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Title: Evaluating the Association Between the Three Different Ejection Fraction Measurement Techniques and Left Ventricle Global Strain

Running Head: Assessment of Left Ventricular Systolic Function

Authors: Ednan Bayram[1], Oktay Gulcu[2], Ugur Aksu[3], Emrah Aksakal[1], Oguzhan Birdal[1], Kamuran Kalkan[3]

Institutions: [1]Department of Cardiology, Atatürk University School of Medicine, Erzurum, Turkey

[2]Clinic of Cardiology, Patnos State Hospital, Erzurum, Turkey

[3]Department of Cardiology, Erzurum Training and Research Hospital, Erzurum, Turkey

Correspondence to: Ugur Aksu, aksuuu001@msn.com

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ABSTRACT

Objective: The prognosis of cardiovascular diseases (CVDs) is directly associated with systolic function based on the measurement of ejection fraction (EF), and many studies have indicated that the left ventricular global strain (LVGS) provides better predictivity than the EF measurement in the diagnosis, prognosis, survival, and CVD staging. However, these studies did not investigate the correlation between the EF measurement and the LVGS parameters, or which parameters are better correlated with LVGS, but we analyzed the association between three EF measurement methods and LVGS.

Materials and Methods: This study included 62 patients that applied to the clinic between October 2015 and March 2016. An echocardiography examination of these patients was performed. The exclusion criteria were atrial fibrillation and suboptimal image quality.

Results: Sixty-two patients (the average age 61.0±12.6 years; 56% male and 44% female) were enrolled in the study. A statistically significant association was found between the visual EF and Simpson EF measurements and the LVGS parameters ($p<0.001$). While the visual EF was moderately correlated with the LVGS parameters (r=0.44), there was a good correlation between the Simpson EF and the LVGS parameters (r=0.710).

Conclusion: In this study, we demonstrate that the Simpson's rule LVEF correlates better with LVGS than the Teicholtz method or visual EF and that it has a better area under the curve value for determining an abnormal LVGS. Therefore, we recommend the use of the Simpson EF for the EF measurement that has a better correlation with the LVGS values in the patients whose ventricle functions should be evaluated.

Keywords: *ejection fraction*, *left ventricular global strain*, *echocardiography*

Introduction

An echocardiographic assessment of the ventricular functions is commonly used in the diagnosis of cardiovascular diseases (CDVs), therapy planning, prognosis, and prediction of adverse events. Also, it is recommended as the first option method in the current guidelines [1-2]. In recent years, echocardiographic techniques and methods have swiftly advanced and come into use in clinical practice. The use of high-frequency transducer, which improves the image quality, harmonic imaging opportunities, digital workstation, and the use of contrast agent are the vital developments that increased the application of echocardiographic methods. Measuring the diameter of cardiac cavities and assessing the ventricular systolic function are the main aims of the echocardiographic examination [3-7]. The prognosis of CVDs is directly associated with systolic function based on the measurement of ejection fraction (EF). The left ventricular systolic function is a consequence of the complex relations between myocardial contractility, pre-load, after-load, and heart rate.

The velocity of myocardial motion can be measured/recorded using the tissue Doppler imaging techniques, and the color Doppler images, which have been recorded previously, can be used to derive other image modalities. The strain (S) echocardiography was developed because of the limitations of the tissue Doppler imaging, including the inability to distinguish between the active and passive wall motion (tethering effect) and the influence on the peak velocity measures of the heart's rotational motions. Strain echocardiography has begun to be increasingly used in clinical investigations, and some studies have indicated that the S echocardiography provides a better predictivity than the EF measurement in the diagnosis, prognosis, survival, and staging of CVDs [8-12]. However, these studies did not investigate the correlation of the EF measurement with the S parameters or which parameters are better correlated with the LVGS. Nonetheless, the present study analyzed the association between the left ventricular EF measured through different methods and left ventricular global strain (LVGS).

Materials and Methods

Study Design

This study was carried out on the patients who underwent coronary angiography due to stable angina pectoris or acute coronary syndrome at our health care center between October 1, 2015 and March 1, 2016, and the study was launched after obtaining an ethics committee approval and the informed consent forms of the patients. While the patients aged over 18 years and who accepted to participate in the trial were included into the study, those who had atrial fibrillation and/or poor echogenicity were excluded from the study.

Definitions

The clinical risk factors including age, gender, hypertension, diabetes mellitus, hyperlipidemia, smoking, and familial history were recorded for each patient. Additionally, the blood pressure, heart rate, and previous medication were recorded, and the serum creatinine, blood glucose, lipids, and hematological indices were measured for all patients before the procedure. The patients who had systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg in at least two measurements taken after the admission and/or who were previously diagnosed with hypertension (HT) and applied an antihypertensive medication were regarded as hypertensive patients. Those patients whose fasting blood glucose was found to be >126 mg/dL in at least two measurements or those who were on oral antidiabetics/insulin were considered to be diabetic. The patients who were still smoking and/or smoked at least one package/year until 1 month before the admission were regarded as patients with a history of smoking.

Echocardiographic Examination

The echocardiographic examinations were performed by two experienced cardiologists, who were unaware of the study data. The the EF objective was to have a different cardiologist who measured all three methods for an evaluation. The measurements were carried out while the patients were in the left lateral decubitus position using the same echocardiography machine (Vivid 7, GE Healthcare, Horten, Norway) in standard precordial positions according to the American Society of Echocardiography (ASE) recommendation. All cases underwent the standard echocardiographic assessment including 2D (two-dimensional), PW (pulsed-wave) Doppler, color Doppler, and M-mode echocardiography. The visual EF was calculated by assessing the parasternal long and short-axis, apical 4- and 2-chamber views through at least three cardiac cycles. The M-mode echocardiography from the parasternal long axis (perpendicular to the long axis of the ventricle at the level of the mitral valve) measured the left ventricular end-diastolic diameter, left ventricular end-systolic diameter, interventricular septum thickness, and posterior wall thickness. These values were used to estimate the ejection fraction through the Teicholz method (Teicholz EF)=(LV end-diastolic dimension)−(LV end-systolic dimension)/(LV end-diastolic dimension). The endocardial contours were traced in the apical 4- and 2-chamber images in the end-diastole and end-systole. The end-diastolic and end-systolic dimensions were calculated according to the modified Simpson EF (Simpson EF)=(LV end-diastolic volume)−(LV end-systolic volume)/(LV end-diastolic volume).

For the LVGS imaging, the patients were positioned in the supine position and after the assessment of the patient's heart rhythm, 2D-imagery data (video clip) were recorded from the apical 2-, 3-, and 4-chamber and parasternal short-axis images that included at least three cardiac cycles at a rate of 50–75 frames/sec, accompanied by regular ECG signals in the tissue velocity imaging mode and subsequently stored for an offline analysis. The offline analysis of the video clips stored in the Vivid 7 GE echocardiography machine was performed using the Echopack software (GE, USA) installed on the Windows-based computer workstation. The endocardial boundary was determined by the same operator following successive points on a single frame. For each patient, the clip, in which the endocardial border was best imaged, was processed. For obtaining a 4-chamber apical view of the left ventricle, the marking was started from the septal mitral annular segment, and three points were marked for each segment. For the apical 2-chamber view, the viewpoints were marked starting from the mitral annulus at the level of the inferior wall. The LVGS was obtained from the sum of the global longitudinal strain measured in apical 4-, 3-, and 2-chamber views (Figure 1).

Statistical Method

Continuous variables were expressed as mean±standard deviation or median (interquartile range) values, whereas categorical variables were presented in percentages. The statistical analyses were conducted using the STATA software (trial version 13.0; Stata Corp, College Station, TX, USA) and the MedCalc (MedCalc Software, Ostend, Belgium) version 16 for Windows. Two-tailed p-values <0.05 were considered to indicate statistical significance. The normal distribution of the groups was verified with the Kolmogorov–Smirnov test. The continuous variables were compared with the Student's T-test and Mann–Whitney U-test, as appropriate. The Pearson's or Spearman's correlation coefficient was applied to identify the correlation between the groups. The correlation rate was expressed with the value *r*. Moreover, agreement between the EF methods and LVGS was assessed by the Bland–Altman plots and 95% confidence intervals. The strain values were divided into two groups according to the median value, and the receiver operating characteristic (ROC) curve analysis was performed for the EF methods.

Results

Considering the inclusion and exclusion criteria, a total of 62 patients (the average age was 61.0±12.6 years, 56% male and 44% female) were included in the study. There was a significant difference between the groups (baseline clinical and biochemical and echocardiographic parameters). The baseline clinical, biochemical, and echocardiographic characteristics of the patients are shown in Table 1.

A statistically significant association ($p<0.001$) and a moderate correlation ($r=0.44$) was found between the visual EF measurements and LVGS parameters (Figure 2A). Also, there was a statistically significant relation ($p<0.001$) and a moderate correlation ($r=0.287$)

between the Teicholz EF assessments and LVGS parameters (Figure 2B). Moreover, the Simpson EFEF measurements and LVGS parameters showed a statistically significant association (p<0.001) and a good correlation (r=0.710) (Figure 2C).

The Bland–Altman analysis was performed to test the limit of agreements between the visual EF, the Teicholz EF, and the Simpson EF respectively, and poor agreements in the Bland–Altman analysis were revealed for the visual (Figure 3A), Simpson (Figure 3B), and Teicholz (Figure 3C) EF, which means that it would not be appropriate to use them interchangeably.

The LVGS values were categorized by the median 19 value, and a ROC curve analysis was performed for the EF methods. The area under the curve (AUC) values for the visual, Teicholz, and Simpson EF methods and the confidence intervals are respectively shown in Table 2. It was indicated as a result of the comparison of the ROC curves that there was no difference between the visual EF and Teicholz, EF while the Simpson EF ensured a better predictivity as compared to the other two methods (Table 3).

Discussion

In this study, we examined the relation between EF values, which were measured using various methods, and LVGS values. We found that the Simpson EF correlates better with LVGS than the Teicholtz EF or visual EF and has a better AUC for determining abnormal LVGS. To the best of our knowledge, this is the first study comparing different EF measurement methods with the LVGS value in the literature.

Cardiac chambers, the ventricular muscle mass, and ventricular function are among the echocardiographic parameters that are primarily desired to be indicated by the clinicians, and ASE, in this regard, defined some standardization and presented it into clinical practice. Although echocardiography came into use as the gold-standard technique for cardiac examination, the standardization in echocardiographic assessment is lower as compared to other techniques. For this reason, various measurement techniques have been developed to overcome this disadvantage, and the measurement of EF is the most commonly applied technique among them [5, 10, 11, 13-16]. The EF is conventionally used for the prediction

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and assessment of CVDs and has been indicated to be potentially associated with the prediction of adverse events and poor outcome in several studies [11, 15].

The EF is a measurement traditionally performed through the modified Simpson EF using the Teicholz formula based on the M-mode imaging or disc method [11, 17].

Gudmundssion et al. [18] reported that the visual EF measurement showed a good correlation with all other formal methods and had an advantage because it could be readily and quickly performed. A comparison was made between the M-mode echocardiography and Simpson EF radionuclide ventriculography, and the overestimation rate (10%) was found to be higher in the M-mode method as compared to the other method. In another study, however, the M-mode method was demonstrated to correlate well with radionuclide ventriculography in the absence of the wall motion disorder. On the other hand, this study indicated the M-mode to have the worst correlation and that the overestimation rate was higher in the M-mode as compared to the other two methods [3, 5, 10-17, 19-24].

It was concluded in another study comparing the visual EF and Simpson EF with the radionuclide ventriculography that the visual EF showed a better correlation, and in the cases where echogenicity is poor and the ventricular wall contours cannot be identified, the Simpson EF may be miscalculated. Even though in the analysis the Simpson EF showed a better correlation with the radionuclide ventriculography than the visual EF measurement, the Simpson EF appeared to be disadvantageous because of the image quality and the failure of ventricular measurements in some patients. Nevertheless, the Simpson EF showed the best correlation with the strain parameter in our study.

It can be suggested in the light of the studies mentioned above that the Simpson EF provided a better correlation and better predictivity in the studies, where a comparison was made in-between the EF measurement methods [12, 19-21, 23, 24]. However, it should be noted that measuring EF, regardless of the method, is a challenging condition that requires experience and has high interobserver variability, and moreover, this assessment provides information only about the radial deformation of the myocardium. Whereas, it is known that the myocardial motion consists of three phases and that the myocardium thickens, shortens, and rotates during systole, and each of these motions separately contributes to the functions of the myocardium [3, 10, 12, 20].

The LVGS is a new parameter that has lately become available for evaluating the LV functions. It offers the main advantages of rapid and accurate diagnosis in the evaluation of LV functions. Furthermore, it has a low intraobserver variability. Its clinical use is estimated to elevate thanks to its independence in terms of high repeatability and the automatic tracking system [10].

LVGS is a sensitive indicator of myocardial dysfunction, which includes ischemia, hypertrophy, infiltration, hypoxia, cardiotoxic drug use, myocardial rejection, and severe systemic disease. Recent studies have found significant association between the LVGS parameters and the patients with known or suspected coronary artery disease, cardiac failure, and diabetes, and those that had chemotherapy or cardiac transplantation, and suggested that the LVGS parameters can be used for diagnosis, clinical progression, and adverse event estimation [10, 12, 17, 20].

Considering this information, it is undoubtedly inevitable that the LVGS will become a crucial method in transthoracic echocardiography because the LVGS measurement is not affected by many parameters, it shows less interobserver variability, and it is not influenced by other parameters that cause an error in the EF measurement. Moreover, the LVGS helps us approach the issue all in all by allowing the simultaneous evaluation of the other cardiac structures and cardiac cavities and giving information about the all structures and functions of the heart.

The prognosis of the CVDs is directly related to the systolic function depending on the EF measurement. However, many studies argued that the LVGS parameter based on the assessment of myocardial deformation offers better predictivity and correlation than EF in the prediction of cardiovascular events, progression, and mortality. Although some of the results of the studies making comparison between the EF measurement methods in the literature are contradictory, the Simpson EF indicated the best correlation with the LVGS in our study, and we did not experience any limitations while conducting the measurements. Therefore, the Simpson EF is a reliable method for measuring EF. According to our literature review, this is the first study comparing three different EF measurement methods with the LVGS, and it may lead the way for further studies.

In conclusion, the EF, which is recommended by the current guidelines, is a popular approach in the clinical practice. As compared to other echocardiographic measurements, the LVGS ensures better CVD predictivity and prognosis. On the other side, the Simpson EF correlates better with the global strain and has a more improved predictivity as compared to other two methods. Therefore, we recommend the use of the Simpson EF for the EF measurement as well as the LVGS parameters in the patients whose ventricle functions should be evaluated.

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Figure Legends

Figure 1: Left ventricular global strain (LVGS) measurement from the apical 4-chamber view

Figure 2: The correlation plots of the (a) visual, (b) Simpson, and (c) Teicholz EF measurement methods by the strain groups

Figure 3: The Bland–Altman analysis plots assessing the level of agreement between the (a) visual, (b) Simpson, and (c) Teicholz EF measurement methods

Variables	N
Age (years)	62.7±10.7
Sex (Male %)	75.4
Previous CAD (%)	48.4
DM (%)	19.7
Hypercholesterolemia (%)	32.8
Smoking (%)	36.1
Weight (kg)	75.3±12.5
Height (cm)	166±7.9
Serum glucose (mg/dl)	117±48.4
Creatinine (mg/dl)	0.91±0.27
Hemoglobin (g/dl)	14.5±2.13
HDL-cholesterol (mg/dl)	40.8±9.49
LDL-cholesterol (mg/dl)	125±36.9
TG (mg/dl)	180±148
Heart Rate (Min)	72.9±12.3
Septal wall thickness (mm)	1.14±0.13
Posterior wall thickness (mm)	1.07±0.108
LVEDD (mm)	4.88±0.64
LVSDD (mm)	3.33±0.84
Visual EF (%)	54.48±11.83
Teicholz EF (%)	56.34±13.8

Simpson EF (%)	53.1±14.4
LVGS (%)	19.71±5.46
TAPSE (mm)	1.96±0.43
Mapse (mm)	1.33±0.221
E velocity (m/s)	0.61±0.159
A velocity (m/s)	0.77±0.21
Deceleration time (msec)	235.8±78.9
Ejection time (msec)	270.2±38.4
Left ventricular twist (%)	14.8±8.02

Figure 4: The comparison of the ROC curves of the (a) visual, (b) Simpson, and (c) Teicholz EF measurement methods

Table 1: The baseline demographic, biochemical, and echocardiographic characteristics of the patients who participated in the study

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; LVEDD, end-diastolic diameter; LVESD, left ventricular end-systolic diameter; EF, ejection fraction; LVGS, left ventricular global strain; TAPSE, tricuspid annular plane systolic excursion; MAPSE, mitral annular plane systolic excursion

Table 2: The ROC curve analysis of the EF measurement methods by the strain groups

Variables	AUC(95 % CI)	Sensitivity	Specificity

Visual EF	0.68(0.54–0.81)	64	62
Teicholz EF	0.59(0.45–0.74)	58	50
Simpson EF	0.86(0.76–0.95)	88	57

Abbreviations: EF, ejection fraction; AUC, area under the curve

Table 3: The comparison of the ROC curve results of the EF measurement methods by the strain groups

Variables	P-Value
Visual EF–Teicholz EF	0.139
Teicholz EF–Simpson EF	0.0003
Simpson EF–Visual EF	0.0063

Abbreviations: EF, ejection fraction