Evaluation of Left Ventricular Stiffness with Echocardiography

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Abstract

Half of patients with heart failure are presented with preserved ejection fraction (HFpEF). The pathophysiology of these patients is complex but increased left ventricular (LV) stiffness is proved to play a key role. However, the application of this parameter was limited since its measurements requires invasive catheterization. With advances in ultrasound technology, new advances have been achieved in the assessment of LV chamber or myocardial stiffness using noninvasive echocardiography. Therefore, this review was carried out to summarize the pathophysiological mechanisms, correlations with invasive LV stiffness constant, applications in different populations as well as the limitations of echocardiography-derived indices for assessment of both LV chamber and myocardial stiffness. LV chamber stiffness indices such as E/e'/LVEDV, E/SRe/LVEDV, and DPVQ were derived on the basis of the relationship between echocardiographic parameters of LVFP and LV size. However, all these methods are surrogate and lumped measurements, relying on E/e' or E/SRe for evaluating LVFP. The limitations of E/e' or E/SRe in assessment of LVFP may contribute to the moderate correlation between E/e'/LVEDV or E/SRe/LVEDV and LV stiffness constant. Even the best validated measurement (DPVQ) is considered unreliable in the individual patient. Compared to E/e'/LVEDV and E/SRe/LVEDV, $I_{PVA/IA}$ and $F_{PVA/FA}$ may display better performance in assessing LV chamber stiffness as evidenced by a higher correlation with LV stiffness constant. However, only one study has been conducted in the literature on the exploration and application of I_{PVA}/I_{A} and F_{PVA}/F_{A}, and its accuracy in assessing LV chamber stiffness remains to be confirmed. In terms of echocardiographic indices for LV myocardial stiffness evaluation, the parameters of EMI/DWS, iVP and SWI were proposed. Despite alteration of DWS and its predictive value of adverse outcomes in various populations have been widely validated, it was found that DWS may be better considered as an overall marker of cardiac function performance instead of pure myocardial stiffness. As for the iVP and SWI, the validities of these two indices in assessing LV myocardial stiffness have not been confirmed in invasive studies. More echocardiographic indices with higher sensitivities and specificities warrant to be further uncovered to evaluate LV stiffness.

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Abstract

Half of patients with heart failure are presented with preserved ejection fraction (HFpEF). The pathophysiology of these patients is complex but increased left ventricular (LV) stiffness is proved to play a key role. However, the application of this parameter was limited since its measurements requires invasive catheterization. With advances in ultrasound technology, new advances have been achieved in the assessment of LV chamber or myocardial stiffness using noninvasive echocardiography. Therefore, this review was carried out to summarize the pathophysiological mechanisms, correlations with invasive LV stiffness constant, applications in different populations as well as the limitations of echocardiography-derived indices for assessment of both LV chamber and myocardial stiffness. LV chamber stiffness indices such as E/e'/LVEDV, E/SRe/LVEDV, and DPVQ were derived on the basis of the relationship between echocardiographic parameters of LVFP and LV size. However, all these methods are surrogate and lumped measurements, relying on E/e' or E/SRe for evaluating LVFP. The limitations of E/e' or E/SRe in assessment of LVFP may contribute to the moderate correlation between E/e'/LVEDV or E/SRe/LVEDV and LV stiffness constant. Even the best validated measurement (DPVQ) is considered unreliable in the individual patient. Compared to E/e'/LVEDV and E/SRe/LVEDV, $I_{PVA/IA}$ and $F_{PVA/FA}$ may display better performance in assessing LV chamber stiffness as evidenced by a higher correlation with LV stiffness constant. However, only one study has been conducted in the literature on the exploration and application of I_{PVA}/I_A and F_{PVA}/F_A, and its accuracy in assessing LV chamber stiffness remains to be confirmed. In terms of echocardiographic indices for LV myocardial stiffness evaluation, the parameters of EMI/DWS, iVP and SWI were proposed. Despite alteration of DWS and its predictive value of adverse outcomes in various populations have been widely validated, it was found that DWS may be better considered as an overall marker of cardiac function performance instead of pure myocardial stiffness. As for the iVP and SWI, the validities of these two indices in assessing LV myocardial stiffness have not been confirmed in invasive studies. More echocardiographic indices with higher sensitivities and specificities warrant to be further uncovered to evaluate LV stiffness.

Background

Rhythmic contraction and relaxation of the heart are the bases for ensuring hemodynamic stability. Various cardiac structural or functional diseases lead to impaired ventricular filling and/or ejection function, which, in turn, leads to heart failure (HF). In recent years, the high prevalence of HFpEF has highlighted the importance of diastolic dysfunction in the development of HF(1-4). Most patients with HFpEF show diastolic dysfunction, such as an abnormal left ventricular (LV) filling pattern and elevated filling pressure(5, 6). Therefore, the evaluation of cardiac diastolic function and its determinants has important clinical significance (7-9).

The diastolic process can be divided into four phases: isovolumic diastole, early diastolic filling, diastasis, and atrial contraction. Isovolumic diastole is the period of time between the closure of the aortic valve and the opening of the mitral valve, when LV pressure falls while volume remains constant, and usually reflects LV compliance. When LV pressure is lower than left atrial (LA) pressure, the mitral valve opens under negative pressure and enters a period of rapid filling, which is influenced primarily by preload and LV relaxation properties. As blood enters the left ventricle, the LV pressure begins to rise, and when it is equal to the LA pressure, the flow enters a state of relative stagnation, the diastasis phase, which can

be influenced by preload, LV geometry, stiffness of the LV chamber, and compliance. Atrial systole is the final phase of diastole, when LA pressure is again higher than LV pressure, and factors affecting this phase include LV compliance and LA systolic function(10). Among the factors affecting diastolic function of the heart, apart from extrinsic factors such as pulmonary-cardiac contact pressure, pericardial restraint and interaction of both ventricles (11), intrinsic factors are mainly LV active relaxation and passive LV chamber stiffness (12). Delayed active relaxation will result in changes in early filling pressures and impaired filling function. In turn, changes in LV chamber stiffness can affect the hemodynamics of early filling, diastole and the atrial systolic phase. When the mitral valve opens during diastole, the pulmonary veins, LA and LV form a common chamber and abnormal diastolic function leads to an increase in left ventricular filling pressure (LVFP) , resulting in pulmonary oedema and heart failure symptoms, which may ultimately lead to the development of HFpEF. The animal study from Yasushi Sakata et al(13) demonstrated that the transition from compensatory LV hypertrophic stage to HFpEF in the hypertensive heart was associated with the increase in the myocardial stiffness constant, but not with the changes in the time constant of LV relaxation. The clinical study also showed that the time constant of LV relaxation was not different between the HFpEF patients and the control subjects, and that the LV stiffness was higher in the HFpEF patients than in the control subjects. These studies proved the important role of LV stiffness in the development of HFpEF. Most importantly, substantial evidences suggested that LV stiffness was associated with worse prognosis in patients with HFpEF. Therefore, early detection of LV stiffness alteration and initiation of early intervetnions may improve the overall prognosis of patients with HFpEF.

The concept of LV stiffness is ambiguous in various studies. Left ventricular stiffness is not the same as myocardial stiffness, and the left ventricular stiffness assessed in many studies is in fact left ventricular chamber stiffness. LV chamber stiffness is an indicator of the relationship between diastolic volume and pressure, and in the operating room, a pressure volume catheter can be used to continuously measure the volume and pressure of the LV to derive the chamber stiffness (dP/dV). Myocardial stiffness, on the other hand, is the degree to which the myocardium undergoes strain as a result of stress, and is a passive physical property of the myocardium itself. Indicators that can influence LV chamber stiffness may include LV geometry, myocardial stiffness and other extra LV factors such as pericardial, right ventricular and interventricular synchrony, etc. At the molecular level, indicators of myocardial stiffness include myosin, microtubule and extracellular matrix composition, etc(14).

However, the application of this parameter is limited since its measurements requires a highly invasive and specialized technique of catheterization. Therefore, an easily applied, noninvasive technique is urgently needed. As a non-invasive, simple and easy-to-use tool for cardiac function evaluation, cardiac ultrasound is increasingly being used in clinical practice, and the combination of multiple indices is particularly important for a comprehensive assessment of cardiac function. Previously, indicators associated with pulsed-wave tracings of mitral inflow including E velocity of mitral inflow, the deceleration time, the velocity of the mitral A wave as well as the ratio of E/A, are frequently used to assess LV filling. However, these indices do not enable indirect measurement of LV stiffness. With advances in ultrasound technology, new advances have been achieved in the assessment of LV chamber or myocardial stiffness using noninvasive echocardiography.

Therefore, this review was carried out to summarize the pathophysiological mechanisms, correlations with invasive LV stiffness constant (Table 1), applications in different populations as well as the limitations of echocardiography-derived indices for assessment of both LV chamber and myocardial stiffness, aiming to improve our abilities in evaluating LV stiffness non-invasively.

Methods

Eligibility

Studies published in full-text form in PubMed or Web of science with [?]10 patients and using cardiac ultrasound techniques to assess LV chamber stiffness or myocardial stiffness were included. Studies published in non-English language journals, published in abstract form, assessing non-cardiac stiffness, assessed by methods other than cardiac ultrasound techniques, or with fewer than 10 subjects were excluded.

Search Strategy

All articles on echocardiography methods for evaluating LV chamber stiffness or myocardial stiffness were computer searched. The study was medically searched through PubMed, Web of science, combining the terms "cardiac echocardiography, left ventricular stiffness, left ventricular chamber stiffness, myocardial stiffness". In addition, a follow-up search of all references listed in the article was performed to find other relevant articles. Any other relevant literature was also identified by the citation tracker.

Study Selection

All abstracts were reviewed by Nanjun Zhang, Linlin Zhang, Liting Tang, Shuran Shao, Qinhui Wang, Li Zhao, Xiaoliang Liu and checked by Chuan Wang. Disagreement was resolved between the two reviewers. Full texts of eligible articles were retrieved for review. If there are studies that report ultrasound methods for assessing LV chamber stiffness or myocardial stiffness, they should be included.

Data Extraction and Collection

Ultimately, there were main 3 review, 2 systematic review and meta-analysis, 1 meta-analysis and 35 articles on evaluation of LV chamber stiffness or myocardial stiffness, including 6 studies on the ratios of echocardiographic surrogates of LV end-diastolic pressure to LV size methods, 18 on the diastolic wall strain (DWS) methods, 5 on the intrinsic velocity propagation of myocardial stretch (iVP) methods, 5 on the myocardial shear wave imaging (SWI) and 1 on the time-velocity integral (TVI) measurements of pulmonary venous and transmitral flows method. Also, data for most articles are entered into a table including echocardiographic method technique, author, year, type of study, main findings, new index statistical differences, correlation with adverse events and predictive value, receiver-operating characteristic analysis, and reproducibility (Table 2).

Quality Assessment

Kaiyu Zhou and Yimin Hua independently assessed the quality of included studies, including inclusion criteria, exclusion criteria, collected data, etc.

Echocardiographic evaluation of LV chamber stiffness and myocardial stiffness.

Ratios of echocardiographic surrogates of LVFP to LV size

The left ventricle, left atrium and pulmonary veins are a common conduit and abnormal diastolic function can all lead to an increase in LV end-diastolic pressure (LVEDP), mean left atrial pressure (MLAP) and pulmonary capillary wedge pressure (PCWP). All these pressures are commonly referred to as LVFP(15). However, there are important pathophysiological differences between these pressures, and different pressure profiles can be drawn by invasive catheter manometry. Invasive monitoring shows three discontinuous pressure changes in LV diastole (Figure 1): the lowest or minimum pressure in early diastole, the second before the ventricular A wave, and the third at the end of diastole. LAP also changes during diastole. LVFP decreases during isovolumic diastole until it falls below LAP, prompting mitral valve opening and subsequent blood flow from the atria to the ventricle. When the two chambers reach pressure equilibrium, blood flow is minimal and LAP matches LVFP until the atria contract, producing a further pressure difference, and blood flows through the mitral valve again until pressure equilibrium is reached and the valve closes. LAP is equal to LVFP until atrial contraction and the generation of an A wave, but is lower than LVEDP after atrial contraction is complete.

The assessment of LVFP is an important component for the evaluation of LV diastolic function and chamber stiffness. Although the use of the Swan-Ganz catheter is the gold standard, several studies in recent years have found that non-invasive cardiac ultrasound measurements of filling pressures do not differ significantly from the gold standard (16, 17). Substantial evidences have proved that the ratio of early diastolic transmitral flow velocity to early diastolic myocardial velocity using tissue Doppler tracing (E/e') correlates well with LVFP (18-24). Meta-analysis study by Rachel Jones et al. demonstrated a moderate correlation between E/e' and invasive LVEDP (r=0.55, 95% CI 0.46-0.62, P=0.01) (25).In addition, with the addition of indices

from speckle tracking technology (STE), a number of new integration metrics have been created. The pooled meta-analysis by Lassen MCH et al. showed a significant correlation between E/early diastolic strain rate (SRe) and LVEDP measured invasively (Cohen's d=5.30 95% CI [2.83–9.96], p<0.001)(26).

According to the definition of LV chamber stiffness, researchers hypothesized that LV chamber stiffness may be indirectly evaluated by applying the ratios of echocardiographyic surrogates of LVFP to LV size (Figure 2A). In line with the hypothesis, Chowdhury SM et al.(27) found in a population of pediatric heart transplant recipients (n=18) that lateral E/e'/LVEDV (r=0.59, P<0.01), septal E/e'/LVEDV(r =0.57, P<0 .01), and (E/circumferential SRe)/LVEDV (r=0.54, P<0.01) significantly correlated with the chamber stiffness constant β, and lateral E/e'/LVEDV displayed a C statistic of 0.93 in detecting patients with abnormal LV stiffness($\beta > 0.015 mL^{-1}$). Furthermore, A lateral E/e'/LVEDV of >0.15 mL^{-1} had 89% sensitivity and 93% specificity in detecting an abnormal β. Thereafter, the DPVQ, whose principle is similar to E/e'/LVEDV, is also a non-invasive parameter obtained by three-dimensional echocardiography (3DE) and Doppler tissue imaging (DTI). The LV volume was measured by 3DE and E/e' was measured by DTI, after which DPVQ was obtained. Kasner et al.(28) applied this index to the HFpEF population and compared it with LV chamber stiffness calculated by invasive cardiac catheterization. Significant differences for DPVQ were found between 23 HFpEF patients and normal controls [0.14(0.12–0.17) vs. 0.07(0.06–0.0.09), P<0.001) and there was a significant correlation between DPVQ and LV chamber stiffness (r = 0.91, P < 0.001).

Although the ratios of echocardiographic surrogates of LVFP to LV size are currently used to evaluate LV chamber stiffness, it still remains an issue of concern that all above mentioned methods(E/e'/LVEDV, E/SRe/LVEDV and DPVQ) are surrogate and lumped measurements, relying on E/e' or E/SRe for evaluating LVFP. However, there are several limitations and controversies for the validities of E/e' in the assessment of LVFP. Firstly, in terms of measurement, both E and e' are strictly limited by the location of the sample and e' is also dependent on the angle of measurement (<20°). Secondly, the ratio is susceptible to a number of factors such as hemodynamics, myocardial synchronization, and ventricular wall segmental motion(29). Park JH et al. also suggested in their review that the use of E/e' may be unreliable in situations such as tachycardia with fusion of E and A velocities, significant mitral regurgitation (>2+), mitral valve repair or replacement, severe mitral annular calcification, significant mitral stenosis and presence of left bundle branch block(30). Most importantly, in terms of diagnostic accuracy, a systematic review and meta-analytic analysis from Sharifov OF et al. pointed out that there was insufficient evidence to support that E/e' could reliably estimate LVFP in patients with preserved LVEF(31). The summary sensitivities and specificities for lateral E/e', mean E/e', and septal E/e' in detecting elevated LVFP were 30% and 92%, 37% and 91%, and 24% and 98%, respectively. Additionally, we reviewed 37 literatures on the correlation between E/e' and each LVFP (LVEDP, M-LVDP, Pre-A LVP, LAP and PCWP) (supplemental material 1). In agreement with previous studies, it was found that in patients with HFrEF and HFpER, the correlation between E/e' and each pressure varied considerably: LVEDP (0.03-0.84 vs 0.11-0.80), M-LVDP (0.40-0.52 vs. 0.49-0.60), Pre-A LVP (0.02-0.63 vs. 0.19-0.76), LAP (0.46-0.52) and PCWP (0.19-0.91 vs. 0.083-0.78)(25, 31, 32). All these disadvantages may limit these indices in clinical use. Other parameters which could reliably and accurately assess LVFP warrant further uncovered.

Encouragingly, the ratio of early filling rate derived from the time derivative of LV volume to SRe (FRe/SRe) (33) has the potential to be a surrogate marker of LVFP. It was reported that in nondilated hearts, FRe/circumferential-SRe and FRe/ area-SRe may be more useful to accurately assess LVFP than E/e'. In addition, LA longitudinal strain derived from STE is also sensitive in estimating intracavitary pressures. It is angle-independent, thus overcomes Doppler limitations and provides highly reproducible measures. Cameli M et al. found that the E/e' correlated poorly with invasive LVFP in a group of patients with advanced systolic heart failure (r=0.15). However, the LA longitudinal deformation (PALS) correlated well with PCWP (r=-0.81, p<0.0001), and a cut-off value of less than 15.1% had a high sensitivity and specificity of 100% and 93% in predicting elevated LVFP(34). Similarly, Cameli M et al. noted in their study that both the PALS and mean E/e' correlated well with LVEDP in patients with preserved (r=-0.79 vs. r=0.72) or mildly reduced LVEF (r=-0.75 vs. r =0.73). However, compared to mean E/e', PALS displayed a better performance in assessment of LVEDP in patients with moderately (r=-0.78 vs. r=0.47) or severely (r =-0.74

vs. r=0.19) reduced LVEF(35). More invasive studies are yet to be performed to further explore and confirm the relationship between the ratio of FRe/SRe or PALS to LV size and LV chamber stiffness.

The time-velocity integral (TVI) measurements of pulmonary venous and transmitral flows

As LV chamber stiffness increases, antegrade trans-micuspid blood flow and pulmonary venous return are affected during atrial contraction because of the increase in chamber pressure. The original invasive study by Rossvoll O, et al. found that pulmonary venous flow reversal beyond the duration of the mitral A wave indicated an exaggerated increase in late left ventricular diastolic pressure. A pulmonary venous systolic fraction <0.4 indicated a significant increase in ventricular filling pressures(36). Based on this, Kazunori Okada et al. (37)proposed to indirectly reflect LV chamber stiffness by velocity-time integral measurements of pulmonary venous and transmicuspid blood flow. The TVI measurements of pulmonary venous and transmitral flows refer to the measurements of the TVI of the backward pulmonary venous (PV) flow during atrial contraction (I_{PVA}) and the ratio of I_{PVA} to the PV flow TVI throughout a cardiac cycle (F_{PVA}) by echocardiography. In addition, the TVI of the atrial systolic forward transmitral flow (I_A) and the ratio of the I_A to the transmitral TVI during a cardiac cycle (F_A) also need to be measured (Figure 2D). Kazunori Okada et al. reported the F_{PVA}/F_A and I_{PVA}/ I_A are well correlated with the LV chamber stiffness (r = 0.79 and r = 0.81) and LV end-diastolic pressure (r = 0.73 and r = 0.77) in 62 patients who underwent cardiac catheterization. The areas under the ROC curve to discriminate LVEDP >18mmHg were 0.90 for I_{PVA}/ I_A (Optimal cut-off value 0.51, Sensitivity 83%, Specificity 80%, P <0.001)and 0.93 for F_{PVA}/F_A(Optimal cut-off value 0.47, Sensitivity 83%, Specificity 82%, P <0.001).

Unfortunately, only one study has been conducted in the literature on the exploration and application of TVI, and its accuracy in assessing LV chamber stiffness remains to be confirmed. In the meanwhile, these indicators are not applicable to patients with dyssynchrony of atrial activity caused by synchronized atrial activity due to arrhythmias such as atrial fibrillation, atrial flutter and complete atrioventricular block, and left ventricular catheterization and echocardiography cannot be performed at the same time. In addition, although there was a good correlation between I_{PVA}/I_A and chamber stiffness, I_{PVA}/I_A was angle dependent. More in-depth studies in different populations with larger samples are further needed.

The Epicardial movement index (EMI) and Diastolic wall strain (DWS)

Researchers hypothesized that the evaluation of epicardial movement during diastole is helpful for the noninvasive assessment of LV wall distensibility following the linear elastic theory(38). Based on the laws of physics, when applying an active external force on the surface of an object, the difference between the movement of the surface and the outside should be equal to the change in the deformation of the object. In soft tissue, the effect of surface movement on the outside is small when the ventricular wall is thinning, and in hard tissue, the opposite result occurs because of less change in the wall thickness. It is assumed that the deformation of the ventricular wall under pressure also follows this principle, which is obtained with the following indices: epicardial movement index (EMI) = (endocardial movement during diastole - epicardial movement during diastole)/(wall thickness at the beginning of diastole × epicardial movement during diastole). Because the movement of the epicardium during diastole is small, to better fit the clinical application, the researchers simplified EMI to obtain the diastolic wall strain (DWS): DWS = (LV posterior wall thickness at end-systole - LV posterior wall thickness at end-diastole) / (LV posterior wall thickness at end-systole) (Figure 2B). In animal model studies, Yasushi Sakata's team(38) not only proved that DWS can replace EMI, but also that there is an inverse correlation between EMI or DWS and the LV myocardial stiffness constant (r = -0.40, r = -0.47, P<0.05, respectively). Preload alteration did not affect EMI or DWS (before 0.48 ± 0.04 vs. after 0.55 ± 0.03 [1/mm], P = 0.18) or DWS (before 0.45 ± 0.02 vs. after 0.48 ± 0.02, P=0.39).

Thereafter, amounts of studies investigated the alterations of DWS in different populations. Both Sakata et al.(38) (0.26 ± 0.02 vs. 0.35 ± 0.02, P<0.05) and Ohtani et al. (39) (0.33 ± 0.08 vs. 0.40 ± 0.07, P<0.001) found DWS was significantly lower in patients with HFpEF compared to healthy controls. Similar findings were also found in patients with paroxysmal atrial fibrillation and structurally normal hearts (40) (0.35 ± 0.07 vs. 0.41 ± 0.06, P<0.001), in adult survivors of childhood leukemias with HFpEF(41) (0.28 ±0.07 vs

0.33 ± 0.07, P<0.001), in patients with repaired tetralogy of fallot (42) (0.38 ±0.10 vs 0.47 ±0.08, P<0.001), in adolescents and young adults after arterial switch operation for transposition of the great arteries(43) (0.30 ±0.09 vs 0.41 ±0.08, P<0.001) as well as in pediatric patients with end stage kidney disease (44) (dialysed group vs transplanted group vs healthy controls: 0.37 ±0.07 vs 0.35 ± 0.05 vs 0.47 ± 0.08, P<0.001).

The decrease in DWS in multiple disease populations is another reminder that LV myocardial stiffness is quietly changing in these patient groups, and may be a precursor to certain adverse events. In a study of patients with paroxysmal atrial fibrillation and structurally normal hearts, Uetake S et al. (40) found that a low DWS (< 0.38) was the strongest indicator of AF prevalence (OR: 1.22, 95% CI: 1.14-1.31 per 0.01 decrease, P<0.001). In 2017, Choij et al.(45) found that patients with stable angina who underwent revascularization had a significantly lower DWS than those who did not (0.26 ±0.08 vs 0.38 ± 0.09, P<0.001) and decreased DWS was associated with coronary revascularization (OR: 0.920, 95% CI 0.862–0.981, P=0.011). Immediately thereafter, Amano M et al.(46) found that DWS was an independent predictor of prognosis in the diagnosis of patients with AL amyloidosis with cardiac involvement during follow-up of patients, and DWS was significantly lower in patients with poor prognosis (all-cause death and cardiac death: HR 0.93 [95% CI 0.88- 0.99], P<.02). The same predictive value of DWS was shown by Obasare E et al.(47) in a retrospective study of patients with severe aortic stenosis, where DWS could predict mortality independently of conventional clinical and echocardiographic parameters (HR 2.5 [95% CI 1.02- 5.90], P<.05). In 2020, Kishima H et al.(48) a retrospective study of patients with PMI study showed that DWS was independently associated with AHREs (HR 0.223, 95% CI 0.137–0.357, P<0.0001), and patients with reduced DWS (<0.33) had a higher risk of incidences of AHREs.

For the patients with preserved ejection fraction, Ohtani et al. (39) in 2012 found that HFpEF patients with DWS [?] 0.33 had a higher rate of death or HF hospitalization than those with DWS > 0.33, even after adjustment for age, sex, log B-type natriuretic peptide, LV geometry and log E/e'. Similarly, Kamimura D et al.(49) in 2017 found DWS to be significantly associated with HF symptoms in patients with AS with preserved ejection fraction (OR: 0.91, CI:0.86-0.96, P<0.005). Immediately thereafter, in 2018,Kamimura D et al.(50) found both continuous and categorical DWS were independently associated with incident HF after adjustment for traditional risk factors and incident coronary artery disease (HR 1.21, 95%CI 1.04–1.41 for 0.1 decrease in continuous DWS, P= 0.014; HR 1.40, 95%CI 1.05–1.87 for the smallest DWS quintile vs other combined quintiles, P = 0.022), and in 2019 a study by Tsujimoto S, et al.(51) showed low DWS ([?] 0.33) was a significant independent predictor of cardiovascular events after adjusting for cardiovascular comorbidities in a multivariable model (HR: 1.87, 95% CI 1.04–3.36, P=0.04). In addition, DWS has also a predictive value even in patients with reduced ejection fraction. In 2017, Soyama Y.et al. (52)found that the incidence rate (HF hospitalization or cardiovascular death) was higher in low DWS than high DWS HFrEF patients who were administrated chronic beta (Log-rank, p = 0.049), and showed DWS was the independent contributor to the event-free time(HR 2.66 [95% CI 1.10- 6.85], P=0.032).

Taken together, these findings suggested that DWS, a simple parameter, might be useful in assessing LV myocardial stiffness and predicting worse outcomes in various populations. However, the relationship between DWS and LV myocardial stiffness constant which is the gold standard to evaluate LV myocardial stiffness, was proved only in a basic experimental study and a correlation of only 0.4 does not "prove" that the LV myocardial stiffness could be accurately reflected by DWS. In addition, despite the animal study from Takeda et al proved that there was a lack of correlation between DWS and LV systolic function, wall thickness at the beginning of diastole, LV chamber size, indices derived from the transmitral flow velocity curves as well as preload alteration, recent clinical studies(43, 46, 47, 50, 53) found that DWS may not be a pure measure of diastolic function since it also correlates with systolic function. Therefore, DWS may be considered as an overall marker of cardiac performance, including systolic and diastolic mechanics. Furthermore, DWS is an abbreviated term from the original equation that sought to quantify LV stiffness, the epicardial motion index (DWS)/(epicardial movement during diastole). Though the epicardial motion index is a more exact marker of LV diastolic stiffness, this formula requires direct measurement of epicardial movement, which is difficult to achieve with 2D echocardiography. The epicardial motion index may better reflect LV diastolic stiffness compared to DWS, but its difficult implementation in routine clinical practice would reduce its

clinical utility. Another important point is that regional assessment of LV stiffness at the posterior wall may not reflect global LV myocardial stiffness. Therefore, the role of DWS in the evaluation of LV myocardial stiffness awaits further study.

Intrinsic velocity propagation of myocardial stretch (iVP)

Left ventricular inflow through the mitral valve during systole and diastole has been well described and evaluated by cardiac ultrasound after a very comprehensive functional study, but in addition to inflow, we can also perform corresponding functional studies from the point of view of myocardial motion. Apart from the functional evaluation of the velocity of annular and ventricular wall motion using tissue Doppler techniques, the perspective of the intrinsic wave transmission of the myocardium has become a new research hotspot. These waves may have a mechanism similar to pulse wave propagation in arteries. An earlier study described a sequential onset of circumferential lengthening in different parts of the LV, which is suggestive of a wave propagating from LV base to apex.(54) Based on this, a hypothesis has been proposed that the ventricular filling that begins after atrial contraction stretches the base of the left ventricle, producing a wave that propagates apically with a velocity proportional to the elasticity of the myocardial wall (Figure 2C). In 2014, Pislaru C, et al.(55) found in basic animal experiments that the main factors determining myocardial longitudinal stretch wave propagation were LV myocardial stiffness and left ventricular geometry and pressure (r^2 model=0.83, p<0.0001), and the stiffer the myocardium, the faster the intrinsic propagation of the myocardium(Vp was higher at reperfusion compared to baseline: 2.6 +- 1.3 vs. 1.3 +- 0.4 m/s, p = 0.005). Thereafter, several studies investigated the alterations of iVP in different populations. Strachinaru M et al. (56)and Zhang J et al.(57) found that iVP was significantly higher in patients with hypertrophic cardiomyopathy (1.8+-0.3m/s vs.1.6+-0.3m/s, P=0.14) and hypertension (1.53+-0.39 m/s vs 1.40+-0.19 m/s, p=0.031) compared to normal healthy controls. Similar findings were also found in patients with aortic Stenosis and mitral regurgitation(58) (AS 2.2+-0.7 m/sec vs MR 1.6+-0.5 m/sec vs control subjects 1.4+-0.2 m/sec, P<0.0001). These studies, side-by-side, hint at changes in LV myocardial stiffness and may be a predictor of poor prognosis. Pislaru C,et al. (58) showed a lower survival free of major adverse cardiac events in patients with high iVP in their study of patients with aortic stenosis and mitral regurgitation (P = 0.002). It is worth noting that iVP also increased in patients with normal left ventricular systolic function (LVEF and GLS), suggesting that increased LV myocardial stiffness may precede systolic dysfunction. This provides a direction for early identification of HFpEF. Measuring the changes of myocardial elasticity is helpful to evaluate the changes of cardiac structure and function caused by the changes of LV myocardial stiffness. However, the iVP still has its limitations: first, there is no gold standard (cardiac catheterization) validation both in animal and clinical studies. Secondly, the heart is not a circular tube and its motion is torsional, which contradicts the original intention of the Moens-Korteweg theory, which postulates that the structure is a cylindrical tube, wall is homogenous and thin compared to radius, thickness is constant, and there are no reflections.Third, because of the extremely high frame rate required, this parameter may not be suitable in patients with enlarged chambers.

Myocardial shear wave imaging(SWI)

SWI is a technique based on ultrasonic mechanical effect, which can be used to evaluate the hardness of soft tissue noninvasively and quantitatively. In the past ten years, it has been used in breast, liver and other diseases, and has certain clinical value. SWI uses the propagation characteristics of shear waves and the speed of wave transmission to estimate the stiffness of the tissue. Shear waves can be induced naturally in the heart when the atrioventricular or ventricular artery valves are closed, but they can also be induced mechanically using an external source. In fact, SWI has been shown to be significantly positively correlated with age, end-diastolic wall thickness, loading status (left atrial size, LVEDP), and MRI cardiac-related fibrosis indicators in healthy volunteers and in some patients with disease(59-63). However, the accuracy of the technique is greatly challenged by the operator's technique, the particular geometry, viscosity, anisotropy, contraction and diastole of the heart, haemodynamics and pathology that will affect the shear wave generation and wave speed.(64) In addition to this, due to the limitations of ultrasound views and sites, the shear waves assessed only reflect local myocardial stiffness and do not reflect the overall level of myocardial stiffness.

With this in mind, there is an urgent need for consistent data collection and reporting as the number of clinical studies of cardiac SWI continues to increase. In a recent review, Caenen A, et al.(64) made some constructive suggestions to improve the accuracy of SWI and to facilitate the comparison of SWE results between studies.

Perspectives and Conclusions

Half of patients with the clinical syndrome of heart failure are presented with preserved ejection fraction. The pathophysiology of HFpEF is complex but increased LV stiffness is proved to play a key role. Additive information about LV stiffness may be helpful in the early diagnosis and management of patients with HFpEF. Determination of LV stiffness has previously relied on invasive cardiac catheterization. The echocardiographic imaging has increasingly been applied recently for non-invasive evaluation of LV chamber and myocardial stiffness. LV chamber stiffness indices such as E/e'/LVEDV, E/SRe/LVEDV, and DPVQ were derived on the basis of the relationship between echocardiographic parameters of LVFP and LV size. However, all these methods are surrogate and lumped measurements, relying on E/e' or E/SRe for evaluating LVFP. The limitations of E/e' or E/SRe in assessment of LVFP may contribute to the moderate correlation between E/e'/LVEDV or E/SRe/LVEDV and LV stiffness constant. Even the best validated measurement (DPVQ) is considered unreliable in the individual patient by Kass and Burkhoff themselves. Compared to E/e'/LVEDV and E/SRe/LVEDV, $I_{PVA/IA}$ and $F_{PVA/FA}$ may display better performance in assessing LV chamber stiffness as evidenced by a higher correlation with LV stiffness constant. However, only one study has been conducted in the literature on the exploration and application of $I_{PVA/IA}$ and $F_{PVA/FA}$, and its accuracy in assessing LV chamber stiffness remains to be confirmed. In terms of echocardiographic indices for LV myocardial stiffness evaluation, the parameters of EMI/DWS, iVP and SWI were proposed. Despite alteration of DWS and its predictive value of adverse outcomes in various populations have been widely validated, it was found that DWS may be better considered as an overall marker of cardiac function performance instead of pure myocardial stiffness. As for the iVP and SWI, the validities of these two indices in assessing LV myocardial stiffness have not been confirmed in invasive studies.

Taken together, it seems that no echocardiography-derived indices could be currently used to reliably and accurately assess LV stiffness despite several parameters were developed. Therefore, the comprehensive evaluation of LV stiffness using all these available parameters may be more accurate and earlier to detect the alterations of LV stiffness. Despite there is a long way to go, indices from STE such as FRe/SRe and PALS have been proved to show good correlations with LVFP and have the potential to become promising indexes for LV stiffness assessment. More echocardiographic indices with higher sensitivities and specificities warrant to be further uncovered to evaluate LV stiffness. Additionally, further cross-sectional and longitudinal studies with large sample size and prospective design of nature are also required to confirm their utilities in different populations and their prognostic values.

Competing interests

All authors have no conflict of interests or any grants to declare.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Competing interests

All authors have no conflict of interests or any grants to declare.

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Authors' contributions

Nanjun Zhang drafted the manuscript, and approved the final manuscript as submitted. Linling Zhang, Liting Tang and Li Zhao contributed to the literature collection, provided supplemental material 1 and Table 1 and 2, and approved the final manuscript as submitted. Shuran Shao, Xiaoliang Liu, and Qinhui Wang contributed to the study design and approved the final manuscript as submitted. Yimin Hua and Kaiyu Zhou provided Figure 1 and 2, funding support, and as well as approved the final manuscript as submitted. All abstracts were reviewed by Nanjun Zhang and checked by Chuan Wang, and Chuan Wang also provided financial support and as well as approved the final manuscript as submitted.

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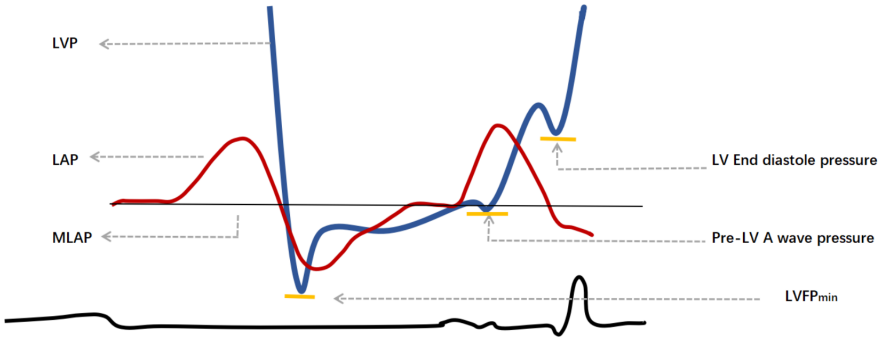
Figure legends

Figure 1: Invasive monitoring shows three discontinuous pressure changes in LV diastole: the lowest or minimum pressure in early diastole, the second before the ventricular A wave, and the third at the end of diastole. LAP also changes during diastole. LVP=Left ventricular pressure, LAP=left atrial pressure, MLAP=mean left atrial pressure, LVFPmin=minimum left ventricular filling pressure, Pre-LV A wave pressure=pressure of ventricular A wave.

Figure 2: A. The LV stiffness constant, defined as the slope of pressure-volume relationship. B. Diastolic wall strain (DWS) = (LV posterior wall thickness at end-systole - LV posterior wall thickness at end-diastole) /(LV posterior wall thickness at end-systole). C. Intrinsic velocity propagation of myocardial stretch (iVP). D. The time-velocity integral (TVI) measurements of pulmonary venous and transmitral flows. The figure shows the correlation between Echocardiography-derived indices and the invasive LV stiffness constant.



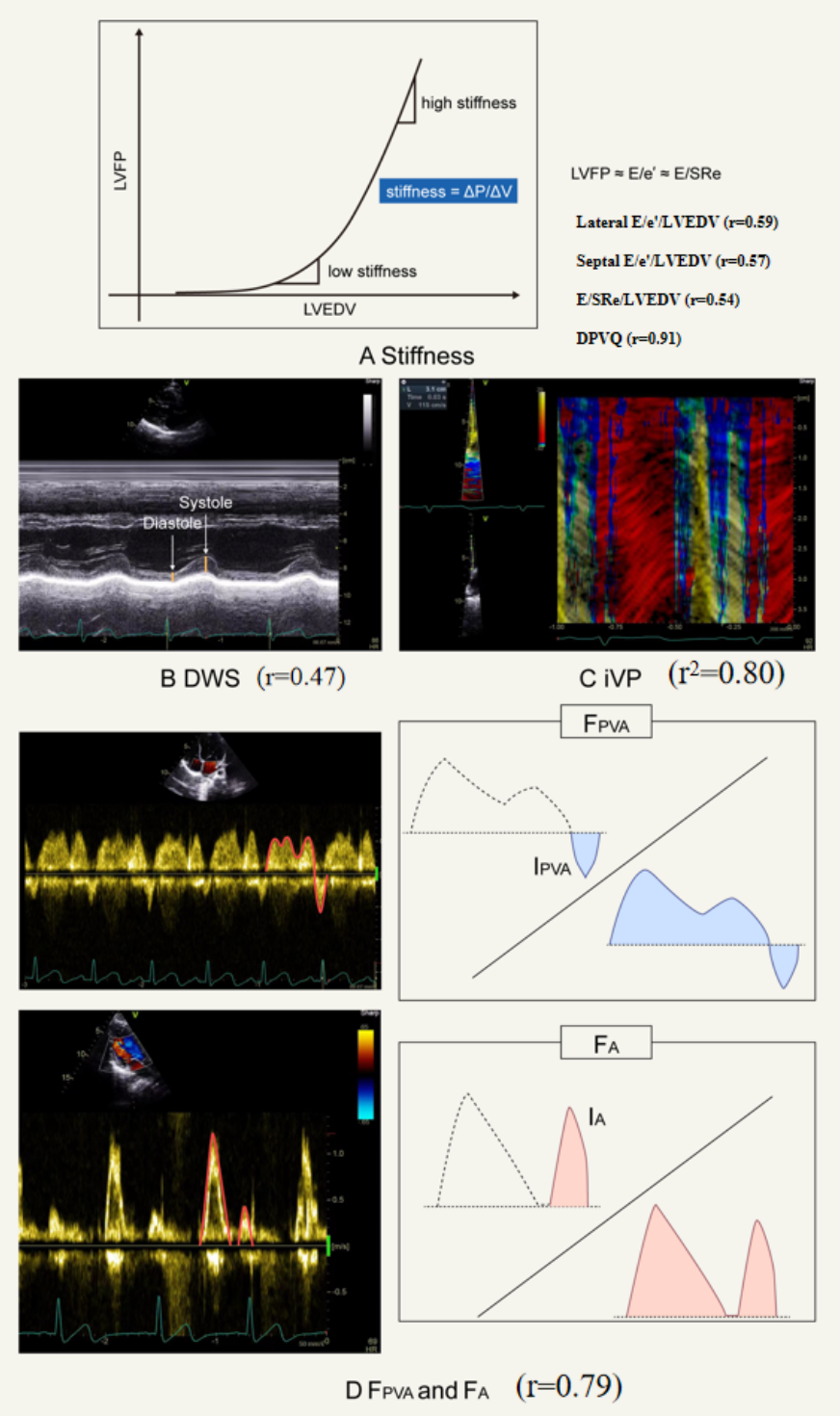


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Table 2.docx available at https://authorea.com/users/369303/articles/635049-evaluation-of-left-ventricular-stiffness-with-echocardiography