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REVIEW

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Reversible left ventricular diastolic dysfunction—Overview and clinical implications

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Abstract

Strong evidence supports a pathophysiological link between left ventricular diastolic dysfunction (LVDD) and symptoms in many patients with heart failure, including those with normal LV ejection fraction. Thus, echocardiographic assessment of LV diastolic function is currently recommended when evaluating patients with dyspnea of suspected or known cardiac origin. Beyond the well-established role in the diagnostic algorithm of heart failure, LVDD is an independent predictor of cardiovascular events in various patient cohorts and in the general population. Moreover, several studies suggested a dynamic link between ventricular relaxation, filling dynamics, and prognosis. Thus, worsening of LVDD emerged as a marker of worse prognosis, whereas its improvement is associated with better outcomes. From this perspective, it is important for clinicians to recognize the potentially reversible causes of LVDD that can be identified and treated with symptomatic and/or prognostic benefits. The purpose of this review is to discuss several clinical conditions associated with reversible LVDD, from possible mechanisms to potential clinical implications.

KEYWORDS

clinical implications, diastolic function, echocardiography, reversible

1 | INTRODUCTION

Evaluation of left ventricular diastolic function has received much attention during the last decade along with its increasing recognition as a key determinant of cardiac performance. There is a strong pathophysiological link between left ventricular diastolic dysfunction (LVDD) and heart failure (HF) symptoms in many patients, including those with normal LV ejection fraction (LVEF).[1] Thus, from a practical perspective, LV diastolic function assessment is particularly useful in patients with dyspnea of suspected or known cardiac origin.

Echocardiography is the most widely used noninvasive technique to assess diastolic function in clinical practice and a large number of echocardiographic parameters have been tested and validated for their correlation with invasively determined diastolic function measurements.[2]

However, the pathophysiological background of LVDD is very complex and the clinical potential of data derived from diastolic function analysis is far from being reached.

We know from previous studies that reversibility of a restrictive filling pattern under optimized treatment predicts a better prognosis in patients with HF and reduced LVEF.[3] However, there are few data in the literature about reversible LVDD, particularly in patients with preserved LVEF. The purpose of this review is to discuss this less studied scenario, addressing several clinical conditions associated with reversible LVDD, from possible mechanisms to potential clinical implications.

2 | LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

Diastolic dysfunction defines the inability of the LV to adequately fill at low or normal atrial pressure, at rest or with exercise. It can result

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from impaired LV myocardial relaxation, with or without reduced restoring forces (responsible for early diastolic suction), and reduced LV compliance or increased chamber stiffness.[2]

There is a wide array of etiological factors associated with LVDD. However, they can be broadly divided in two main categories: intrinsic (related to intrinsic properties of the ventricular chamber) or extrinsic (related to pericardial and right heart disease).[4] While many of these factors are persistent or progressive, it is important to recognize the potentially reversible causes of LVDD that can be identified and treated with symptomatic and/or prognostic benefits.[5] (Table 1).

3 | ECHOCARDIOGRAPHIC ASSESSMENT OF LEFT VENTRICULAR DIASTOLIC FUNCTION

Echocardiography is the primary diagnostic tool used to assess LV diastolic function noninvasively in clinical practice. It allows a comprehensive overview of LV morphology and function, left atrial size and function, pulmonary pressures, the right ventricle, and the pericardium. [2] However, catheterization remains the gold standard whenever the noninvasive assessment is inconclusive. [2]

In the clinical setting, evaluation of LV diastolic function should always start by assessing the presence of clinical risk factors known to be associated with LVDD (eg, hypertension, coronary artery disease, diabetes), by looking for the presence of structural cardiac abnormalities (eg LV hypertrophy, LA dilatation), and by measuring LVEF. Specific settings which may change the way LV diastolic function is evaluated (eg atrial fibrillation, mitral valve disease, conduction abnormalities/pacing rhythm) should also be noted.[2]

In patients with structural heart abnormalities or LV systolic dysfunction (reduced LVEF or impaired global longitudinal strain, GLS), LVDD is assumed to be present, and the echocardiography examination should then focus on the assessment of LV filling pressure (LVFP).[2]

If clinical and 2D-echo findings do not indicate myocardial disease and LVEF is normal, the measurement of four "first-line" parameters is currently proposed for the diagnosis of LVDD: pulsed-wave TDI-derived mitral annular early diastolic velocity *e′*, the *E/e′* ratio, LA volume index (LAVi), and the tricuspid regurgitation velocity.[2] Based on these measurements and on the mitral inflow pattern, proposed algorithms lead to the diagnosis of LVDD and allow the estimation of LVFP.[2]

4 | REVERSIBLE LEFT VENTRICULAR DIASTOLIC DYSFUNCTION—CLINICAL SCENARIOS

4.1 | Acute myocardial ischemia

Acute myocardial ischemia slows LV relaxation and impairs LV distensibility, resulting in one of the most studied mechanisms of potentially reversible LVDD. Previous studies reported that short-term ischemia

TABLE 1 Conditions associated with potentially reversible left ventricular diastolic dysfunction

Clinical condition	Mechanism of LVDD	Potential clinical implications
Acute myocardial ischemia	• Abnormal relaxation (lengthening of the IVRT precedes changes in systolic function) • Increase in LVEDP • Impaired LV distensibility • LV dyssynchrony	• The development of LVDD during stress echocardiography may improve the accuracy of the coronary artery disease diagnosis • The noninvasive diagnosis of LVDD indicates a poor prognosis in patients with an acute coronary syndrome
Acute onset nonischemic cardiomyopathies: • Myocarditis • Takotsubo CMP	• Alterations in early LV relaxation • Impaired active relaxation • Increased LV diastolic stiffness • Increased LVEDP	• Echocardiographic follow-up of patients with recent onset nonischemic cardiomyopathies might improve both prognostication and risk stratification.
Obesity CMP	• Impaired LV relaxation • Reduced LV compliance	• Body weight control strategies are associated with improvements in LV systolic and diastolic function and might have a beneficial effect in preventing or delaying the development of heart failure
"Cardiac fatigue" in athletes	• Decline in preload and/or changes in intrinsic LV relaxation and compliance	• Echocardiographic monitoring of cardiac performance in athletes may provide a better characterization of cardiac remodeling occurring in response to specific forms of exercise, their time sequence, mechanisms, and reversibility
Critically ill patients	• Alterations in LV relaxation/compliance	• Echocardiographic monitoring of LV diastolic function in critically ill patients may have an important role in risk stratification and fluid balance assessment

Note: Abbreviations: CMP = cardiomyopathy; IVRT = isovolumic relaxation time, LVEDP = left ventricular end-diastolic pressure.

(10–20 seconds following coronary artery occlusion) causes lengthening of the isovolumic relaxation period.[6] Wall-motion abnormalities occur 15–30 seconds later, followed by a fall in global LV systolic function. Subsequently, ECG changes and ischemic symptoms may develop.[7] Nevertheless, this cascade of events may be disturbed in relation to the presence of collateral flow and ischemic preconditioning.[8,9]

In studies including patients with preserved LV function and acute myocardial ischemia due to brief coronary artery occlusion or rapid pacing, the first echocardiographic marker of LVDD was the prolongation of the isovolumic relaxation time followed by reduction of the E-wave velocity and the *E/A* ratio.[10] The abnormal relaxation pattern (*E/A* ratio < 1) has also been reported in half of 28 patients with LVEF > 40% during acute STEMI, despite the presence of severely elevated LVFP measured invasively in all patients before percutaneous coronary intervention (PCI).[11] This pattern was accompanied by mildly reduced *e′* velocities, and *E/e′* ratios in the indeterminate range (8–15) in the majority of patients. As a result, neither the mitral flow pattern nor the *E/e′* ratio suggested the increased pre-PCI level of LVEDP. The authors indicated two potential explanations for these findings. One was that the ability of *E/e′* ratio to predict LVFP was validated in studies including mostly stable patients in whom the mitral inflow patterns and TDI velocities reflect chronic changes in LV and LA geometry and function. On the other hand, in the setting of acute coronary occlusion, significant LVDD and elevation of LVFP occur rapidly and the LA has no time to change its size and function. A second explanation relates to the regional nature of the ischemic process. Thus, in stable patients without coronary artery disease (CAD) reduced *e′* velocities reflect a global alteration in early LV relaxation. In contrast, during acute infarction, the significance of *e′* depends more on the site of measurement. It is expected to be reduced in an infarcted segment whereas *e′* may be normal/elevated in an adjacent segment due to compensatory hyperkinesis.[11]

A significant decrease in LVEDP has been reported in the same study following revascularization. However, serial TDI measurements showed persistence of LVDD at three days and then at 1-year follow-up despite successful revascularization.[11]

Further insight into myocardial mechanics of patients undergoing episodes of acute myocardial ischemia emerged from studies using 2-dimensional speckle-tracking echocardiography (2D-STE). Coronary occlusion induced a reduction in both peak radial LV strain and strain changes during the first one-third of diastole expressed as strain imaging diastolic index [SI-DI]. Upon reperfusion (24 hours after PCI), systolic deformation parameters and SI-DI values in the proximal at-risk segment returned to pre-occlusion values, whereas the SI-DI value in the distal at-risk segment was still significantly lower than at baseline.[12]

Clinical implications Stress echocardiography is a good predictor of ischemia, especially when the diastolic function assessment is included in the test interpretation. In several studies, stress-induced changes in diastolic function parameters emerged as more sensitive markers for detection of CAD than nonspecific symptoms or parameters of LV systolic dysfunction.[13]

A reduction in *e′* during dobutamine or exercise stress echocardiography has been reported to discriminate between patients with and without CAD (sensitivity of 78%–93%, specificity of 76%–79%).[13] Persistence of diastolic abnormalities into the recovery phase increases the feasibility and usefulness of this approach in identifying patients with CAD since one of the limitations of applying TDI to stress echocardiography is the merging of early and late mitral annular diastolic waves during stress-induced tachycardia.[13]

In a study using 2D-speckle-tracking imaging to detect exercise-induced regional LVDD in patients with CAD, LVDD was still present 10 minutes after exercise was completed, when systolic function had already returned to normal. This technique detected CAD with a sensitivity of 97% and a specificity of 88%.[14]

The feasibility and added value of LV diastolic function assessment at rest and peak exercise, for the early diagnosis of stress-induced myocardial ischemia, has been assessed in a study using coronary computed tomography angiography (CCTA) as a gold standard test. A good agreement has been demonstrated between the worsening of LV diastolic function and obstructive CAD on CCTA. A change in *E/e′* ≥ 25% and the worsening of diastolic function grade between rest and peak exercise were highly suggestive of positive stress test (new regional WMAs in one or more segments) and increased the likelihood of obstructive CAD.[15]

Moreover, there is increasing evidence that LVDD is a robust predictor of patient outcomes after AMI independent of LV systolic function. This was analyzed in a retrospective study on 463 patients with AMI and preserved LVEF, who underwent successful PCI.[16] Diastolic functional recovery was defined as an improvement of ≥1 grade in LVDD on echocardiography at six months, compared to baseline. Change in the *E/e′* ratio from ≥10 at baseline to <10 at 6-month follow-up was also considered an improvement, regardless of diastolic functional grading. At the end of study, diastolic function deteriorated or did not change in about half of the patients despite the improvement in LV systolic function. The failure to recover LV diastolic function was a significant predictor of long-term major adverse cardiac events. These findings suggest that serial monitoring of diastolic function would be useful in the risk stratification of patients with AMI, regardless of LV systolic function.[16]

4.2 | Acute nonischemic cardiomyopathies

In a sub-study of the IMAC-2 trial, including 147 patients with acute onset nonischemic dilated cardiomyopathy, LVDD was prevalent (up to 80% of the cohort at baseline).[17] Up to 80% of these patients demonstrated LV systolic function recovery (≥10% LVEF units) at 6 months. Diastolic function improved in 58%, was unchanged in 28%, and worsened in 14% of patients at six-month follow-up. Moreover, nearly 40% of patients had complete normalization of LV diastolic function at follow-up. An improvement in LV remodeling (more significant reduction of LV end-systolic volume), as well as worse baseline diastolic function parameters (eg, shorter E-wave deceleration time and increased *E/e′* ratio), was associated with

diastolic function improvement at 6 months in this cohort. Of note, diastolic functional improvement provided incremental prognostic value.[17]

4.2.1 | Myocarditis

Although acute myocarditis often presents with depressed LVEF, LVDD with preserved LVEF may also occur in this setting.[18] In patients with acute myocarditis and preserved LVEF, LVDD is often associated with subtle abnormalities of LV systolic function detectable by echocardiographic deformation imaging techniques.

Decreased early diastolic velocities and impaired longitudinal and circumferential early diastolic strain rates have been detected in a young population with myocarditis and preserved LVEF.[19] The study reported a gradual improvement with time in these markers of early LV relaxation, and however, the changes were still present after 1 year of follow-up. This partial recovery suggests that even patients with apparently mild forms of myocarditis and preserved LVEF at presentation may develop persistent diffuse myocardial injury. Moreover, these findings call into question the conventional concept that in the majority of patients with acute myocarditis without heart failure symptoms at presentation a complete resolution of myocardial injury occur.[19] Of note, in another study on patients with biopsy-confirmed myocarditis, 49% of the cohort developed HFpEF at 6-year follow-up.[20]

A case of acute myocarditis with serial echocardiography studies is presented in Figure 1.

Clinical implications Diastolic functional recovery appears to be as important as systolic function recovery in patients with myocarditis. Thus, continued imaging follow-up, irrespective of the presence or absence of HF at presentation, may provide incremental prognostic value.

4.2.2 | Takotsubo syndrome

Takotsubo syndrome (TTS) is an acute and transient HF syndrome. Although initial studies suggested a rather benign clinical course, recent data have shown higher in-hospital mortality rates (3.5-5%) in patients with TTS.[21]

Acute LVDD has been reported in more than 50% of patients with TTS and is generally considered to develop in association with wall-motion abnormalities.[22,23]

Differences in LV diastolic properties according to the TTS phenotypes have been reported in a study on 114 patients with TTS

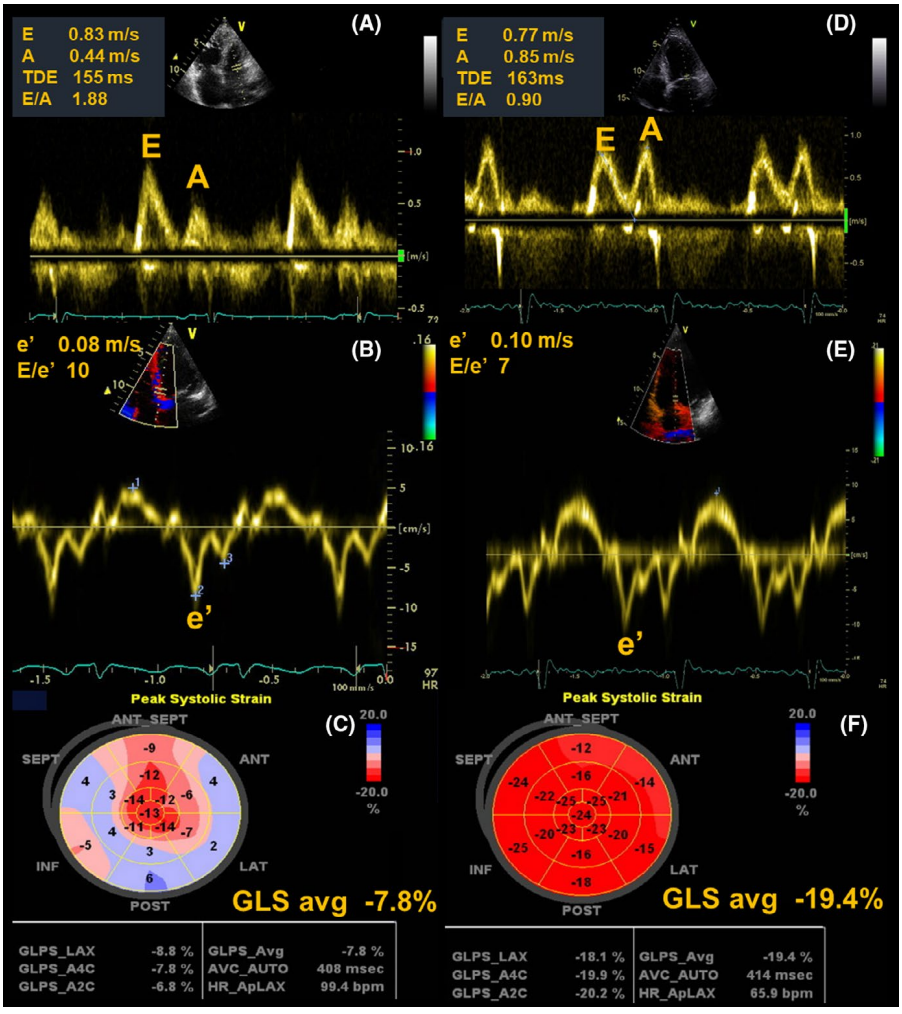

FIGURE 1 The echocardiographic assessment of a fifty-five-year-old man with acute myocarditis is presented at admission and at 1-mo follow-up. Pulsed-wave (PW) Doppler of mitral inflow and PW tissue Doppler of the mitral annulus are presented on admission (A, B) and at 1-month follow-up (D, E). Recovery of LV diastolic function is demonstrated by the transition from a pseudonormal LV filling pattern (A) during the acute phase to an impaired relaxation filling pattern at 1-month follow-up (D), with normalization of *e'* and *E/e'* values (E). Two-dimensional speckle-tracking longitudinal strain analysis shows significantly reduced left ventricular systolic strain values with patchy distribution and severely reduced average GLS (−7.8%) at admission (C). At 1 mo, there is full recovery of left ventricular longitudinal strain, with normalized GLS (−19.4%) (F)

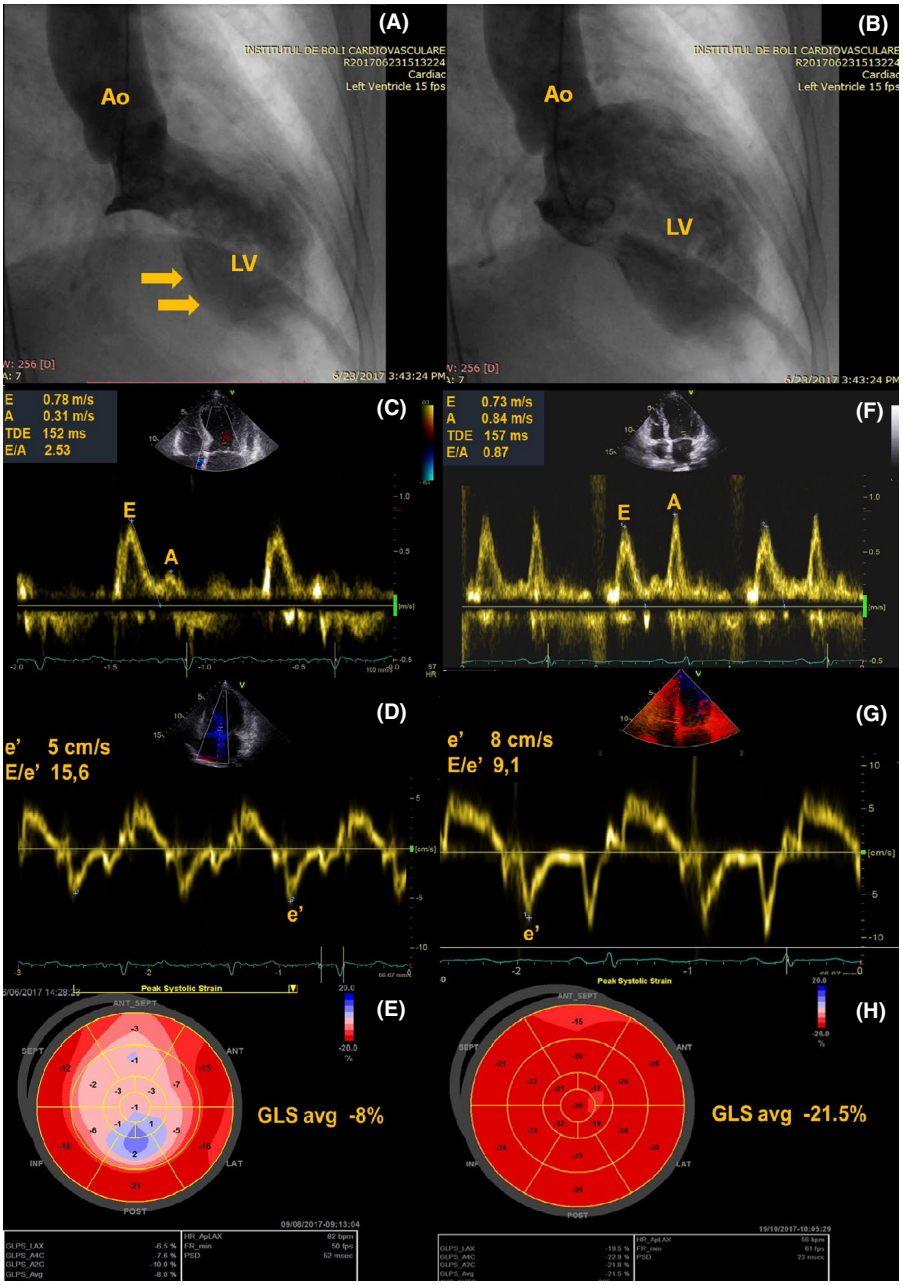

FIGURE 2 Sixty-four-year-old woman with Takotsubo syndrome and dyspnea at presentation. Left ventriculography in right ventricular oblique view at end-systole (A) and end-diastole (B) demonstrates apical ballooning in systole (A, yellow arrows) due to akinesia of the left ventricular (LV) apex which is typically seen in the acute phase of this disease. The echocardiographic assessment of left ventricular function is presented at admission and during the recovery phase, after 1 mo. Full recovery of LV kinetics is observed at 1-mo follow-up. A severe reduction in average global longitudinal strain (GLS: −8%) is seen at admission (E), because of severe abnormalities in the apical and mid-segments of the LV. GLS recovers fully at 1-mo follow-up (−21.5%) with normalization of global and regional longitudinal strain visible on the 2D-STE bull's eye plot (H). Pulsed-wave (PW) Doppler tracings of the mitral inflow and PW tissue Doppler tracings of the mitral annulus are presented at admission (C, D) and after 1 mo (F, G). Note the marked improvement in LV diastolic function, with a transition from a restrictive LV filling pattern in the acute phase to a relaxation filling pattern at 1-mo. There is an increase in *e′* velocity from 5 to 8 cm/sec, and a decrease in *E*/*e′* ratio from 15.6 to 9.1. Of note, this was also paralleled by an increase in S velocity from 3.5 to 7 cm/s, confirming the improvement in LV longitudinal function. Ao = aorta

assessed by LV catheterization. The study reported more severe LVDD in apical ballooning TTS patients, characterized by a higher LVEDP and a marked increase in LV diastolic stiffness, in comparison with midventricular TTS patients.[24]

Complete recovery of diastolic function paralleled by improvement in systolic function has been reported in studies using conventional Doppler and TDI parameters (*E*/*e′* ratio or systolic pulmonary arterial pressure).[25] Several studies using 2D-STE reported either complete recovery of regional LV strain at early follow-up (1 month) or persistence of postsystolic shortening, whereas one study highlighted that patients with ST-segment elevation–type presentation may have delayed recovery, especially of LV diastolic function.[26-28]

Moreover, in patients with apical ballooning and high-risk clinical presentation (ST-segment elevation or malignant arrhythmias), a reduced untwisting rate has been reported compared with control subjects, and persisted at 4-month follow-up, despite normalization of global LV function parameters (LVEF, mitral annular *S*, *e′*, and *E*/*e′*) and preserved LV geometry. Of note, none of these patients exhibited any evidence of fibrosis on cardiac magnetic resonance (CMR). These abnormalities are likely to explain persistent alterations in LV diastolic function observed in some patients after the acute phase and to provide a partial explanation for limited exercise capacity in these patients.[22,29] Moreover, they suggest persistent changes in myocardial structure and function in a condition considered until recently as a fully reversible form of acute cardiomyopathy.[26]

A case of TTS with serial echocardiography studies is presented in Figure 2.

Clinical implications Myocardial function recovery in patients with TTS should be monitored with echocardiography during the acute

phase. Conventional echocardiographic diastolic indices (mitral inflow profile, *e′*, *E/e′*, LA volume, TR velocity, sPAP) should be assessed early and systematically to identify patients at higher risk for acute HF and to guide management.[21]

4.3 | Obesity

Hemodynamic studies reported elevated LVFP as a frequent finding in severely obese subjects.[30] Furthermore, several studies using conventional Doppler parameters identified an increased prevalence of impaired LV diastolic filling in obese compared to normal weight subjects regardless of the severity of obesity.[31-33] Decreased *E/A* ratio, prolonged isovolumetric relaxation time, decreased *e′* velocities are common in obesity.[34,35]

Concentric LV remodeling/hypertrophy emerged as the most prevalent type of LV geometry in obese patients, and waist circumference demonstrated a relationship to LV wall thickness and relative wall thickness, both associations being independent of blood pressure measurements.[36] Studies in obese subjects suggest that not only adverse LV loading conditions, but certain neurohormonal and metabolic alterations commonly associated with obesity may contribute to changes in cardiac structure and function in this setting.[37] Elevated cardiac collagen turnover serum markers, and a high prevalence of diabetes mellitus in obese subjects, propose perivascular, and interstitial LV fibrosis as potential contributors to LV diastolic dysfunction in obese patients.[37] More recently, studies employing TDI and STE have shown significantly higher impairment of *e′* velocities in obese subjects relative to normal weight controls, with a progressive decrease in diastolic velocities and impairment of diastolic strain and strain rate with increasing body mass index (BMI).[37]

The first large-scale study in a randomly selected, elderly cohort, revealed an inverse relationship between BMI and echocardiographic parameters of diastolic function. Higher BMI was associated with lower *E/A* and higher *E/e′* ratio independent of factors influencing LV diastolic function including age, sex, LV mass, hypertension, diabetes, and heart rate. In a subanalysis of subjects without hypertension and diabetes (223 patients), the relation between BMI and *E/e′* ratio was still significant and independent of cardiovascular risk factors associated with obesity, such as hypertension, diabetes, and LV hypertrophy. This finding suggests that different mechanisms may link the increase in BMI with the impairment in LV diastolic properties. Moreover, it is the first study to demonstrate that impairment of diastolic function may already be present in overweight persons.[38]

The relationship between increased BMI and LVDD is relevant since obesity has been demonstrated to be one of the leading causes of HFpEF.[39]

The effects of weight loss on LV diastolic filling have been assessed in several studies using Doppler echocardiography. Significant improvement in LV filling or relaxation was detected in most of these studies. In some studies, these improvements were associated with a reduction in LV mass.[40,41]

Clinical implications Substantial weight loss can reverse many of the hemodynamic, neurohormonal, and metabolic alterations associated with obesity. These may result in reverse cardiac remodeling, improvement in ventricular function in obese patients, and improved functional capacity in those with HF.[37] Improved LV systolic and diastolic function associated with therapeutic measures promoting optimal body weight might be a step toward preventing or delaying the development of HF, a hypothesis that deserves further investigation.[38]

4.4 | Critically ill patients

In critically ill patients, diastolic function is at least as important as systolic function and plays a major prognostic role.[42] The incidence of LVDD in selected populations of critically ill patients ranges between 40% and 80%.[43]

Septic shock is a significant cause of morbidity and mortality, and sepsis-induced myocardial dysfunction is increasingly being recognized.[44-46] Recent studies in patients with sepsis demonstrated that LVDD may occur de novo during septic shock and resolves as the infective condition is treated. In a study that included patients with severe sepsis or septic shock, 38% had isolated diastolic dysfunction.[42] Furthermore, sepsis-induced LVDD was associated with myocardial injury, as indicated by increased troponin I.

When septic shock patients present with increased cTnI, physicians should assess the possibility of elevated LVFP, despite the absence of global LV systolic dysfunction. Previous studies have validated the use of *E/e′* as an accurate predictor of pulmonary capillary wedge pressure in septic shock and other critical scenarios.[47,48] Thus, echocardiographic estimation of LVFP may be used to guide therapy in septic shock associated with fluid overload, increased cTnI, and hypoxemia.[49]

Reversible impairment of echocardiographic LV relaxation parameters (*e′*, flow velocity propagation Vp) associated with transient increases in troponin-I and inflammatory markers have been reported in 20% of 54 septic shock patients studied.[49] Moreover, in a study on 21 septic shock patients, the *E/e′* ratio emerged as an independent predictor of mortality, better than cardiac biomarkers.[50] Furthermore, *e′* and *E/e′* were the strongest independent predictors of early mortality, even after adjusting for other independent predictors of mortality (the APACHE-II score, low urine output, low LV stroke volume index, hypoxemia), in a group of 262 patients with severe sepsis and septic shock.[42]

Clinical implications Bedside Doppler echocardiography is well suited for the diagnosis of LVDD in critically ill patients and should be performed repeatedly to detect transient alterations of LV relaxation and/or compliance.[51] The diagnosis of isolated, reversible sepsis-induced LVDD is important and has treatment implications. Excessive fluid loading of the noncompliant LV may aggravate lung congestion, leading to pulmonary hypertension, RV dysfunction, and a further decrease in LV volumes.[52] Moreover, high positive fluid balance is associated with greater mortality in septic patients. Thus,

echocardiography may have an essential role in assessing cardiac response to fluids in this setting.[42]

4.5 | Transient diastolic dysfunction in athletes

There have been reports suggesting that intense exercise can result in a transient deterioration of LV systolic and diastolic function in subjects with an otherwise normal heart. [53,54] The duration of these changes is variable, ranging from a few days to 1 month and the reversal of these alterations during recovery has suggested the term "cardiac fatigue".[55]

Different degrees of transient systolic and diastolic dysfunction soon after prolonged or strenuous exercise have been reported in elite athletes. In a study aimed at assessing the effects of repetitive competitive high altitude running on LV performance in trained athletes, transient alterations in LV relaxation have been reported (reduced *E/A* ratio soon after the race, mainly due to reduction in peak *E* velocity).[56] Repetitive racing reproduced similar changes without evidence of a cumulative effect.[56]

The effect of exercise on diastolic function has also been reported in recreational runners.[53,57,58] These studies have consistently demonstrated transient impairment in LV diastolic function (a variable combination of reduced mitral *E* velocity, increased *A* and *E/A* ratio, and reduced or unchanged *e′* velocity) after prolonged exercise (ie, more than 2 hours).

It has been suggested that reduced LV preload associated with acute volume loss (eg, postexercise dehydration) might explain the decrease in early diastolic flow velocity after prolonged exercise, which may be reversed by rehydration. However, other investigators challenged this hypothesis and indicated myocardial dysfunction as a key player in this setting.[53]

Clinical implications The increasing popularity of recreational marathon running, exposing subjects with different levels of physical training to supraphysiological stress requires better characterization of cardiac structural and functional alterations occurring in response to such forms of stress. [53] Since an impairment in LV myocardial mechanics has been demonstrated in healthy individuals participating in strenuous or prolonged exercise, future studies are needed to understand the duration of training required for recreational runners.[53] Further studies are also needed to clarify the mechanisms and reversibility of such myocardial dysfunction..

5 | REVERSIBILITY OF ELEVATED LEFT VENTRICULAR FILLING PRESSURE

The increase in LVFP is the ultimate consequence of LVDD, representing the final pathway for HF, regardless of etiology. Conventional Doppler echocardiography has been widely used to analyze the LV filling patterns. Several studies demonstrated the high feasibility and accuracy of a restrictive filling pattern in identifying HFrEF patients with elevated LVFP.[59,60] Moreover, a short (≤125 ms) mitral DT has been identified as a powerful independent predictor of poor prognosis in both symptomatic and asymptomatic patients with LV systolic dysfunction.[61]

Further studies showed that LVFP is not fixed, and Doppler filling patterns may change over time in relation to the clinical course of the disease or with treatment. Reversible restrictive physiology was defined as the Doppler restrictive filling pattern that changes into abnormal relaxation pattern with treatment or preload reduction, while irreversible restrictive physiology refers to the restrictive filling pattern that remains unchanged.[61] This observation led to the hypothesis that induction of specific changes in the filling pattern by means of controlled manipulation of ventricular loading (eg, valsalva maneuvre, nitroprusside treatment) may add value to the echocardiographic study.[59,61]

It has been shown that changes in transmitral flow pattern after loading manipulations or long-term optimized therapy in patients with systolic HF are correlated with changes in hemodynamic variables and functional capacity.[60,61] Moreover, the prognostic value of a reversible restrictive LV filling pattern in patients with systolic dysfunction in response to various loading manipulations has been previously reported. The restrictive pattern was defined in many of these studies by an *E/A* ratio ≥ 2 or by the combination of an *E/A* ratio between 1 and 2 and a DT ≤ 140 ms.[62,63]

In a study on a similar population, a persistently short DT (≤125 ms) was found to be the single most powerful indicator of poor prognosis. In contrast, a prolongation of an initially short DT was associated with a 66% risk reduction of cardiac mortality. Furthermore, a persistently short DT was the most important predictor of hospital admission for worsening HF and cumulative cardiac events (death, urgent transplantation and hospital admission for HF).[3]

Serial echocardiographic studies at admission and after treatment are presented in Figure 3 for a patient with HFpEF and in Figure 4 for a patient with HFrEF.

Clinical implications In clinical practice, a restrictive filling pattern is commonly seen in patients with LV dilatation and severe systolic dysfunction and is a strong predictor of mortality in this setting, particularly if it is not reversible with treatment.[64,65] Thus, monitoring the changes in LV filling pattern may be useful in tracking the course of the disease and assessing the effects of long-term therapy in patients with LV dysfunction. Moreover, it allows more accurate prediction models as patients with a persistently restrictive filling pattern under optimal medical treatment have worse outcomes.

6 | CONCLUDING REMARKS

Numerous studies have analyzed and highlighted the diagnostic relevance and independent prognostic value of LV diastolic dysfunction in various clinical settings. However, in contrast to studies analyzing LV systolic function, few studies have evaluated LVDD reversibility and very few studies have proposed LVDD reversibility as a

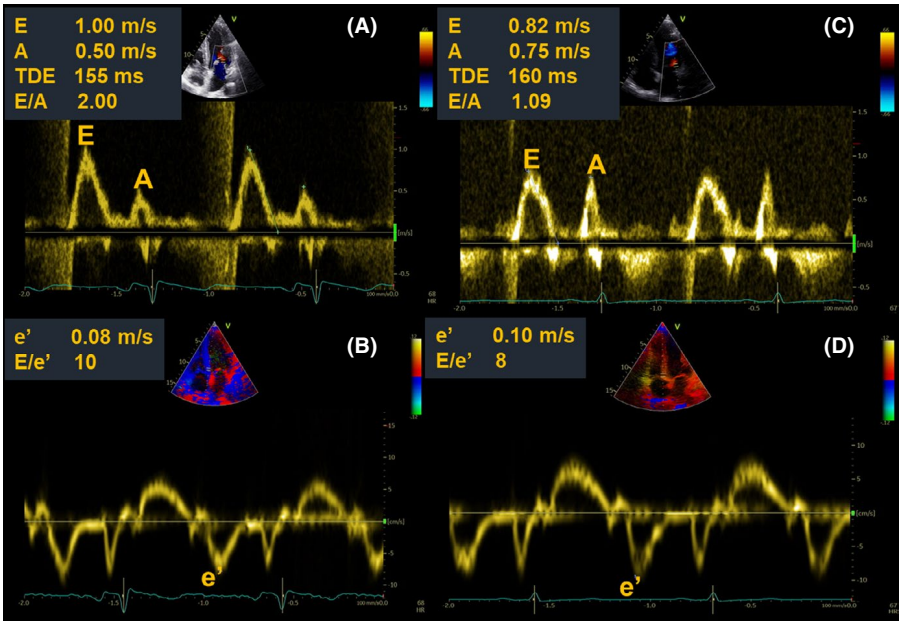

FIGURE 3 The echocardiographic assessment of a forty-eight-year-old man with heart failure and preserved ejection fraction (LVEF: 55%) complaining of dyspnea on exertion is presented at baseline and after 6 mo of heart failure therapy including diuretics. Pulsed-wave (PW) Doppler tracings of the mitral inflow and PW tissue Doppler tracings of the mitral annulus at baseline (A, B) and after 6 mo of therapy (C, D) are presented. The baseline restrictive filling pattern (A) reverses after therapy (C). This is paralleled by an increase in TDI early diastolic velocity from 8 cm/s (B) to 10 cm/s (D) and a decrease in *E/e′* ratio from 10 to 8

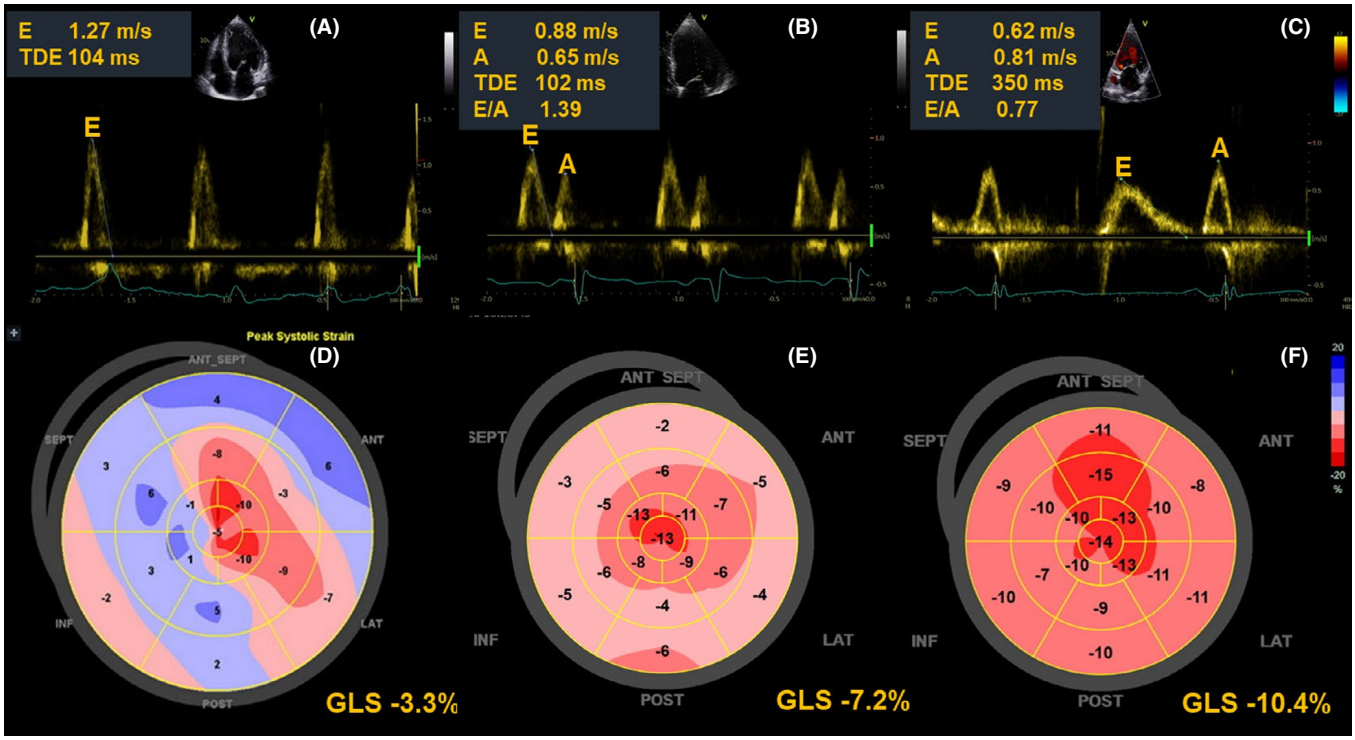

FIGURE 4 Echocardiographic assessment of a fifty-two-year-old man with heart failure and reduced ejection fraction (LVEF: 25%) due to nonischemic dilated cardiomyopathy, admitted with orthopnea. Serial studies of left ventricular function at admission, after 1 wk, and 1 mo of heart failure therapy are shown: mitral inflow patterns (A,B,C) and global longitudinal strain bull's eye plots (D,E,F). Pulsed-wave Doppler of the mitral inflow at admission shows atrial fibrillation with a restrictive filling pattern (A). The restrictive pattern reverses to a pseudonormal filling pattern at 1 wk (B) and to abnormal relaxation pattern at 1-month follow-up (C) under optimal heart failure therapy and restoration of sinus rhythm. Two-dimensional speckle-tracking longitudinal strain analysis shows severe reduction in average global longitudinal strain (GLS −3.3%) at admission (D). At 1-wk (E) and 1-mo follow-up (F), there is progressive recovery of left ventricular longitudinal function (GLS of −10.4% at 1-mo follow-up)

therapeutic target. This is somewhat surprising given that LVDD is a dynamic process but can be explained by the fact that for a longtime LVDD was considered a bystander rather than a major pathophysiological factor.

By using both conventional methods and advanced techniques, echocardiography is the most suitable method for characterizing LVDD as a dynamic process. When searching the literature, we identified a wide range of conditions for which serial

echocardiographic evaluation objectified the reversibility of LVDD in relation to an index moment. We selected for the purpose of this review some of the most clinically relevant settings in which echocardiography allows identification of potentially reversible causes of LVDD that can be treated with symptomatic or even prognostic benefits (Table 1). However, many areas of uncertainty remain, beginning with a crisp definition of reversible LVDD. Establishing for each pathology a waiting horizon in which the normalization of diastolic function could be expected, selecting the echocardiographic parameters which best reflect reversibility of LVDD and the prognostic relevance of this information, all these require further clarification.

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