sengeløv M, Jørgensen PG, et al. Global longitudinal strain corrected by RR interval is a superior predictor of all-cause mortality in patients with systolic heart failure and atrial fibrillation. ESC Heart Fail. 2018; 5: 311-318.

97 Nahum J, Bensaid A, Dussault C, et al. Impact of longitudinal myocardial deformation on the prognosis of chronic heart failure patients. Circ Cardiovasc Imaging. 2010; 3: 249-256.

98 Melenovsky V, Hwang SJ, Redfield MM, et al. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. Circ Heart Fail. 2015; 8: 295-303.

99 Melenovsky V, Hwang SJ, Lin G, et al. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J. 2014; 35: 3452-3462.

100 Yang H, Negishi K, Wang Y, et al. Echocardiographic screening for non-ischaemic stage B heart failure in the community. Eur J Heart Fail. 2016; 18: 1331-1339.