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LITERATURE REVIEWS
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Left ventricular global function index: diagnostic and prognostic value in cardiovascular diseases

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Left ventricular global function index (LVGFI) is a novel indicator for assessing LV function, considering the main components of cardiac remodeling, obtained using magnetic resonance imaging and echocardiography. Works with the assessment of normal LVGFI values were analyzed. The review provides data on the diagnostic and prognostic efficacy of LVGFI in various cardiovascular diseases, such as heart failure, myocardial infarction, cardiomyopathy, and amyloidosis. Examples of LVGFI calculation in healthy patients and in those with listed pathologies are also presented.

Keywords: left ventricle, function, global function index, ejection fraction, left ventricular remodeling, echocardiography.

Relationships and Activities: none.

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Key messages

- We demonstrated the potential of a novel indicator of left ventricular function — global function index for assessing the prognosis of various cardiovascular diseases.

In most European countries, the incidence of cardiovascular diseases (CVD) decreases; recently, the main risk factors (RFs) for these diseases have been identified. However, they still remain the leading cause of morbidity and mortality. In this regard, the search for new risk factors and improving the prevention of CVDs does not lose relevance [1]. Modern imaging techniques occupy an important place in the diagnosis, choice of treatment and prognosis of patients with CVDs [2].

Assessment of left ventricular (LV) systolic function remains an important issue in clinical decision making and risk stratification in various CVDs [3]. The LV ejection fraction (EF) is by far the most important and widely used echocardiographic parameter for assessing heart failure (HF). It is also important to note that LVEF is the main criterion for inclusion in most randomized clinical trials related to cardiology [4].

However, despite the importance and widespread use of LVEF, there are some limitations in assessing cardiac function in HF [5-8]. First, a decrease in LVEF does not reflect its underlying process, since various heart diseases can lead to LVEF [9]. Secondly, the normal LVEF values are influenced by physiological factors, such as, for example, age

and sex [10]. Thirdly, there are limitations of echocardiography itself, including poor imaging, interobserver variability, and dependence on geometric assumptions of the Simpson method.

In addition to the above limitations, LVEF does not fully take into account LV myocardial remodeling.

Pathological LV remodeling is closely associated with the activation of neuroendocrine, paracrine, and autocrine secretion after myocardial injury under conditions of increased LV wall tension and hemodynamic disorders [11]. Modern outlooks say that the sequence of these events is a compensatory response to various pathological influences; however, the remodeling process is favorable for a short time [12]. The development of any of the LV remodeling patterns (concentric remodeling, eccentric hypertrophy, concentric hypertrophy) is associated with a gradual increase in the risk of composite endpoints [13].

Thus, along with the importance of assessing LV volumes, the evaluation of LV remodeling has additional information for prognosis.

Concentric and eccentric LV hypertrophy (LVH) are the predominant phenotypes associated with LV remodeling in patients with HF [14]. Modern echocardiography makes it possible to quantify the mass and left ventricular geometry as part of a routine diagnostic examination [15]. The detection of increased LV mass is a strong independent predictor of cardiovascular risk in adults [16].

Concentric LVH is more common in HF patients with preserved EF. This is explained by maintenance of normal myocardial torsion function, despite impaired longitudinal and circumferential strain [17]. In addition, progression of LV diastolic dysfunction contributes to HF with preserved EF [18].

Eccentric LVH, on the contrary, is more often associated with HF with reduced EF, which occurs due to myocardial infarction (MI), dilated cardiomyopathy and LV volume overload (for example, with mitral or aortic regurgitation) [19]. Fibrosis and synthesis of new sarcomeres predominate, elongating myocardial fibers [11, 20, 21], resulting in a change in LV geometry in the form of a transition from an elliptical to a spherical configuration of LV chamber with its subsequent expansion [22, 23] and a loss of cardiomyocyte orientation with impairment of all types of LV strain [24, 25].

LVH increases the risk of cardiovascular events and is the most important risk factor compared to other risk factors for morbidity and mortality [26]. Currently, echocardiography is a common, widely used in everyday diagnostic practice and a simple method for diagnosing LVH.

Taking into account the above data, such an important echocardiographic indicator as LVEF does not completely take into account LV remodeling, including LV mass.

Mewton N, et al. [27] in 2013 for the first time proposed a novel parameter — LV global function index (GFI), obtained using magnetic resonance imaging (MRI), which includes stroke volume (SV), end-diastolic volume (EDV), end-systolic volume (ESV), as well as LV mass.

LV GFI was calculated by the following equation:

$$\text{LV GFI} = \frac{\text{SV}}{\left(\frac{\text{LV EDV}+\text{LV ESV}}{2}\right) + \text{LV myocardial volume}} * 100\%,$$

where SV is stroke volume, LV EDV — left ventricular end-diastolic volume, LV ESV — left ventricular end-systolic volume. LV volume was calculated as LV mass/LV density, where LV density was 1,05 g/mL.

Subsequently, a number of researchers also published data, including LV GFI obtained by MRI in various pathological conditions [28-33], including in MI, hypertrophic cardiomyopathy (HCM), and cardiac amyloidosis. Given that the parameters required for LV GFI can be obtained using transthoracic echocardiography, there were studies appearing from 2019 on this method, analyzing healthy individuals, patients with MI and chronic HF (CHF) [34-37].

The aim of this review is to analyze the potential and limitations of LV GFI in clinical practice.

Literature search was performed using electronic bibliographic databases (Medline, PubMed, Elibrary) without publication date range.

LV GFI in healthy individuals

To date, there have been no targeted studies to determine the normal LV GFI values. There are several publications related to LV GFI, which include groups of relatively healthy people [27, 30, 34].

Mewton N, et al. (2013) [27] for the first time presented LV GFI assessed by MRI as a novel marker for the prediction of cardiovascular events using the database of a Multi-Ethnic Study of Atherosclerosis. In 4425 patients of the control group with a mean age of 61±10 years and approximately the same ratio of men and women, LV GFI was 40±7%.

In addition, in the study on the differential diagnosis of amyloidosis and HCM by MRI [30], there was a control group of patients, quantitatively significantly inferior to the previous publication. Thirty-five relatively healthy patients aged 51±9 years with a uniform sex distribution with LV GFI 51±7,3% were included. It is possible that higher LV GFI values were obtained due to the younger age of patients in the group.

LV GFI by echocardiography in relatively healthy individuals was proposed in a publication investigating the predictive value of LV GFI in relation to HF and CVD in young adults [34]. After analyzing 3900

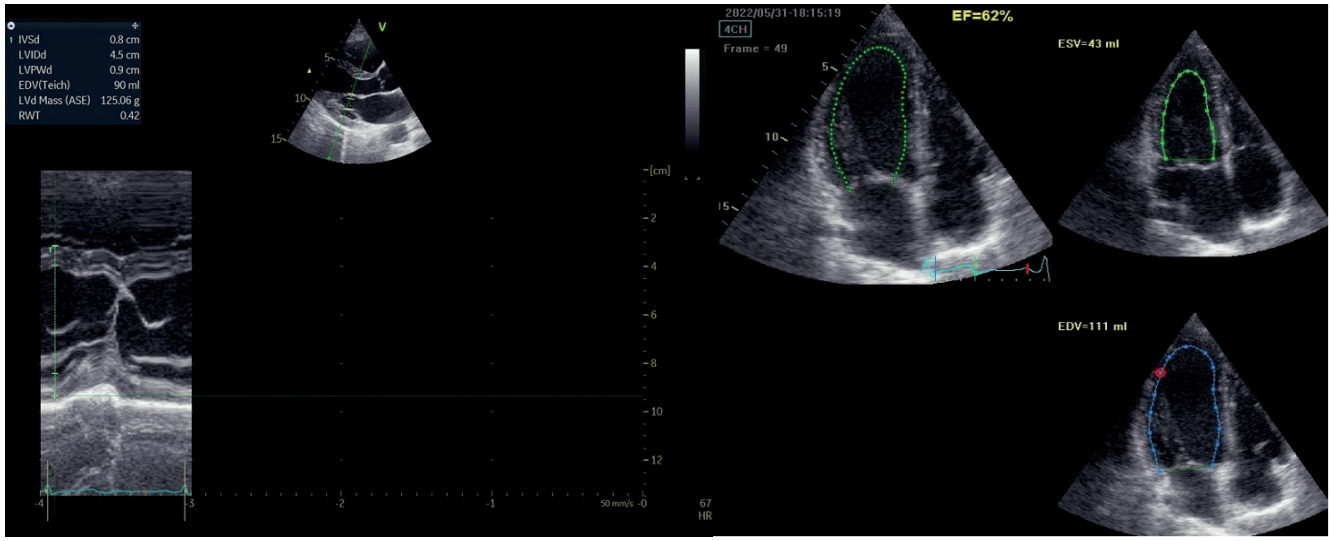

Figure 1. Estimation of LV mass and LVEF in a healthy patient.

people in the control group aged 29,9±3,6 years, LV GFI of 34,6±6,4% were obtained. Apparently, the lower values in comparison with the previous data are due to different methods of LV GFI assessment — MRI and echocardiography.

Figure 1 shows the parameters for calculation and an example of calculating the LV GFI in a healthy 35-year-old patient with the following echocardiographic parameters — LV EDV — 111 ml, LV ESV — 43 ml, LV SV — 68 ml, LV mass — 147 g, LVEF — 62%, LV GFI — 31%.

Thus, the search for reference values of LV GFI remains relevant, including the dependence of these values on the method (echocardiography or MRI), age and sex.

LV GFI in HF

Mewton N, et al. (2013) [27] in a multiethnic study of atherosclerosis revealed the significance of a decrease in LV GFI and LVEF in relation to HF development, along with an increase in myocardial mass, heart rate, N-terminal pro-brain natriuretic peptide, and the presence of diabetes in patients with an average age of 68±8 years. In addition, LV GFI <35% was associated with a 1,5-fold increased risk of HF.

Similar study but in young people (29,8±3,7 years) [34], for 25 years, showed that with LV GFI <30,7%, there is a significantly higher risk of HF. When comparing LV GFI with LVEF, the former showed the best predictive value for HF risk as follows: AUC, 0,80 and 0,66, respectively.

There are data on the significance of LV GFI in patients with HF with preserved EF over 60 years [35], for which LV GFI below 21,1% had an independent predictive value in relation to a death and had greater sensitivity and specificity compared to LVEF (sensitivity: 73,3% vs 66,7%; specificity: 70,0% vs 68,0%).

LV GFI in MI

The first study of LV GFI using MRI in patients with acute MI [28] included 795 patients who underwent coronary artery stenting (within 12 hours from the onset) followed by repeat MRI a week later. The follow-up period was 1 year. LV GFI <31,2% in multivariate analysis proved to be an independent predictor of adverse endpoints (all-cause mortality, recurrent MI, HF). Only the Thrombolysis In Myocardial Infarction (TIMI) score showed similar predictive value. Compared with LVEF, LV GFI showed a greater predictive value for all-cause mortality (AUC, 0,73 and 0,65, respectively, p=0,05).

In a study of patients with acute ST-segment elevation MI [29], which included 200 people, the incidence of adverse cardiovascular events (all-cause death, recurrent MI, HF) was analyzed during 3,1-year follow-up. In total, 20 such cases were identified, among which there were significantly lower values of both LV GFI and LVEF in comparison with the group without adverse cardiovascular events. In the ROC analysis, LV GFI and LVEF also showed comparable predictive values — AUC 0,73 and 0,74, respectively. Thus, LV GFI was a strong predictor of adverse cardiovascular events over 3 years in post-MI patients, but was inferior to LVEF.

In another publication [31], 235 patients with coronary artery disease were examined and, according to MRI, 3 following groups were identified: patients with MI (n=67), without a history of MI, but detected on MRI (n=48) and without MI (n=120). There were no

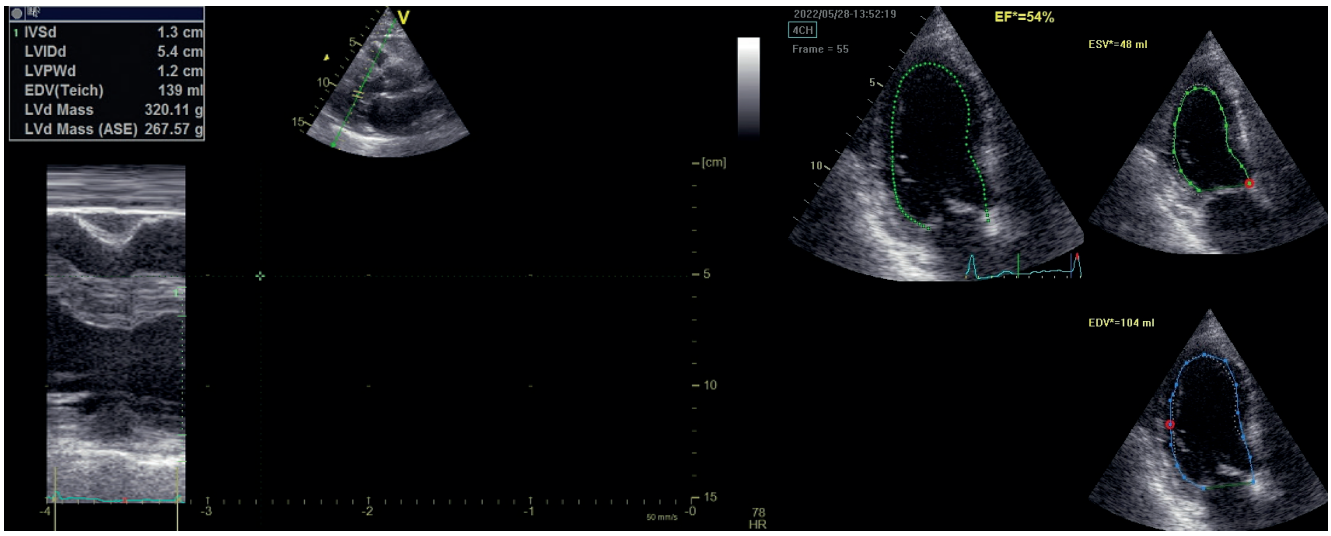

Figure 2. Estimation of LV mass and LVEF in a patient with impaired local contractility.
Note: LV EDV — 104 ml, LV ESV — 48 ml, LV SV — 56 ml, LV mass — 320 g, LVEF — 54%, LV GFI — 16%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

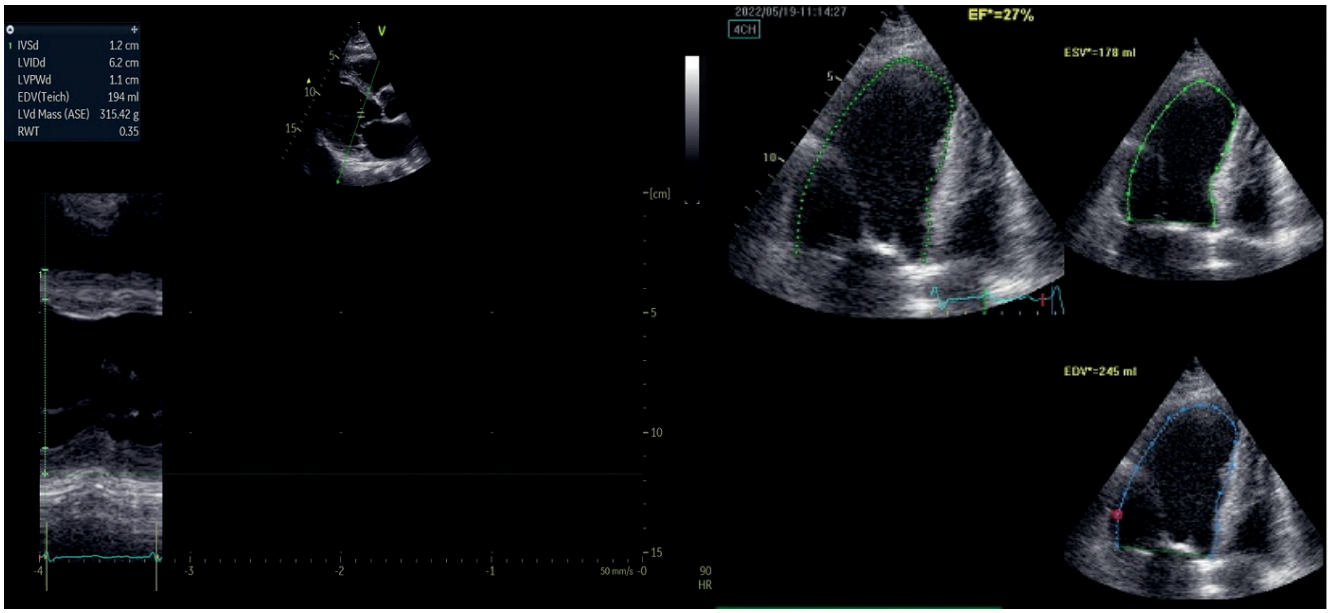

Figure 3. Estimation of LV mass and LVEF in a patient with reduced LVEF and eccentric LVH.
Note: LV EDV — 245 ml, LV ESV — 178 ml, LV SV — 67 ml, LV mass — 398 g, LVEF — 27%, LV GFI — 12%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

significant differences between groups 1 and 2 for either LVEF or LV GFI, but there was a significant difference between the groups 1+2 and group 3. Thus, the role of LV GFI as an additional parameter in the assessment of LV function in patients with coronary artery disease was shown, which, along with the data already presented, speaks in favor of greater prognostic value.

The studies assessing LV GFI in patients with acute coronary syndrome showed that a decrease in LV GFI <22,6% [36] is associated with an unfavorable outcome of ACS, correlates with the risk of all-cause death and adverse coronary events, along with age, prior MI, HF, diabetes and peripheral atherosclerosis. There was no significant difference in LVEF between the groups of survivors and deceased patients, in contrast to the LV GFI. LV GFI <27% [37] predicted obstructive coronary artery disease and had a high predictive value (AUC, 0,80) when

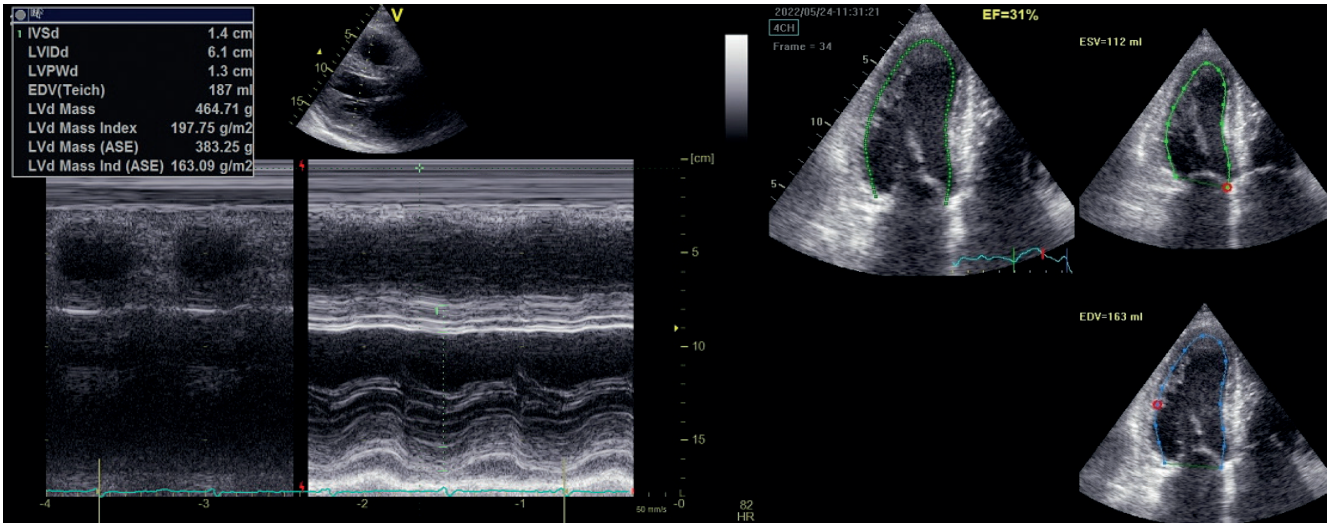

Figure 4. Estimation of LV mass and LVEF in a patient with reduced LVEF and concentric LVH.
Note: LV EDV — 163 ml, LV ESV — 112 ml, LV SV — 51 ml, LV mass — 465 g, LVEF — 31%, LV GFI — 9%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

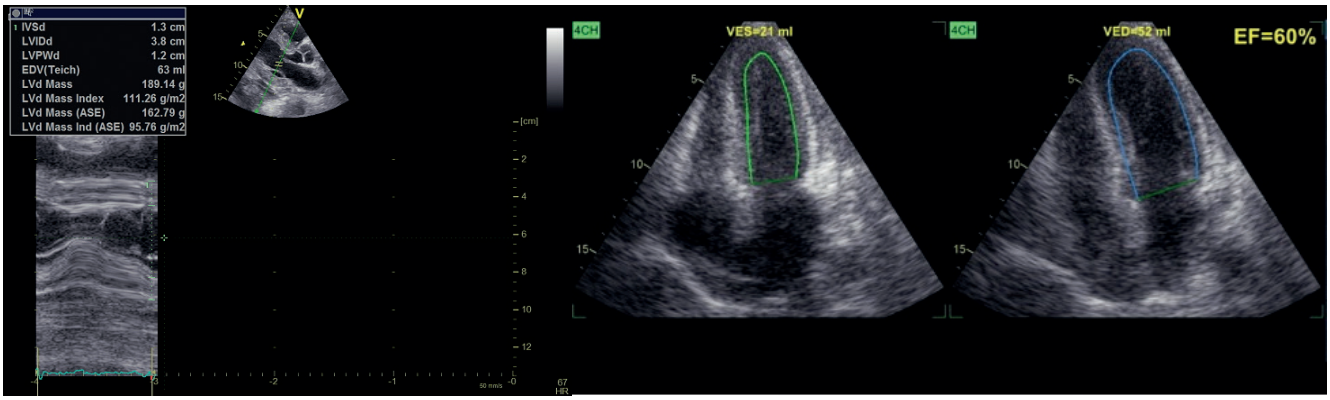

Figure 5. LV mass and LVEF in a patient with amyloidosis.
Note: LV EDV — 52 ml, LV ESV — 24 ml, LV SV — 28 ml, LV mass — 179 g, LVEF — 60%, LV GFI — 13%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

combined with LVEF, LV global longitudinal systolic strain, low-density lipoprotein level, and age.

Figure 2 shows an example of LV GFI calculation in a 73-year-old patient with concentric LVH, impaired local LV contractility (hypokinesia of the middle anterolateral and middle posterolateral segments) with a history of myocardial infarction, type 2 diabetes, and grade 3 hypertension, lower limb peripheral arterial disease.

Noteworthy is a significant decrease in LV GFI with normal LVEF and normal LV volumes.

Figures 3 and 4 illustrate the calculation of LV GFI in patients 77 and 67 years old with reduced LVEF, LVH (eccentric and concentric, respectively), prior MI, grade 3 hypertension, and multivessel coronary disease.

The calculations showed a significant decrease in LV GFI in patients with reduced LVEF in both eccentric LVH and concentric LVH.

LV GFI in cardiomyopathies and amyloidosis

LV GFI is of particular interest in patients with HCM, because EF does not take into account the relationship between LV mass and dimension. In a publication [30] including 90 patients with HCM and 68 patients with amyloidosis (66% with AL-amyloidosis), LV GFI demonstrated a comparable ability to late gadolinium uptake in the differential diagnosis of amyloidosis and HCM, superior to LVEF.

Figure 5 shows an example of LV GFI calculation in a 67-year-old patient with amyloidosis.

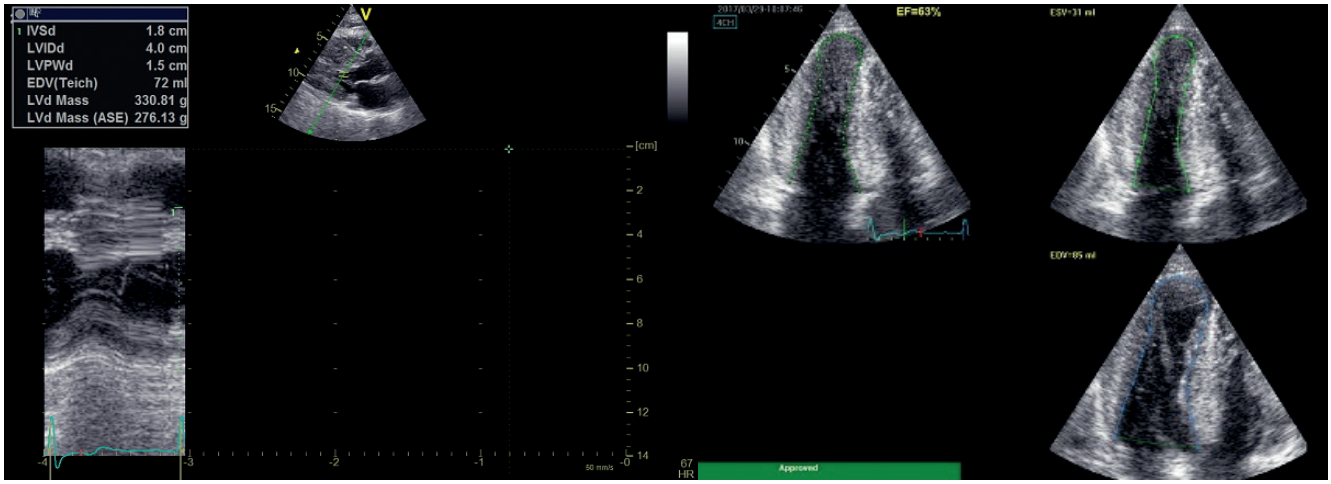

Figure 6. LV mass and LVEF in a patient with HCM.
Note: LV EDV — 85 ml, LV ESV — 31 ml, LV SV — 54 ml, LV mass — 331 g, LVEF — 63%, LV GFI — 15%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

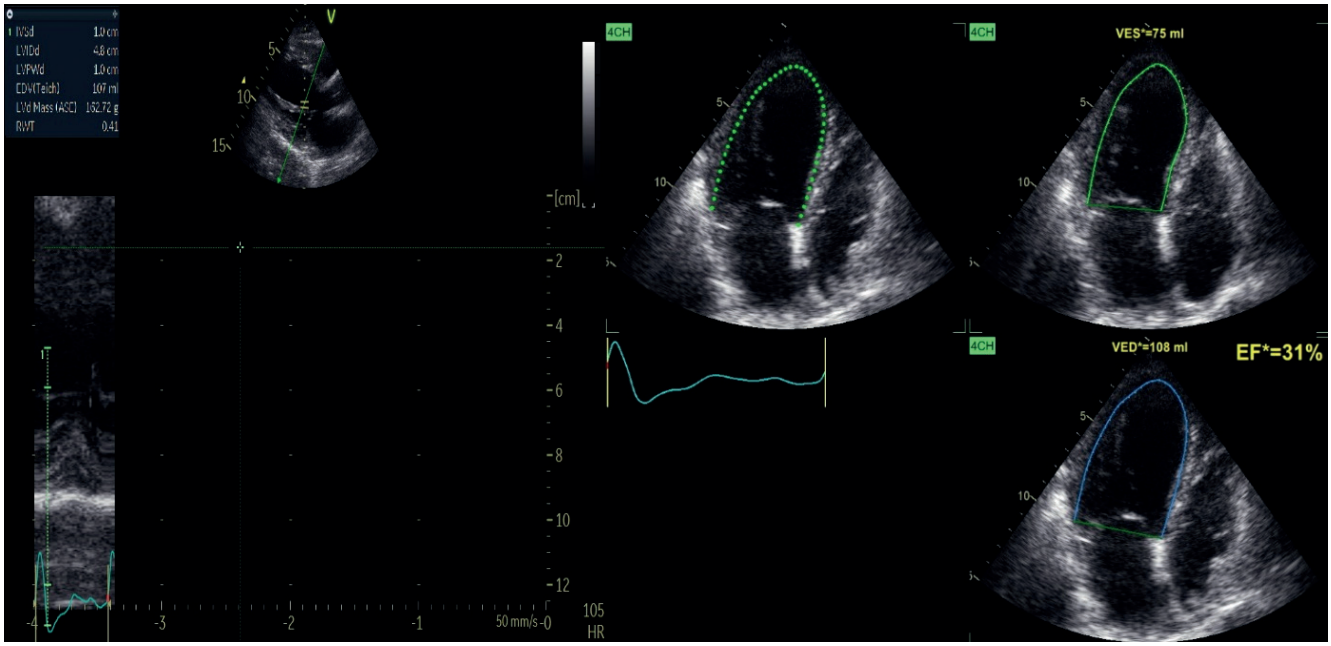

Figure 7. LV mass and LVEF in a patient with takotsubo cardiomyopathy.
Note: LV EDV — 108 ml, LV ESV — 75 ml, LV SV — 33 ml, LV mass — 163 g, LVEF — 31%, LV IGF — 10%.
Abbreviations: GFI — global function index, EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, SV — stroke volume, EF — ejection fraction.

As shown in Figure 5, LV GFI is significantly reduced, while LVEF and myocardial mass are normal, and LV volumes are low.

With a larger sample of patients (n=681), an analysis of LV GFI in HCM with LVEF >55% [33] was conducted during a 6,1-year follow-up period. LV GFI <37% was associated with the risk of all-cause death and ICD shock.

Figure 6 shows the parameters for calculating the LV GFI in a 68-year-old patient with HCM.

The presented calculations show a decrease in LV GFI with normal LVEF and LV volumes, but with increased myocardial mass.

Separate publications [32] showed differences in LV GFI in patients with myocarditis and takotsubo cardiomyopathy, which were more pronounced

when using LV GFI modification. However, the authors noticed significantly complicated estimation of this indicator.

Figure 7 shows the parameters for calculating LV GFI in a 68-year-old patient with takotsubo cardiomyopathy.

There is a decrease in LV GFI with a normal LV volume and mass, but with a decrease in LVEF.

Thus, LV GFI is an indicator of LV function, which can be easily estimated using standard echocardiography and does not require any additional methods. This is a huge advantage of LV GFI for wide diagnostic use. There is evidence of its prognostic significance in the development of adverse cardiovascular events in healthy individuals, patients with myocardial infarction, heart failure, heart failure with preserved LVEF, HCM. In addition, the effectiveness of LV GFI in the differential diagnosis of HCM and cardiac amyloidosis has been shown.

However, LV GFI also has a number of mathematical, methodological, and clinical limitations. Of course, LV GFI is mathematically related to LVEF and has similar disadvantages. For example, dependence on the quality of cardiac imaging on ultrasound is a major limitation for both EF and LV GFI. Impaired intracardiac hemodynamics with LV volume overload can also significantly affect both EF and LV GFI. Despite these limitations, the additional predictive value of LV GFI and its advantages mentioned above allow its wider use in a number of clinical situations.

According to the available data, LV GFI is not evaluated in routine diagnostic practice, not included in current guidelines, and currently purely research in nature. More studies are needed to evaluate in healthy groups of people and in various CVDs. In sum, these results indicate that LV GFI, which combines structural changes and LV functional state, can be useful and promising both in predicting subsequent cardiovascular events and as an indicator of LV structural and functional remodeling.

Relationships and Activities: none.

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