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Prediction of elevated left ventricular filling pressures in patients with preserved ejection fraction using longitudinal deformation indices of the left ventricle†

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Aims Estimation of left ventricular (LV) filling pressures is a clinical challenge in patients with preserved ejection fraction (EF). In the present study, we investigated whether LV and atrial longitudinal strain and strain rate (SR) parameters derived by speckle tracking echocardiography (STE) could be used to predict invasively measured LV end-diastolic pressure (LVEDP) in this patient population.

Methods and results LVEDP was measured before coronary angiography was performed in 65 patients with preserved EF (≥50%) referred to elective cardiac catheterization; besides, patients enrolled underwent comprehensive echocardiographic examination before the procedure. In addition to conventional echocardiographic parameters used to evaluate diastolic function LV longitudinal strain and SR, as well as peak atrial longitudinal strain during LV systole, measurements were performed using STE. Only log-diastolic blood pressure, systolic SR, early diastolic SR, SR during isovolumetric relaxation (SRIVR), and mitral early diastolic flow velocity/SRIVR significantly correlated with LVEDP. When age-adjusted stepwise linear regression analysis was performed, SRIVRT values ($\beta = -20.682$, $t = -3.292$; $P = 0.002$) and log-diastolic blood pressure levels ($\beta = 21.118$, $t = 3.784$; $P < 0.001$) were independently correlated with LVEDP.

Conclusion When compared with conventional echocardiographic parameters, other longitudinal strain, and SR indices, SRIVRT independently predicted LVEDP in conjunction with log diastolic blood pressure. We suggest that SRIVRT is a valuable parameter to evaluate diastolic function in patients with preserved EF.

Keywords Speckle tracking echocardiography • Diastolic dysfunction • Left ventricular end-diastolic pressure • Left ventricular longitudinal strain

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a prevalent and growing public health problem associated with significant morbidity and mortality. HFpEF currently accounts for ≥50% of the general heart failure population.[1] Impairment in left ventricular (LV) diastolic function has been proposed as a key pathophysiologic mediator.[2,3] To be able to diagnose diastolic dysfunction, non-invasive estimation of LV filling pressures is a clinical requisite.[4] The estimation of LV filling pressures in patients with normal ejection fraction (EF) is more challenging than in those with depressed EF. LV filling index *E*/*E*′ with its wide borderline values has also some limitations in the diagnosis of diastolic function particularly when left atrial (LA) pressure is low.[5–8] This involves clinical circumstances like young patients with borderline symptoms and risk factors for diastolic dysfunction.

Recently, several investigations have highlighted the key role of the longitudinal diastolic function of the LV in the pathophysiology of HFpEF, also suggesting that in patients with diastolic dysfunction

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the myocardial systolic function of the LV is not preserved.[9–11] Myocardial strain and strain rate (SR) were recently introduced as echocardiographic parameters for quantification of diastolic function. LV diastolic SR signals can be recorded during early filling (SRE), late diastole (SRA), and isovolumetric relaxation (SRIVR). The ratio of early mitral flow (*E*) to SRIVR predicted LV filling pressure in patients in whom the *E*/e′ ratio was inconclusive and was more accurate than the *E*/e′ ratio in patients with normal EF and those with regional dysfunction.[12] Additionally, peak LA longitudinal strain (PALS, peak atrial longitudinal strain) during LV systole was also presented as a new index of diastolic function.[13]

The evaluation of diastolic function by deformation imaging is promising, but needs more study of its incremental clinical value. Therefore, longitudinal deformational parameters of LV and LA, detected by speckle tracking echocardiography (STE), and conventional echocardiographic indicators of diastolic dysfunction were compared in our study to predict invasively measured LVEDP in a patient population with preserved EF (>50%).

Methods

Our patient population consisted of 65 patients with preserved EF who underwent elective cardiac catheterization for the diagnosis of coronary artery disease or re-evaluation after coronary intervention. Patients were excluded if they had non-sinus rhythm, more than mild aortic and mitral regurgitation or stenosis, LV systolic dysfunction (EF <50%), acute coronary syndrome, renal failure, or prosthetic mitral valve. One hundred and two consecutive patients referred to catheterization from outpatient clinic were evaluated and 65 of them were included. These patients underwent comprehensive echocardiographic examination ≤15 min before cardiac catheterization and measurement of LVEDP was also performed in addition to conventional coronary angiography. The study was approved by the institutional ethical committee of Kartal Kosuyolu Heart Training and Research Hospital; oral and written informed consent was obtained from all study participants.

Risk factors

Arterial hypertension was defined as blood pressure of >140/90 mmHg or in patients receiving anti-hypertensive therapy. Diabetes mellitus was defined as a fasting blood glucose level of >126 or >200 mg/dL 2 h after an oral glucose tolerance test or in patients receiving permanent medical anti-diabetic therapy. Hyperlipidaemia was defined as blood total cholesterol levels of >180 mg/dL or low-density lipoprotein of >130 mg/dL or when patients were receiving permanent treatment with lipid-lowering agents. Coronary artery disease was defined as a history of myocardial infarction, coronary artery disease bypass grafting, percutaneous coronary intervention, or an angiographic evidence of a significant coronary artery stenosis (≥50%).

Conventional echocardiographic examination

All echocardiographic examinations were performed before the patient was admitted to cardiac catheterization laboratory, using a commercially available system (iE 33, Philips, Bothel, USA) equipped with an S5-1 probe and recorded for offline analysis (Xcelera Workstation and QLAB; Advanced Quantification Software V.8.1, Philips). Individuals were instructed to hold their breath, and images were coupled with electrocardiographic recordings. Measurements were done offline later by a single investigator who was blinded to the clinical and catheterization data.

M-mode measurements were performed according to the criteria of the European Association of Cardiovascular Imaging. Three consecutive cycles were averaged for every parameter. LA dimension and LV end-systolic (LVESD) and end-diastolic diameters were measured. LV ejection fraction was estimated by biplane Simpson's rule. Maximum LA volume was calculated at end-systole of the left ventricle using the biplane Simpson's method and indexed to BSA.[14] Early (*E*) and late (*A*) wave velocities, *E*/*A* ratio, and *E* deceleration time (DT) were measured from the mitral inflow profile. Isovolumetric relaxation time (IVRT) was also measured using pulsed-wave Doppler using previously validated and recommended methods.[7] To acquire tissue Doppler imaging data, the Nyquist limit was set at 15–20 cm/s, and minimal optimal gain was used. The myocardial systolic (*S*′), early diastolic (*E*′), and late diastolic (*A*′) velocities were obtained at the septal and lateral mitral annulus by placing a sample volume. The *E*/*E*′ ratio was subsequently calculated for septal and lateral measurements; besides, it was also averaged. Mitral regurgitation severity was semiquantified from none to severe based on integrated assessment. LV diastolic dysfunction was classified according to previously defined standard criteria as normal (DT = 160–240 ms, *E*/*A* ratio = 0.9–1.5, *E*′ ≥ 10 cm/s), impaired relaxation; grade I (DT > 240 ms, *E*/*A* ratio < 0.9, *E*′ < 10 cm/s), pseudonormalized pattern; grade II (DT = 160–240 ms, *E*/*A* ratio = 0.9–1.5, *E*′ < 8 cm/s) and restrictive pattern; grade III (DT < 160 ms, *E*/*A* ratio > 2.0, *E*′ < 5 cm/s).[7]

Speckle tracking imaging

For speckle tracking analysis, three cycles were recorded at a frame rate of ≥45 fps, and were averaged for strain analysis. Aortic valve opening and closing times were measured from the LV outflow Doppler profile and were incorporated in the speckle tracking strain profile in order to exclude post-systolic components. From three manually selected landmark points (lateral and septal mitral annulus and LV apex) in apical views, LV endocardial borders were automatically detected by the software. Subsequently, automatic tracking of myocardial speckles was performed throughout the whole cardiac cycle. Manual corrections of the border tracings were avoided as far as possible. Global longitudinal strain (GLS) and SR curves were obtained for apical four-chamber, three-chamber, and two-chamber views; subsequently, the software (Q LAB V8.1 application for two-dimensional strain analysis) provided LV model consisting of all segments. Systolic GLS was obtained by averaging peak longitudinal strain of 17 segments (*Figure 1*). Similarly, peak global SR during systole (SRS), SRE, SRA, and during SRIVR were determined (*Figure 2*). *E*/SRIVR was also calculated.

Two-dimensional echocardiographic images for the LA were obtained from the apical four-chamber and two-chamber views. From three manually selected landmark points (lateral and septal mitral annulus and LA apex), endocardial borders were automatically detected by the software. Myocardial speckles were tracked automatically throughout the cardiac cycle and typical LA strain curves were obtained for each patient. A peak LA strain value during LV systole was measured in apical four and two-chamber images. Then measurements from these two views were averaged to obtain the peak atrial longitudinal strain (PALS) value for the index patient.

Cardiac catheterization

Cardiac catheterization was performed after the echocardiographic image acquisition was completed. During catheterization, heart rate and blood pressure were continuously monitored. In all patients, a fluid-filled 6-F pigtail catheter was inserted percutaneously from the right femoral artery and advanced to the LV. Before the contrast agent was injected into the coronary arteries, the LV pressure was obtained. After 10

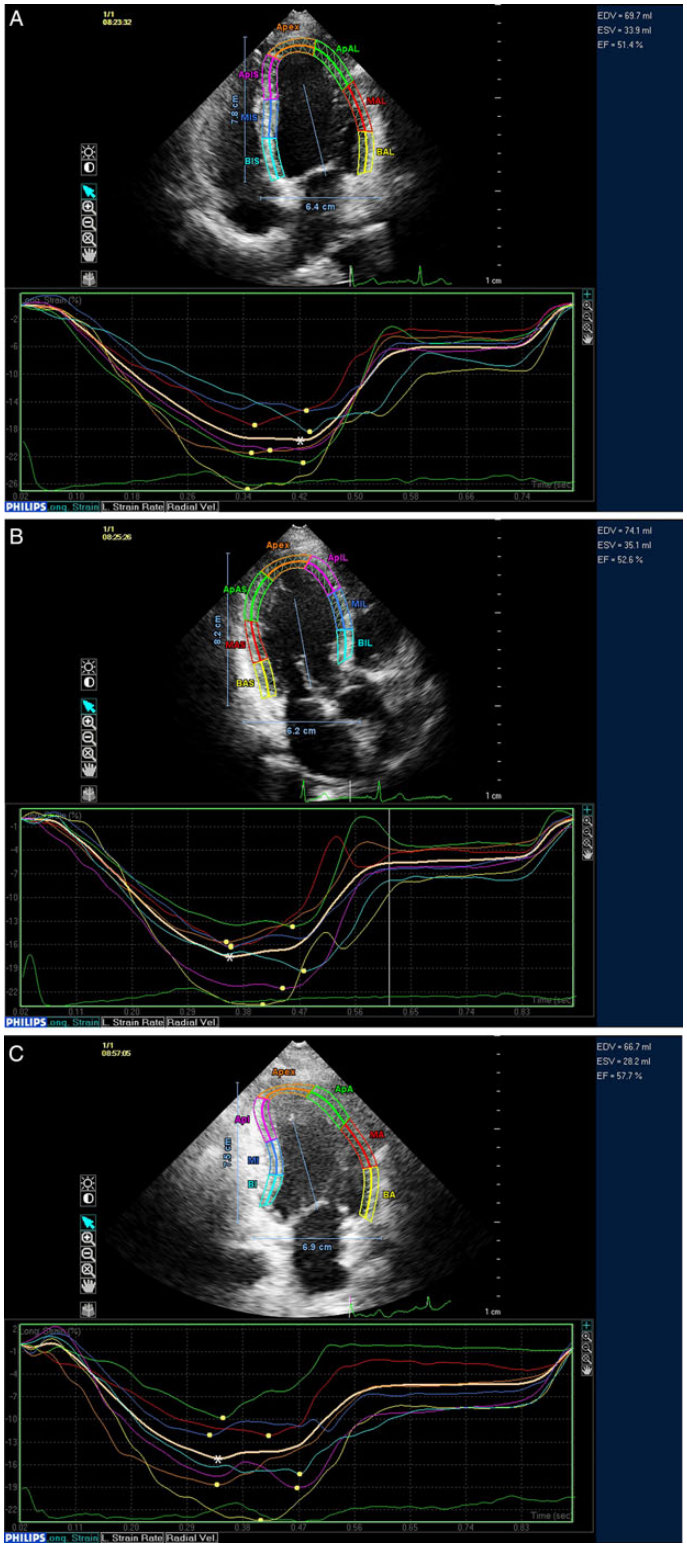

Figure 1 GLS measurement. The asterisk in (*A*) shows the average of peak strain values obtained from apical four-chamber view segments. Likewise, (*B* and *C*) show the average values obtained from each segment in three-chamber and two-chamber views, respectively. The GLS was obtained by averaging the values obtained from each view in a 17-segment model representation of the left ventricle provided by the software. The yellow dots represent peak systolic longitudinal strain of individual segments analysed in the 17-segment left ventricle model.

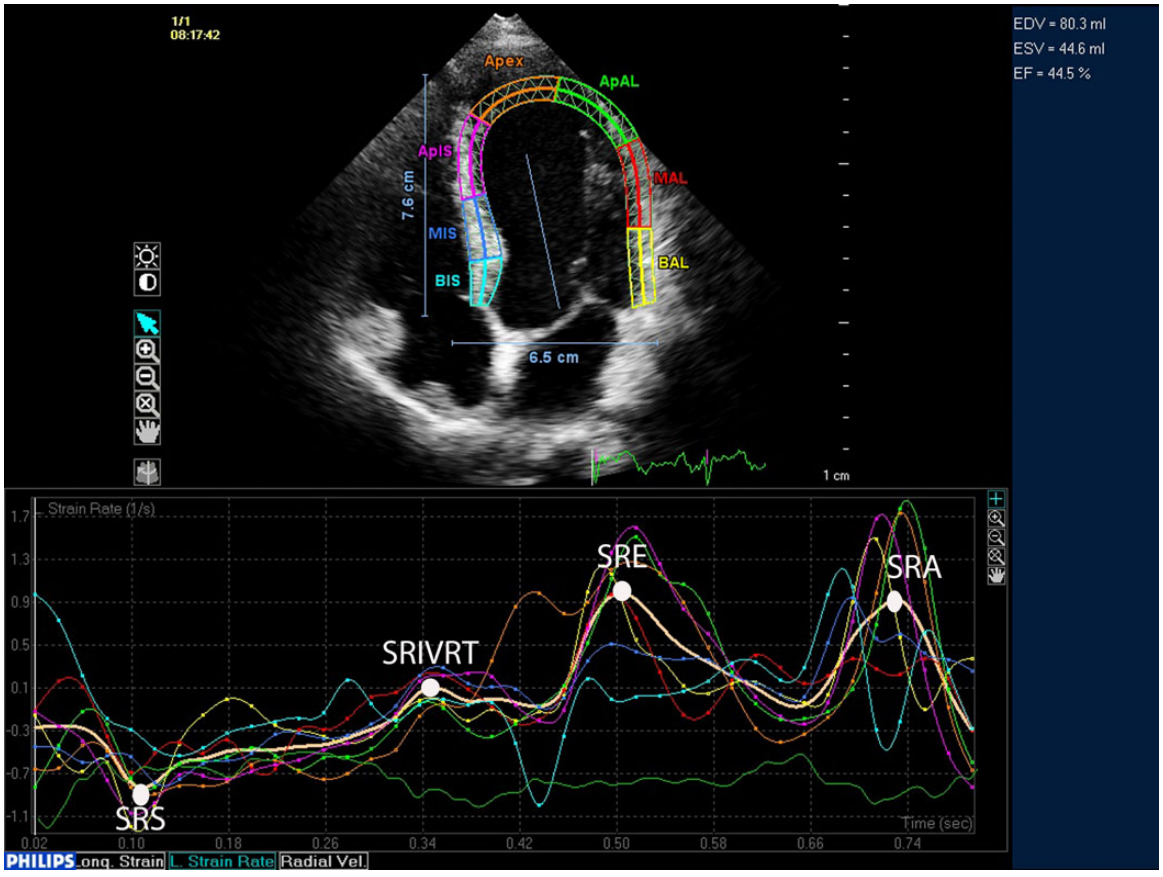

Figure 2 An example of SR measurement from the apical four-chamber view. The final values were obtained by averaging the corresponding measurements from apical four-chamber, two-chamber, and three-chamber views. SRS, systolic strain rate; SRIVRT, strain rate during isovolumetric relaxation; SRE, strain rate during early diastole; SRA, strain rate during atrial filling.

consecutive beats were recorded, the measurement of LVEDP was made at the peak of R-wave on electrocardiography and average of measurements made for five consecutive beats was recorded as LVEDP for the index patient.

Statistical analysis

The data were presented as mean ± SD for continuous variables and as percentage for categorical variables. For normality and homogeneity of data, Kolmogorov–Smirnov test was used. Diastolic blood pressure levels, *E*/SRIVR, IVRT, and LVESD had skewed distribution; therefore, data were log-transformed. The Pearson's correlation analysis was used to test the possible associations between LVEDP and the study variables. Prediction of independent variables was obtained by a stepwise linear regression model including potential confounders. The coefficient of determination (R^2) and adjusted coefficient of determination (R_a^2) were evaluated to control the power of model.

The intraclass correlation coefficient (ICC) and its 95% CI were used to assess intraobserver reliability for the first echocardiographer. Cronbach's α was used to evaluate internal consistency. The interobserver reliabilities were assessed by Bland and Altman plots.

A *P*-value of <0.05 was considered statistically significant. Statistical analysis was performed using the MedCalc 13 Software (Mariakerke, Belgium).

Results

One hundred and two consecutive patients referred for catheterization were evaluated; 8 patients were excluded for more than mild valvular disease, 6 for having AF, 12 had LV systolic dysfunction, and 11 were excluded for having insufficient echocardiographic images. The indication for catheterization was stable angina pectoris in 36 (55%) patients, myocardial ischaemia detected by stress imaging in 20 (31%) patients, and exercise electrocardiography test positivity in 9 (14%) patients. Mean age of the 65 (29 females and 36 males) patients enrolled was 57 ± 9.5 years. Patients' clinical characteristics and data from echocardiographic examination are presented in *Table 1*. Mean LVEDP of patients was 16 ± 3.9 mmHg. Sixteen patients (24.6%) had a normal diastolic filling pattern, 40 (61%) patients had impaired relaxation (Grade I), and 9 (13.8%) patients had pseudonormalized pattern (Grade II). All of our patients had NHYA functional class I or II symptoms.

Among the non-invasive parameters analysed in our study, only systolic and log-diastolic blood pressure, SRS, SRE, SRIVR, and E/SRIVR were significantly correlated with LVEDP. Correlation coefficients for these parameters are presented in *Table 2*. Examples of SR curves for individual patients with normal and elevated filling

Table 1 Clinical, echocardiographic, and laboratory characteristics of the study population

Variables	n = 65
Clinical characteristics	
Age, years	57 ± 9.5
Men, *n* (%)	36 (55.4%)
Body mass index, kg/m^2	28 ± 4
Body surface area, m^2	1.8 ± 0.17
Hypertension, *n* (%)	31 (47.7%)
Diabetes, *n* (%)	18 (27.7%)
Hypercholesterolaemia, *n* (%)	32 (49.2%)
Coronary artery disease, *n* (%)	27 (41.5%)
Smoking, *n* (%)	14 (21.5%)
Heart rate, bpm	74.2 ± 9.8
Systolic blood pressure, mmHg	154 ± 25
Diastolic blood pressure, mmHg	90 (80,110 [30])[a]
LV and LA structure and function	
LVEDD, cm	4.7 ± 0.48
LVESD, cm	3 (2.8, 3.4 [0.6])[a]
LV ejection fraction, %	63 ± 7.5
LA, cm	3.4 ± 0.37
LA volume, mL/m^2	26.1 ± 7.3
LV diastolic function	
E, cm/s	67 ± 16
A, cm/s	75 ± 12
E/*A* ratio	0.91 ± 0.29
E/*E*′ average	8.3 ± 2.04
IVRT, ms	90 (80,100 [20])[a]
DT, ms	217 ± 43
Myocardial deformation indices	
GLS, %	−15.1 ± 2.0
PALS, %	21.2 ± 4.9
SRS, s^{-1}	−0.74 ± 0.13
SRE, s^{-1}	0.77 ± 0.20
SRA, s^{-1}	0.80 ± 0.16
SRIVR, s^{-1}	0.16 ± 0.06
E/SRIVR	4.15 (2.85, 6.86 [4.01])[a]

LVEDD, indicates left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LV, left ventricle; LA, left atrium; *E*, mitral early diastolic inflow; *A*, mitral late diastolic inflow; *E*′, early diastolic mitral annular velocity; IVRT; isovolumetric relaxation time; DT; deceleration time of mitral inflow; GLS, global longitudinal strain; PALS, peak left atrial systolic strain; SRS, systolic strain rate; SRE, early diastolic strain rate; SRA, late diastolic strain rate; SRIVR, strain rate during isovolumetric relaxation.
[a]Median (25th, 75th percentile [interquartile range]) was used for variables that were not distributed normally.

pressures are also provided in *Figure 3*. *E*/*E*′ was not correlated with LVEDP in our patient population ($r = 0.133$; $P = 0.292$).

Age-adjusted stepwise linear regression analysis was performed; while LVEDP was regarded as a dependent variable, log-diastolic blood pressure and other study variables including SRS, SRE, SRIVRT, and age were assumed as independent variables (*Table 3*). We found that only SRIVRT values ($\beta = -20.682$, $t = -3.292$; $P = 0.002$) and log-diastolic blood pressure levels ($\beta = 21.118$, $t = 3.784$; $P < 0.001$) were independently correlated with LVEDP. Although systolic blood pressure levels were correlated with LVEDP, they were not included in the regression analysis because they were strongly correlated with diastolic blood pressure. The relationship between LVEDP and SRIVR is shown by using a scatter plot representation in *Figure 4*.

Table 2 Correlation of LVEDP with echocardiographic and clinical findings

Variable	r	p
Systolic blood pressure	0.364	0.003
Log-diastolic blood pressure	0.463	<0.001
SRS	0.249	0.045
SRE	−0.256	0.040
SRIVR	−0.420	<0.001
Log-*E*/SRIVR	0.300	0.015

SRS, systolic strain rate; SRE, early diastolic strain rate; SRIVR, strain rate during isovolumetric relaxation; *E*, early diastolic mitral inflow.

Reliability analysis

Reproducibility of strain measurements was assessed in 25 randomly selected patients. GLS, SRS, SRE, and SRIVR were re-measured by the original reader and a second echocardiographer who was blinded to the first measure. For intraobserver reliability, ICCs were significant for GLS 0.848 (0.655–0.937), SRS 0.975 (0.939–0.990), SRE 0.882 (0.727–0.952), and SRIVR 0.930 (0.832–0.972).

The interobserver agreements for the same measurements were assessed by Bland and Altman plots. Bland–Altman plotting of the two echocardiographers' results was within the correlation limits of 1.96 (95% confidence interval; *Figure 5*).

Discussion

LV global longitudinal SR parameters, except SRA, correlated significantly with LVEDP in conjunction with systolic and log-diastolic blood pressure in patients with preserved EF. The present study showed that SRIVR measured by STE and log-diastolic blood pressure are independent predictors of LVEDP in this patient population. To the best of our knowledge, this is the first study comparing invasively measured filling pressures and GLS, SR parameters, as well PALS in patients with preserved EF and various degrees of diastolic function.

STE is a sensitive tool to evaluate myocardial mechanics and it is independent from translational motion and other through-plane motion effects in contrast to myocardial velocities. Data regarding accuracy, validity, and clinical application of STE are rapidly accumulating.[15,16] Since the endocardium is most susceptible to the deleterious effects of interstitial fibrosis and hypoperfusion, the abnormal longitudinal function can be detected at an earlier stage by examining subendocardial function, by means of GLS and SR measurements.[12,17]

Direct measurement of LV filling pressures with cardiac catheterization is the gold standard to determine the extent of diastolic dysfunction.[3] There are currently no unified criteria specified in the major

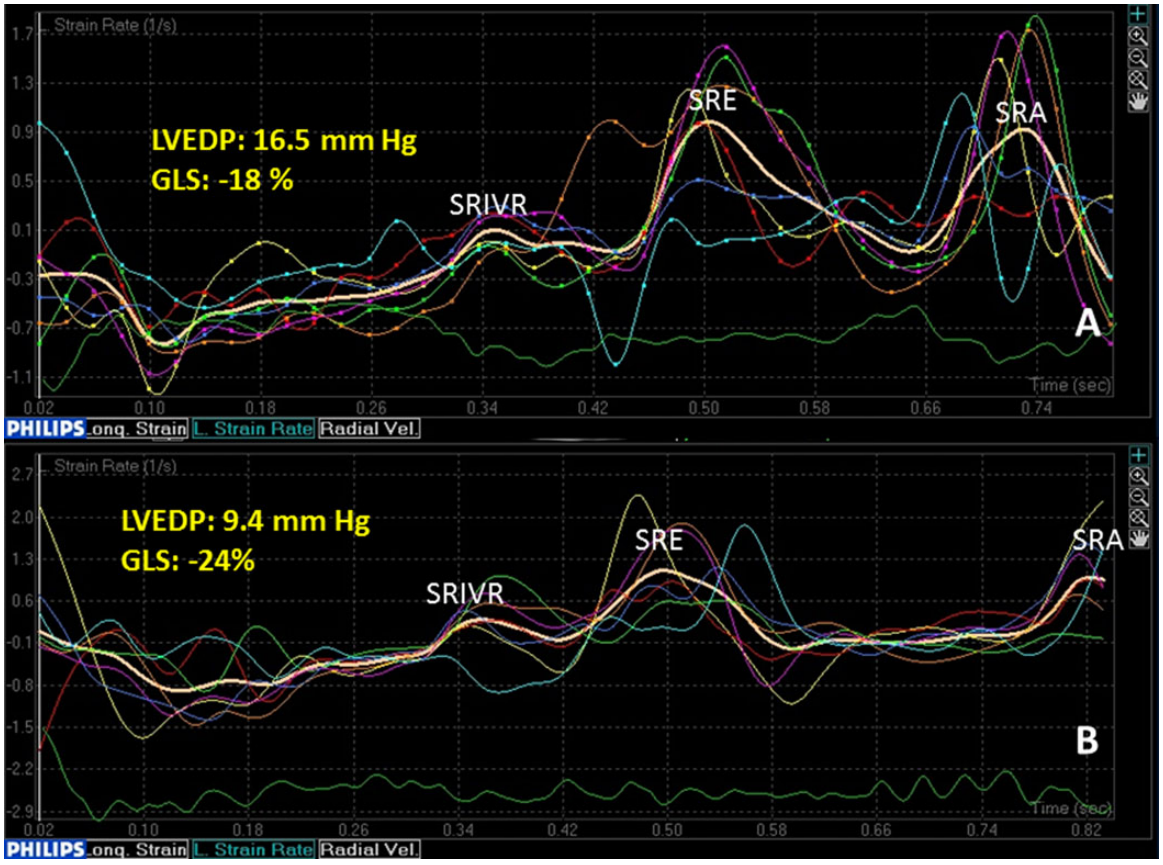

Figure 3 Comparison of SR curves from an index patient with elevated LV end-diastolic pressure (*A*) and from a patient with normal filling pressures (*B*). The patient in (A) has an SRIVR value of 0.1 s^{-1}, GLS −18%, and LVEDP 16.5 mmHg. (B) The curves from a patient with an SRIVR value of 0.4 s^{-1}, GLS −24%, and LVEDP 9.4 mmHg. GLS, global longitudinal strain; LVEDP, LV end-diastolic pressure; SRIVRT, strain rate during isovolumetric relaxation; SRE, strain rate during early diastole; SRA, strain rate during atrial filling.

Table 3 Stepwise linear regression analysis data that were performed to determine independent predictors of LV end-diastolic pressure

Variables	Unstandardized coefficients	t	p
Log-diastolic blood pressure	21.118	3.784	<0.001
SRIVR	−20.682	−3.292	0.002
Age	−0.012	−0.117	0.907
SRE	−0.127	−1.141	0.258
SRS	0.171	1.648	0.104

SRE, early diastolic strain rate; SRIVR, strain rate during isovolumetric relaxation; SRS, systolic strain rate.
R^2: 0.575; adjusted R^2: 0.331; standard error of the estimate: 3.263.

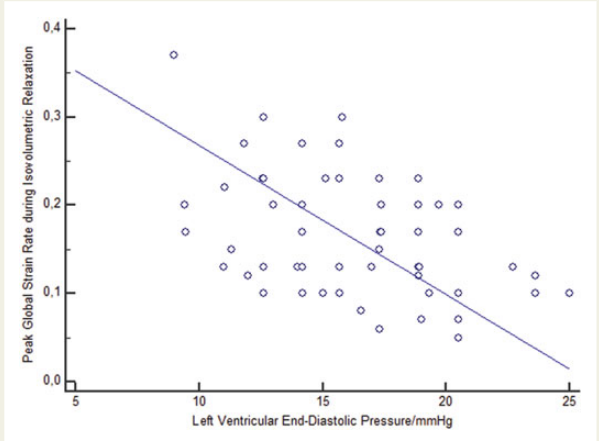

Figure 4 The relationship between LVEDP (mmHg) and peak SR value (s^{-1}) during isovolumetric relaxation.

guidelines for diagnosing diastolic dysfunction in patients with preserved EF. The value of the *E*/*E*′ ratio as a reliable estimate of LV filling pressures was endorsed by European and American consensus statements on diastolic HF and diastolic LV dysfunction.[3,7] However, the existence of a 'grey zone' between 8 and 13 represents a limitation for the application of *E*/*E*′ ratio in clinical practice.[18] This may be particularly relevant among patients with normal EF, for whom the

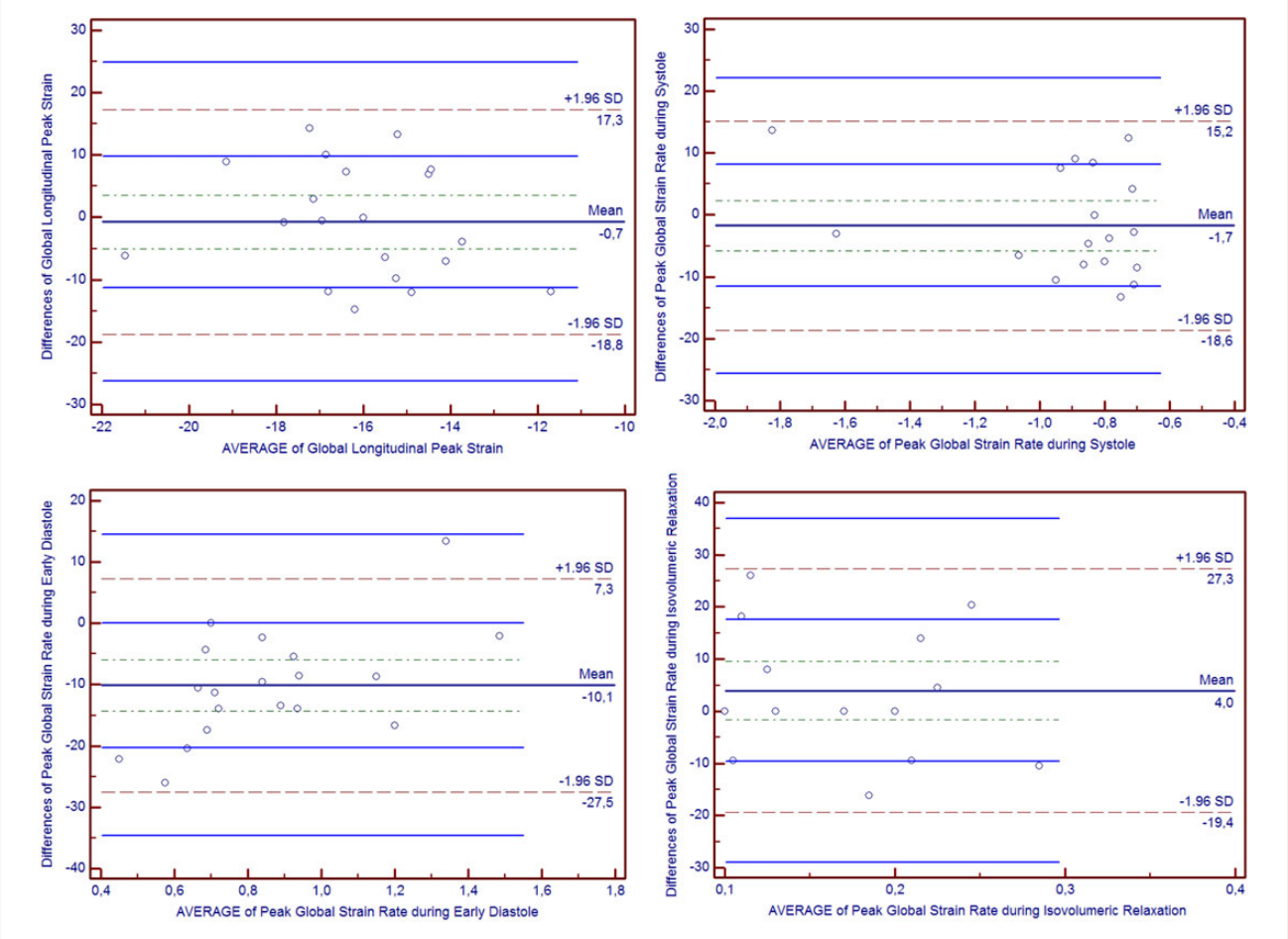

Figure 5 Bland–Altman plots of LV GLS, SRS, SRIVRT and SRE.

possibility of correctly estimating LV filling pressures is of key importance for the diagnosis of heart failure with preserved EF. Mean *E*/*E*′ of our study population was in the 'grey zone' and patients enrolled had many risk factors for diastolic dysfunction. Therefore, we tested the reliability of GLS and SR parameters for the prediction of LVEDP in comparison with *E*/*E*′ and other conventional echocardiographic diastolic indices.

Wang *et al.*[12] were first to suggest the use of global diastolic SR for the assessment of LV relaxation and filling pressures. Consistent with our findings, they reported that global SRIVR derived by STE related well to haemodynamic indices of LV relaxation both in animal models and in patients. They also stated that SRE was also dependent on LV relaxation in humans and this association was weaker than that of SRIVR, which is parallel to our findings. In their study, *E*/SRIVR predicted LV filling pressures with reasonable accuracy, particularly in patients with an E/E_a ratio of 8 to 15, those with normal EF, and those with regional dysfunction. However, in our patients, SRIVR was superior to *E*/SRIVR for the prediction of filling pressures. This may have resulted from the different patient populations studied as they have also included patients with dilated cardiomyopathy and more than mild valvular disease. A number of variables other than LV diastolic function and filling pressures affect mitral inflow, including heart rate and rhythm, PR interval, cardiac output, mitral annular size, and LA function. In patients with coronary artery disease or hypertrophic cardiomyopathy, in whom EF is preserved LV filling patterns have a U-shaped relation with LV diastolic function, with similar values seen in healthy normal subjects and patients with cardiac disease.[7] A better predictive value of SRIVR than *E*/SRIVR can be explained by this phenomenon. SRIVR was also reported to be a reliable parameter to assess invasively measured LV relaxation in patients with hypertrophic obstructive cardiomyopathy.[19]

In contrary to our findings, Kasner *et al.* concluded that, in patients with HFpEF, STE is accurate in detecting increased LV stiffness, but is not superior to *E*/*E*′. They also reported that, in patients with HFpEF, SRIVR was reduced and SRE and SRA did not differ compared with controls. However, the patient populations studied are different in these studies and in our study *E*/*E*′ was not even correlated with LVEDP. This is consistent with the data reported previously by Previtali *et al.*[5], indicating that the mitral *E*/*E*′ ratio is of limited clinical value in patients without heart failure.

SRIVR occurs before the mitral valve opens and therefore is less dependent from load condition and chamber stiffness, and it is expected that SRIVR better reflects the intrinsic myocardial characteristics of the LV during early LV expansion. An SRE value is dependent on the balance between LV relaxation and LA pressure. In patients in whom

myocardial expansion is delayed such that it occurs after the LA–LV pressure crossover, SRE is influenced mainly by LV relaxation. However, when it occurs earlier than this time point, it is affected as well by LA pressure. In that regard, SRE appears to have determinants similar to those of *E′*.[20]

Consistent with previous studies, we found that SR during the late diastolic filling (SRA) was not related to LVEDP. In addition, we did not find significant correlation between PALS and LVEDP in our study, which was previously reported to correlate strongly and negatively with invasively determined LVEDP.[13] However, the populations studied were different mainly in regard to LVEF.

Despite the fact that, in patients with diastolic dysfunction, the myocardial systolic function of the LV is not preserved, average values of GLS were lower than we would expect in a population with preserved LVEF.[9–11] Patients enrolled had many risk factors for diastolic dysfunction like diabetes mellitus, hypertension, and coronary artery disease, which may also have resulted in subclinical LV systolic dysfunction.[21–23] In patients with diabetes mellitus, it was suggested that GLS deterioration proceeds and/or coexists with LV diastolic dysfunction as a consequence of diabetic cardiomyopathy.[23] Possibly, other explanation is that GLS reflects predominantly longitudinal motion which is affected more frequently and earlier in the evolution of diastolic dysfunction; however, LVEF is more global or even more a reflection of circumferential contraction.[20]

The main limitation of our study was the small size of the study population. This fact may explain to a certain extent the weak, although significant, correlations observed with some of the STE parameters. Besides, LVEDP was obtained using fluid-filled pigtail catheters. Although micromanometer-tipped catheters would have been ideal, our method used to measure LVEDP is standard in the clinical setting and well validated. The patients in this study were classified by LVEF and LV filling pressure, not enrolled according to clinical heart failure criteria. Therefore, this investigation was a study of the relation of myocardial mechanics to cardiac load. Our study could only detect cross-sectional relationships between the studied variables; long-term outcome studies are needed.

With the present study, we have demonstrated that SRIVR has an incremental value in patients with preserved EF for the estimation of LV filling pressures when compared with conventional echocardiographic parameters and recently suggested global longitudinal deformational indices of LV and LA (GLS, SRS, SRIVR, SRE, SRA, and PALS).

Authors' contributions

S.H. and N.O. designed the study protocol; R.B.B. and S.H. performed data analysis/interpretation; S.H. and O.C. drafted the article; N.O. and C.G. critically revised the manuscript; G.B.G. and C.D. performed statistical analysis; data collection was performed by S.H., T.U., C.D., C.G., and O.C.

Conflict of interest: The authors alone are responsible for the content and writing of paper.

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