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Original Article

Echocardiography Core Laboratory Validation of a Novel Vendor-Independent Web-Based Software for the Assessment of Left Ventricular Global Longitudinal Strain

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ABSTRACT

BACKGROUND: Global longitudinal strain (GLS) is an accurate and reproducible parameter of left ventricular (LV) systolic function which has shown meaningful prognostic value. Fast, user-friendly, and accurate tools are required for its widespread implementation. We aim to compare a novel web-based tool with two established algorithms for strain analysis and test its reproducibility.

METHODS: Thirty echocardiographic datasets with focused LV acquisitions were analyzed using three different semi-automated endocardial GLS algorithms by two readers. Analyses were repeated by one reader for the purpose of intra-observer variability. CAAS Qardia (Pie Medical Imaging) was compared with 2DCPA and AutoLV (TomTec).

RESULTS: Mean GLS values were −15.0 ± 3.5% from Qardia, −15.3 ± 4.0% from 2DCPA, and −15.2 ± 3.8% from AutoLV. Mean GLS between Qardia and 2DCPA were not statistically different (p = 0.359), with a bias of −0.3%, limits of agreement (LOA) of 3.7%, and an intra-class correlation coefficient (ICC) of 0.88. Mean GLS between Qardia and AutoLV were not statistically different (p = 0.637), with a bias of −0.2%, LOA of 3.4%, and an ICC of 0.89. The coefficient of variation (CV) for intra-observer variability was 4.4% for Qardia, 8.4% 2DCPA, and 7.7% AutoLV. The CV for inter-observer variability was 4.5%, 8.1%, and 8.0%, respectively.

CONCLUSIONS: In echocardiographic datasets of good image quality analyzed at an independent core laboratory using a standardized annotation method, a novel web-based tool for GLS analysis showed consistent results when compared with two algorithms of an established platform. Moreover, inter- and intra-observer reproducibility results were excellent.

Keywords: Left ventricular global longitudinal strain; Echocardiography; Core Lab; Validation; Reproducibility

INTRODUCTION

Global longitudinal strain (GLS) assessed with 2-dimensional (2D) echocardiography has evolved as an important marker of left ventricular (LV) systolic function and impaired GLS

has been associated with worse outcomes in patients with cardiovascular disease.[1] Notably, GLS is an independent predictor of death, heart failure hospitalizations, and LV remodeling in patients presenting with aortic stenosis,[2][3] acute myocardial infarction,[4][5] or congestive heart failure.[6] Notwithstanding, GLS is not sufficiently used in clinical routine and ongoing efforts exist to promote its wider clinical use.

Development in quantitative assessment of GLS occurred simultaneously through several manufacturers, leading to the existence of multiple approaches to measure strain as well as diverse algorithms.[7] Approaches include the assessment of epicardial, mid-wall, or endocardial strain; peak, systolic, or post-systolic strain; assessment of 1, 2, or 3 views (4 chamber [4CH], 4CH + 2CH, 4CH + 2CH + 3CH); 2D vs. 3D GLS; among others. These factors led to prominent standardization efforts which showed that GLS values are vendor-dependent[7]; that test-retest, intra-observer and inter-observer variability within a vendor are adequate[7][8]; that the use of vendor-independent GLS analysis software is feasible and adequate[7-9]; and that in terms of accuracy and reproducibility, endocardial GLS was associated with lower inter-vendor bias.[10]

Further implementation of GLS use in clinical routine may benefit from the availability of a standardized methodology to annotate endocardial borders towards lower variability; user-friendly, fast, vendor independent GLS analysis software; and standardized methodology to test intra- and inter-observer variability within an echocardiography core laboratory. In this work we, an independent core laboratory, utilized a standardized annotation methodology and test the accuracy and reproducibility of a novel web-based 2D-derived endocardial GLS analysis software using three apical views compared to a reference vendor-independent software.

METHODS

Study datasets

This study included 30 fully anonymized 2D transthoracic echocardiographic DICOM datasets used for internal validation purposes at an Echo Core Laboratory (Cardialysis, Rotterdam, The Netherlands). Each of the 30 datasets consisted of apical 4CH, 3CH, and 2CH views, and required good image quality as well as sinus rhythm. Good image quality was defined when all endocardial segments (16-segment American Heart Association model) were visible at end-diastolic and end-systolic phases. Once the 30 datasets were selected, 3 copies (i.e., the labelled datasets A, B, and C) were created with new randomly-ordered identifiers. Dataset A was used for the first analysis of observer 1, dataset B for the second analysis of observer 1 (intra-observer variability), and dataset C for the analysis of observer 2 (inter-observer variability). Fully anonymized datasets were provided by an affiliated academic institution (Erasmus University Medical Center, Rotterdam, The Netherlands), and all acquisitions were performed in the context of diverse prospective investigations that required patient consent and were approved by the Institutional Review Board at the same institution (Erasmus Medical Center).

Software and methodology

All cases were previously analyzed by the same readers for internal validation purposes at the Echo Core Lab. The algorithms used to quantify endocardial GLS were 2DCPA GLS (TomTec Arena 2.20.01; TOMTEC Imaging Systems GmbH, Unterschleissheim, Germany) and AutoLV (TomTec Arena 2.20.01; TOMTEC Imaging Systems GmbH); this TomTec algorithm is different to 2DCPA and this version provides GLS results as well. 2DCPA uses up to three apical views for determination of GLS, while AutoLV uses only up to two apical views (2CH and 4CH views). For the purpose of this comparison, 30 sets of Philips DICOM data were reanalyzed using CAAS Qardia 1.0 (Pie Medical Imaging, Maastricht, The Netherlands), which uses up to 3 apical views for GLS determination (**Figure 1**). All results are reported for the first time. The time between the first and second analysis of observer 1 was 4 weeks at least, to address memory bias. The analyses were performed by two experienced Echo Core Lab readers (CR and ES).

Qardia quantifies GLS using DICOM echo images as input. To calculate GLS, a dedicated strain analysis workflow within Qardia is used. The workflow starts at the end-diastolic frame where the endocardial contour is determined using a minimum cost segmentation algorithm that is initiated from three anatomical landmark points as set by the user, i.e., the left and right mitral annular hinge points and the LV apex (**Figure 1**). The end-diastolic frame is automatically identified using ECG information obtained from the DICOM echo images. Subsequently, the LV endocardial border is tracked along the cardiac cycle using cross-correlation based speckle tracking (**Figure 1**). GLS is calculated as the ratio between endocardial contour length changes and the initial endocardial contour length obtained from the tracked edge positions. Qardia can be installed using the so-called client-server approach in which the software is operated at the client via the web browser on any PC that is connected to the center's server. As a vendor-neutral software platform, there are no specific additional requirements

to use Qardia as compared to conventional echo analysis software platforms.

The Cardialysis Echo Core Lab methodology for annotation of endocardial borders was utilized. The method includes drawing the endocardial contours of the left ventricle after precise identification of the hinge points: 1) 2CH view: mitral annular plane (at mitral leaflet hinge points) and apex; 2) 3CH view: mitral leaflet hinge point, aortic annulus and apex; and 3) 4CH view: mitral annular (at mitral leaflet hinge points) and apex. Characteristically, in this method the apex is placed close to epicardium to ensure consistency and accuracy, at both end-systole and end-diastole.

Statistical analysis

Continuous variables were compared using the Student's t-test and the association between them was tested using Pearson correlation, intraclass correlation coefficient and Bland-Altman analysis. Intra- and inter-observer variability were expressed as coefficient of variation (CV) calculated as the standard deviation of inter- and intra-observer difference divided by the population mean. Normal distribution was confirmed with use of the

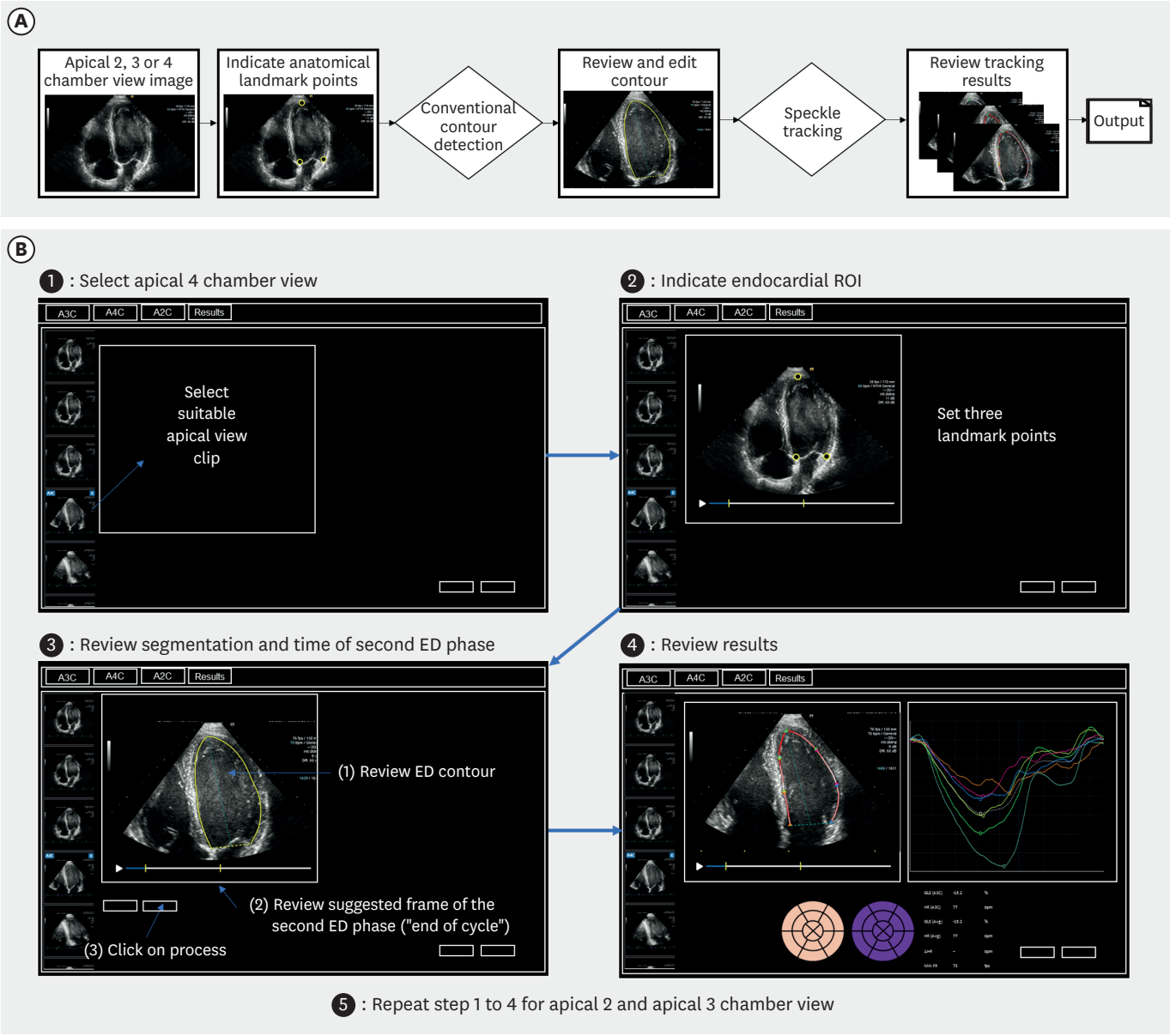

Figure 1. CAAS Qardia global longitudinal strain analysis flow (A) and analysis steps (B).
ED, end-diastole; ROI, region of interest.

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Shapiro-Wilk test. Statistical analyses were performed with SPSS 23.0 (IBM Corp., Armonk, NY, USA). All probability values were 2-tailed, and a value of p<0.05 was considered significant.

RESULTS

Baseline characteristics and echocardiographic findings are presented in **Supplementary Table 1**. In brief, 77% of datasets were from male patients and the mean age was 47 years. 43% had a presumably normal LV systolic function, 47% had ischemic cardiomyopathy, and 10% had non-ischemic cardiomyopathy.

GLS

After automatic endocardial contour delineation, manual correction was performed using all three algorithms in the end-diastolic phase. End-systolic phase corrections were performed when using 2DCPA and AutoLV, but Qardia does not allow manual corrections on the end-systolic phase per design. The mean time required for the analysis of each dataset was 228 ± 87 seconds for Qardia, 360 ± 46 seconds for 2DCPA, and 170 ± 18 seconds for AutoLV. For Qardia and 2DCPA, 3 views were used in every instance for determination of LV GLS. For AutoLV, 2 views were used in every instance. It is noteworthy that the reported time starts at the opening of the case in the analysis platform, continues with selection of each view, contour determination, contour correction (when possible and needed), and data capture or export, as applicable.

Mean GLS values were –15.0 ± 3.5% for Qardia, –15.3 ± 4.0% for 2DCPA, and –15.2 ± 3.8 for AutoLV (**Table 1**, **Figures 2** and **3**). The Mean GLS values between Qardia and 2DCPA were statistically not different (p = 0.359), with a bias of –0.3% and limits of agreement of 3.7%. The intra-class correlation coefficient was 0.88. Likewise, the mean GLS values between Qardia and AutoLV were statistically not different (p = 0.637), with a bias of -0.2% and limits of agreement of 3.4%. The intra-class correlation coefficient was 0.89. Individual measurements are provided in **Supplementary Table 2**.

Inter- and intra-observer reproducibility

Reproducibility results are presented in **Table 2**. The coefficient of variation for intra-observer variability was 4.4% for Qardia, 8.4% for 2DCPA, and 7.7% for AutoLV. Similarly, the coefficient of variation for inter-observer variability was 4.5%, 8.1%, and 8.0%.

Table 1. Comparison of global longitudinal strain measured with CAAS Qardia vs. TomTec 2DCPA vs. TomTec AutoLV algorithms

Variables	CAAS Qardia	2DCPA	AutoLV
Mean ± SD	−15.0 ± 3.5%	−15.3 ± 4.0%	−15.2 ± 3.8%
p-value	-	0.359	0.637
Bias	-	−0.3%	−0.2%
LOA	-	± 3.7%	± 3.4%
r	-	0.88	0.89
ICC	-	0.88	0.89

ICC, intraclass correlation coefficient; LOA, limits of agreement; r, Pearson correlation r; SD, standard deviation.

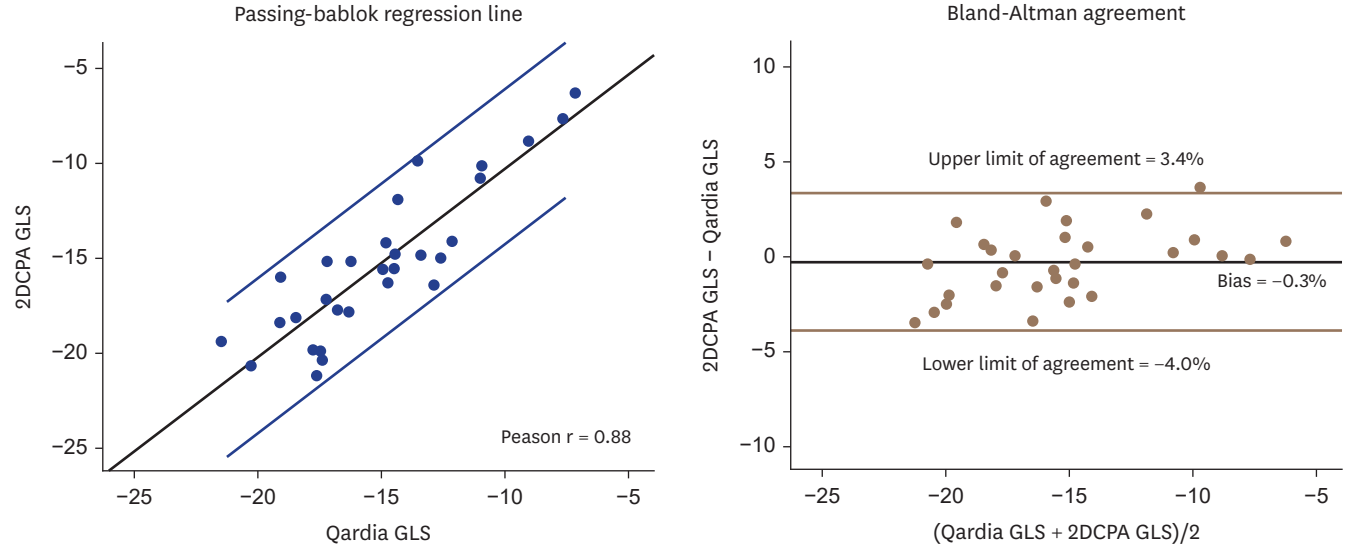

Figure 2. Regression and Bland-Altman plot for the comparison of global longitudinal strain measured with CAAS Qardia vs. TomTec 2DCPA. GLS, global longitudinal strain.

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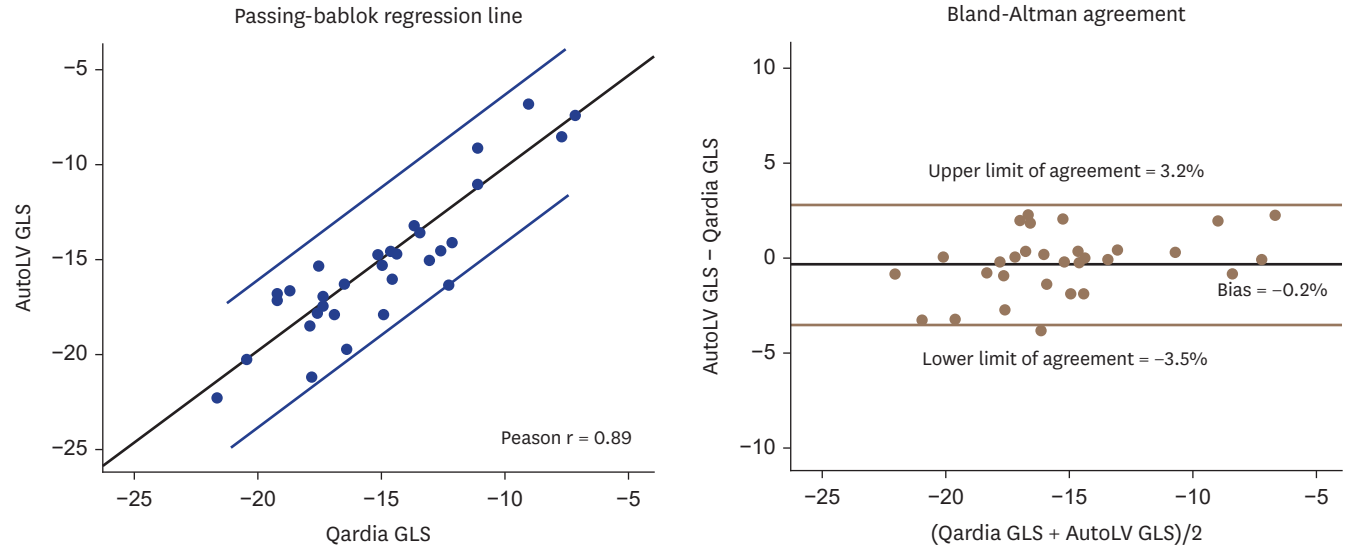

Figure 3. Regression and Bland-Altman plot for the comparison of global longitudinal strain measured with CAAS Qardia vs. TomTec AutoLV.
GLS, global longitudinal strain.

Table 2. Intra- and inter-observer reproducibility (n = 30)

Analysis algorithm	CV intra-observer	CV inter-observer
CAAS Qardia	4.4%	4.5%
2DCPA	8.4%	8.1%
AutoLV	7.7%	8.0%

CV, coefficient of variation.

DISCUSSION

The main findings of our investigation are:

- Measurement of endocardial GLS using a web-based tool (CAAS Qardia) is feasible and yields comparable results when compared with commercially available desktop software (TomTec 2DCPA and TomTec AutoLV).
- The inter- and intra-observer reproducibility with CAAS Qardia, are comparable (if not superior) to those with TomTec 2DCPA and TomTec AutoLV.

Assessment of accuracy typically requires a gold standard reference. However, in the study of LV GLS, the scientific community agreed over time that there is no such gold standard. This is explained by the fact that GLS determined with echocardiography or cardiac magnetic imaging are vendor and software dependent, and intrinsic methodologies of each may vary. The closest gold standard is a well-established method, which in this work refers to the 2DCPA software, which has been extensively studied and compared to other algorithms.[7] Similar to 2DCPA, Qardia utilizes up to three views to calculate LV GLS. Both are vendor independent, however, Qardia has the advantage of being web-based, not requiring desktop installation of software. In addition, we decided to compare the assessment with AutoLV, given that this method uses only 2 views (2CH and 4CH), which is consistent with the Simpson's approach for LV ejection fraction assessment.[1] In our Core Lab, we use the same contouring method for LV volumes, ejection fraction, and strain analysis, all being endocardial. It is noteworthy that from the user perspective, the web-based platform appeared faster and user-friendly. Qardia does not allow changes of end-systolic endocardial contours, which differs from other systems. However, the manufacturer confirmed that this restriction is per design and in-line with the algorithm functionality.

An important hurdle in the implementation of strain analysis in clinical practice it its high variability. This is inherited from LV ejection fraction analysis variability which unfortunately has not fully evolved into a quantitative parameter.[11] In many European centers, LV ejection fraction is still qualitatively assessed and documented, partly explained by the time required to draw the endocardial borders in end-diastole and end-systole, and by the lack of standardized methodologies to annotate the endocardium. In our experience, a critical source of variability is where the mitral annular hinge points are positioned, and more importantly the apex. As much as the apex position has a relatively less important effect in ejection fraction calculation, it has a bigger effect in volume assessment, and even larger effect in strain assessment.[12] Beyond the implementation of a standardized method, the use of automation may soon expedite the increased use of quantitative parameters in clinical routine. In addition, user-friendliness and vendor-independence may play a role.

The European Association of Cardiovascular Imaging (EACVI)/American Society of Echocardiography (ASE)/Industry Task Force to Standardize Deformation Imaging have defined an acceptable test-retest variability of 10%,[10)13)] and normal values have been defined within –18% to –20%,[8)] consequently, a bias of less than 2% in absolute GLS values would be considered acceptable.[10)13)] This is conceptually important, since this approach suggested back in 2015, would require changes > 2 GLS % units to define a real change (i.e., not due to observer variability). However, in patients with reduced GLS, the absolute change that defines a real chance would be much lower than 2 GLS % units. For example, in a patient with GLS of –7.0%, an absolute change of 0.7% would be considered a real change not due to variability. In this investigation, the coefficient of variation was less than 10% for all comparisons for intra- and inter-observer variability. Furthermore, the differences among Qardia and the other two methods showed a small change (≤ 0.3%), although the limits of agreement were up to 3.7%.

Our results have to be interpreted in view of the following limitations. First, only datasets with good image quality and in sinus rhythm were included. Extrapolation to daily medical practice is not possible since moderate or poor image quality are frequent, as well as rhythm disorders. Similarly, data is insufficient to conclude the accuracy of GLS in specific sub-groups, such as non-ischemic cardiomyopathy patients, LV hypertrophy patients, among other specific conditions. Second, only experienced Core Lab readers participated in the analysis, which would bias results towards better reproducibility numbers. However, the same readers were involved for all comparisons, making the comparisons valid. As lack of gold standard in strain analysis, a experienced reader in this field is essential for a validation study. Third, Qardia does not allow manual changes in end-systole, which may limit the reader's need for manual corrections and may explain the better reproducibility. Fourth, this analysis did not provide other echocardiographic measurements such as ejection fraction or segmental strain, which should be considered in future studies. As next steps of this validation study, the feasibility of using this algorithm with different levels of reader expertise, with different image quality, and in different rhythm conditions, needs to be further investigated.

In conclusion, assessment of LV global longitudinal strain with CAAS Qardia renders comparable results as those of TomTec 2DCPA and TomTec AutoLV, with excellent reproducibility, in the presence of sinus rhythm and good image quality.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Demographic characteristics

Click here to view

Supplementary Table 2

Individual measurements using three GLS algorithms

Click here to view

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Conflict of Interest

Dr. Spitzer reports institutional contracts for which he receives no direct compensation with Boston Scientific, Cardiawave, Edwards Lifesciences, Medtronic, Shanghai Microport Medical Co. Ltd., NVT GmBH, Pie Medical Imaging, and Siemens Healthcare GmBH. Other authors declare no conflicts of interest.

Author Contributions

Conceptualization: Spitzer E, Camacho B, Mrevlje B, Brandendburg HJ, Ren CB; Data curation: Spitzer E, Ren CB; Formal analysis: Spitzer E, Ren CB; Funding acquisition: Spitzer E; Investigation: Spitzer E, Camacho B, Mrevlje B, Brandendburg HJ, Ren CB; Methodology: Spitzer E, Camacho B, Mrevlje B, Brandendburg HJ, Ren CB; Project administration: Spitzer E; Resources: Spitzer E; Software: Spitzer E; Supervision: Ren CB; Writing - original draft: Spitzer E, Ren CB; Writing - review & editing: Spitzer E, Camacho B, Mrevlje B, Brandendburg HJ, Ren CB.

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