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Quantitative Measurement of Left Ventricular Function: Comparison of Two-Dimensional Speckle-Tracking Echocardiography with Two-Dimensional and Three-Dimensional Ejection Fraction

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ABSTRACT

Background:A thorough measurement of left ventricular (LV) function is critical in order to assist treatment and prognosis. Aim: We envisaged to assess the accuracy of global strains derived from two-dimensional (2D) speckle tracking echocardiography (STE) compared to 2D ejection fraction (EF) and three-dimensional (3D) EF for LV function assessment, as well as determined the intra- and inter-observer variation while measuring 2D STE-derived global strains and 3D EF.**Material and Methods:**A total of 100 patients with LV systolic dysfunction underwent 2D and 3D echocardiography and 2D STE. The 2D global longitudinal strain (GLS) and global circumferential strain (GCS) were measured and correlated with 2D EF and 3D EF. Independent and blinded observers assessed the reproducibility and practicality to conduct 2D STE and 3D EF.**Results:**Correlation between change in global strains and change in 2D EF and 3D EF across different baseline LVEF subgroups was improved significantly at lower LVEF. Following were discovered to have a significant strong correlation: a) 2D EF and 3D EF (r=0.963, p=0.01), b) 2D STE GLS and 2D EF (r=0.724, P=0.01), c) 2D STE GCS and 2D EF (r=0.652, P=0.01), d) 2D STE GLS and 3D EF (r=0.717, P=0.01] and e) 2D STE GCS and 3D EF (r=0.632, P=0.01). Good reproducibility in terms of intra- and inter-observer variability was reported in 3D EF and 2D STE-derived strain parameters.**Conclusion:**2D STE was a useful technique for LV function estimation with the potential for extensive clinical usage due to its accuracy and good reproducibility, as evidenced by minimal inter- and intra-observer variability. 2D STE-derived global strains were discovered to be possible alternate marker to measure LV function beyond LVEF.

Keywords: Ejection fraction, left ventricular function, echocardiography, strain, two-dimensional, three-dimensional.

Introduction

Left ventricular ejection fraction (LVEF) is the most well-studied echocardiographic parameter to quantify global left ventricular (LV) function. It has been proven as an important prognostic predictor of cardiac mortality and morbidity, as well as routinely utilised by clinicians to aid in patient management.[1] Howbeit, 2-dimensional (2D) echocardiographic assessment of LVEF, both qualitative and quantitative, is hindered due to issues with reproducibility, dependence on image quality, subjective interpretation, and LV

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geometric assumptions. To address these limitations, recent development in the field of three-dimensional echocardiography (3DE) have rendered better reproducibility and higher accuracy as compared to two-dimensional echocardiography (2DE) for the evaluation of LV size and function, as it averts apical foreshortening and is reliant on direct volumetric assessments without geometrical assumptions.[2] However, 3DE is impeded due to insufficient acoustic window and inferior image quality.[3]

Currently, 2D speckle tracking echocardiography (2D STE) is an emerging method that offers a more comprehensive assessment of LV function than conventional LVEF estimation. It provides multidimensional myocardial mechanics which includes rotation as well as longitudinal and circumferential motion.[4] Furthermore, both 3DE and cardiac magnetic resonance imaging have demonstrated that myocardial global strains measured by 2D STE correlate well with LVEF.[5] Despite the benefits of this strategy being emphasized in relevant literature[6-14], there is paucity of data on the usage of 2DSTE over conventional techniques. In considering the foregoing, the present study compared the accuracy of 2D STE-derived global strains to that of 2D EF and 3D EF to verify the novel technique of 2D STE as a substitute for the assessment of LV function. In addition, we assessed intra- and inter-observer variation while measuring 2D STE-derived global strains and 3D EF.

Material &Methods

This was a single-centre, prospective, and observational study conducted in the cardiology department of CMC Vellore between October-2012 and December-2014. The study was approved by the Institutional Review Board and adhered with the tenets of Declaration of Helsinki. A total of 100 consecutive patients in the age group of 18-80 years with LV systolic dysfunction (defined as patient with 2D EF<50%) who were willing to provide informed consent to participate in the study were included. Patients aged below 18 years, patients with poor echo window, severely dilated LV, atrial fibrillation, atrial flutter, or frequent ectopic, clinically unstable patients, or patients who were not willing to provide informed consent form were excluded.

Data regarding baseline characteristics, history of cardiovascular morbidities, clinical risk factors, probable cause of LV systolic dysfunction and status of coronary artery disease were collected as per predefined proforma.

All the patients were subjected to a thorough echocardiogram that included 2D STE, 2DE and 3DE. Following echocardiographic variables were noted: a) 2D EF, b) 3D EF, c) 2D global longitudinal strain (GLS) and d) 2D global circumferential strain (GCS). Each participant in this study had a transthoracic echo in the left lateral decubitus position in expiratory apnoea performed by a 5-1 Hz Matrix probe on IE 33 (Philips Medical System).

Standard 2D echocardiographic images were acquired from standard transthoracic echocardiography views (parasternal long and short axis, apical 4 chambers, long axis and 2 chamber). Standard 3D echocardiographic images were collected in full volume mode in expiratory apnoea in order to remove the lung field coming across the front wall of the left ventricle. Biplane Simpson's method was used to calculate 2D ejection fraction. 2D ejection fraction was represented as percentages.

The GLS was computed in offline mode with the help of 2D STE in following views: a) apical four chamber, b) apical long axis, and c) apical two chamber. Three views in parasternal short axis at basal, papillary muscle, and apical level were collected for the estimation of 2D STE GLS.

Endocardial borders were automatically monitored with the help of QLAB software, and a zone of interest that included the entire myocardium was chosen. The endocardial border was manually monitored if these measurements were not precise. The outcomes of the LV strain

analysis were shown by default as following: a) seventeen-segment polar map model with seventeen regional strain values and b) a meal global value for the entire myocardium.
The 3D ejection fraction was calculated using 3DQ Adv software. Following adjusting the images in three axes i.e., a) apical four chamber, b) two chamber and c) short axis, endocardial borders were manually traced.
End diastolic and end systolic images were chosen as per electrocardiogram (ECG).End diastolic and end systolic was obtained at the peak of R wave and at the end of T wave, respectively. All the parameters were recorded as per the recommendations of the American Society of Echocardiography.
Sample size was estimated with the help of correlation coefficient of 0.86 for comparing 2D GLS with 2D EF and 3D EF (based on previous studies) (Table 1).
Data entry was performed with the help of Epidata software program. Statistical analysis was done using statistical packages for social sciences (SPSS) software version 18.0 (Chicago, SPSS Inc.). Quantitative variables were characterised as mean ± standard deviation. Qualitative variables were expressed as frequency and percentages. Linear regression analysis with Pearson's correlation coefficient was used to assess the correlation between strain measurements and LVEF. A p value of <0.05 was regarded statistically significant. Assessment of intra- and inter-observer variation while measuring 2D STE-derived global strains and 2D EF and 3D EF was done using coefficient of variation (COV), intra-class correlation coefficient (ICC) and standard error of measurement (SEM). Out of 100 patients, 10 patients were randomly selected for inter-observer and intra-observer variations. Measurement of inter-observer variation was done among two cardiologists. Intra-observer variation was measured offline one week apart with blinding to the earlier result.

Results

The mean age of the study population was 50 ± 12.4 years, with male preponderance (75%). Majority of the patients were aged between 40-60 years. The male to female ratio was approximately 3:1.Most of the patients had ischemic heart disease (56%) and diabetes mellitus (44%), followed by hypertension (37%) and dyslipidemia (18%). Out of 100 patients, only 50 patients underwent coronary angiography. Coronary angiogram revealed that majority of the patients had multi-vessel coronary artery disease [double vessel disease (28%) and triple vessel disease/ left main (20%)]. Thirteen patients (26%) had single vessel disease and 13 patients (26%) had normal coronary artery. Fifty-six patients (56%) had LV dysfunction due to ischemic heart disease. Other aetiologies of LV dysfunction in the study population were uraemia, chemotherapy, and cardiomyopathies.

Table 1: Regression methods - Sample size for correlation coefficient analysis (testing against population value)

Sample correlation coefficient	0.86	0.86
Population correlation coefficient	0.6	0.05
Power (1- beta) %	90	90
Alpha error (%)	5	5
1 or 2 Sided	2	2
Required sample size	32	10

The mean end diastolic volume and mean end systolic volume was 123.8 ± 45.9 ml and 84.5 ± 31.4 ml, respectively. The mean 2D EF and mean 3D EF was 34 ± 7.5% and 34.2 ± 7.6%. The mean GLS and GCS was -8 ± 3.2% and -10.6 ± 4.3%. Remaining clinical and echocardiographic characteristics of the patients is delineated in Table 2.

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Table 2: Clinical and echocardiographic characteristics of the study population

	Total patients (N=100)
Clinical Characteristics	
Age, years	50 ± 12.4
Male	75 (75%)
Male: female	3:1
Body surface area, m^2	1.63±0.23
Heart rate, beats per minute	70±12
Risk factors	
Diabetes mellitus	44 (44%)
Smoker	31 (31%)
Hypertension	37 (37%)
Dyslipidaemia	18 (18%)
Ischemic heart disease	56 (56%)
Echocardiographic characteristics	
End diastolic LV volume, ml	123.8 ± 45.9
End systolic LV volume, ml	84.5 ± 31.4
2D left ventricular ejection fraction, %	34 ± 7.5
3D left ventricular ejection fraction, %	34.2 ± 7.6
Strain	
Global longitudinal strain, %	-8 ± 3.2
Global circumferential strain, %	-10.6 ± 4.3

Data are presented as n (%) or mean ± S.D.
§ 2D: 2-dimensional; 3D: 3-dimensional; S.D.: standard deviation.

Correlations between change in global strains and changes in 2D EF and 3D EF across different baseline LVEF subgroups was improved significantly at lower LVEF (Table 3).

Table 3: Correlations between change in global strains and changes in 2D EF and 3D EF across different baseline LVEF subgroups

	GLS		**GCS**	
2D EF (%)	**r**	**P value**	**r**	**P value**
<30(n=31)	-0.36	0.09	-0.75	**0.03**
30-39(n=43)	-0.67	**0.015**	-0.62	**0.02**
40-50(n=26)	-0.25	**0.009**	-0.59	**0.006**

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3D EF (%)	r	P value	r	P value
<30 (n=30)	-0.32	0.071	-0.628	**0.02**
30-40 (n=46)	-0.76	**0.013**	-0.720	**0.01**
40-50(n=24)	-0.26	**0.009**	-0.55	**0.007**

§ 2D: 2-dimensional; 3D: 3-dimensional; GLS: global longitudinal strain; GCS: global circumferential strain; LVEF: left ventricular ejection fraction; r: Pearson coefficient

A significant strong correlation was found between change in 2D EF and 3D EF with Pearson correlation coefficient (r=0.963, P=0.01) as shown in Figure 1.As outlined in Figure 2, change in GLS and GCS was significantly related to the change in the 2D EF with Pearson correlation coefficient (r=0.724,P=0.01) and (r=0.652,P=0.01), respectively. There was a considerably significant correlation found between change in global strains [GLS (r=0.717, P=0.01] and GCS (r=0.632, P=0.01)] and change in the 3D EF.

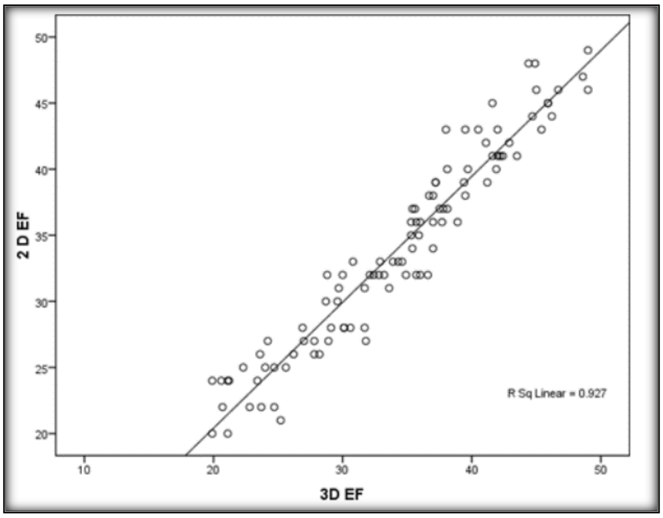

Figure 1:Scatter diagram demonstrating correlation between 2D EF and 3D EF
§ 2D: 2-dimensional; 3D: 3-dimensional; EF: ejection fraction

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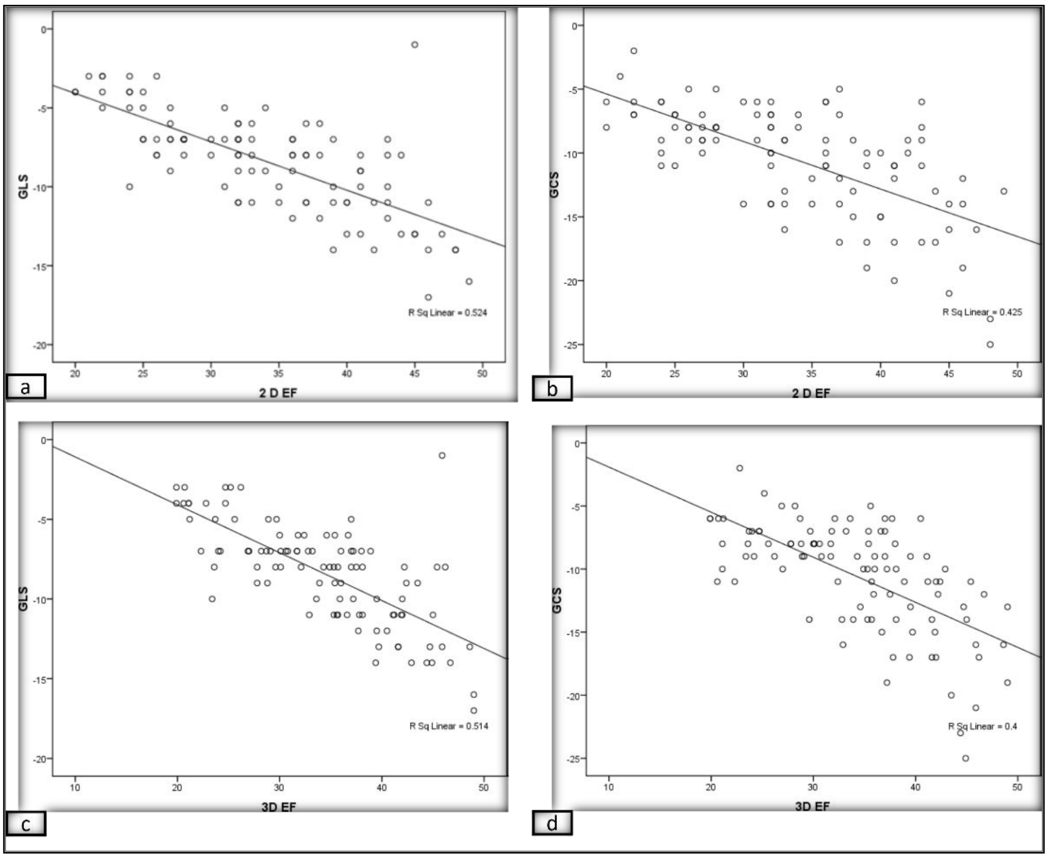

Figure 2:Scatter diagram demonstrating correlation between 2D STE-derived global strains and 2D EF and 3D EF: a) correlation between 2D EF and 2D STE GLS, b) correlation between 2D EF and 2D STE GCS, c) correlation between 3D EF and 2D STE GLS, and d) correlation between 3D EF and 2D STE GCS

§ 2D: 2-dimensional; 3D: 3-dimensional; EF: ejection fraction; GCS: global circumferential strain; GLS: global longitudinal strain; STE: speckle tracking echocardiography

There was good reproducibility for 3D EF in terms of intra-and inter-observer variability as ICC was 0.96 (CI: 0.85-0.98) for intra-observer and ICC of 0.94(CI: 0.86-0.98) for inter-observer. Similar results were found with GLS and GCS (Table 4).

Table 4: Intra- and inter-observer variability of 2D STE-derived global strains and 3D EF

	Intra-observer variability			**Inter-observer variability**		
Variable	**ICC(95% CI)**	**SEM**	**COV**	**ICC(95% CI)**	**SEM**	**COV**
GLS	0.99(0.96-0.99)	0.8	0.27	0.98(0.69-0.98)	0.9	0.46
GCS	0.99(0.97-0.99)	0.8	0.25	0.96(0.85-0.99)	1.0	0.43
3D EF	0.96(0.85-0.98)	1.0	0.43	0.94(0.86-0.98)	1.3	0.49

§ COV: coefficient of variation; 2D: 2-dimensional; 3D: 3-dimensional; EF: ejection fraction; GCS: global circumferential strain; GLS: global longitudinal strain; ICC: Intra-class correlation coefficient; SEM: standard error of measurement.

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Discussion

To our knowledge, this might be the first study to demonstrate that 2DSTE was a more reproducible and accurate method for the quantification of LV function than conventional techniques i.e., 2D EF and 3D EF. The principal findings of the present study are as follows: (i) Strong co-relation was noted between 2D STE-derived global strains and 2DEF, as well as between 2D STE-derived global strains and 3D EF. ii) Low inter- and intra-observer variability was found while assessing 2D STE-derived global strains and 3D EF. The findings of this study back up the growing clinical usage of 2DSTE as a diagnostic tool for the assessment of LV function. This technique has the potential to be clinically effective due to its reduced processing time and minimal observer variability.

As an alternative technique to evaluate LV function, our findings revealed robust relationships between 2D STE-derived global strains and LVEF. The 2D speckle-tracking echocardiographic parameters (GLS, GCS) corresponded well with LVEF acquired by 2D and 3D echocardiography in assessing LV function. In our cohort, the greatest predictor of LVEF was 2D GCS (with 2D EF: r=0.724; P=0.01 and 3D EF: r=0.717, P=0.01). The 2D GLS demonstrated the low correlation with LVEF when compared to 2D GCS, albeit still having a substantial link. However, this is not particularly surprising given the fact that the vast majority of cardiac myofibers are oriented circumferentially, with a proportionately lesser number oriented longitudinally in a histologic myocardial study. Despite regional heterogeneity, with a higher proportion of circumferential fibres in the basal segments than the cardiac apex, the circumferential to longitudinal fibre orientation's ratio has been observed to be around 10: 1.[15] Streeter et al.[15] has demonstrated that circumferentially oriented fibres contribute the most to LV myocardial function. Similarly, in a comparative study of 100 subjects with EF ranging from 16% to 72%, Stokke et al.[16] demonstrated that the alteration in GCS by each percentage had a 1.6 times larger effect on LVEF compared to GLS. Likewise, Cho et al. (4) found that 2D GCS (HR: 1.15, 95% CI: 1.04 to 1.28; P=0.006) was a more powerful predictor of adverse cardiac events and found to be a better parameter than ejection fraction in 201 patients with acute heart failure, regardless of age and LVEF. In patients with Duchenne Muscular Dystrophy–Associated Cardiomyopathy, Siddiqui et al.[17] also exhibited that 2D GCS was a powerful echocardiographic parameter than 2D GLS to prognosticate Duchenne muscular dystrophy–associated cardiomyopathy prior to the development of LV failure. In line with previous studies[4,16,17], the present study suggest that GCS is a new metric that has to be explored in future studies to assess its prognostic implications beyond LVEF.

Like put forth by Luis et al.[18], the present study also demonstrated that subgroup analysis of 2D EF and 3D EF into three groups (<30%, 30-40% and 40-50%) showed higher relationship with lower LVEF across 2D STE parameters. Inter- and intra-observer variability in LVEF and 2D STE-derived global strains outperforming LVEF has been previously documented in earlier investigations.[19-21] During the assessment of global strains and LVEF, there are several causes of error in both image acquisition and image analysis which may influence the measurement and outcomes.[22] We noted low inter- and intra-observer variability in 3D EF. This concurs well with Tan et al.[23] In addition, the present study discovered low inter- and intra-observer variability in 2D STE-derived global strains parameters. On the account of low inter- and intra-observer variability noted in 2D STE-derived global strains parameters, these parameters were a reliable marker of LV function that can be widely used in clinical practice. This may overcome the shortcomings of LVEF such as poor inter-observer reproducibility, limited acoustic windows, and variations in measurement technique.[24]

Altogether, our study has confirmed the accuracy and practicability of 2D speckle-tracking echocardiographic estimation throughout a broad variety of LV function, encompassing patients with LV systolic dysfunction (2D and 3D echocardiographic LVEF range, <30%–

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50%), and LV size (LV end diastolic volume range, 78-169 ml and end systolic LV volume range 53-115 ml). The 2DSTE outperformed both 2D EF and 3D EF in terms of higher accuracy and reproducibility. The approach of semi automated speckle tracking algorithm used in 2DSTE could be rationale for the improved accuracy and reproducibility in 2D STE when compared to EF. This is because one source of variability of the traditional technique for the assessment of EF is the necessity to visually distinguish the end-diastolic and end-systolic frames for analysis that is not perfectly reproducible. There still remains a confusion in the chamber quantification guidelines from the American Society of Echocardiography regarding frame selection.[22] On the other hand, assessment of global strains depends on speckle tracking technology that follows the myocardium throughout the cardiac cycle and therefore encompasses every single frame in each analysis which eliminates this source of variability.

Limitations

There are some drawbacks in the current study that must be addressed. The study is limited by the fact that it was a single-centre, prospective, observational study, which implies that it did not reflect the entire Indian population but rather a specific region. The study also lacked a comparison to the non-invasive gold standard for LVEF i.e., cardiac magnetic resonance imaging. Further large-scale comparative research studies that investigatethe use of 2D STE over conventional technique to assess LV systolic function is warranted.

Conclusion

Taken together, our results show an outperformance of 2D STE over 2D EF and 3DEF in terms of estimation of LV systolic function. 2D STE had comparatively less intra-observer and inter-observer variability and a strong correlation was found between 2D STE and 2D EF as well as between 2D STE and 3D EF. This study strengthens the case for the application of 2D STE strain parameters in echocardiographic investigations for the quantitative assessment of LV function.

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