Semiautomatic Quantification of Left Ventricular Ejection Fraction and Volumes by Two-Dimensional Echocardiography: Comparison with Automatic Three-Dimensional Echocardiography

Quantificação Semiautomática da Fração de Ejeção e Volumes do Ventrículo Esquerdo ao Ecocardiograma Bidimensional: Comparação com o Ecocardiograma Tridimensional Automático

Rafael Borsoi[1], Miguel Morita Fernandes da Silva[1], Silvio Henrique Barberato[1]
Quanta Diagnosis and Therapy – Curitiba, PR, Brazil.

Abstract

Background: Left ventricular ejection fraction is one of the most used echocardiographic parameters in clinical practice. Its estimation by two-dimensional manual method (Simpson method) has limited reproducibility and accuracy, and semi-automatic methods have been proposed. It becomes necessary to compare the semi-automatic two-dimensional method with more accurate methods of assessing left ventricular ejection fraction, such as measurement by automatic three-dimensional echocardiography.

Objective: To compare the left ventricular ejection fraction, and left ventricular end-diastolic and end-systolic volumes estimates by the semi-automatic two-dimensional method with those obtained using the automatic three-dimensional method.

Method: Observational cross-sectional study, including patients in sinus rhythm, left ventricular ejection fraction > 50% and without significant structural heart disease, submitted to transthoracic echocardiography. Student's t test, Pearson's coefficient and Bland-Altman analysis were used in the statistical analysis.

Results: Forty patients were included, 53% women, 35% with arterial hypertension, 25% with dyslipidemia, 10% diabetic, 10% smokers and 13% with previous angioplasty. The mean values of left ventricular ejection fraction by three-dimensional and two-dimensional were 62.1 ± 5.8% and 61.7 ± 5.9% (p = 0.50), respectively. There was a strong correlation between left ventricular ejection fraction determined by two-dimensional and three-dimensional (r = 0.75; p <0.001), as well as with left ventricular end-diastolic (r = 0.75; p <0.001) and end-systolic (r = 0.76; p < 0.001). There was good agreement between two-dimensional and three-dimensional left ventricular ejection fraction (mean difference: -0.39; 95% confidence interval -1.7-0.9).

Conclusion: Left ventricular ejection fraction estimated by the two-dimensional semi-automatic method showed good agreement with the automatic three-dimensional method. The findings suggest the two-dimensional semi-automatic method as a reliable alternative for assessing volumes and left ventricular ejection fraction.

Keywords: Echocardiography, Doppler; Echocardiography, Three-Dimensional; Stroke Volume; Ventricular Function, Left.

Resumo

Fundamento: *A fração de ejeção do ventrículo esquerdo é um dos parâmetros ecocardiográficos mais utilizados na prática clínica. Sua estimativa pelo método bidimensional manual (método de Simpson) tem reprodutibilidade e acurácia limitadas, e métodos semiautomáticos têm sido propostos. Torna-se necessário comparar o método bidimensional semiautomático com métodos mais acurados de avaliação da fração de ejeção do ventrículo esquerdo, como a medida pela ecocardiografia tridimensional automática.*

Objetivo: *Comparar as estimativas da fração de ejeção do ventrículo esquerdo e dos volumes diastólico final e sistólico final do ventrículo esquerdo pelo método bidimensional semiautomático com as obtidas pelo método tridimensional automático.*

Método: *Estudo observacional transversal, com pacientes em ritmo sinusal, fração de ejeção do ventrículo esquerdo >50% e sem cardiopatia estrutural significativa, submetidos ao ecocardiograma transtorácico. Teste **t** de **Student**, coeficiente de Pearson e análise de Bland-Altman foram usados na análise estatística.*

Resultados: *Foram incluídos 40 pacientes, sendo: 53% mulheres, 35% hipertensos, 25% dislipidêmicos, 10% diabéticos, 10% tabagistas e*

Mailing Address: Rafael Borsoi •
R. Alm. Tamandaré, 1000 - Alto da XV, Curitiba - PR, 80045-170
E-mail: rafaelborsoi@yahoo.com.br
Manuscript received 3/9/2020; revised 3/26/2020; accepted 4/17/2020

DOI: 10.47593/2675-312X/20203304eabc98

13% com angioplastia prévia. Os valores médios da fração de ejeção do ventrículo esquerdo aos métodos tri e bidimensionais foram 62,1 ± 5,8% e 61,7 ± 5,9% (p = 0,50), respectivamente. Houve forte correlação da fração de ejeção do ventrículo esquerdo determinada melos métodos bi e tridimensional (r = 0,74; p<0,001), assim como com o volume diastólico final (r = 0,75; p<0,001) e o sistólico final (r = 0,76; p<0,001). Houve boa concordância entre a fração de ejeção do ventrículo esquerdo bi e tridimensional (diferença média: -0,39; intervalo de confiança 95% -1,7-0,9).

Conclusão: *A fração de ejeção do ventrículo esquerdo estimada pelo método bidimensional semiautomático mostrou boa concordância com o método tridimensional automático. Os achados sugerem que o método bidimensional semiautomático represente uma alternativa confiável para avaliação dos volumes e fração de ejeção do ventrículo esquerdo.*

Palavra-chave: Ecocardiografia Doppler; Ecocardiografia Tridimensional; Volume Sistólico; Função Ventricular Esquerda.

Introduction

The assessment of left ventricular ejection fraction (LVEF) and volumes is among the primary indications of transthoracic echocardiography; thus, it is essential that these measurements be accurately and reproducibly estimated.[1-3] Two-dimensional (2D) echocardiography, traditionally used for this purpose, has important limitations, such as broad intra- and interobserver variability and ventricular volume obtention through geometric presumptions.[4,5] Three-dimensional (3D) echocardiography allows for more reliable volumetric and functional left ventricular (LV) analyses and boasts greater reproducibility than manual 2D echocardiography (Simpson's method) and greater precision than cardiac magnetic resonance (CMR).[6-11] Three-dimensional echocardiography results are close to the volumes obtained by CMR, considered the gold standard, while 2D manual echocardiography significantly underestimates LV measurements.[7-9] In the first years using the method, image acquisition difficulties and delayed analysis limited the routine use of 3D echocardiography and decreased its spread.[12-14] Recent improvements in quantification methods made its use faster and simpler in daily practice.[15-18] The commercially available automatic 3D Philips HeartModel software can obtain cardiac chamber LVEF and volumes in approximately 30 seconds while requiring minimal operator training and maintaining a strong correlation with CMR results.[19-22] Similarly, 2D echocardiography quantification methods have also progressed by providing semiautomatic LVEF and volumes in addition to other relevant information for clinical practice, such as global longitudinal strain (GLS). However, no studies comparing semiautomatic LVEF 2D quantification software with the 3D echocardiographic method, which has proven greater accuracy, were found in the literature.

This study aimed to compare LVEF and end-diastolic LV (EDV) and end-systolic LV (ESV) estimates of the semiautomatic 2D and automatic 3D methods.

Methods

This observational cross-sectional study included an outpatient population referred for transthoracic echocardiography by their attending physician. The included patients had sinus rhythm and an LVEF > 50% without significant structural heart disease (moderate to severe aortic, mitral or tricuspid insufficiency; any degree of valve stenosis; congenital heart disease with any degree of hemodynamic repercussion; pericardial effusion; LV segment contractility; and moderate to severe myocardial hypertrophy) and with a high-quality acoustic window. After a complete standardized echocardiographic examination, 2D and 3D images were also acquired to analyze and compare LVEF, ESV, and EDV using the automatic 3D and semiautomatic 2D methods. The examinations were performed on an EPIQ 7 ultrasound machine (Philips) with an X5 transducer. The images for volume and LVEF assessment were obtained by the semiautomatic 2D method in four- and two-chamber apical windows. Additionally, the apical three-chamber view was obtained to calculate the GLS. Reference points were defined in the mitral annulus (septal and lateral, anterior and inferior) and in the apex at each of the windows. From these reference points, the semiautomated aCMQ software (Philips) detected the systolic and diastolic LV endocardial borders, providing LVEF, ESV, and EDV estimates (Figure 1). When necessary, manual adjustments were made to optimize identification of the cardiac borders.

Images were obtained by the automatic 3D method in the four-chamber apical window during controlled apnea to estimate LVEF and volumes. After acquisition, the images were analyzed by the HeartModel software, which uses an adaptive analytical algorithm to automatically detect the interface between the endocardial borders and the blood. At the touch of a single button on the HeartModel's screen, the software automatically calculated LVEF and volumes (Figure 2). If necessary, manual adjustments were made to optimize the identification of the endocardial borders.

The Statistical Package for Social Science software version 22.0.0.0 was used for the statistical analyses; values of $p < 0.05$ were considered statistically significant. The results are presented as mean and standard deviation. Student's t-test (numerical differences), Pearson's coefficient (correlation), and Bland-Altman analysis (concordance) were used in the statistical evaluation.[23]

Results

Of the 44 patients included in the study, four were excluded due to a lack of data or inadequate echocardiographic image quality, resulting in a final sample of 40 patients. The mean age was 58 ± 15 years and the body mass index was 26 ± 3; 52.5% (n = 21) of the patients were women, 35% (n = 14) were hypertensive, 25% (n = 10) had dyslipidemia, 10% (n = 4) were diabetic, 10% (n = 4) were smokers, and 12.5%

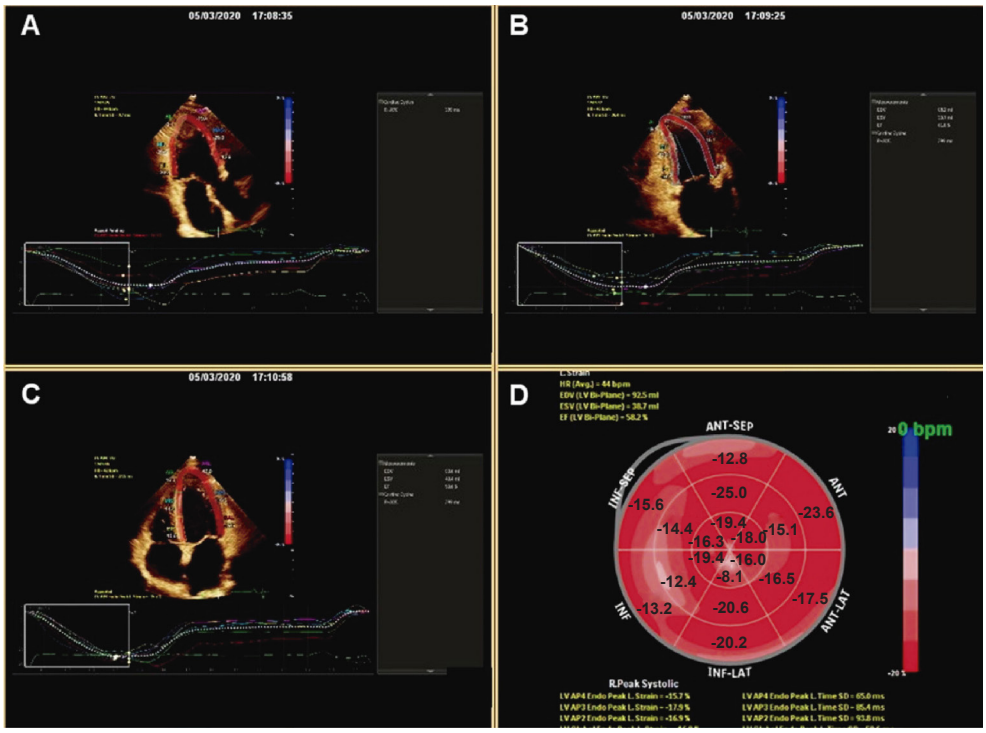


Figure 1 – *Left ventricular ejection fraction estimation by the aCMQ software from two- and four-chamber apical sections (B and C). The apical three-chamber view (A) and the bullseye graph with global longitudinal strain calculation (D) are shown.*

LV, left ventricle; LA, left atrium.

Figure 2 – *Sample three-dimensional reconstruction produced by the HeartModel software representing the left ventricle and other cardiac chambers. The software automatically calculates left ventricular ejection fraction and end-systolic and diastolic volumes.*

(n = 5) previously underwent coronary angioplasty. These and other clinical characteristics are shown in Table 1.

Regarding the echocardiographic parameters of the study population, 38% (n = 15) had grade I diastolic dysfunction (all others were normal), 18% (n = 7) had mild concentric LV hypertrophy, and 10% (n = 4) had a slightly increased LA. The mean GLS was 18.1 ± 2.7% (absolute value). The echocardiographic parameters are shown in Table 2.

The mean 3D and 2D FEVE values were 62.1 ± 5.8% and 61.7 ± 5.9% (p = 0.50), respectively. There was a strong correlation between 2D and 3D LVEF (r = 0.74; p < 0.001), EDV (r = 0.75; p < 0.001), and ESV (r = 0.76; p < 0.001) values. The Bland-Altman analysis (Figure 3) showed good concordance between 2D and 3D LVEF estimates (mean difference, -0.39; 95% confidence interval, -1.71 to -0.9; concordance, -8.67 to 7.89).

Table 1 - Demographic and clinical characteristics of the study population.

Characteristic	
Age, years	58 ± 15 (28-84)
Women	21 (52.5)
BMI	26 ± 3 (19-35)
Beta-blocker use	8 (20)
ACEI or ARB use	11 (27.5)
CCA	3 (7.5)
Diuretic	3 (7.5)
ASA use	8 (20)
Statin	7 (17.5)
SAH	14(35)
Dyslipidemia	10(25)
DM	4 (10)
Sedentary lifestyle	5 (12.5)
Smoking	4 (10)
Family history of CAD	3 (7.5)
CT or RxT	3 (7.5)
Prior CAD	6 (15)
Previous revascularization	5 (12)

Results expressed as mean ± standard deviation (range) or n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; CAD, coronary artery disease; CCA, calcium channel antagonist ; CT, chemotherapy; DM, diabetes mellitus; RxT, radiotherapy; SAH, systemic arterial hypertension.

Table 2 - Echocardiographic characteristics of the study population.

Characteristic	Value
LV mass, g/m²	87 ± 21
LA volume, mL/m²	26 ± 6
E/A ratio	1.1 ± 0.44
Septal e' wave, cm/s	7.2 ± 2.2
Lateral e' wave, cm/s	9.6 ± 2.9
Wave and 'mean, cm/s	8.4 ± 2.4
Septal E/e' ratio	10.9 ± 3.9
Lateral E/e' ratio	8.3 ± 2.9
Mean E/e' ratio	9.7 ± 3.8
GLS, %	18.1 ± 2.7

Values are shown as mean ± standard deviation. GLS, global longitudinal strain; LA, left atrium; LV, left ventricle.

Discussion

LV systolic function estimation by LVEF is a cornerstone of modern cardiology that has great use in clinical practice, with transthoracic echocardiography being the first-line examination for this purpose. Although 3D echocardiography enables a more reliable, accurate, and reproducible analysis, manual 2D echocardiography (Simpson's method) is still the most widely available and commonly used method for estimating LVEF. The evaluation of LV systolic performance using manual 2D echocardiography is based on endocardial border tracing, taking care to maximize the areas and avoid LV volume underestimation.[11,24] On the other hand, on 3D echocardiography, LV volume reduction is less relevant since the method is not based on geometric assumptions.[9-11] In cases of good image quality, the accuracy of the 3D method is comparable to that of CMR, with a tendency to obtain slightly smaller volumes.[6,7] In the present study, the good concordance between the results of the semiautomatic 2D and automatic 3D methods suggests that semiautomatic 2D echocardiography may be a reliable alternative for LVEF and volume evaluation. The calculated bias was low in the Bland-Altman analysis, i.e., the differences between methods seemed clinically acceptable. No previous study comparing the semiautomatic 2D and automatic 3D methods was found in a literature review.

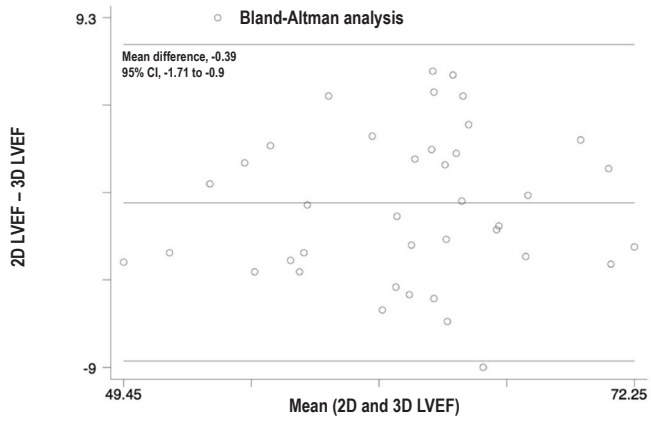
Semiautomatic 2D echocardiography showed good practical applicability and processing time. The broad use of traditional 3D echocardiography was recently limited by image acquisition difficulties and delayed analysis[12-14] in addition to its limited availability. Although the present study did not specifically evaluate image acquisition and processing time, evaluations using the semiautomatic 2D method tended to be faster than those with the manual 2D and traditional 3D methods, enabling its inclusion in the standard echocardiography routine.[11,13]

Economically, the semiautomatic 2D echocardiography method is a more accessible option, considering that equipment using 3D technology has higher cost due to the greater complexity of its components (transducers and software). The disadvantages of using the semiautomatic 2D echocardiography method include an inadequate echocardiographic window or certain types of structural cardiac changes that can lead to incorrect recognition of the endocardial borders and atrioventricular junction. Manual adjustments can optimize the identification of the borders, but they require a longer analysis time. Likewise, arrhythmias or inappropriate electrocardiographic tracings can impair the identification of end-systolic and/or diastolic conditions, providing inaccurate or incorrect estimates. On the other hand, the same technical difficulties are observed in the automatic 3D echocardiography method, comprising common limitations to the two methods.[23] To minimize these difficulties, this study included only patients with an adequate thoracic acoustic window, a regular heart rhythm, and no significant structural heart changes. Prospects point to the development and optimization of software and automatic platforms for cardiac chamber volumetric and functional calculations. The progression of these platforms should enable more agile and precise measurements despite the current limitations.

The limitations of this study include its relatively small sample, absence of simultaneous measurement by traditional non-automatic methods (manual 2D and semiautomatic 3D), and lack of intra- and interobserver variability estimations. In addition, the findings cannot be extended to patients with arrhythmias, LV systolic dysfunction (LVEF < 50%), and/or moderate to severe structural heart disease.

Conclusion

This study is the first to demonstrate good concordance between LVEF and ventricular volumes estimated by the semiautomatic 2D and automatic 3D methods in patients without arrhythmias and/or significant structural heart disease.



2D, two-dimensional; 3D, three-dimensional; 95% CI, 95% confidence interval; LVEF, left ventricular ejection fraction.

Figure 3 – *Bland-Altman analysis of two- and three-dimensional left ventricle ejection fraction.*

Thus, 2D transthoracic echocardiography with automatic quantification software was proven reliable for measuring LVEF and volumes in this group of participants.

Authors' contributions

Research creation and design: Borsoi R, Barberato SH; Data acquisition: Borsoi R, Barberato SH; Data analysis and interpretation: Borsoi R, Barberato SH, Silva MMF; Statistical analysis: Barberato SH, Silva MMF; Manuscript writing: Borsoi R, Barberato SH, Silva MMF; Critical revision of the manuscript for important intellectual content: Borsoi R, Barberato SH, Silva MMF.

Conflict of interest

The author have declared that they have no conflict of interest.

References

1. Wong M, Johnson G, Shabetai R, Hughes V, Bhat G, Lopez B, et al. Echocardiographic variables as prognostic indicators and therapeutic monitors in chronic congestive heart failure. Veterans Affairs cooperative studies V-HeFT I and II. V-HeFT VA Cooperative Studies Group. Circulation. 1993;87(6 Suppl):VI65-70. PMID: 8500242.

2. Kaufmann BA, Min SY, Goetschalckx K, Bernheim AM, Buser PT, Pfisterer ME, et al. How reliable are left ventricular ejection fraction cut offs assessed by echocardiography for clinical decision making in patients with heart failure? Int J Cardiovasc Imaging. 2013;29(3):581-8. doi: 10.1007/s10554-012-0122-5

3. Cameli M, Mondillo S, Solari M, Righini FM, Andrei V, Contaldi C, et al. Echocardiographic assessment of left ventricular systolic function: from ejection fraction to torsion. Heart Fail Rev. 2016;21(1):77-94. doi: 10.1007/s10741-015-9521-8

4. Jacobs LD, Salgo IS, Goonewardena S, Weinert L, Coon P, Bardo D, et al. Rapid online quantification of left ventricular volume from real-time threedimensional echocardiographic data. Eur Heart J. 2006;27(4):460-8. doi: 10.1093/eurheartj/ehi666

5. Hoffmann R, Barletta G, von Bardeleben S, Vanoverschelde JL, Kasprzak J, Greis C, et al. Analysis of left ventricular volumes and function: a multicenter comparison of cardiac magnetic resonance imaging, cine ventriculography, and unenhanced and contrast-enhanced two-dimensional and three-dimensional echocardiography. J Am Soc Echocardiogr. 2014;27(3):292-301. doi: 10.1016/j.echo.2013.12.005

6. Jenkins C, Bricknell K, Hanekom L, Marwick TH. Reproducibility and accuracy of echocardiographic measurements of left ventricular parameters using real-time three-dimensional echocardiography. J Am Coll Cardiol. 2004;44(4):878-86. doi: 10.1016/j.jacc.2004.05.050

7. Kühl HP, Schreckenberg M, Rulands D, Katoh M, Schafer W, Schummers G, et al. High-resolution transthoracic real-time three-dimensional echocardiography: quantitation of cardiac volumes and function using semi-automatic border detection and comparison with cardiac magnetic resonance imaging. J Am Coll Cardiol. 2004;43(11):2083-90. doi: 10.1016/j.jacc.2004.01.037

8. Caiani EG, Corsi C, Zamorano J, Sugeng L, MacEneaney P, Weinert L, et al. Improved semi-automated quantification of left ventricular volumes and ejection fraction using 3-dimensional echocardiography with a full matrix-array transducer: comparison with magnetic resonance imaging. J Am Soc Echocardiogr. 2005;18:779-88.

9. Mor-Avi V, Jenkins C, Kuhl HP, Nesser HJ, Marwick T, Franke A, et al. Real-time 3-dimensional echocardiographic quantification of left ventricular volumes: multicenter study for validation with magnetic resonance imaging and investigation of sources of error. JACC Cardiovasc Imaging. 2008;1(4):413-23. doi: 10.1016/j.jcmg.2008.02.009

10. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T, Faletra FF, Franke A, Hung J, de Isla LP, Kamp O, Kasprzak JD, Lancellotti P, Marwick TH, McCulloch ML, Monaghan MJ, Nihoyannopoulos P, Pandian NG, Pellikka PA, Pepi M, Roberson DA, Shernan SK, Shirali GS, Sugeng L, Ten Cate FJ, Vannan MA, Zamorano JL, Zoghbi WA; American Society of Echocardiography; European Association of Echocardiography. EAE/ASE recommendations for image acquisition and display using threedimensional echocardiography. J Am Soc Echocardiogr. 2012;25(1):3-46. doi: 10.1016/j.echo.2011.11.010

11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular

Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003

12. Pepi M, Tamborini G, Pontone G, Andreini D, Berna G, De Vita S, et al. Initial experience with a new on-line transthoracic three-dimensional technique: assessment of feasibility and of diagnostic potential. Ital Heart J. 2003;4(8):544-50.

13. Soliman OI, Krenning BJ, Geleijnse ML, Nemes A, van Geuns RJ, Baks T, et al. A comparison between QLAB and TomTec full volume reconstruction for real time three-dimensional echocardiographic quantification of left ventricular volumes. Echocardiography. 2007;24(9):967-74.

14. Tsang W, Kenny C, Adhya S, Kapetanakis S, Weinert L, Lang RM, et al. Interinstitutional measurements of left ventricular volumes, speckle tracking strain, and dyssynchrony using three-dimensional echocardiography. J Am Soc Echocardiogr 2013;26(11):1253-7. doi: 10.1016/j.echo.2013.07.023

15. Muraru D, Badano LP, Piccoli G, Gianfagna P, Del Mestre L, Ermacora D, et al. Validation of a novel automated border-detection algorithm for rapid and accurate quantitation of left ventricular volumes based on threedimensional echocardiography. Eur J Echocardiogr. 2010;11(4):359-68. doi: 10.1093/ejechocard/jep217

16. Thavendiranathan P, Liu S, Verhaert D, Calleja A, Nitinunu A, Van Houten T, et al. Feasibility, accuracy, and reproducibility of real-time full-volume 3D transthoracic echocardiography to measure LV volumes and systolic function a fully automated endocardial contouring algorithm in sinus rhythm and atrial fibrillation. J Am Coll Cardiol Img. 2012;5(3):239-51. doi: 10.1016/j.jcmg.2011.12.012

17. Shibayama K, Watanabe H, Iguchi N, Sasaki S, Mahara K, Umemura J, et al. Evaluation of automated measurement of left ventricular volume by novel real-time 3-dimensional echocardiographic system: validation with cardiac magnetic resonance imaging and 2-dimensional echocardiography. J Cardiol. 2013;61(4):281-8. doi: 10.1016/j.jjcc.2012.11.005

18. Zhang QB, Sun JP, Gao RF, Lee AP, Feng YL, Liu XR, et al. Feasibility of single-beat full-volume capture real-time three-dimensional echocardiography for quantification of right ventricular volume: validation by cardiac magnetic resonance imaging. Int J Cardiol. 2013;168(4):3991-5. doi: 10.1016/j.ijcard.2013.06.088

19. Tsang W, Salgo IS, Medvedofsky D, Takeuchi M, Prater D, Weinert L, et al. Transthoracic 3D echocardiographic left heart chamber quantification using an automated adaptive analytics algorithm. J Am Coll Cardiol Img. 2016;9(7):769-82. doi: 10.1016/j.jcmg.2015.12.020

20. Otani K, Nakazono A, Salgo IS, Lang RM, Takeuchi M. Three-dimensional echocardiographic assessment of left heart chamber size and function with fully automated quantification software in patients with atrial fibrillation. J Am Soc Echocardiogr. 2016;29(10):955-65. doi: 10.1016/j.echo.2016.06.010

21. Medvedofsky D, Mor-Avi V, Amzulescu M, Fernández-Golfín C, Hinojar R, Monaghan MJ, et al. Three-dimensional echocardiographic quantification of the left-heart chambers using an automated adaptive analytics algorithm: multicentre validation study. Eur Heart J Cardiovasc Imaging. 2018;19(1):47-58. doi: 10.1093/ehjci/jew328

22. Tamborini G, Piazzese C, Lang RM, Muratori M, Chiorino E, Mapelli M. Feasibility and accuracy of automated software for transthoracic three-dimensional left ventricular volume and function analysis: comparisons with two-dimensional echocardiography, three-dimensional transthoracic manual method, and cardiac magnetic resonance imaging. J Am Soc Echocardiogr. 2017;30(11):1049-58. doi: 10.1016/j.echo.2017.06.026

23. Bland JM, Altman DG. Statistical method for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307-10.

24. Knackstedt C, Bekkers SC, Schummers G, Schreckenberg M, Muraru D, Badano LP, et al. Fully automated versus standard tracking of left ventricular ejection fraction and longitudinal strain the FAST-EFs multicenter study. J Am Coll Cardiol. 2015 Sep 29;66(13):1456-66. doi: 10.1016/j.jacc.2015.07.052