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Left ventricular strain and twisting in heart failure with preserved ejection fraction: an updated review

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Abstract Despite the high prevalence of the patients with heart failure with preserved ejection fraction (HFpEF), our knowledge about this entity, from diagnostic tools to therapeutic approach, is still not well established. The evaluation of patients with HFpEF is mainly based on echocardiography, as the most widely accepted tool in cardiac imaging. Identification of left ventricular (LV) diastolic dysfunction has long been considered as the only responsible for HFpEF, and its evaluation is still "sine qua non" of HFpEF diagnostics. However, one should be aware of the fact that identifying cardiac dysfunction in HFpEF might be very challenging and often needs more complex evaluation of cardiac structure and function. New echocardiographic modalities such as 2D and 3D speckle tracking imaging could help in the diagnosis of HFpEF and provide further information regarding LV function and mechanics. Early diagnosis, medical management, and adequate monitoring of HFpEF patients are prerequisites of modern medical treatment. New healthcare approaches require individualized patient care, which is why clinicians should have all clinical, laboratory, and diagnostic data before making final decisions about the treatment of any patients. This is particularly important for HFpEF that often remains undiagnosed for quite a long time, which further prolongs the beginning of adequate treatment and brings into question outcome of these patients. The aim of this article is to provide the overview of the main principles of LV mechanics and summarize recent data regarding LV strain in patients with HFpEF.

Keywords Heart failure with preserved ejection fraction · Left ventricle · Strain

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Introduction

Although the incidence of cardiovascular diseases in developed countries reduced over the last two decades, the prevalence of patients with heart failure (HF) is constantly increasing, and currently it is between 1 and 2% [1]. The number of hospitalizations, which only in USA exceeds 1 million per year, significantly increases the costs of treatment of these patients [2]. The study that investigated the trend of deaths attributed to HF in seven developed European countries over a period of 20 years showed that the mortality significantly decreased [1]. However, US statistics showed that 5-year mortality is still higher than 50% [2]. Considering the fact that population is aging and the fact that the number of patients with different risk factors for HF development such as coronary artery disease, hypertension, diabetes, and obesity is continuously rising, an adequate diagnostic and therapeutic approach of HF is necessary.

HF represents a clinical diagnosis, characterized by typical symptoms and signs and increments of important biomarkers such as brain natriuretic peptide (BNP or pro-BNP). However, for a long time, HF was exclusively ascribed to the reduced left ventricular (LV) function, and relatively recently, it was recognized that even patients with preserved LV function

could have HF. First appeared the term "diastolic HF," which soon evolved to "HR with preserved LV ejection fraction" (HFpEF). Considering the fact that mortality is the same in HF patients with reduced and preserved EF [3], as well as the statistics that show the significant reduction of mortality in HF with reduced EF (HFrEF) over the last several decades, but not in HFpEF patients [3], it is of great importance to make diagnoses and start treatment of HFpEF as soon as possible.

The aim of this review article is to summarize current clinical usefulness of LV strain and twist assessment in patients with HFpEF.

HFpEF definition

The cutoff value for EF in HFpEF is challenging, and it has been changed over time. It was recognized that reduced EF is 40%, but there was no consensus regarding the definition of preserved EF. The American guidelines from 2013 defined that HFpEF is EF ≥50%, whereas EF between 41 and 49% was considered as "borderline" HF and finally EF ≤40% defined HFrEF [4].

The latest European guidelines introduced the term "mid-range" HF for the patients with EF between 40 and 49% [5].

However, LVEF in the majority of conducted or ongoing studies ranges 35–50% as the cutoff value for preserved LVEF. The lack of agreement regarding LVEF opens a large space for other echocardiographic parameters that could (and should) be used in diagnostics of the HF patients in everyday clinical practice. This predominantly refers to sophisticated two- and three-dimensional speckle tracking imaging parameters that provide insight in LV mechanics.

Role of left ventricular mechanics in HFpEF

Left ventricular contraction and relaxation are complex and dynamic associated changes in muscle length and shape that consist of shortening, lengthening, narrowing, widening, twisting, and uncoiling. The timing of the movement and the strength of each layer dictate the direction and velocity of the dominant motion. There are several theories regarding layer architecture and myocardial fiber organization. Some authors claimed that LV myocardium consists of two layers; others reported three layers; whereas there are also those who suggested a four-layer LV myocardial structure [6]. The majority of investigators agree that LV myocardium contains three layers: endocardial, mid-myocardial, and epicardial. It is also widely accepted that fibers in the subendocardium and subepicardium are mainly longitudinally oriented while fibers in the mid-myocardium are circumferentially oriented. The subepicardial LV fibers with an average orientation of about −60° produce helices with almost horizontal mid-myocardial fibers and form a left-handed helix, whereas the mid-myocardial fibers and the subendocardial fibers with an average angle of about +60° form the right-handed helix. Additionally, the circular muscle of the basal loop contracts and rotates the LV, whereas the descending and ascending helical fibers shorten or lengthen the LV and also rotate the chamber. It is not the same at which angle myocardial fibers are. A mathematical model demonstrated that contraction of purely longitudinally or circumferentially organized myocytes would produce ejection fractions of 15 and 28%, respectively [7]. On the other hand, fibers with 60° angle from the horizontal would achieve ejection fractions >60%.

The first studies on animal models published almost half a century ago showed that the LV myocardial wall has a well-ordered distribution of fiber angles varying from 60° (from the circumferential direction) at the inner surface to −60° on the outer surface [8]. The greatest change in angle with respect to wall thickness occurs at the endocardium and epicardium. The authors [9, 10] reported that fiber angles did not change significantly during the changeover from diastole to systole, despite a 28% increase in wall thickness.

Considering the orientation of different LV myocardial layers, one would expect that epicardial and endocardial layers are responsible only for longitudinal strain, whereas mid-myocardial fibrils are responsible only for circumferential strain. However, the latest analyses with multilayer strain showed that each layer is contributing to global longitudinal, circumferential, and radial motion [11–14]. The layer-specific strain analysis shows that longitudinal, circumferential, and radial strains gradually decreased from the endocardium to epicardium, and none of these layers shows a strain value of 0% (or even close to 0%), which confirms the hypothesis that each layer contributes to multidirectional LV strain. The reason is the different angle between various layers. Namely, myocardial layers are not perpendicular to each other which is why the contraction of longitudinally organized myocytes in endocardial and epicardial layers will not produce isolated shortening in LV length, without changing the LV circumference or LV thickness and vice versa; contraction of the mid-myocardial layer will not induce solely circumferential shortening but also change in length and thickness.

Besides longitudinal, circumferential, and radial motion (thickening), basal and apical rotation together twist and untwist. The base rotates clockwise, while the apex rotates significantly more pronounced counterclockwise, which is why torsion represents important and prominent cardiac motion. Twist is a consequence of contraction of individual myofibers interacting with their three-dimensional architecture.

Untwisting is best termed the reversal of twisting and occurs as a consequence of relaxation of the myofibers interacting with their three-dimensional architecture. The first 40–60% of untwisting occurs during an approximately 90-ms post-ejection isovolumic interval that precedes rapid filling.

Different factors that influence LV mechanics

There are many factors that could influence LV strain in HFpEF patients. Namely, these patients usually have comorbidities such as arterial hypertension, diabetes, obesity, metabolic syndrome, renal failure, or obstructive lung disease that at the same time contribute to HF development and impairment of LV mechanics [3–5].

These conditions induce structural myocardial abnormalities from organ level such as concentric hypertrophy with associated alterations in shape and fiber orientation, to fibrosis with altered tethering of myocardial layers, to changes at a molecular level that modify acto-myosin kinetics. Different mechanisms could induce myocardial fibrosis in HFpEF: increase in concentration of proinflammatory cytokines and matrix metalloproteinase, oxidative stress, and renin-angiotensin-aldosterone system [15].

There are a limited number of studies that explain molecular mechanisms of LV strain changes in HFpEF. An animal model of streptozotocin-induced diabetes showed that LV deformation in the early stages of diabetes is related with the delay of Ca(2+) transients in cardiomyocytes due to the reduced phosphorylation of CaMKII [16]. Adenine nucleotide translocator (ANT) exports mitochondrial adenosine triphosphate into the cytosol and has a role in the regulation of the intrinsic apoptosis pathway. The investigations in mouse model showed that mitochondrial energy deficiency induced by ANT mutation induced LV circumferential, radial, and rotational mechanics [17]. Histopathologic analysis revealed myocyte hypertrophy, fibrosis, and calcification in the mutant mice compared with control mice. Additionally, elevated cytoplasmic cytochrome c levels and caspase 3 activation were noticed in the mutant mice [17].

In patients with end-stage dilated cardiomyopathy, Cordero-Reyes et al. [18] showed that longitudinal, circumferential, and radial strains are associated with messenger ribonucleic acid levels of molecules implicated in cardiac fibrosis and function (transforming growth factor beta, titin isoforms, collagen type I, collagen type III, sarcoplasmic reticulum Ca(2+)-ATPase, phospholamban, protein levels of SERCA2a, phosphorylated phospholamban). Kilic et al. [19] showed that the abundance of sodium/calcium exchanger type 1 protein, in addition to major calcium-handling proteins—sarcoplasmic reticulum Ca(2+)-ATPase and phospholamban—correlates with strain. However, it should be emphasized that the majority of these studies show the correlation, but not necessarily the causal relation between molecular mechanisms and strain.

All risk factors that could induce HFpEF could also be responsible for LV geometry changes. Uchino et al. [20] showed that LV geometry is quite different in patients with HFrEF and HFpEF with predominance of concentric over eccentric LVH in HFpEF. Considering the results of previous studies that indicate the importance of LV geometry on survival [21, 22], it is not difficult to understand the relationship between LV geometry, strain, and mortality in HF patients. However, the mechanisms of this relationship remain unclear.

Strain measurements in HFpEF and clinical correlates

Longitudinal strain

The Karolinska Rennes study [23] included 539 HFpEF patients with an average EF 56 ± 7% who were hospitalized due to symptoms and signs of HF. Control echocardiographic examination was performed in the period between 4 and 8 weeks after hospitalization and showed that LV EF was significantly higher (62 ± 7%) and global longitudinal strain (GLS) was −14.6 ± 3.9% [23]. Table 1 summarizes current findings regarding LV mechanics in patients with HFpEF [23–43].

Kosmala et al. [24] performed cardiopulmonary exercise test to 207 HFpEF symptomatic patients (NYHA II and III) and 60 asymptomatic HFpEF subjects with normal exercise tolerance, diastolic dysfunction, LV hypertrophy, and/or reduced GLS. After exercise test, the E/e' ratio in asymptomatic HFpEF patients slightly decreased (9.7 ± 1.7 vs. 9.0 ± 1.9), whereas in symptomatic patients the E/e' ratio significantly increased (11.6 ± 3.6 vs. 15.3 ± 5) [24]. On the other hand, GLS increased after exercise in both groups. However, the increment was significantly higher in the asymptomatic group. A receiver operator characteristic (ROC) curve showed that exercise GLS represents the best predictor of symptomatic HFpEF (AUC 0.78), significantly better than LVEF and E/e' [24]. Henein et al. [28] showed similar changes in LV diastolic strain rate and E/e' ratio in HFpEF subjects during exercise.

Liu et al. [25] showed proportional reduction in GLS from controls, throughout HFpEF to HFrEF (−19.7 ± 2.4 vs. −14.0 ± 4.5 vs. −8.1 ± 3.4, $p < 0.001$). Interestingly, the increase in the E/e' ratio was not that proportional (12.6 ± 3.5 vs. 15.9 ± 7.2 vs. 25.0 ± 14.0, $p < 0.001$) [25]. This shows higher sensitivity of LV GLS over the E/e' ratio to detect LV dysfunction, which represents an important clinical implication.

Similar results were obtained by Carluccio et al. [26] who correlated LV longitudinal mechanical function with tissue characterization derived by 2D echocardiography. The investigators demonstrated that myocardial fibrosis negatively correlated with GLS ($r = -0.68$, $p < 0.001$) and positively with the E/e' ratio ($r = 0.46$, $p < 0.001$) [26].

An investigation which showed that galectin-3, a new biomarker in heart failure which correlates good with inflammation and fibrosis, is significantly higher in diabetic patients with HFpEF than in controls did not reveal a difference in GLS between HFpEF and controls (−19.4 ± 3.2 vs. −20.2 ± 2.6%, $p = 0.7$) [27].

Table 1 Left ventricular mechanics in HFpEF patients

Reference	Sample size	Age (years)	Female (%)	Ejection fraction (%)	E/e'	GLS (%)	GCS (%)	GRS (%)	Twist (°)	Devices
Donal et al. [23]	539	77 ± 9	303 (56)	56 ± 7	12.9 ± 6.1	−14.6 ± 3.9	–	–	–	Unknown
Kosmala et al. [24]	207	63 ± 8	152 (73)	72 ± 9	11.6 ± 3.6	−18.4 ± 3.3	–	–	–	GE
Liu et al. [25]	26	63 ± 18	10 (43)	63 ± 8	15.9 ± 7.2	−14.0 ± 4.5	–	–	–	GE
Carluccio et al. [26]	46	75 ± 8	24 (52)	60 ± 6	16.7 ± 6.8	−15.4 ± 3.5	–	–	–	GE
Flores-Ramírez et al. [27]	76	55 ± 11	46 (61)	62 ± 6	10.7 ± 2.9	−19.5 ± 3.3	–	–	–	GE
Kraigher-Krainer et al. [29]	219	72 (66–78)	131 (61)	59.2 (53.7–63.6)	14.7 (11.5–18.8)	−14.6 ± 3.3	−22.9 ± 5.9	–	–	TomTec
Biering-Sørensen et al. [30]	85	53 ± 8	64 (75)	64 ± 8	7.7 (5.7–10.7)	−18.2 ± 2.2	−25.9 ± 3.3	–	–	TomTec
Santos et al. [31]	130	71 ± 9	80 (62)	60 ± 7	13.2 ± 6.5	−15.1 ± 3.1	–	–	–	TomTec
Hasselberg et al. [32]	37	58 ± 11	12 (32)	62 ± 7	11 ± 5	−17.5 ± 3.2	–	–	–	GE
Wang et al. [33]	80	66 ± 8	29 (29)	62 ± 5	14.4 ± 6.6[a] 13.3 ± 5.5[b]	−17.5 ± 3.7[a] −18.8 ± 2.9[b]	−21.1 ± 4.9[a] −22.3 ± 3.5[b]	26.3 ± 5.9[a] 28.3 ± 4.9[b]	20.3 ± 8.9[a] 20.7 ± 8.9[b]	GE
Gregorova et al. [34]	46	63 ± 8	26 (57)	67 ± 6	8.2 ± 1.9	−18.6 ± 3.7	−20.8 ± 4.4	42.0 ± 16.5	–	GE
Wenzelburger et al. [35]	62	71 ± 8	41 (66)	60 ± 7	11.3 ± 4.2	−18.3 ± 3.3	–	41.8 ± 14.5	–	GE
Wang et al. [36]	20	63 ± 16	7 (35)	63 ± 6	–	−12 (−13–8)	−15 ± 5	28 ± 9	13 ± 6	GE
Shah et al. [37]	447	70 ± 10	240 (54)	60 ± 8	15.8 ± 6.9	−15.8 ± 3.4	–	–	–	TomTec
Yip et al. [38]	112	74 ± 12	67 (64)	61 ± 6	19.9 ± 9.7	−15.9 ± 3.9	−20.8 ± 4.9	32.9 ± 10.6	–	GE
Stampehl et al. [39]	100	60 ± 1	76 (76)	58 ± 4	17.4 ± 3.7	−11.6 ± 0.4[a] −16.5 ± 0.3[b]	−17.5 ± 0.7[a] −19.7 ± 0.8[b]	–	–	GE
Luo et al. [44]	58	70 ± 10	23 (40)	62 ± 8[c]	16 ± 6	14.0 ± 2.7 14.3 ± 3.6[d]	15.2 ± 2.4 33.1 ± 6.7[d]	30.9 ± 8.6 24.8 ± 10.5[d]		Toshiba

GE general electric (vivid), *GLS* global longitudinal strain, *GCS* global circumferential strain, *GRS* global radial strain, *E/e'* the ratio between early transmitral flow evaluated with pulsed and tissue Doppler

[a] HFpEF with adverse event (all-cause death and/or HF hospitalizations)

[b] HFpEF patients without adverse event

[c] 3D LV EF

[d] 3D LV strain

The PARAMOUNT study [29] confirmed that GLS is significantly lower in HFpEF patients than in controls and hypertensive patients (−20.0 ± 2.1 vs. −17.07 ± 2.04 vs. −14.6 ± 3.3%, respectively, $p < 0.001$ for all). GLS was associated with LVEF ($r = -0.46$; $p < 0.001$) in HFpEF individuals, but not with standard echocardiographic measures of LV diastolic function (e' or E/e'). Lower GLS was associated with higher pro-BNP, even after adjustment for LVEF, parameters of LV diastolic function, and LV filling pressure [29]. The authors showed that GLS gradually increased from HFpEF with EF 45–50%, throughout HFpEF with EF 50–55%, to HFpEF patients with EF >55%. The PARAMOUNT trial [31] also showed that LV dyssynchrony assessed by 2D speckle tracking was related to worse diastolic function. The relationship with LV diastolic function (e') remained even after adjusting for age, gender, systolic blood pressure, LV mass index, and LVEF [31].

The investigation that used right heart catheterization together with echocardiography and cardiopulmonary test revealed the association between lower GLS at rest and larger increment in pulmonary arterial wedge pressure at peak exercise ($r = 0.23$, $p = 0.034$). Higher global circumferential strain (GCS)/GLS ratio was the best predictor of elevated wedge pressure during exercise ($r = 0.30$, $p = 0.015$). The CS/LS ratio had the highest specificity for the presence of rest- or exercise-induced pulmonary venous hypertension [30]. Nguyen and coworkers [40] also showed that LV filling pressure significantly correlated with GLS, longitudinal systolic strain rate, radial and circumferential systolic strain rate, torsion, and torsion rate. Additionally, GLC, GCS, global radial strain (GRS), and torsion were deteriorated in HFpEF patients with LV filling pressure >15 mmHg comparing with those patients with filling pressure <15 mmHg [40].

Hasselberg et al. [32] showed that GLS and peak pulmonary arterial systolic pressure were independently associated with peak VO2 in HFpEF. Reduced GLS was proved to be superior to EF and E/e' in detection of patients with impaired functional capacity (peak VO2 <20 ml/kg/min). Furthermore, GLS was better than LVEF associated with E/e′ ($r = 0.45$, $p = 0.005$) and left atrial volume index ($r = 0.48$, $p = 0.003$) in patients with HFpEF [22]. Wenzelburger et al. [33] reported similar findings—lower GLS in HFpEF patients at rest, improvement of GLS during exercise in HFpEF patients and controls, and higher increase in GLS in controls than in HFpEF subjects.

During the 3-year follow-up of HFpEF patients, Wang et al. [33] did not find any difference in GLS between HFpEF who suffered adverse event and patients without event. Interestingly, GLS increased during the exercise test only in HFpEF subjects with no event (from 18.8 ± 2.9 to 21.4 ± 3.9%, $p < 0.001$), which again underlines the importance of GLS evaluation in these patients. Elevated E/e' ratio and GLS were significantly associated with adverse events, but only impaired GLS during exercise remained an independent predictor of adverse events with a sensitivity of 84% and a specificity of 61% [33]. In another study, Wang et al. [36] hypothesized that increased LV twist in HFpEF patients represents a sort of compensation for the reduced LV strains (GLS, GCS, and GRS) that is necessary in order to maintain normal LVEF.

The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial [37] showed not only that GLS was significantly decreased in HFpEF but also that reduced GLS (defined as <−15.8%) was the predictor of the composite outcome (cardiovascular death, HF hospitalization, or aborted cardiac arrest), cardiovascular death alone, and HF hospitalization alone independently of clinical and conventional echocardiographic parameters. It has been shown that GLS represents the strongest echocardiographic predictor of the composite outcome, stronger than E/e' [37]. However, the combination of reduced GLS, increased E/e', and LV hypertrophy was the most responsible for unfavorable outcome in the study population. Similar investigation showed that patients with GLS ≤−15% have significantly more adverse events (re-hospitalizations and cardiac death) than patients with GLPS > −15% in the period of 1 year [39]. The authors [41] reported that GLS was a better predictor than LVEF for adverse events in HFpEF patients.

Yip et al. [38] reported significantly deteriorated multidirectional LV strain (GLS, GCS, and GRS) in comparison with controls, but there was no difference in any of these strain parameters when investigators compared HFpEF patients with and without coronary artery disease.

Interesting research by Smith et al. [42] demonstrated that endocardial and epicardial GLS of basal, mid-, and apical LV segments is significantly lower in HFpEF individuals. This demonstrates that the whole thickness of the myocardium is affected in HFpEF, and not only the subendocardial part. These findings also confirm the hypothesis that HFpEF affects all myocardial fibers, irrespective of angle and orientation in different myocardial layers.

Luo et al. [43] showed that 3D GLS was significantly higher in patients with HFpEF than those with HFrEF (all $p < 0.001$), but still lower than that in normal controls (all $p < 0.05$). The 3D LV area strain, combination of longitudinal and circumferential strain, and a very good predictor of LV systolic function, showed the best correlation with LVEF.

Circumferential strain

The results regarding circumferential strain in the HFpEF population are conflicting. HFpEF patients enrolled in the abovementioned PARAMOUNT trial [29] showed significantly lower global circumferential strain (GCS) in comparison to both controls and hypertensive patients (−27.1 ± 3.1 vs. −30.1 ± 3.5 vs. −22.9 ± 5.9%, respectively; $p < 0.001$ for all).

GCS is associated with LVEF ($r = -0.51$; $p < 0.001$) in HFpEF individuals, but not with standard echocardiographic measures of LV diastolic function (e' or E/e'). The authors [17] showed that GCS gradually increased from HFpEF with EF 45–50%, throughout HFpEF with EF 50–55%, to HFpEF patients with EF >55%.

Biering-Sørensen et al. [30] showed that higher GCS at rest predicts a larger increase in wedge pressure ($r = -0.27$, $p = 0.032$). Higher GCS/GLS ratio was the best predictor of elevated wedge pressure during exercise ($r = 0.30$, $p = 0.015$) with the highest specificity for the presence of pulmonary hypertension [30]. However, other studies did not show difference in GCS between HFpEF patients who suffered adverse event and those without adverse event, which implies that GCS was not the predictor of all-cause death and/or HF hospitalizations in HFpEF patients [35].

There are authors who did not find any difference in GCS between patients with HFpEF and healthy controls [34, 39], and those who reported significant GCS reduction in HFpEF patients [38, 42, 43]. Smith et al. [42] even succeeded to show that endocardial and epicardial GCS of basal, mid-, and apical LV segments is significantly lower in HFpEF than in controls, which again confirms that all myocardial layers are affected in HFpEF.

Using 3D speckle tracking imaging, Luo et al. [43] showed that GCS is significantly lower in HFpEF patients, which completely corresponds with 2D strain results of this study.

Radial strain

Global radial strain (GRS) is poorly explored in HFpEF. There are only a few investigations that included this LV mechanical parameter, and the results are conflicting.

The results from the follow-up study showed that GRS was not associated with adverse event occurrence in the HFpEF population [33]. However, the increment of GRS during the exercise test seems to be higher in HFpEF patients without adverse event than in those who suffered an event [33]. The increase in GRS was significantly higher than for GLS or GCS, but it was not further evaluated or commented by the authors. The absence of difference in GRS between HFpEF and controls was also reported by the other authors [34].

Wenzelburger et al. [35] revealed that GRS was significantly lower in HFpEF patients compared with controls. As expected, GRS increase during the exercise test was higher in controls than in HFpEF individuals [31]. Other authors also reported decreased GRS in HFpEF patients [38].

Luo et al. [43] reported significantly lower values of 2D and 3D GRS in HFpEF patients, which represents the first study which at the same time used two methods for the strain assessment.

We would like to stress several reasons for the inconsistence of GCS and GRS in the prediction of disease severity and outcome in HFpEF. First, most of the vendors require the additional software packages for calculation of GCS and GRS, which is often time demanding and not suitable for everyday clinical practice in busy echocardiographic laboratories. This is the reason why determination of GLS is part of everyday clinical practice and large number of investigations, unlike GCS and GRS. Second, studies showed that interobserver and intraobserver variability is much higher for GCS and particularly GRS. Third, there is still a large intervendor variability for GCS and GRS.

Twist

Although LV twist represents a good parameter of LV function and mechanics, it has still not been fully investigated in HFpEF patients.

Wang et al. [33] did not find a difference between HFpEF patients who experienced some adverse event and HFpEF patients with no event. However, it seems that during exercise LV twist significantly more improved in HFpEF patients with no event [33].

Wenzelburger et al. [35] did not investigate twist, but they provided information regarding LV apical rotation that was significantly lower in HFpEF patients than in controls before and after the exercise test. An increase in apical rotation was significantly higher in healthy controls than in HFpEF subjects [35].

Wang et al. [36] showed how LV twist could compensate significantly decreased LV mechanical function (GLS, GCS, and GRS) in HFpEF and maintain completely normal LVEF. The authors also showed the high level of negative correlation between LV twist and GLS ($r = -0.58$, $p < 0.001$) and GCS ($r = -0.73$, $p < 0.001$).

Interestingly, Yip et al. [38] reported that LV torsion, which is only derived from twist, is significantly lower in HFpEF patients than in controls. However, when HFpEF subjects with and without coronary artery disease were compared, there was no difference in LV torsion [38]. Stampehl et al. [39] did not find any difference in LV torsion between HFpEF and controls.

A study that investigated layer-specific strains and rotation showed that endocardial and epicardial basal rotation is significantly higher in HFpEF patients, whereas only endocardial apical rotation is lower in these patients [42]. Considering the fact that the subepicardial fibers are mainly responsible for LV twist, it is understandable why LV twist remains normal at the beginning. However, with disease progression, midmyocardial and subepicardial layers become more impaired, which further induces LV twist reduction in advanced stages of HFpEF.

Three-dimensional LV architecture is an important determinant of LV twist and torsion [43]. Namely, cardiac electric and mechanical activation starts in the apical

subendocardial region. During isovolumic contraction, the subendocardial myofibers shorten and the subepicardial myofibers stretch, which results with a short clockwise apical rotation and a counterclockwise LV basal rotation. During ejection, the subendocardial and subepicardial layers shorten simultaneously. The subepicardial fibers dominate the direction of twist, producing apical counterclockwise rotation and clockwise basal rotation, respectively. During isovolumic relaxation, the subepicardium stretches in basal-apical direction, whereas the subendocardium stretches in the opposite direction. The early diastole is characterized by relaxation in both layers with minimum untwisting. The prompt decline in LV pressure during this phase is caused by active myocardial relaxation and LV elastic recoil. LV elastic recoil—untwisting—generates the energy for LV filling.

LV strain and heart failure symptoms

Investigations that study symptoms and LV strain in HF population are scarce. Kosmala et al. [45] showed significant improvement in symptoms and functional capacity in HFpEF patients treated with spironolactone. However, the authors did not find any difference in LVEF and GLS after 6-month therapy, but only for e' and E/e' [45]. Hasselberg et al. [42] revealed a significant correlation between functional capacity (peak VO2), NYHA class, GLS, and E/e'. Interestingly, only GLS and mitral E/e', and not NYHA class, remained independently associated with peak VO2. A study that included HFpEF patients and patients with dyspnea without criteria for HFpEF showed that patients with higher NYHA class have significantly lower GLS and GCS [34]. The TOPCAT study [37] showed that GLS is a good predictor of hospitalization due to HF, which represents a reliable indicator of HF symptoms.

It should be emphasized that the straightforward relationship between HF symptoms and strain could not be established. However, the LV strain represents an additional tool to make distinction among patients with different etiologies of dyspnea. Usage of GLS together with other echocardiographic parameters (E/e', E/A, LAVI) and biomarkers such as pro-BNP could significantly help to establish the diagnosis of HFpEF. A recently published study [46] demonstrated strong correlations between speckle tracking parameters and the conventional indices of diastolic dysfunction and LV filling pressures. A multivariable analysis [47] also allowed estimation of E/e' and pulmonary capillary wedge pressure by speckle tracking parameters. However, GLS still should not be used for the estimation of LV filling pressures, which was claimed in the latest guidelines.

Conclusion

Advanced echocardiographic approach significantly changes our perception of HFpEF, improves our knowledge, and spreads our diagnostic horizon. Clinical implications of LV strain evaluation of HFpEF patients are wide. LV strain represents a better predictor of outcome than traditional LVEF; it is associated with functional capacity; and it provides more accurate, reproducible, and detailed information regarding LV function and mechanics. The assessment of GLS is feasible and rapid and provides many answers that could completely change the therapeutic approach, which is why it should be a "sine-qua-non" of every echocardiographic examination in patients HFpEF.

Compliance with ethical standards

Conflict of interest The authors do not declare any conflict of interest that could be perceived as prejudicing the impartiality of this review article. We did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector in order to write this article. MT, EPK, and DAM were involved in the design and writing of the article. CC, MG, KZ, NAW, and BP were involved in drafting and revising critically for important intellectual content.

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