



Reproducibility of right ventricular function by longitudinal strain and other echocardiographic parameters in the ELSA-Brasil study

Eduardo G. Pianca¹ · Giulia B. Schmitz^{1,2} · Bruce B. Duncan³ · Murilo Foppa^{1,2} · Angela B. S. Santos^{1,2}

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Abstract

Right ventricular (RV) free wall longitudinal strain (RVFWLS), and four-chamber longitudinal strain (RV4CLS) using speckle tracking echocardiography have demonstrated increased accuracy and discrimination to measure right ventricular function in different clinical conditions. Reproducibility data of these measures are scarce and mainly tested in small or reference populations. The main objective of this study was to investigate their reproducibility, and of other traditional RV parameters, from unselected participants of a large cohort study. RV strain reproducibility was analyzed using echocardiographic images of 50 participants from a randomly selected sample from The ELSA-Brasil Cohort. Images were acquired and analyzed following the study protocols. The mean RVFWLS was $-26.9 \pm 2.6\%$ and the mean RV4CLS was $-24.4 \pm 1.9\%$. The intra-observer reproducibility parameters of RVFWLS demonstrated a coefficient of variation (CV) of 5.1% and an intraclass correlation coefficient (ICC [95%CI] 0.78[0.67–0.89]), and for RV4CLS were CV = 5.1% and ICC = 0.78[0.67–0.89]. Reproducibility for RV fractional area change was CV = 12.1%; ICC = 0.66 [0.50–0.81] and for RV basal diameter was CV = 6.3%; ICC = 0.82 [0.73–0.91]. The inter-observer reproducibility for RVFWLS was CV = 8.3%; ICC 0.54[0.34–0.74] and for RV4CLS, CV = 6.3%; ICC = 0.53[0.34–0.73], following the same pattern among conventional RV parameters. We found adequate reproducibility of RV longitudinal strain parameters. This information is relevant for the long-term follow-up of cohort participants and reinforces the utility of RV longitudinal strain as a tool to monitor subclinical changes in RV systolic function.

Keywords Right ventricular reproducibility · Speckle-tracking echocardiography · Global longitudinal strain · Free wall longitudinal strain

Introduction

Assessment of right ventricular (RV) function is important to the management of patients with heart failure [1], pulmonary hypertension [2], and congenital heart diseases [3]. Traditional RV systolic parameters such as tricuspid lateral annular peak systolic velocity by pulsed tissue Doppler

imaging (s') and tricuspid annular plane systolic excursion (TAPSE) remain the recommended measures to estimate RV systolic function [4]. However, these parameters have limitations such as angle and load dependence and inaccuracy in evaluating a global RV systolic function since they represent only the function of the basal segment [4].

Two-dimensional speckle tracking echocardiography (2DSTE) is an increasingly used technique to quantify RV global and regional myocardial function. RV longitudinal strain measurement has been demonstrated to increase the diagnostic accuracy of multiple heart conditions, such as pulmonary hypertension [5], pulmonary embolism [6], arrhythmogenic right ventricular dysplasia [7], and to further stratify the prognosis in patients with heart failure [8], acute coronary syndromes [9] and heart transplantation [10].

Previous studies evaluating the RV longitudinal strain reproducibility are scarce and were done in small or reference populations [11]. Consequently, data regarding RV

✉ Angela B. S. Santos
absantos@hcpa.edu.br

¹ Postgraduate Program in Cardiology and Cardiovascular Sciences, Medical School, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

² Cardiology Division, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos, 2350, Sala 2061, Porto Alegre, Rio Grande do Sul, RS ZIP Code 90035-903, Brazil

³ Postgraduate Program in Epidemiology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

longitudinal strain reproducibility in community scenarios and cohort populations are limited. Therefore, the main objective of this study was to investigate the inter- and intra-observer reproducibility of 2DSTE right ventricular longitudinal strain parameters and other traditional RV parameters from The ELSA-Brasil study participants.

Methods

Study population

The ELSA-Brasil study is a cohort study of 15,105 civil servants (men and women aged 35–75 years old) in Brazil aiming to investigate the incidence, progression, and determinants of diabetes and cardiovascular diseases, and was detailed elsewhere [12, 13]. The study protocol was approved by each institutional review board and written informed consent was obtained from all participants.

Echocardiography was performed at the study baseline (between 2008 and 2010), and 2DSTE parameters were measured in a predefined random subsample comprising 10% of the entire cohort. Exclusion criteria were inadequate echocardiography images and cardiac arrhythmias in acquired images. Fifty participants were selected from the random sample for the right ventricular global longitudinal strain reading and analysis, similar sample size to our previously published left ventricular strain reproducibility [14].

Two-Dimensional echocardiography

Transthoracic echocardiography images were acquired by trained echocardiographers following study protocols according to the North American and European Societies of Cardiology guidelines [15, 16]. All studies were performed in identical equipment (Aplio XG; Toshiba Corporation, Tokyo, Japan), using a 2.5 MHz sectorial transducer, and the frame rate for the acquisition ranged from 40 to 60 frames per second. Cine loops and static images of 3 cardiac cycles were selected in each acoustic window for posterior central reading. Cine loops and static images of 3 cardiac cycles were selected in each acoustic window for posterior central reading.

In the reading center, all studies were blindly read for clinical parameters in a dedicated workstation (ComPACS Review Station 10.5, Medimatic Solutions Srl, Italy) according to a prespecified protocol [17]. RV basal diameter was obtained from the apical four-chamber view and calculated as a mean of 3 consecutive heart cycles (Fig. 1A). RV fractional area change (FAC) was obtained from the apical four-chamber view and calculated as the difference in the end-diastolic area and the end-systolic area divided by the end-diastolic area (Fig. 1B).

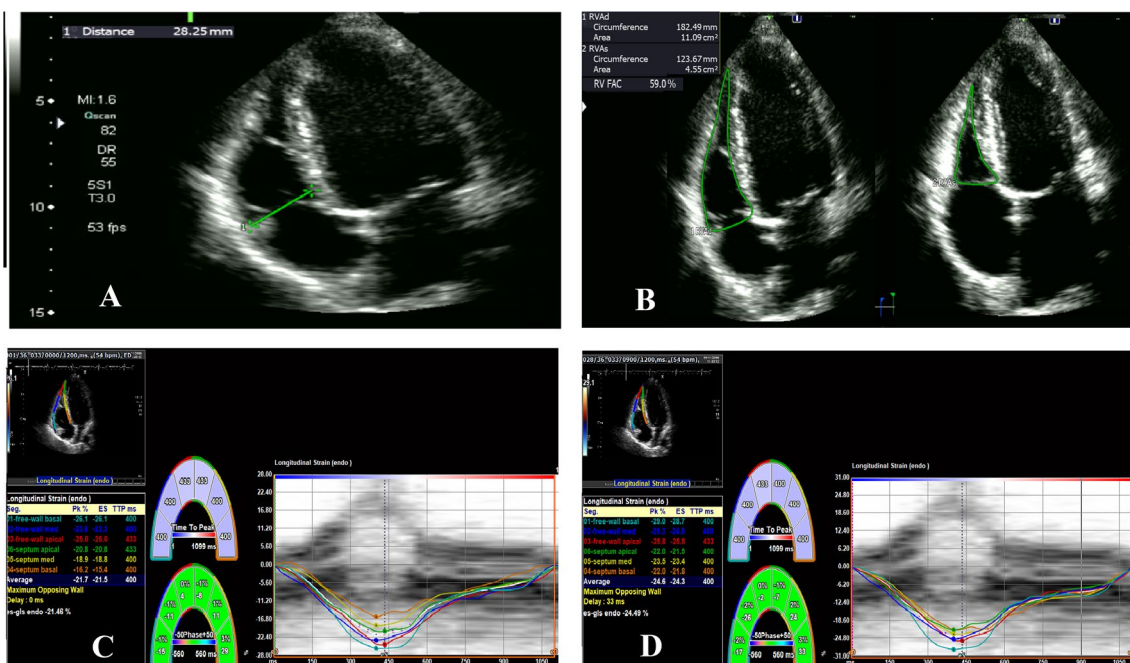


Fig. 1 Examples of right ventricular measurements: **A** RV basal diameter; **B** RV endocardial border tracing at end-diastole and end-systole to calculate the fractional area change (FAC); **C** observer 1

RV strain; **D** observer 2 RV strain. The colored lines represent strain curves of each of the six segments of the right ventricle

RV longitudinal strain

The quantitative evaluation of right ventricular global longitudinal strain followed current guidelines and recommendations [18, 19], using a previously validated and commercially available software dedicated to RV analysis (2 D Cardiac Performance Analysis©, TomTec-Arena™ 1.2 Imaging Systems, Unterschleißheim, Germany) [20].

For deformation analysis, the software tracks speckles along the endocardial border and myocardium throughout the cardiac cycle, and unacceptable image quality was defined as a lack of a full cardiac cycle or when two or more segments could not be properly tracked. The RV strain could be obtained in all subjects of this subsample. End-diastole was manually defined as the peak of the R-wave from the QRS electrocardiogram tracing, whereas end-systole was defined as a tricuspid valve opening from the four-chamber view. The RV free wall and interventricular septum are both divided into three segments (apical, mid, and basal). RV free wall longitudinal strain (RVFWLS) is the average value from three RV free wall segments and four-chamber longitudinal strain (RV4CLS) is a measurement obtained from the average of the values from all six segments, including septal segments, and the dedicated software calculated both final values (Fig. 1C).

The strain analysis had a mean duration of 10–15 min per participant and was made by two investigators with different grades of training in RV strain measurements: investigator 1 (EGP), an echocardiographer with 500 analyses performed, and investigator 2 (GBS), echocardiographer on training with 100 analyses performed. To assess intra-observer reproducibility, each investigator repeated the analysis on the same set of images after 2 months, blinded to the first reading.

Statistical analysis

Data are presented as mean \pm standard deviation (SD). For reproducibility, intra-observer and inter-observer coefficients of variation (CV) were calculated as the ratio of SD to mean, expressed in percentage. Intraclass correlation coefficient (ICC) and 95% confidence intervals (95% CI) were calculated using a two-way mixed model. [21]. Bland & Altman graphics were plotted to demonstrate the inter-observer rate of agreement and to assess the relationship between the observer's measurements. All statistical analyses were performed using Stata® (version 13.0).

Results

The mean age of the study sample's participants was 51.3 ± 9.7 years and 57% were female. The mean heart rate was 65 ± 6 beats per minute. Other clinical and demographic

Table 1 Intra-observer reproducibility of right ventricular function parameters (N = 50)

	Measure 1	Measure 2	CV	ICC
RVFWLS, %				
Observer 1	-26.9 ± 2.6	-26.5 ± 2.5	6.6	0.77 (0.65–0.88)
Observer 2	-27.6 ± 3.4	-27.3 ± 2.6	10.6	0.62 (0.46–0.79)
RV4CLS, %				
Observer 1	-24.4 ± 1.9	-24.1 ± 1.9	5.1	0.78 (0.67–0.89)
Observer 2	-24.6 ± 2.0	-24.5 ± 1.6	8.2	0.67 (0.52–0.82)
FAC, %				
Observer 1	41.8 ± 5.3	40.2 ± 7.1	12.1	0.66 (0.50–0.81)
Observer 2	41.6 ± 4.6	40.7 ± 4.1	11.1	0.44 (0.22–0.66)

RVFWLS right ventricular free wall longitudinal strain, *RV4CLS* right ventricular four chamber longitudinal strain, *FAC* right ventricular fractional area change; Values noted as Mean \pm SD, *CV* coefficient of variation, %; *ICC* intraclass coefficient correlation (95% CI)

Table 2 Inter-observer reproducibility of right ventricular function parameters (N = 50)

	Observer 1	Observer 2	CV	ICC
RVFWLS, %				
	-26.5 ± 2.5	-27.3 ± 2.6	8.3	0.54 (0.34–0.74)
RV4CLS, %				
	-24.1 ± 1.9	-24.5 ± 1.6	6.3	0.53 (0.34–0.73)
FAC, %				
	40.2 ± 7.1	40.7 ± 4.1	17.6	0.22 (0–0.51)

RVFWLS right ventricular free wall longitudinal strain, *RV4CLS* right ventricular four chamber longitudinal strain, *FAC* right ventricular fractional area change; Values noted as Mean \pm SD; *CV* coefficient of variation, %; *ICC* intraclass coefficient correlation (95% CI)

characteristics of study participants in The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) were described previously [14].

Intra- and inter-observer reproducibility

The intra-observer reproducibility of the RV global longitudinal strain was similar for free wall and four chamber analysis (Table 1). Considering RVFWLS, observer 1 had an excellent CV (6.6%) and intra-observer agreement (ICC [95%CI]: 0.77[0.65–0.86]). Considering RV4CLS, observer 1 had, also, an excellent CV (5.1%) and intra-observer agreement (ICC: 0.78 [0.67–0.89]).

Table 2 shows inter-observer reproducibility for RVFWLS and RV4CLS. Both longitudinal strain parameters had a fair inter-observer agreement (RVFWLS ICC: 0.54 [0.34–0.74]), (RV4CLS ICC: 0.53 [0.34–0.73]), and CV of 8.3% and 6.3%, respectively. An inter-observer Bland & Altman analysis shows a mean difference of 0.17 ± 1.55 for RVFWLS (Fig. 2A) and 0.54 ± 2.2 for RV4CLS (Fig. 2B).

The reproducibility of more common RV parameters demonstrated that FAC had worse intra-observer (ICC: 0.66 [0.50–0.81], CV: 12.1%) and inter-observer agreement (ICC:

0.22 [0–0.51], CV: 17.6%) (Tables 1 and 2), while RV basal diameter had an excellent intra-observer agreement (ICC: 0.82 [0.73–0.91], CV: 6.3%).

Comparison of the first 25 readings to the last 25 in the less experienced observer demonstrated improved intra-observer agreement in the last measurements for RVFWLS (ICC: 0.28 [0–0.64], vs. 0.55 [0.27–0.82]; CV: 14.5% vs 10.4%) and RV4CLS (ICC: 0.2 [0–0.58] vs. 0.56 [0.29–0.83]; CV: 12.5% vs. 6.5%) (Table 3).

Discussion

In this sample from a multicentric Brazilian free-dwelling middle-aged individuals, there was adequate reproducibility and level of agreement in right ventricular longitudinal strain measurements. The more traditional FAC appeared to show worse reproducibility while RV basal diameter, a dimension parameter, had excellent intra-observer reproducibility.

In a previous study, *Mirea et al.* prospectively selected 200 subjects who underwent echocardiography examination, and they found excellent intra-observer agreement in RVFWLS and RV4CLS (ICC > 0.75) with the worse inter-observer agreement [11], similar to our study. Another study that included 35 subjects (5 healthy controls and 30 subjects with pulmonary hypertension), found an inter-reader RV4CLS CV of 9.6% and intra-reader CV of 8.5% [22], and this degree of variability was consistent with our sample, using a not selected sample based on a disease condition and in a clinical research context. RV longitudinal strain by cardiovascular magnetic resonance feature tracking also demonstrated excellent reproducibility [23]. However, *Erley et al.* studied the agreement in RV longitudinal strain measurement between cardiovascular magnetic resonance

Table 3 Echocardiographer on training's intra-observer reproducibility of right ventricular longitudinal strain measurements according to the case number

	CV	ICC
Readings 1–25		
RVFWLS	14.5	0.28 (0–0.64)
RV4CLS	12.4	0.20 (0–0.58)
Readings 26–50		
RVFWLS	10.4	0.55 (0.27–0.82)
RV4CLS	6.5	0.56 (0.29–0.83)

RVFWLS right ventricular free wall longitudinal strain, *RV4CLS* right ventricular four chamber longitudinal strain, *CV* coefficient of variation, %; *ICC* intraclass coefficient correlation (95% CI)

(CMR) and echocardiography, and found only moderate inter-modality agreement, concluding that different modalities and techniques should not be used interchangeably to determine and monitor RV strain. [24]

Regarding traditional RV function parameters, *Ruotsalainen et al.* analyzed FAC in 51 hypoplastic left heart syndrome children and found an inter-observer ICC of 0.774 [0.427–0.922] and an intra-observer ICC of 0.205 [0.498–0.269], similarly to our numbers [25]. In addition, *Genovese et al.* compared RV size and function parameters obtained from RV-focused and apical four-chamber views, and the test–retest variability between these two views in 50 patients undergoing clinically indicated transthoracic echocardiography. Their intra-operator RV basal diameter test–rest had an excellent agreement (ICC: 0.92 [0.87–0.96]), comparable to our study. In contrast, they found better intra-operator agreement than our study for FAC (ICC: 0.89 [0.81–0.93]), RVFWLS (ICC: 0.97 [0.94–0.98]), and RV4CLS (ICC: 0.90 [0.84–0.94]) [26]. These discrepancies could be explained

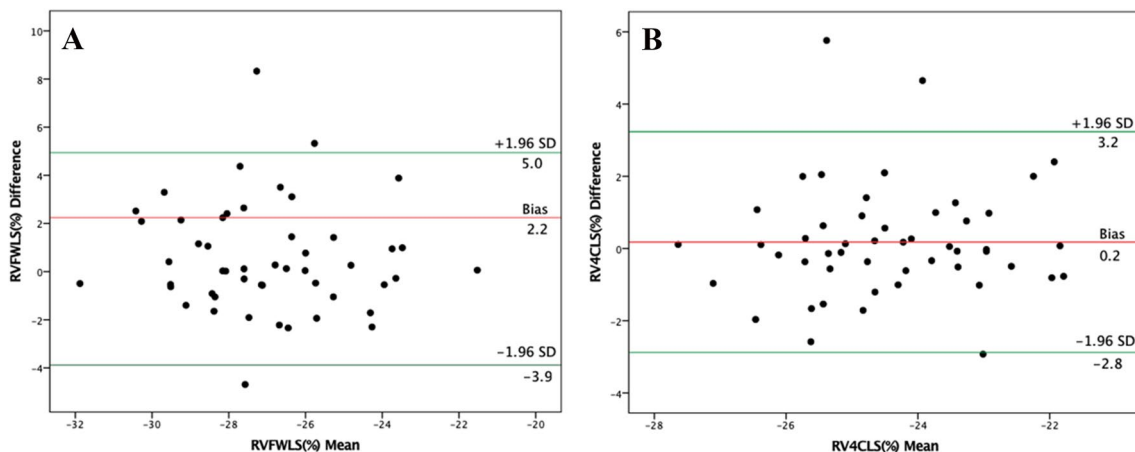


Fig. 2 Bland & Altman plot of inter-observer for RVFWLS (A) and RV4CLS (B). The red solid lines indicate the mean difference, and the green solid lines indicate the 95% limits of agreement (LOA).

RVFWLS right ventricular free wall longitudinal strain, *RV4CLS* right ventricular four chamber longitudinal strain

by better image quality obtained in RV-focused views, allowing better visualization of endocardial borders to calculate FAC and longitudinal strain. Furthermore, *Srinivasan et al.* evaluated the correlation of 2D echocardiographic assessment of RV size and function with CMR imaging in 23 patients with repaired Tetralogy of Fallot and 13 controls. In contrast to the left ventricle, 2D echocardiographic indices of RV size and function did not correlate with CMR data and qualitative assessment of the RV showed poor interobserver agreement. [27] The lack of accuracy in assessing RV function by 2D echocardiography is likely due to the complex geometry of the RV and dynamic volumetric measures as those derived from 3D echocardiographic images [28] or cardiac resonance, which has been considered the gold standard, may be more accurate and reliable, however, these modalities require more advanced and less available resources, which limits its wider use in most conditions. Nevertheless, RV strain 2D-parameters had been shown a better correlation with RV ejection fraction using magnetic resonance imaging than conventional RV measures [29] and seemed to detect subtle RV longitudinal systolic abnormalities despite preserved RV conventional measurements [30].

Additionally, we observed an improvement in RV intraobserver reproducibility in the last exams compared to the first exams analyzed by the less experienced observer, suggesting a quick learning curve for this method, reinforcing its potential utility in less specialized scenarios. *Chamberlain et al.* demonstrated that a minimum of 100 studies was required to achieve an expert level of competency (intraclass correlation coefficient > 0.90) among all novice observers, whereas left ventricular longitudinal strain required only 50 studies to achieve level III competency [31]. Possible explanations for these findings include difficulty to visualize the true RV apex because of foreshortening during image acquisition, increased prevalence of apical trabeculation and moderator bands, and the placement of the markers too close to the tricuspid annulus which can also affect strain analysis results.

Some limitations of RV strain 2D analyses should be considered. RV echocardiographic strain is influenced by image quality, reverberation, and artifacts and the thin RV free wall may make it difficult to limit the myocardium. The global analyses of RV function are from a single view (4-chamber) and may not represent a global assessment of RV function.

Conclusion

This study showed that measurements of right ventricular global longitudinal strain by speckle tracking echocardiography are reproducible in a clinical research context. This information is crucial for the long-term follow-up of cohort participants and reinforces the utility of RV longitudinal

strain as a tool to monitor subclinical changes in RV systolic function.

Author contributions All authors contributed to the study's conception and design. Data collection was performed by EGP and GBS. Material preparation and data analysis were performed by EGP. The first draft of the manuscript was written by EGP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Because it is a multicenter study, ELSA-Brasil's research protocol was approved not only by the ethics committee of each institution but also by the National Research Ethics Committee.

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