Ultrazvočna ocena okvare levega prekata z doplersko ehokardiografijo in izračunom indeksa okvare levega prekata (iLVI) pri bolnikih s kroničnim srčnim popuščanjem

Assessment of left ventricular impairment by calculating left ventricular impairment index using doppler echocardiography in chronic heart failure patients

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Izvleček

Namen: *Pri oceni globalne okvare levega prekata (LP) pri bolnikih s kroničnim srčnim popuščanjem (SP) je potrebno upoštevati tako funkcijske kot strukturne spremembe prekata. Z upoštevanjem utripnega volumna (angl. stroke volume = SV) kot pokazatelja funkcije LP, končnega diastoličnega premera (LVEDD) kot enostavnega pokazatelja strukturnih sprememb LP in z upoštevanjem bolnikove višine (angl. height = H) je moč izračunati indeks okvare levega prekata (iLVI). Z raziskavo smo želeli ugotoviti diagnostični pomen iLVI pri bolnikih s kroničnim SP.*
Metode: *V raziskavo je bilo vključenih 50 bolnikov s kroničnim SP in 50 zdravih preiskovancev. Pri vseh smo opravili standardno dvodimenzionalno ehokardiografijo, iLVI pa smo izračunali po formuli iLVI = SV x H / LVEDD2 [mL/cm].*

Abstract

Purpose: *In order to assess global left ventricular impairment in chronic heart failure (HF) patients, it is necessary to consider both functional and structural changes of the left ventricle (LV), in particular, stroke volume (SV) and left ventricular end-diastolic diameter (LVEDD). Based on SV as a marker of LV function, LVEDD as a simple indicator of structural LV changes, and height of an individual patient (H), the left ventricular impairment index (iLVI) can be calculated. The purpose of this study was to assess the diagnostic value of iLVI in chronic HF patients.*
Methods: *This prospective study included a total of 50 chronic HF patients and 50 healthy individuals, who underwent standard two-dimensional echocardiography. The iLVI was calculated according to the formula: iLVI = SV x H / LVEDD2 (mL/cm).*

Rezultati: *Ugotovili smo, da iLVI najbolj zanesljivo loči zdrave preiskovance od bolnikov (AUC = 0,989). Občutljivost in specifičnost iLVI (oboje 96,0 %) sta za ugotavljanje bolnikov s kroničnim SP v primerjavi z iztisnim deležem (angl. ejection fraction = EF), indeksom utripnega volumna (angl. stroke volume index = SVI) in razmerjem SV/H največja. Klinični učinek iLVI je velik (Cohen's d = 3,2) in presega klinični učinek tako EF kot tudi klinični učinek SVI in SV/H.*

Zaključek: *Z raziskavo smo ugotovili, da iLVI predstavlja enostaven in odličen pokazatelj globalne funkcijske in/ali strukturne okvare LP pri bolnikih s kroničnim SP.*

Results: *The iLVI accurately separated healthy subjects from patients (AUC = 0.989), with the highest sensitivity and specificity for proper identification of HF (96.0% each), in comparison with ejection fraction (EF), stroke volume index (SVI), and SV/H. The iLVI effect was strong (Cohen's d=3.2), exceeding that of EF, SVI, and SV/H.*

Conclusion: *The study concluded that the iLVI, which can be readily calculated, represents an excellent clinical marker for global functional and/or structural LV impairment in chronic HF patients.*

INTRODUCTION

Chronic heart failure (HF) represents a major health care burden with an estimated prevalence of 1–2% in populations aged around 70 years old in developed countries. This prevalence is even higher (above 10%) in populations with individuals over 70 years of age. Population ageing and prolonged life expectancy due to modern pharmacological treatments and procedures give rise to the chronic HF epidemic characteristics (1–3).

The main treatment goals for chronic HF patients are to improve quality of life, prevent hospital admissions, and increase survival (4). Despite continued improvements in chronic HF patient treatment, the mortality rate remains high. Any improvement in diagnostic or therapeutic procedures is useful and should be considered.

Echocardiography is of key importance for early diagnosis, treatment, follow-up, and prognostic assessment in HF patients (5, 6). Global left ventricular systolic function is most frequently assessed by measurement of the ejection fraction (EF) using two-dimensional echocardiography, as a ratio between the end-diastolic volume (EDV) and end-systolic volume (ESV) (7). Recent ESC (European Society of Cardiology) guidelines categorize HF patients by their EF measurements into categories with reduced EF < 40% (HFrEF), mid-range EF 40–49% (HFmrEF), and preserved EF ≥ 50% (HFpEF) (4). EF is not only the most frequently used marker of left ventricular (LV) function but also an outcome predictor in several cardiovascular conditions (4, 8–10).

EF measurements are simple, informative, and useful, although occasionally imprecise due to poor acoustic window and suboptimal presentation of the LV endocardium, frequently requiring estimation of EF by an experienced echocardiographer (11–13). In clinical practice, EF correlates weakly with clinical condition, especially in patients with significant mitral regurgitation (MR) or severe LV enlargement (14).

Doppler echocardiography enables us to measure the LV outflow tract velocity time integral (VTI) and to calculate stroke volume (SV) and SV index (SVI), which also reflect global LV systolic function (15, 16). Lower SVI is a strong indicator of poor outcome in patients with severe aortic stenosis (17, 18). SV measurements can be used to assess the contractile reserve of LV by using dobutamine stress echocardiography (19). On the other hand, SV and SVI overestimate LV function in patients with important aortic regurgitation. In chronic HF patients with dilated LV, SV and SVI do not provide any information on LV dimensions or structural impairment.

LV end-diastolic diameter (LVEDD) can be easily measured in most patients using 2-D echocardiography (20). LVEDD thus provides significant diagnostic and prognostic data. Enlarged LVEDD is one of the most important echocardiographic criteria for dilatative cardiomyopathies and important risk factors for adverse cardiovascular events in coronary and chronic HF patients (21–23). LVEDD also correlates with the left atrial volume, LV thrombus appearance in patients with dilatative cardiomyopathy and preserved sinus rhythm, and serious cardiac events in chronic HF patients undergoing physical activity. It also enables monitoring of LV dilatation under septic conditions as an adaptation response in these patients to maintain or elevate the LV stroke volume (24–26). Increased LVEDD is associated with failure of the resynchronization treatment (27). Measurement of LVEDD makes it possible to assess the range of the so-called reverse LV remodeling and treatment success in HF patients (28). Pre-operatively, LVEDD predicts the success of surgical revascularization and mitral annuloplasty (29).

The purpose of this study was to demonstrate that, when integrating SV as an indicator of global LV systolic function, LVEDD as an indicator of LV size, and the patient's body height (H), a simple and informative indicator of LV impairment (iLVI) is obtained, particularly in cases when EF, SV, or SVI are less informative due to their limitations.

MATERIAL AND METHODS

A prospective echocardiographic, non-interventional study was conducted in the Department of Cardiology and Angiology of the University Medical Centre Maribor, Slovenia. The study group consisted of 100 subjects, including 50 healthy subjects and 50 patients with established diagnoses of symptomatic HF. All of the included individuals were over 18 years old, regardless of their sex and associated non-cardiac conditions. All of the subjects were in sinus rhythm. Exclusion criteria included atrial fibrillation, electrosystolic rhythm, myocardial hypertrophy, and a known or newly diagnosed aortic regurgitation.

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (75/04/15). Written informed consent was obtained from all of the included individuals. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and good clinical practice. We/I certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers/animals were followed during this research.

Before ultrasound examinations were performed, medical records of all of the included subjects were reviewed. Clinical history, focusing on cardiovascular conditions, was obtained and documented. All of the included individuals were clinically examined in order to measure and record blood pressure, body height, and body weight. Body surface area (BSA) was also calculated. Finally, subject functional status according to the NYHA (New York Heart Association) classification was assessed.

Asymptomatic patients without any limitations to physical acitivity were included in NYHA class I. NYHA class II patients were mildly symptomatic during daily activities and NYHA class III patients were markedly symptomatic during daily activities and were comfortable only at rest. NYHA class IV patients were symptomatic even at rest (4).

In every patient a standard 12-lead ECG (electrocardiography) was recorded and echocardiography performed. Two-dimensional echocardiography was performed according to the standard protocol.

LVEDD was measured in the parasternal longitudinal view at or just before the opened mitral valve level, perpendicular to the longitudinal left ventricular axis, reaching from the LV endocardium septal to posterior wall. Mean ± SD (standard deviation) normal LVEDD levels in healthy male and female subjects were 5.02 ± 0.41 and 4.50 ± 0.36 cm, respectively (7). Alternatively, LVEDD measurements were also performed in the apical four-chamber view perpendicular to the ventricular longitudinal axis, running from the mitral ring to the left ventricular apex at the level corresponding to one-third of the longitudinal axis from the mitral ring. The biplane method of disks (modified Simpson’s rule) was used to calculate left ventricular EF (30).

Pulsed Doppler was used to measure maximal velocity (Vmax) in LVOT (left ventricular outflow tract) during the ejection phase in the apical five-chamber view with the sample volume located immediately below the aortic valve and with clear visibility of the aortic valve closure on the Doppler display of the velocity profile (31). LVOT was displayed in the parasternal longitudinal view, where the outflow tract area was zoomed in on and the LVOT diameter was measured at a distance of 0.5–1.0 cm from and parallel to the aortic valve in LV systole. LVOT area was then calculated.

SV was calculated using a standard formula with VTI and LVOT diameter measurements as follows: SV = CSA x VTI, where CSA = cross-sectional area (cm2) of the LVOT, and VTI = velocity-time integral (cm) (30). SV was indexed according to the subject's BSA to determine SVI and also according to the subject's height only (SV/H). Both structural and functional components were considered when calculating the iLVI.

The structural component was expressed as a relationship between the subject's H (cm) and LVEDD (cm): H/LVEDD. The functional component was expressed as a relationship between the subject's SV (mL) and LVEDD (cm): SV/LVEDD (mL/cm). Both of these relationships (structural and functional) must be normal for LV to be in normal condition. However, in chronic HF patients, at least one of these components is impaired. Therefore, the iLVI represents the product of both of these proportional ratios. For the iLVI calculation in the current study, the following equation was used:iLVI = SV x H / LVEDD2 (mL/cm).

A single investigator measured all of the ultrasound parameters using the same ultrasound device Phillips iE 33 with transthoracic probe X5–1 x MATRIX (Philips Ultrasound, Andover, Massachusetts, USA).

The summary statistics were presented as mean values ± standard deviations or as frequencies or percentages. Cohen's d method (32) was used for the effect size calculations of EF, SV/H, SVI, and iLVI. Cohen's d was calculated as the difference between group means divided by pooled standard deviation, which was defined as the root mean square of the two standard deviations. The coefficient d ≥ 0.8 represented a significant effect or difference in parameters between the two groups. To compare clinical characteristics between the two groups, a t-test for independent samples was used. Correlations between iLVI, age, and BMI (body mass index) were calculated using the Pearson's correlation coefficient.

Normal distribution of the numerical values was verified using the Kolmogorov-Smirnov test. Sensitivity and specificity of the analysed parameters were tested using the receiver operating characteristic (ROC) curve. Statistical analysis was performed using the IBM SPSS 22.0 (IBM Corp., Armonk, NY, USA), where $p \leq 0.05$ was considered to be statistically significant.

Reliability of measurements was calculated using a previously published method as the mean percentage error and by using intraclass correlation coefficients (ICC) for absolute agreement (33). A dataset of 20 randomly selected participants was analysed for the iLVI. Measurements of echocardiographic records were repeated on a different day, and a second observer, blinded to the authors' results, measured the same echocardiographic records. Percentage error in intraobserver reliability was 5.2% (95% confidence interval (CI) 3.7–6.8%) and ICC was 0.963 (95% CI 0.932–0.988). Percentage error in interobserver reliability was 6.1% (95% CI 4.2–7.9%) and ICC was 0.949 (95% CI 0.921–0.975).

RESULTS

Echocardiography was performed on 100 subjects (50.0% males and 50.0% females). There were 50 (50.0%) healthy subjects and 50 (50.0%) patients with established HF. In each group there were 25 (50.0%) males and 25 (50.0%) females. A comparison of baseline characteristics between patients and healthy subjects is presented in Table 1.

There were no significant differences in baseline characteristics between healthy subjects and HF patients (Table 1). All healthy subjects were in class I, according to the NYHA. The remaining patients were distributed among the NYHA classes II–IV as follows: 22 (44.0%) patients in NYHA class II, 20 (40.0%) patients in NYHA class III, and 8 (16.0%) patients in NYHA class IV.

There were 27 (54.0%) patients with ischemic cardiomyopathy, 17 (34.0%) with dilatative cardiomyopathy, five (10.0%) with valvular cardiomyopathy, and one (2.0%) with undefined cardiomyopathy. In addition, there were nine (18.0%)

Table 1: Comparison of baseline characteristics between patients and healthy subjects

Variables (mean ± SD)	Healthy (n = 50)	Patients (n = 50)	p
Age (years)	55.1 ± 9.3	58.4 ± 10.9	0.107
BMI (kg/m2)	26.2 ± 3.7	27.7 ± 4.1	0.057
Heart rate (/min)	73.1 ± 11.8	74.4 ± 12.7	0.619
Systolic BP (mm Hg)	131.8 ± 15.3	126.7 ± 19.7	0.151
Diastolic BP (mm Hg)	81.9 ± 10.8	77.9 ± 12.0	0.079

BMI: body mass index, BP: blood pressure.

subjects without MR, 16 (32.0%) with mild MR, 17 (34.0%) with moderate MR, and eight (16.0%) with severe regurgitation in the patient group. Patients received the following treatments: 30 (60.0%) patients received diuretics, 30 (60.0%) angiotensin-converting enzyme inhibitors, 10 (20.0%) angiotensin II receptor blockers, 41 (82.0%) beta-blockers, 29 (58.0%) mineralocorticoid receptor antagonists, 13 (26.0%) amiodarone, three (6.0%) digoxin, eight (16.0%) calcium channel blockers, 22 (44.0%) statins, 30 (60.0%) aspirin, and 11 (22.0%) anticoagulant therapy.

Important echocardiographic parameters in healthy subjects and HF patients are presented in Table 2. Mean values for LVEDD, LVESD, ESV, LAV, LAVI,

Table 2: Comparison of ejection fraction, index of left ventricular impairment, and other important echocardiographic parameters in healthy subjects and patients

Variables (mean ± SD)	Healthy (n = 50)	Patients (n = 50)	p	Cohen's d
LVEDD (cm)	4.2 ± 0.4	5.4 ± 0.7	<0.001	2.1
LVESD (cm)	3.0 ± 0.4	4.5 ± 1.1	<0.001	1.8
EDV (mL)	76.9 ± 18.6	156.2 ± 54.2	<0.001	2.0
ESV (mL)	30.0 ± 9.1	95.6 ± 43.8	<0.001	2.1
LAV (mL)	54.1 ± 20.2	91.1 ± 35.3	<0.001	1.3
LAVI (mL/m²)	31.1 ± 12.9	46.2 ± 16.7	<0.001	1.0
E/A	1.8 ± 1.1	2.2 ± 1.2	0.085	0.3
E/E'	7.5 ± 1.1	20.2 ± 9.4	<0.001	1.9
RVP (mmHg)	32.0 ± 9.9	41.5 ± 9.5	<0.001	1.0
EF (%)	65.1 ± 6.9	38.9 ± 17.1	<0.001	2.0
SV/H (mL/m)	37.1 ± 7.1	25.9 ± 7.7	<0.001	1.5
SVI (mL/m2)	33.8 ± 6.3	22.9 ± 6.5	<0.001	1.7
iLVI (mL/cm)	602.0 ± 98.6	267.2 ± 109.3	<0.001	3.2
H/LVEDD	40.5 ± 3.2	31.8 ± 3.9	<0.001	2.4
SV/LVEDD (mL/cm)	14.9 ± 2.3	8.3 ± 2.8	<0.001	2.6

LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, EDV: end-diastolic volume, ESV: end-systolic volume, LAV: left atrial volume, LAVI: left atrial volume index, E/A: ratio of the early (E) to late (A) ventricular filling velocities, E/E´: the ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E´), RVP: right ventricular systolic pressure, EF: ejection fraction, SV/H: stroke volume indexed to subject's height, SVI: stroke volume index, iLVI: index of left ventricular impairment, H: height, SV: stroke volume.

E/E', RVP, and EDV were significantly higher in the patient group. On the other hand, patient mean values for EF, SV/H, SVI, and iLVI were significantly lower in comparison to healthy subjects (Table 2).

Next, clinical significance for the identification of patients with chronic HF according to Cohen's d method was calculated for all indicators of LV function. All markers exhibited significant differences between healthy subjects and patients. The iLVI components H/LVEDD (Cohen's d = 2.4) and SV/LVEDD (Cohen's d = 2.6) resulted in similarly significant effects between the two groups (healthy subjects vs. patients). The iLVI, being defined as a multiplication of both components (H/LVEDD and SV/LVEDD), showed the strongest effect (Cohen's d = 3.2) compared to EF (Cohen's d = 2.0), SV/H (Cohen's d = 1.5), SVI (Cohen's d = 1.7), and other important echocardiographic parameters.

The iLVI did not show a significant correlation with age (r = -0.190, p = 0.188) or BMI (r = 0.033; p = 0.819) in the group of healthy subjects. The iLVI in healthy male subjects was not significantly different than that in healthy female subjects (264.1±106.3 vs. 279.4±126.0, p=0.696), nor was the iLVI in male patients significantly different from that in female patients (632.2±81.0 vs. 581.8±105.2, p=0.077).

Sensitivity and specificity for EF, SV/H, SVI, and iLVI were tested using the ROC curve (Figure 1). Area under the curve (AUC) for iLVI (AUC = 0.989, 95% CI 0.974–1.000) was the highest, followed by EF (AUC = 0.897, 95% CI 0.824–0.970), SVI (AUC = 0.891, 95% CI 0.826–0.955), and SV/H (AUC = 0.856, 95% CI 0.783–0.929).

Sensitivity of 96.0% and specificity of 96.0% were calculated for the iLVI. Sensitivity for the EF was 92.0% and specificity 86.0%, sensitivity for SVI was 88.0% and specificity 82.0%, and sensitivity for SV/H was 84.0% and specificity 76.0% (Figure 1).

Considerable differences in the iLVI were found between healthy subjects and patients, since patient iLVI values did not exceed the iLVI mean value of 602.0 ± 98.6 mL/cm for the healthy subjects (Figure 2).

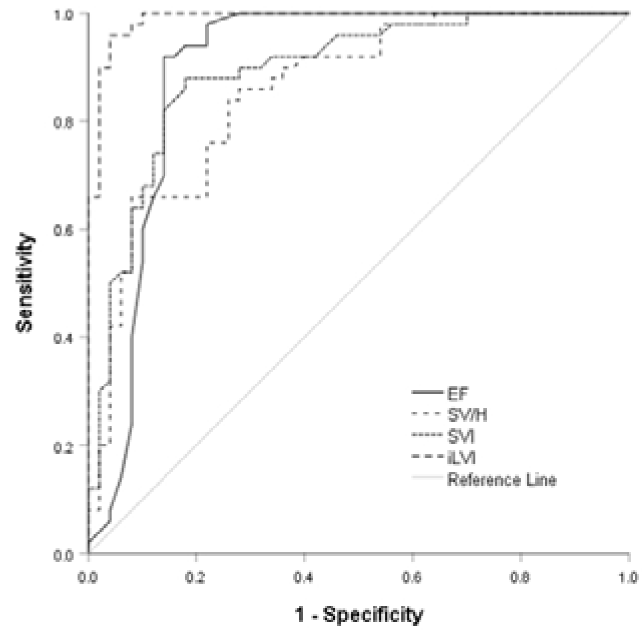

Figure 1. ROC curve for EF, SV/H, SVI, and iLVI (EF: ejection fraction, SV/H: stroke volume indexed to subject's height, SVI: stroke volume index, iLVI: index of left ventricular impairment)

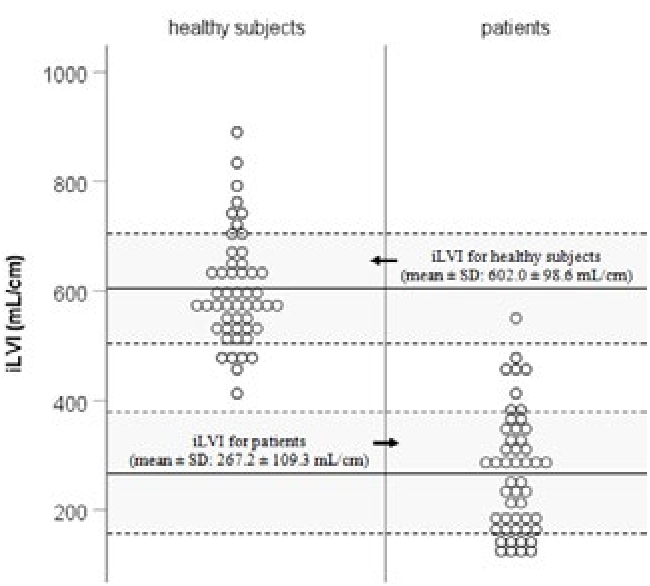

Figure 2. Index of left ventricular impairment values in healthy subjects and patients (iLVI: index of left ventricular impairment, M: mean, SD: standard deviation)

DISCUSSION

In an echocardiographic study, LV impairment in chronic HF patients was estimated with a simple index (iLVI) using data from the 2-D and Doppler echocardiographic measurements. SV, body H, and LVEDD were considered for the iLVI calculation. Assessment of both the LV size (LVEDD) and its global systolic function in chronic HF patients plays an important role in both diagnostics and follow-up assessment of treatment efficacy. Among echocardigraphic parameters of the LV function, such as EF, SVI, SV/H, and iLVI, iLVI seemed to be the most promising in detecting patients with chronic HF, as demonstrated in our study.

In clinical practice, EF is the usual marker for LV systolic function or contractility and is an important criterion for the start of pharmacological therapy, interventional procedures, or cardiac surgery in HF patients. Recommendations for treatment with mineralocorticoid receptor inhibitors, neprilysin inhibitor, biventricular electrostimulation, and ivabradine therapy include EF in the therapeutic algorithm for the HF patients (4). There are also a number of possible errors that are associated with EF measurements that could under- or overestimate the LV function.

Doppler echocardiography enables adequate differentiation between healthy subjects and symptomatic patients (34). To assess the LV impairment using measured SV, it is also necessary to consider structural LV changes. Namely, if the systolic function of severe dilated LV is impaired, SV remains relatively increased and therefore less informative about the LV impairment. In order to improve the informative value and clinical applicability of ultrasound-measured SV, LVEDD was also considered in the calculation of the LV impairment index, along with H.

Normal LV can be assumed when two prerequisites are fulfilled: normal LV size according to the subject's height and normal LV function. According to these facts, the clinical hypothesis in this study assumed that the product of two well-known proportional ratios, H/LVEDD and SV/LVEDD, would better distinguish between healthy subjects and patients with chronic heart failure than would EF, SV, or LVEDD alone.

The LVEDD/H relationship is well known and defines the size of LV relative to the subject's H (7). An inverse relationship between H and LVEDD (H/LVEDD) was used to calculate the iLVI. The SV/LVEDD relationship is very similar to EF. The difference represents the use of LVEDD instead of EDV in the formula for assessing the end-diastolic size of the LV. In clinical practice, iLVI represents the LV systolic volume, indexed to the LV size, with consideration for the subject's body H.

In this study, statistically significant differences was observed between patients and healthy subjects with respect to the mean values for EF, SV/H, SVI, and iLVI (Table 2). Cohen's d test confirmed a major contribution of the iLVI for a proper identification of patients with chronic HF in comparison to EF, SV/H, and SVI. Also, sensitivity and specificity of chronic HF detection were highest using the iLVI. These results also demonstrate that both of the components (H/LVEDD and SV/LVEDD) involved in the calculation of the iLVI had similar clinical effects on the HF assessment.

Despite the fact that LVEDD is less accurate in assessment of LV size in comparison to EDV measurements, using the Simpson method, LVEDD was used in the formula for calculating the iLVI. LVEDD still remains an excellent marker for LV size, especially when ultrasound visibility is not optimal (35, 36).

It was demonstrated that the iLVI is readily obtained and that it has an advantage over EF, because it is more accurate in the diagnosis of chronic HF patients. While EF is less informative, iLVI measurements are poised to become relevant in clinical practice, especially in cases of patients with HF when poor ultrasound image quality makes EF measurements impossible. In these cases, even newer ultrasound techniques, such as three-dimensional echocardiography and global longitudinal strain definition, which have demonstrated positive results in some studies, fail and echocardiographers can perform only a visual EF assessment (12, 13, 37).

This study has several limitations. The study was conducted in a subgroup of HF patients in sinus rhythm without associated aortic regurgitation and severe myocardial hypertrophy. A number of errors are also posssible when calculating SV due to incorrect LVOT measurements. However, these problems can be resolved. To decrease such errors, the same LVOT diameters should be used in the same patient when an examination is repeated (16). The formula for calculating iLVI included LVEDD as an approximate estimate of the LV size, which is otherwise a 3-D parameter (38).

Further research is needed to test the importance of iLVI, using a larger cohort of patients with MR, in particular before corrective mitral valve surgery. In these patients, EF is preserved for longer periods of time and is less informative. However, LV functional stability and dimensions are of particular importance in these cases (39).

Using the iLVI, it was confirmed that, in chronic HF patients, the assessment of LV size and its global systolic function at the same time is very important during diagnostic procedures. In addition, further studies are needed to investigate the possibility that iLVI measurements can be useful in monitoring the efficacy of pharmacological treatment in chronic HF patients.

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