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ORIGINAL PAPER

3D echocardiographic global longitudinal strain can identify patients with mildly-to-moderately reduced ejection fraction at higher cardiovascular risk

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Abstract
Severely reduced left ventricular (LV) ejection fraction (EF) derived from 2D echocardiographic (2DE) images is associated with increased mortality and used to guide therapeutic choices. Global longitudinal strain (GLS) is more sensitive than LVEF to detect abnormal LV function, and accordingly may help identify patients with mildly-to-moderately reduced LVEF who are at a similarly high cardiovascular (CV) risk. We hypothesized that 3D echocardiographic (3DE) measurements of EF and GLS, which are more reliable and reproducible, may have even better predictive value than the 2DE indices, and compared their ability to identify such patients. We retrospectively studied 104 inpatients with 2DE-derived LVEF of 30–50% who underwent transthoracic echocardiography during 2006–2010 period, had good quality images, and were followed-up through 2016. Both 2DE and 3DE images were analyzed to measure LVEF and GLS. Kaplan–Meier survival curves were generated for two subgroups defined by the median of each parameter as the cutoff. Of the 104 patients, 32 died of CV related causes. Cox regression revealed that 3D GLS was the only variable associated with CV mortality. Kaplan–Meier curves showed that 2D LVEF, 2D GLS and 3D EF were unable to differentiate patients at higher CV mortality risk, but 3D GLS was the only parameter to do so. Because 3D GLS is able to identify patients with mildly-to-moderately reduced LVEF who are at higher CV mortality risk, its incorporation into clinical decisions may improve survival of those who would benefit from therapeutic interventions not indicated according to the current guidelines.

Keywords Left ventricular function · Global longitudinal strain · Mild to moderately reduced ejection fraction · Outcomes · Risk assessment

Abbreviations

2DE	Two-dimensional echocardiographic
3DE	Three-dimensional echocardiographic
BSA	Body surface area
CV	Cardiovascular
EF	Ejection fraction
GLS	Global longitudinal strain
LV	Left ventricular
STE	Speckle tracking echocardiography

Introduction

Left ventricular (LV) function is usually assessed using 2D echocardiographic (2DE) ejection fraction (EF), which was found to be associated with hospitalizations and mortality [1–4]. While severely reduced LVEF was found to predict poor outcomes, the relationship between mildly-to-moderately reduced LVEF and cardiovascular (CV) risk is not well established. It is known that some patients with LVEF > 30% may also be at risk, but there are no tools today to reliably identify this subpopulation. Importantly, foreshortened 2DE views and image quality affect the quantitative evaluation of LVEF [5].

Recently, global longitudinal strain (GLS), assessed by speckle tracking echocardiography (STE), has emerged as an alternative to quantify LV function, with the advantages of better reproducibility and ability to detect subtle changes in myocardial function that precede changes in EF [6–8]. Furthermore, GLS was found to predict mortality, potentially

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better than EF [9–15]. Therefore, we hypothesized that GLS may be able to identify a subset of patients with mildly-to-moderately reduced LVEF who are at a similar CV risk level as those with severely reduced LVEF. Moreover, the vast majority of outcomes studies have been based on 2DE methodology of LV function assessment.

As 3D echocardiographic (3DE) evaluation of LV size and function avoids apical foreshortening and utilizes direct volumetric measurements without geometrical assumptions, it is more accurate and reproducible than the 2DE assessment [16]. Accordingly, 3D GLS may also be more accurate and reproducible than 2D GLS [17, 18]. In our recent publication, which included patients with a wide range of LV function [19], we found that 3DE-derived functional indices are indeed important for prognostic purposes, as 3DE EF had a superior predictive ability over 2DE EF, and also that the addition of 3D GLS improved the association with outcomes. The current study was designed to test the hypothesis that in patients with mildly-to-moderately reduced LV EF, 3DE-based functional indices may have better predictive value than their 2DE equivalents.

Table 1 Clinical characteristics of the study group

Baseline characteristics	%
Dyslipidemia	53
Hypertension	53
Diabetes mellitus	18
Smoker	41
Paroxysmal atrial fibrillation	18
s/p Ventricular tachycardia	6
Glomerular filtration rate < 60 ml/min/1.73 m^2	39
Coronary artery disease	47
s/p Myocardial infarction	18
Ischemic cardiomyopathy	24
Non ischemic cardiomyopathy	18
Pulmonary hypertension	18
Valvular cardiomyopathy	6
Implantable cardioverter defibrillator	5
Pacemaker	7

Methods

Population and study design

Our retrospective analysis included 416 inpatients, who were referred for a clinically indicated transthoracic echocardiography during 2006–2010 period, and had 2DE and 3DE images of sufficient quality to allow both LV volume measurements and STE-based LV deformation analysis. To test our hypothesis, we included 104 patients with LVEF between 30 and 50% measured by 2DE in the final analysis (age 61 ± 16 years, 60 males and 44 females, BSA 1.8 ± 0.2 m^2). This was a subset of the study cohort described in our previous study [19]. Patients with atrial fibrillation or other arrhythmias during echocardiographic examinations were excluded. Clinical characteristics of our cohort are summarized in Table 1. We collected mortality data, including CV mortality, from hospital records and the Social Security Death Index through 2016 (mean follow-up of 5 ± 3 years). 2DE and 3DE images were used to measure EF and GLS. The risks for CV mortality associated with these indices were determined using Cox regression and Kaplan–Meier analyses. The study was approved by the Institutional Review Board (Protocol # 16800B) for retrospective analysis with a waiver of consent.

Echocardiographic imaging and analysis

2DE and 3DE imaging was performed using commercial equipment (Philips iE33 imaging system with a fully sampled matrix array transducer). 2DE imaging included apical 2-, 3- and 4-chamber views. LVEF was measured using the biplane method of disks from the 2- and 4-chamber views (Xcelera, Philips Medical Systems, Andover, MA) and GLS using 2D STE in all three views (Philips QLab). 3DE imaging included multi-beat full-volume datasets, while maximizing frame rate, which was 18 ± 3 Hz. 3DE images were analyzed using widely used and previously validated commercial software (4D LV-Function, TomTec Imaging Systems, Unterschleissheim, Germany) to quantify LVEF by semi-automated detection of the endocardial boundaries with minimal manual editing as judged necessary to optimize border position and tracking throughout the cardiac cycle, and GLS by automated 3D STE analysis (Fig. 1).

Statistical analysis

Continuous variables are presented as mean ± SD, and categorical variables as numbers and percentages. Echocardiographic variables of the subgroups were compared using non-paired Student's t-tests. Cox proportional hazards model was used to calculate hazard ratios (HRs) for CV mortality risk, while the non-CV deaths were censored. Due to the limited number of events (CV deaths), only three covariates related to our hypothesis were included in the Cox model: age, body surface area (BSA) and one of the LV functional indices found significant in the unadjusted regression analysis. Survival analysis included Kaplan–Meier curves for 5 years, because this was the mean follow-up time of the study. These curves were constructed for the 4 LV function parameters: EF and GLS measured by 2DE and separately 3DE. Comparisons of cumulative events across strata were performed using the log-rank test. Cutoffs for EF and GLS

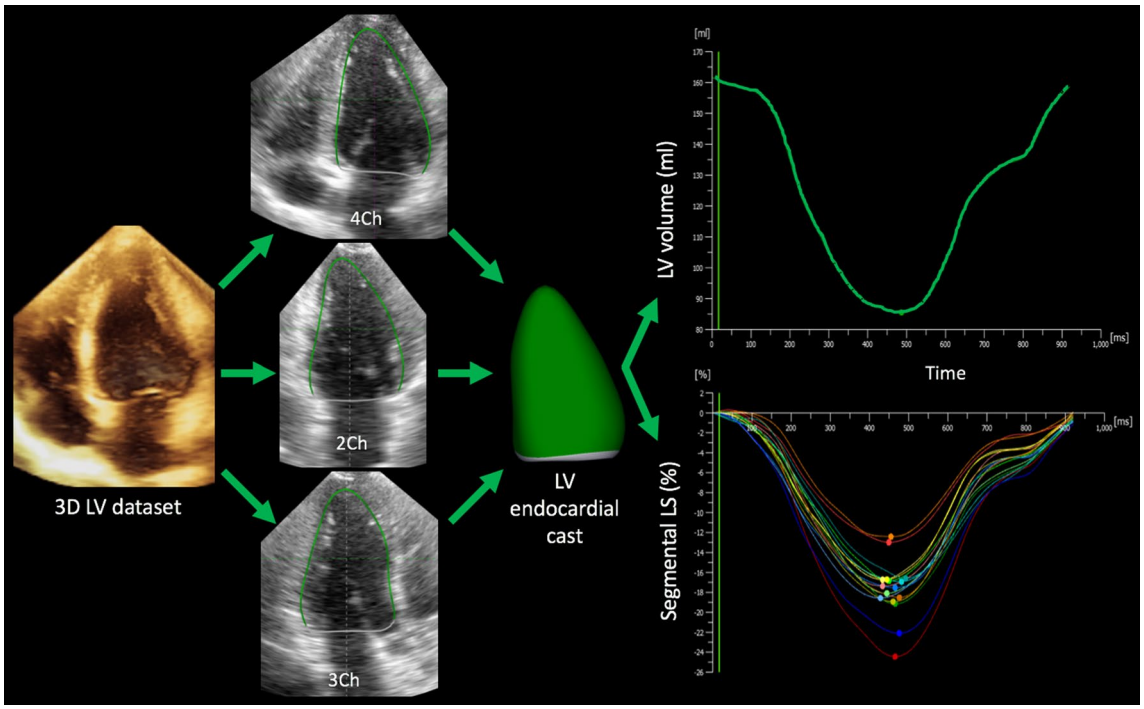

Fig. 1 Three-dimensional echocardiographic volume and deformation analyses. Example of 3DE dataset of the left ventricle (left). Endocardial boundaries initialized in 3 crossectional views extracted from the 3D dataset (center-left) are used to create a dynamic 3D cast of the ventricle (center-right), from which both dynamic volume (top, right) and longitudinal strain (LS) (bottom, rigth) are calculated (see text for details)

for each 2DE and 3DE measurements, were determined by dividing the study group into two subgroups using the median of each parameter as the cutoff. All analyses were performed using SPSS software version 22 (IBM, Armonk, New York). Statistical significance was inferred at $p < 0.05$.

Results

During the follow-up period, 53/104 (51%) patients died, including 21 patients (20%) who died of non-CV causes, while the remaining 32 (31%) were CV-related deaths. Table 2 shows the results of the 2DE- and 3DE-derived LV size and function parameters for the entire study group, as well as separately for the subgroups of survivors and non-survivors. We found no significant differences between these subgroups regarding age, BSA, 2DE-derived LVEF and GLS and 3DE-derived LVEF. Importantly, 3D GLS was the only parameter that separated the two subgroups, with the survivors having a significantly higher 3D GLS magnitude.

Due to the limited number of events, we included only three covariates in the Cox proportional hazards analysis, to avoid overfitting. Table 3 shows the results of the multiple regression for CV mortality, including the results of both unadjusted (left) and adjusted (right) analyses. The unadjusted regression revealed that only 3D GLS was

Table 2 Summary of results of all 2DE- and 3DE-derived LV size and function parameters mild to moderately reduced LV function subgroup defined by 2D LVEF

N	2D EF 30–50%			*p* value
	Total 104	Survivors 72	CV-mortality 32	
General				
Age (years)	61 ± 16	60 ± 18	64 ± 12	0.12
BSA (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.3	0.71
2DE				
Biplane EDV (ml)	176 ± 54	171 ± 56	186 ± 49	0.19
Biplane ESV (ml)	103 ± 34	100 ± 34	109 ± 33	0.18
Biplane EF (%)	42 ± 5.7	42 ± 5.8	41 ± 5.4	0.78
GLS (%)	− 13.5 ± 3.5	− 13.9 ± 3.7	− 12.8 ± 3.0	0.11
3DE				
EDV (ml)	212 ± 64	210 ± 63	216 ± 67	0.66
ESV (ml)	125 ± 49	122 ± 49	132 ± 50	0.36
EF (%)	42 ± 12	42 ± 13	39 ± 10	0.19
GLS (%)	− 13.9 ± 4.9	− 14.7 ± 5.0	− 12.2 ± 4.3	0.01

BSA body surface area, *EDV*, *ESV* end-diastolic, end-systolic volume, *EF* ejection fraction, *GLS* global longitudinal strain

Table 3 Results of Cox regression analysis of LV function indices obtained from 2DE and 3DE images: assessment of risks of long-term CV mortaility in inpatients referred for echocardiographic examination

Cox regression: CV mortality (N = 104)						
	Unadjusted			Adjusted		
	p-value	HR	95% CI	p-value	HR	95% CI
Age	0.116	1.02	0.99–1.05	0.336	1.01	0.99–1.04
BSA	0.610	0.693	0.17–2.83	0.508	0.637	0.17–2.42
2D EF	0.474	0.774	0.39–1.60			
2D GLS	0.142	0.592	0.29–1.19			
3D EF	0.090	0.543	0.27–1.10			
3D GLS	0.022	2.40	1.13–5.07	0.046	0.453	0.21–0.99

BSA body surface area, *EF* ejection fraction, *GLS* global longitudinal strain, *CV* cardiovascular, *HR* hazard ratio, *CI* confidence interval

associated with CV mortality (Table 3). Due to the limited number of events, we included only three covariates also in the adjusted regression analysis: after the addition of age and BSA, 3D GLS remained associated with CV mortality. The above associations with CV mortality were confirmed by Kaplan–Meier curves (Fig. 2), which demonstrated that only 3D GLS was able to differentiate between subgroups defined by the median of each LV function index. Not surprisingly, differences in the median values of EF and GLS by between 2DE and 3DE were minimal: 42.7 versus 41.1% and 13.0 versus 13.5%, respectively.

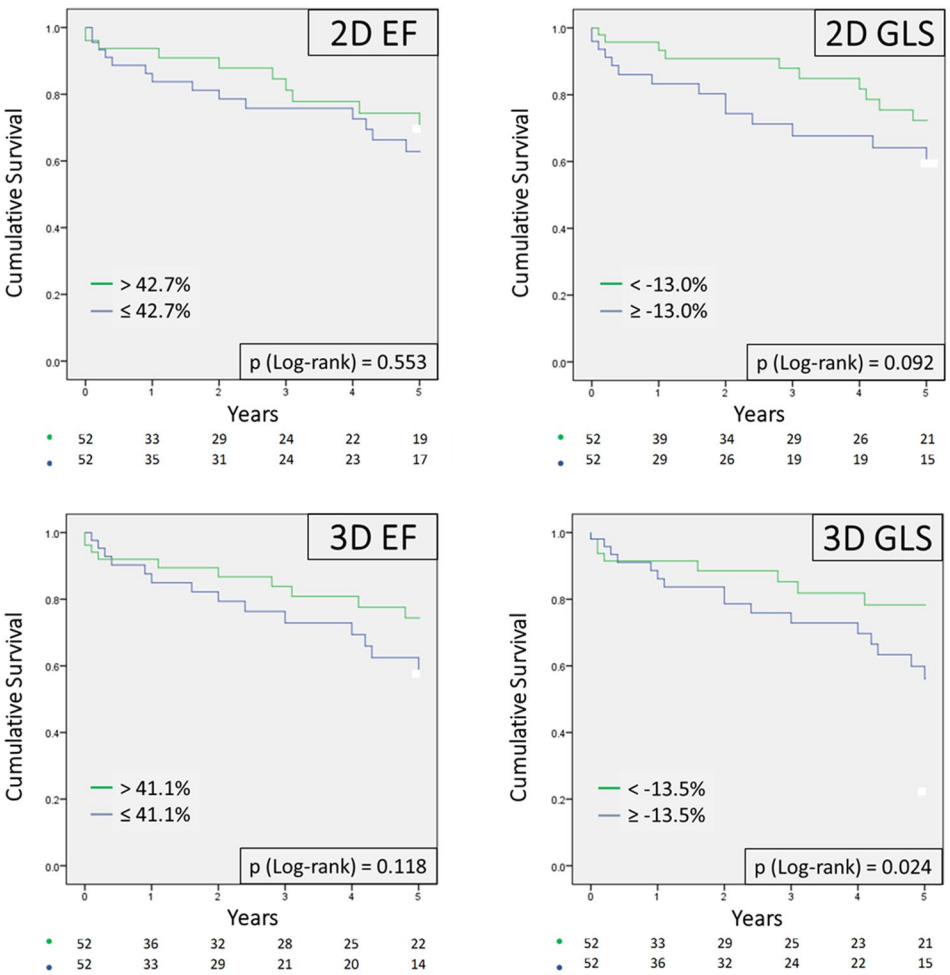

Fig. 2 Kaplan-Meier survival curves for 2DE- and 3DE-based left ventricular ejection fraction (EF) and global longitudinal strain (GLS), stratified by receiver-operating curves derived cut offs (see text for details)

Discussion

Although clinical indications for specific therapies are well established in the subgroup of patients with severely reduced LV function, these were incorporated into the guidelines following multiple studies based on 2DE-derived EF, despite the limitations of this parameter, which is routinely utilized to guide patient management including indications for cardiac valvular surgery [20, 21], cardiac resynchronization therapy and defibrillator implantation [22–24], chemotherapy [25], and advanced heart failure [26, 27]. Limitations of 2DE EF include limited accuracy and reproducibility, compared to 3DE because of the dependence on imaging plane and the geometrical assumptions. Over the last decade, GLS has become an indispensable parameter to assess LV function, as for both 2DE and 3DE, GLS was found to be superior to EF [1–4, 9–15]. The recommendations in the recent guidelines emphasize quantification of LV function by measuring both 3D EF and 2D GLS [28]. In a previous publication [19], we showed that 3DE derived indices of LV function are important for prognostic and not only diagnostic purposes. In this current substudy, we focused on patients with mildly-to-moderately reduced LVEF defined by 2DE-derived EF in the range of 30–50. Our results show that EF by 2DE and 3DE and 2DE GLS were unable to distinguish patients who were at higher risk of mortality in this subgroup. In contrast, 3DE GLS was able to achieve this goal, thereby demonstrating the potential clinical implications of this index of myocardial deformation in patients with mildly-to-moderately reduced LVEF.

Our findings are important as patients at higher CV mortality risk in the mildly-to-moderately reduced LV function group may be routinely undertreated. The 2DE 30–50% LVEF subgroup of patients is a heterogeneous population with patients who are difficult to select for more active therapies. While the common clinical practice recommendations by guidelines include referral for CRT-D implantation in those with 2DE LVEF below 30%, this cutoff may be imperfect [29]. Moreover, decisions about surgical treatment of valvular heart disease or initiation/termination of chemotherapy treatment are also determined by 2D LVEF. Accordingly, other indices of LV function have the potential to better guide indications and timing for challenging clinical decision making. Still, nowadays the vast majority of published studies that guide clinical practice are based on 2D LVEF [22–24].

As previously described [19], this study was possible because of the availability of a unique 3DE database including hundreds of studies dating from 2006, which allowed us an up to a decade-long follow-up in order to investigate the relationship between 3DE-derived indices of LV function and long-term mortality. The inclusion criteria for this study was the availability of good quality 2DE and 3DE images performed in inpatients referred for a clinically indicated echocardiographic examination. This reflects the feasibility of acquiring 3D LV full-volume datasets of adequate quality already in 2006, which provided the basis for the new chamber quantification guidelines [28] that recommend this methodology whenever possible. We also followed these guidelines' recommendation for 2D GLS measurements using 2-, 3-, and 4-chamber views, which underscores the true superiority of 3D over 2D GLS measurements.

One might question the high all-cause mortality rate in our patient cohort, which was approximately 50% over a 10-year period. We believe that this reflects the high acuity and long-term mortality of inpatients referred for cardiac ultrasound examinations in a tertiary referral hospital. This may also reflect the fact that our hospital is located in an underserved urban area, where patient non-compliance is known to be high due to socioeconomic factors, as well as the prevalence of co-morbidities, also confirmed in our study (Table 1).

Our finding that in the 2DE derived 30–50% LVEF group, the predictive power of GLS is better than that of EF, may be related to its superior accuracy, when measured by 3DE [17, 18]. A possible reason for the improved reproducibility and accuracy compared to EF may be related to the methodology of the semi-automated speckle tracking algorithm. This is because one source of variability of the conventional technique for EF measurement is the need to visually identify the end-diastolic and end-systolic frames for analysis, which is not perfectly reproducible. Even the chamber quantification guidelines are ambiguous with regard to this frame selection [28]. In contrast, GLS measurements are based on speckle tracking technology, which follows the myocardium throughout the cardiac cycle and thus includes every single frame in each analysis, avoiding this source of variability.

Interestingly, Kaplan–Meier curves (Fig. 2) showed that 3D GLS was able to differentiate patients at higher mortality risk in our study group, while 2DE EF and GLS and 3DE EF failed to do so. This finding may reflect the improved sensitivity of 3D functional assessment by GLS, which may manifest itself in better predictive power in even the mildly-to-moderately reduced LV function subgroup. This is in contrast to 2D EF which was historically associated with higher mortality only in the severe LV dysfunction group. The Cox and Kaplan–Meier curve analysis showed that 3D EF and 2D GLS showed only a trend towards being associated with CV mortality. It is possible that these analyses were underpowered and, in a bigger cohort of patients, these LV function indices would have been found significant. However, to ensure sufficient power, we would need to perform separate power analysis for each of the many variables included in the

study, which would likely indicate the need for a different sample size for each variable. This would be an impossible goal to achieve in a study based on retrospective analysis of existing historical clinical data with available multi-year outcomes information.

Limitations

One limitation is the retrospective nature of this study, which might have biased the patient selection. For example, we focused on inpatients with good quality images, thus limiting the generalizability of our findings. Obese patients and those with suboptimal images due to other conditions such as lung disease, may not be adequately represented in our cohort. Accordingly, our results cannot be extrapolated to consecutive patients or outpatients with a wide range of image quality, some of which may not be suitable for 3D speckle-tracking based strain analysis. In fact, we cannot estimate the feasibility of 3D analysis in this historical cohort of patients who were selected on the basis of image quality over a decade using imaging equipment available at the time. Finally, this study only analyzed patients in sinus rhythm during imaging. Thus, these results also cannot be extrapolated to patients with atrial fibrillation or other types of arrhythmia.

Conclusions

Our study is the first to demonstrate a superior predictive ability of 3D GLS over 2D GLS and 2D/3D EF in the subgroup of patients with mildly-to-moderately reduced LV function defined by 2D EF. 3D GLS was found to be a superior survival prognostic index in this subgroup of patients. This study adds credence to the use of 3D GLS in echocardiographic examinations to help identify patients with mildly-to-moderately reduced LV function who are at higher CV mortality risk. Accordingly, incorporation of 3D GLS into clinical decisions has the potential to improve survival in the subgroup of patients with mildly-to-moderately reduced LVEF who may benefit from therapeutic interventions that are not indicated according to the current guidelines.

Compliance with ethical standards

Conflict of interest AN was supported by funding from the NIH T32 Training Grant (#(5T32HL7381). The remaining authors have no relevant financial disclosures or conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The study was approved by the Institutional Review Board with a waiver of consent.

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