Validation of Estimating Left Ventricular Ejection Fraction by Mitral Annular Displacement Derived From Speckle-Tracking Echocardiography: A Neglected Method for Evaluating Left Ventricular Systolic Function

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Abstract

Background The accurate measurement of left ventricular (LV) ejection fraction (EF) is highly dependent on professional experience and adequate visualization. The tissue motion of mitral annular displacement (TMAD) can be easily and quickly assessed using speckle tracking echocardiography (STE) for evaluating the LV systolic function, even in patients with poor acoustic windows. Therefore, this study aimed to validate whether LVEF can be estimated using the STE-derived TMAD when LVEF is not available. Methods Four-hundred fifty-six outpatients were consecutively enrolled in this study. An optimized regression model for LVEF-TMAD was developed in the derivation set (n=287), and its reliability was verified in the validation set (n=123) and regional wall motion abnormalities (RWMA) set (n=46). Results In the derivation set, the power models had the highest F-value, and the power equations were chosen to estimate LVEF according to TMAD in the validation set. Near-zero bias and a narrow range of differences were observed between the observed and estimated LVEF. The highest intra-class correlation coefficient was observed between the observed LVEF and estimated LVEF according to the normalized TMAD at the midpoint of mitral annular (nTMADmid). Moreover, there were no significant differences between the observed and estimated LVEF in the RWMA set. Conclusion The LVEF can be estimated with the STE-derived TMAD using a power equation, even for patients with RWMA, and the nTMADmid may be the optimal parameter. The proposed method may provide a clinically acceptable alternative for evaluating LV systolic function when the direct measurement of LVEF is not available.

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Abstract

Background

The accurate measurement of left ventricular (LV) ejection fraction (EF) is highly dependent on professional experience and adequate visualization. The tissue motion of mitral annular displacement (TMAD) can be easily and quickly assessed using speckle tracking echocardiography (STE) for evaluating the LV systolic function, even in patients with poor acoustic windows. Therefore, this study aimed to validate whether LVEF can be estimated using the STE-derived TMAD when LVEF is not available.

Methods

Four-hundred fifty-six outpatients were consecutively enrolled in this study. An optimized regression model for LVEF-TMAD was developed in the derivation set (n=287), and its reliability was verified in the validation set (n=123) and regional wall motion abnormalities (RWMA) set (n=46).

Results

In the derivation set, the power models had the highest F -value, and the power equations were chosen to estimate LVEF according to TMAD in the validation set. Near-zero bias and a narrow range of differences were observed between the observed and estimated LVEF. The highest intra-class correlation coefficient was observed between the observed LVEF and estimated LVEF according to the normalized TMAD at the midpoint of mitral annular (nTMADmid). Moreover, there were no significant differences between the observed and estimated LVEF in the RWMA set.

Conclusion

The LVEF can be estimated with the STE-derived TMAD using a power equation, even for patients with RWMA, and the nTMADmid may be the optimal parameter. The proposed method may provide a clinically acceptable alternative for evaluating LV systolic function when the direct measurement of LVEF is not available.

Keywords: Left ventricular ejection fraction, Mitral annular displacement, Systolic function, Speckle-tracking, Echocardiography

Introduction

Echocardiographic assessment of the left ventricular (LV) systolic function plays a central role in the management of patients with cardiac disease, which provides a reliable basis for the evaluation of disease severity, therapeutic efficacy, prognosis, and corresponding clinical decisions.[1-3] Therefore, the accurate assessment of the LV systolic function is of pivotal importance in routine clinical settings.

The LV ejection fraction (LVEF) is widely recognized as a key variable for evaluating the LV systolic function. The LVEF measured using the two-dimensional biplane Simpson's method plays a ubiquitous role in the characterization and management of cardiac disease and pervades a number of guidelines and clinical practices.[4-6] However, the measurement of the LVEF is highly dependent on professional experience and adequate visualization of the LV endocardium.[7, 8] Therefore, an approach that is more widely available and is independent of the image quality or operators' experience is desired for assessing the LV systolic function in daily clinical practice.

Mitral annular displacement can quantitatively reflect the movement of the mitral annulus towards the apex and accurately assess the LV global longitudinal systolic function independent of the image quality or operators' experience.[9] Mitral annular displacement can be used for identifying structural heart disease and for predicting mortality.[10, 11] Speckle-tracking echocardiography (STE) can automatically track mitral annular motion and measure tissue motion of mitral annular displacement (TMAD) without angle dependence, which is superior to the conventional M-mode ultrasound and tissue Doppler techniques.[12, 13] More importantly, the STE-derived TMAD can be easily and quickly obtained with high reproducibility, and its measurement is independent of the suboptimal endocardial definition or presence of reverberations.[9, 14] However, currently no normal reference values of STE-derived TMAD are available in clinical practice. Therefore, it is highly warranted to investigate the relationship between the biplane LVEF and STE-derived TMAD and study whether the LVEF can be estimated using the STE-derived TMAD when the LVEF is not available.

In view of this discussion, this study aimed to investigate the relationship between the biplane LVEF and STE-derived TMAD, develop the best-fitting regression models and equations, and further validate the reliability of the optimum equations for quantitatively estimating the biplane LVEF according to the STE-derived TMAD in a large group of patients, which might provide an alternative for evaluating the LV global systolic function when the LVEF is not available or the LVEF values are highly variable.

Methods

Study population

This study prospectively and consecutively enrolled patients who underwent transthoracic echocardiography in the outpatient echocardiographic laboratory of our hospital between May 2019 and December 2019. Patients whose LVEF measurements remained challenging, such as patients with atrial fibrillation, left bundle branch block, severe pulmonary hypertension, and constrictive pericarditis were excluded from this study.[6] Moreover, patients with mitral annulus calcification and mitral valve replacement, which may confound the TMAD value, were also excluded.

Four-hundred fifty-six patients (mean age 51.6±16.2 years, 204 females) met the eligibility criteria during the study period. Of these patients, 46 (mean age 58.6±12.9 years, 5 females) had regional wall motion abnormalities (RWMA). The remaining 410 patients (mean age 50.8±16.3 years, 199 females) were randomly divided into a derivation set [n=287 (70%)] and a validation set [n=123 (30%)]. The derivation set was used to study the relationship between the biplane LVEF and STE-derived TMAD and to develop optimized regression models and equations for the LVEF-TMAD. The validation set was used to verify their reliability by assessing the agreements between the observed LVEF and estimated LVEF using the chosen regression equations. To avoid interference from RWMA, we developed and verified regression equations in the derivation and validation sets without RWMA patients. Then, we further, independently, validated the accuracy of estimating the LVEF using the chosen equation in the patients with RWMA.

Written informed consent was obtained from all patients before enrollment. The study protocol was approved by the China Medical University Ethics Committee and was conducted in line with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Echocardiographic analysis

Patients underwent transthoracic echocardiography using an iE33 imaging system (Philips Healthcare, Andover, MA) equipped with an S5 transducer. Echocardiographic images were acquired from standard views with an optimal frame rate between 50 and 70 frames per second according to the guidelines for performing a comprehensive transthoracic echocardiographic examination from the American Society of Echocardiography (ASE).[15] Careful attention should be made to avoid the presence of LV foreshortening in the apical views. At least three consecutive cardiac cycles were stored digitally for offline analysis using QLAB software (Philips Healthcare, USA). Image measurements and quantitative assessments were performed in accordance with the recommendations for cardiac chamber quantification from the Chinese Society of Ultrasound in Medicine.[16]Echocardiographic images were acquired and measured by two experienced cardiologists who

were blinded to any clinical data.

The LVEF was measured using the biplane Simpson's method in the apical 4-chamber and 2-chamber views, and the decrease in the LVEF was defined as an LVEF <53%.[16]All patients underwent TMAD measurement in the apical 4-chamber view. Initially, three points were selected as user-defined anatomic landmarks in a diastolic frame, including the septal and lateral mitral annulus and LV apical myocardium. Subsequently, the software automatically tracked the selected points of the mitral annulus frame by frame, calculated their displacements toward the LV apex throughout the cardiac cycle, and plotted the displacement–time curves of each tracked point**(Figure 1)** . Displacements in the septal and lateral mitral annulus (TMADsep and TMADlat) and the displacement of the midpoint of the two (TMADmid) were obtained. To normalize TMADmid, the ratio of TMADmid and the LV long-axis length at end-diastole (nTMADmid) was calculated. The mean of three measurements of three cycles was used for further analysis.

To investigate the variability of TMAD from the apical 4-chamber or 2-chamber view, we randomly sampled 120 subjects from the included patients who underwent TMAD in both apical 4-chamber and 2-chamber views (anatomic landmarks including the anterior and inferior aspects of the mitral annulus and LV apical myocardium).

Time and reproducibility of nTMADmid measurement

The total time taken for automatically tracking, measuring, and reporting TMAD was recorded in the measurements of each patient. Twenty patients were randomly selected to test the reproducibility of measuring nTMADmid. To assess intra-observer reproducibility, the same observer repeated the same measurements 3 months after the initial measurements. Another independent observer repeated the measurements twice to assess inter-observer reproducibility.

Statistical analysis

IBM SPSS version 21.0 statistical software (IBM Corp, Armonk, NY) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analyses. Normality plots with tests were performed using the Shapiro–Wilk test. Categorical data are presented as frequencies and percentages, and continuous data are presented as mean ± standard deviation (SD) or median (interquartile range). Differences between the derivation and validation sets in categorical variables were compared using the chi-square test or Fisher's exact test, and continuous variables were compared using independent samples t-test or Mann–Whitney U test, as appropriate. In the derivation set, correlations between the LVEF and TMAD were assessed with Pearson's correlation coefficients for normally distributed data and the Spearman's rho test for non-normal data. Receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) were used to evaluate the ability of the TMAD to identify the decrease in the LVEF. The best-fitting regression models for the LVEF and TMAD were developed, including linear, logarithmic, quadratic, cubic, compound, power, S, growth, and exponential and regression equations with the highest F -values chosen to estimate the LVEF in the validation set. Comparisons between the observed and estimated LVEF by each equation and the comparisons of the TMAD between the apical 4-chamber and 2-chamber views were performed by paired samples t-test or Wilcoxon test, as appropriate. The results of the paired samples t-test were internally validated via bootstrapping based on 1000 repetitions. Bland-Altman analyses were used for the assessment of bias and limits of agreement (LOA) between the observed and estimated LVEF. Intra-class correlation coefficients were also calculated using a two-way random-effects model. Bland-Altman analyses were also used to estimate intraobserver and interobserver variabilities. A two-tailed P -value <0.05 was considered statistically significant.

Results

Of the 456 enrolled patients, 158 (34.6%) had abnormal echocardiographic findings, including 46 (10.1%) patients with RWMA, 56 (12.3%) with LV hypertrophy due to hypertension, 41 (9.0%) with valvular heart disease, and 57 (12.5%) with decreased LVEF. Among patients with RWMA, there were anteroseptal, inferoseptal, inferior, inferolateral, anterolateral, and anterior wall involvement in 13 (28.3%), 15 (32.6%), 25

(54.3%), 5 (10.9%), 1 (2.2%), and 8 (17.4%) patients, respectively.

Table I shows the demographic characteristics and echocardiographic measurements of the derivation and validation sets. The age, sex distribution, body surface area, and body mass index were similar between the derivation and validation sets, and there were no statistical differences between the two sets in TMADsep, TMADlat, TMADmid, and nTMADmid.

Analysis in the derivation set

The LVEF was significantly correlated with the TMADsep (r=0.62,P <0.001), TMADlat (r=0.62, P <0.001), TMADmid (r=0.66, P <0.001), and nTMADmid (r=0.72,P <0.001). Moreover, when ROC analyses were performed to discriminate between the patients with normal and decreased LVEF, TMADsep, TMADlat, TMADmid, and nTMADmid, statistical significance was noted for all parameters, and the nTMADmid had the highest AUC (AUC, 0.98; sensitivity, 97.06%; specificity, 89.33%; **Figure 2**).

Table II presents the best-fitting regression models for computing the LVEF based on the TMAD in the derivation set, and all power models had the highest F -value (r^2 =0.57, F =376.40,P< 0.001 for the TMADsep;r^2 =0.46, F =244.03,P <0.001 for the TMADlat;r^2 =0.58, F =391.19,P <0.001 for the TMADmid; andr^2 =0.65, F =524.47,P <0.001 for the nTMADmid). Therefore, each regression equation of the power model was chosen to estimate the LVEF (**Table III**).

Analysis in validation set

In the validation set, the LVEFs were estimated from the TMADsep, TMADlat, TMADmid, and nTMADmid according to the aforementioned regression equations. In comparisons of the observed LVEF and estimated LVEF based on the TMADsep, TMADlat, TMADmid, and nTMADmid, no significant differences were noted (**Figure 3 and Table IV**).

In the Bland-Altman analysis, the estimated LVEF based on the TMADsep, TMADlat, TMADmid, and nTMADmid revealed a negative bias of 0.54% (LOA, -14.38 to 15.46%), 1.17% (LOA, 13.40 to 15.75%), 0.90% (LOA, 13.87 to 15.66%), and 0.95% (LOA, -12.70 to 14.59%), respectively compared with the observed LVEF (**Table IV and Figure 4**). All ranges of difference were acceptable, and the narrowest range of difference was shown between the observed LVEF and estimated LVEF based on the nTMADmid.

Table V shows the intra-class correlations and 95% confidence interval between the observed and estimated LVEF. The highest intra-class correlation coefficient was observed between the observed LVEF and estimated LVEF based on the nTMADmid [ρ , 0.76 (0.67-0.82); P <0.001].

Analysis in RWMA set

There were no significant differences between the observed LVEF and estimated LVEF based on the nTMADmid (57.48±7.41% vs. 56.87±4.74%, P =0.57) for the patients with RWMA, and there were still no significant differences after internal validation using the bootstrapping method (mean difference of -0.03 mm, 95% CI 1.55–2.64, P =0.58).

Comparisons of the TMAD between the apical 4-chamber and 2-chamber view

There were no significant differences in the TMADmid (11.67+-3.49% vs. 11.83+-3.73%, P =0.40) and nTMADmid (13.60+-4.18% vs. 13.56+-4.28%, P =0.86) between the apical 4-chamber and 2-chamber views, and there remained no significant differences after internal validation using the bootstrapping method (mean TMADmid difference of -0.001 mm, 95% CI -0.56–0.21, P =0.39; mean nTMADmid difference of -0.002 mm, 95% CI -0.38–0.45, P =0.85).

Time and reproducibility of the nTMADmid measurement

The automatic tracking, measuring, and reporting of the TMAD was performed in 10.6+-2.2 s. There was high intra- and inter-observer reproducibility for the nTMADmid measurement (**Figure 5**). The intra-

observer reproducibility for the nTMADmid had a bias of 0.04% (LOA, -1.96 to 2.04%), and inter-observer reproducibility had a bias of 0.08% (LOA, -2.50 to 2.66%).

Discussion

This study developed a series of best-fitting regression models and equations for the relationships between the LVEF and STE-derived TMAD in the derivation set, and further validated the reliability of the chosen optimum equations for estimating the LVEF based on the TMAD in the validation set. The results showed that the LVEF can be estimated with the STE-derived TMAD using a power equation, and the nTMADmid may be the optimal parameter. We then validated the accuracy of the estimation of the LVEF by the nTMADmid in the independent RWMA set and found that the power equation was also useful and reliable in patients with RWMA. To the best of our knowledge, this is the first prospective study to develop and validate the optimum equations for quantitatively estimating the biplane LVEF using the STE-derived TMAD in a large population with a wide range of LVEF.

The LVEF is a widely used variable for evaluating the LV systolic function. The two-dimensional biplane Simpson's disk summation method is the most common approach used to measure the LVEF by manually delineating the LV endocardial boundary.[17, 18] The inherent measured process of this method accounts for the associated inevitable limitations, such as dependence on the adequate visualization of the endocardial boundary, susceptibility to operator experience for identifying the blood-tissue interface, vulnerability to geometrical assumptions, and resultant low reproducibility and consistency.[7]When the LV cavity is compromised by suboptimal image quality, LV opacification with ultrasound enhancing agents is recommended to improve the endocardial delineation; however, the LVEF assessed with this method is different from that obtained using the biplane Simpson's method, and its normal reference range has not been well established.[19] Although the LVEF measured using three-dimensional echocardiography is much closer to the actual clinical value, the measurement is more dependent on image quality. Notwithstanding, the LVEF measured using the two-dimensional biplane Simpson's method plays a ubiquitous role in the characterization and management of cardiac disease and pervades a number of guidelines and practice.[20-22] Therefore, rapid and quantitative estimation of the biplane LVEF for assessing the LV systolic function using another method that is more easily available and independent of the image quality or operators' experience is desirable in daily clinical practice.

Movement of the mitral annulus in the longitudinal direction plays a leading role on LV stroke, because the position of the apex is relatively stationary throughout the cardiac cycle.[23]Mitral annular displacement can be used to quantitatively assess the movement of the mitral annulus, and accurately reflect LV global systolic function.[9, 24] Although the traditional motion mode (M-mode) and tissue Doppler imaging can measure mitral annular displacement, these methods are dependent on the angle between the ultrasound beam and the moving direction of mitral annulus.[12] Two-dimensional STE is a reliable technique to measure TMAD by automatically tracking the mitral annulus frame by frame without angle dependency.[25] As only the visualization of the mitral annulus and LV apex is required, the STE-derived TMAD is independent of the image quality, and, thus, more robust than the LVEF when parts of the LV wall were poorly visualized or reverberations were present.[14] Moreover, because only three anatomic landmarks should be defined without delineating the LV endocardial boundary, the measurement of TMAD can be rapidly and easily performed and is independent of the operator's experience. Our results also revealed that STE-derived TMAD is highly reproducible with low inter- and intra-observer variability, and its automated track, measurement, and report can be completed in a few seconds, which was similar to the findings of previous studies.[26, 27] In view of the above, we hypothesized that STE-derived TMAD, which is easy, rapid, highly reproducible, and independent of the image quality and operator experience, may be competent in accurately estimating the biplane LVEF. Our study validated this hypothesis, which may provide a clinically acceptable alternative to evaluate LV global systolic function when directly measured LVEF is not available or is highly variable.

With the STE method, the default TMAD, including TMAD of the septal and lateral aspects of the mitral annulus and TMAD of their midpoint, can be obtained from the apical 4-chamber view, which has been utilized in most studies. However, several previous studies also simultaneously measured TMAD of the

anterior and inferior aspects of the mitral annulus and their midpoint from the apical 2-chamber view for analyses.[9, 26] Our study compared the TMADmid and nTMADmid between the apical 4-chamber and 2-chamber views, and showed that there were no significant differences, even after internal validation by bootstrapping. These findings indicate that it may be adequate to estimate the biplane LVEF by TMAD from the single apical 4-chamber view. The present study used the TMAD from apical 4-chamber view to estimate the biplane LVEF, which may further improve the convenience for estimating the LVEF.

Among the four TMAD indices from the apical 4-chamber view, nTMADmid exhibited a much stronger association with LVEF and better discrimination for LVEF reduction compared with the other TMAD indices in our results. The estimated LVEF by nTMADmid showed a better agreement with the observed LVEF. These findings indicated that the nTMADmid may be the optimal indicator for estimating the LVEF and assessing the LV systolic function. The underlying mechanisms may be explained as follows. First, the nTMADmid represents the mean level of the TMADsep and TMADlat, which may better reflect the LV global systolic function. Moreover, the TMADmid values may vary with heart size in different individuals; therefore, the nTMADmid according to the LV length makes comparisons between individuals more easy and objective. Additionally, the nTMADmid is independent of age, BSA, and heart rate,[28] thereby, being more suitable for developing regression equations and estimating LVEF.

Severe coronary artery disease is one of the main reasons for RWMA, which may reduce local annular motion, and possibly correspond to confounding of the TMAD value and the relationship between the LVEF and TMAD. However, our study validated the accuracy of the estimation of the LVEF using the nTMADmid in the independent RWMA set and showed that there was no significant difference between the observed LVEF and estimated LVEF in the patients with RWMA, even after internal validation by bootstrapping. These findings were in agreement with those of a previous publication,[29] and may further support the robustness and generalization of the developed regression equations in the present study.

Although DeCara et al.[30] previously provided a bilinear regression formula to estimate biplane LVEF by STE-derived TMADmid in a derivation set including 32 subjects, the formula was developed based on a limited population, inadequate comparisons of multiple best-fitting regression models, and a lack of careful selection of multiple variables from STE-derived TMAD. Notably, our study developed a series of best-fitting regression models in a large population and validated the reliability of the chosen optimum equations in patients with and without RWMA. We found that the LVEF can be better estimated with the STE-derived TMAD using a power equation, even for patients with RWMA, and the nTMADmid may be the optimal parameter to estimate the LVEF. The proposed method may provide an alternative for evaluating the LV global systolic function when the direct measurement of the LVEF is not available or the LVEF values are highly variable.

Limitations

There were several limitations in our study. First, measured LVEF was not accurate in patients with high variation from beat to beat caused by atrial fibrillation and paradoxical septal motion caused by left bundle branch block, severe pulmonary hypertension, or constrictive pericarditis. Mitral annulus calcification and mitral valve replacement may also confound the TMAD value. Therefore, in order to develop optimum regression equations, we excluded these patients, which may limit extrapolation of our findings in these patients.

In addition, in order to control selection bias in the present study, enrollment of the patients was consecutive and unselected, which resulted in a relatively low percentage of patients with RWMA. However, we performed bootstrapping for internal validation in the limited patients with RWMA, and the analysis results were like the initial analyses.

Moreover, we did not follow up these patients to compare the differences between the observed LVEF and estimated LVEF based on the TMAD in the prognosis and risk stratification, which should be investigated in a future prospective multicenter study with a follow-up and larger number of patients.

Conclusion

The LVEF can be estimated using the STE-derived TMAD using a power equation, even for the patients with RWMA. The nTMADmid according to the LV long-axis length may be the optimal parameter for estimating the LVEF. This proposed method may provide a clinically acceptable alternative for evaluating the LV global systolic function when the direct measurement of the LVEF is not available or the LVEF values are highly variable.

Author contributions

CYM, YHW: Conception and design, analysis and interpretation of data, drafting and final approval of manuscript. YHW, CYM, JY, SL: Drafting and final approval of manuscript. JL, YZ, GYL, FXK, ZYG: Collection and interpretation of data, drafting and final approval of manuscript.

References

1. Nauta JF, Jin X, Hummel YM, et al: Markers of left ventricular systolic dysfunction when left ventricular ejection fraction is normal. Eur J Heart Fail 2018:20:1636-1638.
2. Pibarot P, Messika-Zeitoun D, Ben-Yehuda O, et al: Moderate Aortic Stenosis and Heart Failure With Reduced Ejection Fraction: Can Imaging Guide Us to Therapy? JACC Cardiovasc Imaging 2019:12:172-184.
3. Ormerod JO, Frenneaux MP, Sherrid MV: Myocardial energy depletion and dynamic systolic dysfunction in hypertrophic cardiomyopathy. Nat Rev Cardiol 2016:13:677-687.
4. Bristow MR, Kao DP, Breathett KK, et al: Structural and Functional Phenotyping of the Failing Heart: Is the Left Ventricular Ejection Fraction Obsolete? JACC Heart Fail 2017:5:772-781.
5. Ponikowski P, Voors AA, Anker SD, et al: 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016:18:891-975.
6. Marwick TH: Ejection Fraction Pros and Cons. J Am Coll Cardiol 2018:72:2360-2379.
7. Lang RM, Badano LP, Mor-Avi V, 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 2015:28:1-39 e14.
8. Oh JK, Pellikka PA, Panza JA, et al: Core lab analysis of baseline echocardiographic studies in the STICH trial and recommendation for use of echocardiography in future clinical trials. J Am Soc Echocardiogr 2012:25:327-336.
9. Buss SJ, Mereles D, Emami M, et al: Rapid assessment of longitudinal systolic left ventricular function using speckle tracking of the mitral annulus. Clin Res Cardiol 2012:101:273-280.
10. Watanabe K, Kishino T, Sano J, et al: Relationship between epicardial adipose tissue thickness and early impairment of left ventricular systolic function in patients with preserved ejection fraction. Heart Vessels 2016:31:1010-1015.
11. Zahid W, Johnson J, Westholm C, et al: Mitral annular displacement by Doppler tissue imaging may identify coronary occlusion and predict mortality in patients with non-ST-elevation myocardial infarction. J Am Soc Echocardiogr 2013:26:875-884.
12. Gjesdal O, Vartdal T, Hopp E, et al: Left ventricle longitudinal deformation assessment by mitral annulus displacement or global longitudinal strain in chronic ischemic heart disease: are they interchangeable? J Am Soc Echocardiogr 2009:22:823-830.
13. Black DE, Bryant J, Peebles C, et al: Tissue motion annular displacement of the mitral valve using two-dimensional speckle tracking echocardiography predicts the left ventricular ejection fraction in normal children. Cardiol Young 2014:24:640-648.
14. Yuda S, Inaba Y, Fujii S, et al: Assessment of left ventricular ejection fraction using long-axis systolic function is independent of image quality: a study of tissue Doppler imaging and m-mode echocardiography. Echocardiography 2006:23:846-852.
15. Mitchell C, Rahko PS, Blauwet LA, et al: Guidelines for Performing a Comprehensive Transthoracic

Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr 2019:32:1-64.
16. Yao GH, Deng Y, Liu Y, et al: Echocardiographic measurements in normal chinese adults focusing on cardiac chambers and great arteries: a prospective, nationwide, and multicenter study. J Am Soc Echocardiogr 2015:28:570-579.
17. Muraru D, Badano LP, Peluso D, et al: Comprehensive analysis of left ventricular geometry and function by three-dimensional echocardiography in healthy adults. J Am Soc Echocardiogr 2013:26:618-628.
18. Kerkhof PLM, van de Ven PM, Yoo B, et al: Ejection fraction as related to basic components in the left and right ventricular volume domains. Int J Cardiol 2018:255:105-110.
19. Porter TR, Mulvagh SL, Abdelmoneim SS, et al: Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update. J Am Soc Echocardiogr 2018:31:241-274.
20. Yancy CW, Jessup M, Bozkurt B, et al: 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017:70:776-803.
21. Mebazaa A, Yilmaz MB, Levy P, et al: Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. Eur J Heart Fail 2015:17:544-558.
22. Bozkurt B, Aguilar D, Deswal A, et al: Contributory Risk and Management of Comorbidities of Hypertension, Obesity, Diabetes Mellitus, Hyperlipidemia, and Metabolic Syndrome in Chronic Heart Failure: A Scientific Statement From the American Heart Association. Circulation 2016:134:e535-e578.
23. de Knegt MC, Biering-Sorensen T, Sogaard P, et al: Concordance and reproducibility between M-mode, tissue Doppler imaging, and two-dimensional strain imaging in the assessment of mitral annular displacement and velocity in patients with various heart conditions. European Heart Journal - Cardiovascular Imaging 2014:15:62-69.
24. Ylanen K, Eerola A, Vettenranta K, et al: Speckle tracking echocardiography detects decreased cardiac longitudinal function in anthracycline-exposed survivors of childhood cancer. Eur J Pediatr 2016:175:1379-1386.
25. Asada D, Okumura K, Ikeda K, et al: Tissue Motion Annular Displacement of the Mitral Valve Can Be a Useful Index for the Evaluation of Left Ventricular Systolic Function by Echocardiography in Normal Children. Pediatr Cardiol 2018:39:976-982.
26. Chiu DY, Abidin N, Hughes J, et al: Speckle tracking determination of mitral tissue annular displacement: comparison with strain and ejection fraction, and association with outcomes in haemodialysis patients. Int J Cardiovasc Imaging 2016:32:1511-1518.
27. Liu S, Ren W, Zhang J, et al: Incremental Value of the Tissue Motion of Annular Displacement Derived From Speckle-Tracking Echocardiography for Differentiating Chronic Constrictive Pericarditis From Restrictive Cardiomyopathy. J Ultrasound Med 2018:37:2637-2645.
28. Roberson DA, Cui W: Tissue Doppler imaging measurement of left ventricular systolic function in children: mitral annular displacement index is superior to peak velocity. J Am Soc Echocardiogr 2009:22:376-382.
29. Tsang W, Ahmad H, Patel AR, et al: Rapid Estimation of Left Ventricular Function Using Echocardiographic Speckle-Tracking of Mitral Annular Displacement. J Am Soc Echocardiogr 2010:23:511-515.
30. DeCara JM, Toledo E, Salgo IS, et al: Evaluation of left ventricular systolic function using automated angle-independent motion tracking of mitral annular displacement. J Am Soc Echocardiogr 2005:18:1266-1269.

Figure Legends

Figure 1. Method of TMAD measurement. *TMAD* tissue motion of mitral annular displacement, *TMADsep*

septal TMAD,*TMADlat* lateral TMAD, *TMADmid* midpoint TMAD

Figure 2. Receiver operating characteristic curve analysis to evaluate the discrimination of TMAD for LVEF <53% in the derivation set. *LVEF* left ventricular ejection fraction,*TMAD* tissue motion of mitral annular displacement, *TMADsep*septal TMAD, *TMADlat* lateral TMAD, *TMADmid* midpoint TMAD,*nTMADmid* normalized TMADmid

Figure 3. Comparisons of the observed LVEF and estimated LVEF from TMAD in the validation set. *LVEF* left ventricular ejection fraction, *TMAD* tissue motion of mitral annular displacement,*TMADsep* septal TMAD, *TMADlat* lateral TMAD, *TMADmid*midpoint TMAD, *nTMADmid* normalized TMADmid

Figure 4. Bland-Altman analyses of the observed and estimated LVEF from TMAD in the validation set. *LVEF* left ventricular ejection fraction, *TMAD* tissue motion of mitral annular displacement, *TMADsep* septal TMAD, *TMADlat* lateral TMAD,*TMADmid* midpoint TMAD, *nTMADmid* normalized TMADmid

Figure 5. Bland-Altman analyses for intra-observer and inter-observer reproducibility of nTMADmid. *nTMADmid* normalized TMADmid

Table I Demographic characteristics and echocardiographic measurements of the population

Variable	Derivation set (n=287)	Validation set (n=123)	*P*-value
Age (years)	50.8±16.5	50.9±15.9	0.95
Female [n (%)]	142 (49.5%)	57 (46.3%)	0.56
Body surface area (m^2)	1.79±0.20	1.77±0.19	0.44
Body mass index (kg/m^2)	23.98±4.43	24.01±6.80	0.96
Heart rate (bpm)	71.99±11.49	72.87±11.02	0.55
Left atrial diameter (mm)	35.85±5.82	36.25±5.41	0.62
Mitral E/A	1.23±0.58	1.12±0.42	0.11
Mitral E/e'	10.66±4.76	10.21±3.74	0.47
LV end-diastolic diameter (mm)	50.93±7.97	50.70±8.92	0.83
LV end-diastolic volume (mL)	102.65±53.73	102.81±43.50	0.98
LV stroke volume (mL)	57.37±15.47	58.48±14.60	0.50
LVEF (%)	59.93±10.42	60.51±11.17	0.61
TMADsep (mm)	10.95±3.52	11.19±3.41	0.52
TMADlat (mm)	12.47±3.85	12.48±3.87	0.99
TMADmid (mm)	12.27±3.62	12.39±3.57	0.77
nTMADmid (%)	14.71±4.45	14.76±4.37	0.92

Values shown are mean±SD or frequency (percentages). *E* early diastolic flow peak velocity, *A* late diastolic flow peak velocity, *e'* early diastolic annular peak velocity, *LV* left ventricle, *LVEF* LV ejection fraction, *TMAD* tissue motion of mitral annular displacement, *TMADsep* septal TMAD,*TMADlat* lateral TMAD, *TMADmid* midpoint TMAD,*nTMADmid* normalized TMADmid

Table II Regression models for computing LVEF from TMAD in the derivation set

Equation	r^2	*F*-value	*P*-value	Constant	*β1*	*β2*	*β3*
TMADsep (n=287)							
Linear	0.39	181.66	¡0.001	39.72	1.85		
Logarithmic	0.53	321.83	¡0.001	21.87	16.45		
Quadratic	0.57	191.11	¡0.001	18.20	6.82	-0.25	
Cubic	0.59	135.07	¡0.001	9.69	10.41	-0.65	0.01
Compound	0.39	185.42	¡0.001	37.19	1.04		
Power	**0.57**	**376.40**	¡0.001	24.26	0.38		

Equation	r^2	F-value	P-value	Constant	$\beta1$	$\beta2$	$\beta3$
S	0.52	312.81	¡0.001	4.24	-1.49		
Growth	0.39	185.42	¡0.001	3.62	0.04		
Exponential	0.39	185.42	¡0.001	37.19	0.04		
TMADlat (n=287)							
Linear	0.39	180.73	¡0.001	38.91	1.68		
Logarithmic	0.45	230.18	¡0.001	25.26	14.19		
Quadratic	0.50	143.83	¡0.001	21.31	5.37	-0.17	
Cubic	0.50	95.59	¡0.001	21.97	5.09	-0.14	-0.001
Compound	0.39	178.85	¡0.001	36.69	1.04		
Power	**0.46**	**244.03**	¡0.001	26.65	0.32		
S	0.18	62.06	¡0.001	4.12	-0.46		
Growth	0.39	178.85	¡0.001	3.60	0.04		
Exponential	0.39	178.85	¡0.001	36.69	0.04		
TMADmid (n=287)							
Linear	0.44	224.91	¡0.001	36.43	1.91		
Logarithmic	0.54	328.34	¡0.001	18.51	17.00		
Quadratic	0.59	208.20	¡0.001	14.31	6.65	-0.22	
Cubic	0.59	138.34	¡0.001	13.74	6.89	-0.25	0.001
Compound	0.44	226.83	¡0.001	34.61	1.04		
Power	**0.58**	**391.19**	¡0.001	22.37	0.40		
S	0.33	142.10	¡0.001	4.16	-0.85		
Growth	0.44	226.83	¡0.001	3.54	0.04		
Exponential	0.44	226.83	¡0.001	34.61	0.04		
nTMADmid (n=287)							
Linear	0.51	300.87	¡0.001	35.25	1.68		
Logarithmic	0.61	437.84	¡0.001	15.80	16.91		
Quadratic	0.66	275.09	¡0.001	15.14	5.45	-0.15	
Cubic	0.66	183.00	¡0.001	13.82	5.93	-0.19	0.001
Compound	0.51	292.18	¡0.001	33.88	1.04		
Power	**0.65**	**524.47**	¡0.001	21.11	0.39		
S	0.35	151.14	¡0.001	4.15	-0.87		
Growth	0.51	292.18	¡0.001	3.52	0.04		
Exponential	0.51	292.18	¡0.001	33.88	0.04		

Abbreviations as Table 1

Table III Regression equations for computing LVEF from TMAD in the validation set.

Regression equations	Regression equations
LVEF-TMADsep	$\text{LVEF} = 24.26 \times \text{TMADsep}^{0.38}$
LVEF-TMADlat	$\text{LVEF} = 26.65 \times \text{TMADlat}^{0.32}$
LVEF-TMADmid	$\text{LVEF} = 22.37 \times \text{TMADmid}^{0.40}$
LVEF-nTMADmid	$\text{LVEF} = 21.11 \times \text{nTMADmid}^{0.39}$

Table IV Comparisons and Bland-Altman analyses of observed and estimated LVEF from TMAD in the validation set

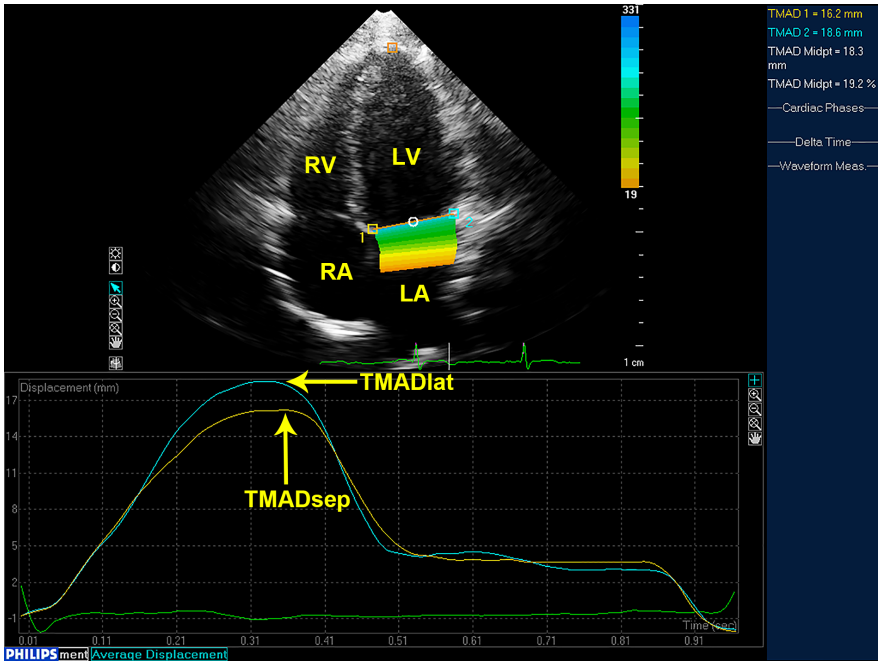
	Mean±SD	*P*-value*	Mean difference	95% CI of mean difference	Limits of agreement (low, high)
LVEF-TMADsep (%)	59.97±8.60	0.43	0.54	-0.82 to 1.90	-14.38, 15.46
LVEF-TMADlat (%)	59.33±7.48	0.08	1.17	-0.15 to 2.50	-13.40, 15.75
LVEF-TMADmid (%)	59.61±8.30	0.19	0.90	-0.45 to 2.24	-13.87, 15.66
LVEF-nTMADmid (%)	59.56±8.66	0.14	0.95	-0.30 to 2.19	-12.70, 14.59

* *P* -value in the comparisons of estimated LVEF and observed LVEF (60.51 ± 11.17 %). *CI* confidence interval, other abbreviations as Table 1

Table V Intra-class correlations between observed and estimated LVEF in the validation set

	Coefficient	95% CI	*P*-value
LVEF-TMADsep	0.71	0.61 to 0.79	¡0.001
LVEF-TMADlat	0.69	0.59 to 0.77	¡0.001
LVEF-TMADmid	0.71	0.61 to 0.78	¡0.001
LVEF-nTMADmid	0.76	0.67 to 0.82	¡0.001

CI confidence interval, other abbreviations as Table 1



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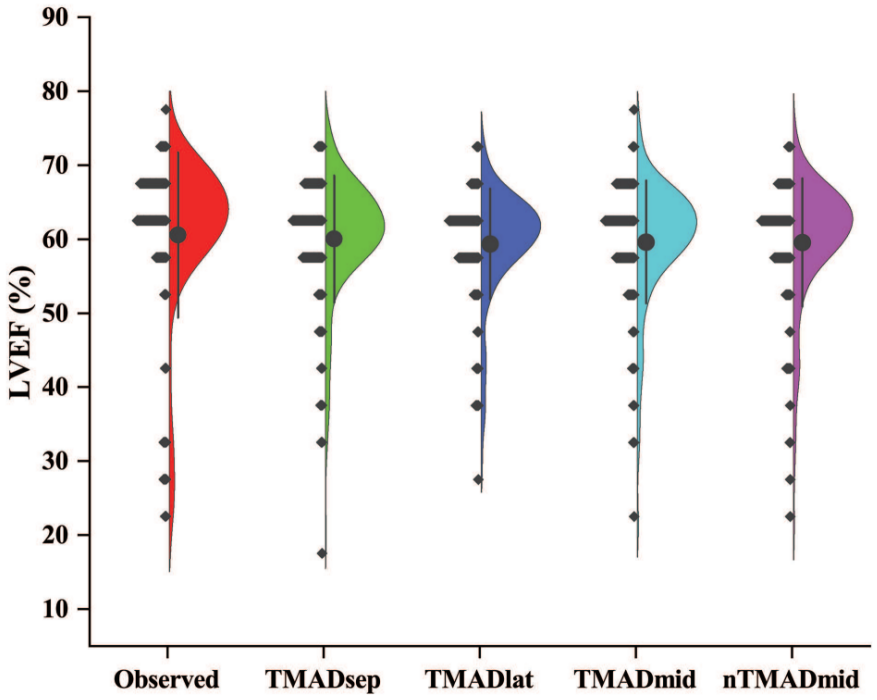

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