Test–retest reliability of left and right ventricular systolic function by new and conventional echocardiographic and cardiac magnetic resonance parameters

Reproducibility and deformation imaging techniques

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ABSTRACT

Reproducible evaluation of left (LV) and right ventricular (RV) function is crucial for clinical decision-making and risk stratification. We evaluated whether speckle-tracking echocardiography (STE) and cardiac magnetic resonance feature-tracking (cMR-FT) global longitudinal (GLS) and circumferential strains allow better test–retest reproducibility of LV and RV systolic function than conventional cMR and echocardiographic parameters.

Thirty healthy volunteers and 20 chronic heart failure patients underwent cMR and STE twice on separate days to evaluate test–retest coefficient of variation (CV), intraclass correlation coefficient (ICC) and estimated sample sizes for significant changes in LV and RV function. Among LV parameters, cMR-left ventricular ejection fraction (LVEF) had the highest reproducibility (CV = 6.7%, ICC = 0.98), significantly better than cMR-FT-GLS (CV = 15.1%, ICC = 0.84), ~~and~~ global circumferential strains (CV = 11.5%, ICC = 0.94) and echocardiographic LVEF (CV = 11.3%, ICC = 0.93). STE-LV-GLS (CV = 8.9%, ICC = 0.94) had significantly better reproducibility than cMR-FT-LV-GLS. Among RV parameters, STE-RV-GLS (CV = 7.3%, ICC = 0.93) had significantly better CV than cMR-right ventricular ejection fraction (RVEF) (CV = 13%, ICC = 0.82). cMR-FT-RV-GLS (CV = 43%, ICC = 0.39) performed poorly with significantly lower reproducibility than all other RV parameters. Owing to their superior interstudy reproducibility, cMR-LVEF (*n* = 12), cMR-RVEF (*n* = 41), ~~and~~ STE-LV-GLS and STE-RV-GLS (both *n* = 14) were the parameters allowing the lowest calculated sample sizes to detect 10% change in LV or RV systolic function.

STE-LV-GLS and STE-RV-GLS showed higher test–retest reliability than other echocardiographic measurements of LV and RV function. They also allowed smaller calculated sample sizes, supporting the use of STE-LV and RV-GLS for longitudinal follow-up of LV and RV function.

Keywords: strain reproducibility cardiac MRI speckle-tracking echocardiography left ventricle right ventricle

Introduction [AQ3]

Evaluation of systolic left ventricular (LV) and right ventricular (RV) function is decisive for risk stratification and clinical decision-making in many cardiac conditions such as myocardial infarction,[1,2] heart failure,[3] valve disease,[4–6] heart failure and reduced ejection fraction,[7] pulmonary hypertension, tricuspid regurgitation, arrhythmogenic cardiomyopathy,[8] and several grown up congenital cardiac diseases. In many of these clinical situations, and particularly in cardio-oncology,[9] it is crucial to serially and accurately follow changes of cardiac systolic function over time to monitor for potential deleterious cardiotoxic effects of drugs or medications.

Echocardiography is the most commonly used imaging technique to assess the systolic function of both ventricles. However, it has well-recognized limitations in evaluating chamber volumes and ejection fraction due to its two dimensional (2D) characteristics. This is particularly true for the RV, where there is no geometric model that enables an estimate of its volumes based on 2D measurements. Therefore, right ventricular ejection fraction (RVEF) derived from RV volumes by 2D echocardiography is not recommended. Indeed, current guidelines propose the use of a combination of surrogate parameters to assess RV systolic function by echocardiography.[10] Cardiac magnetic resonance (cMR) is currently considered the reference standard for reproducible evaluation of left ventricular ejection fraction (LVEF) and RVEF.[11] It has this huge advantage to offer a full 3D coverage of the entire LV irrespectively of the cardiac or body shape with high contrast and sharpness between blood pool and endocardial borders of the myocardium. More recently, deformation imaging techniques have become popular[12] promising higher accuracy and reproducibility of LV and RV function assessment. Yet, most studies evaluated only their inter- or intraobserver variability, and only limited data exist on their test–retest reliability.

Therefore, the aim of this study was to investigate test–retest reliability and minimal detectable changes of speckle-tracking-derived strain echocardiography (STE) and cMR feature tracking (FT) in comparison to conventional echocardiographic and cMR parameters of systolic LV and RV function. Further, we also sought to compute the sample sizes needed to demonstrate significant changes of prespecified differences in LV and RV function by different methods in order to identify which parameter would be most conclusive in design of prospective drug trials, Hence, we performed head-to-head comparison of test–retest reliability of these methods in a prospective trial of 50 subjects with a wide range of LV function undergoing both echocardiography and cMR simultaneously on two separate days.

Methods

Study population and protocol

The study protocol was approved by the ethics committee of our institution (Comité Ethique Hospitalo-Facultaire de l'Université Catholique de Louvain, Brussels, Belgium: 19MAR2019 CARDIO-EVAL-ECHO-IRM) and informed written consent was obtained from each subject before participation in the study. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. We prospectively included 50 subjects including 30 healthy volunteers with no history of cardiovascular disease and 20 patients with stable chronic heart failure (CHF) who had LV systolic dysfunction (LVEF < 50%). Stable CHF was defined as the absence of increase in severity of symptoms or signs of heart failure within 30 days. Exclusion criteria were non-sinus rhythm (atrial fibrillation or flutter), severe chronic kidney disease defined as a glomerular filtration rate <30 mL/min/1.73 m^2, or others generally accepted contraindications of cMR (cardiac devices, cerebral aneurysm clips, and claustrophobia).

Each subject underwent, respectively, two cMR and two echocardiography exams in random order within a maximal delay of 5 days for healthy volunteers and 1 day for CHF patients to avoid changes in haemodynamic conditions, and within ~20 min between each technique. The same acquisition protocols with the same cMR and echocardiographic systems were used for all the patients. Importantly, the same operator (L.H.) performed both acquisitions. Both studies (Study 1 and 2) were anonymized and analysed offline by the same operator (L.H.). For intra- and interobserver variability, the same experienced reader (L.H.) re-analysed 20 random cMR and echocardiography studies 6 weeks later blinded to prior measurements. A second reader (S.M.) performed the analysis on the same 20 cMR and echocardiography studies also blinded to prior measurements. For all participants, age, sex, body mass index, body

surface area, and medical history was collected at baseline. Additionally, blood pressure and heart rate were measured at each visit.

2D transthoracic echocardiography

Standardized comprehensive transthoracic echocardiography exams were acquired using Philips EPIQ 7 ultrasound system (Philips Medical Systems, Andover, MA, USA) equipped with a X5-1 probe in harmonic imaging (2.6/1.3 MHz), stored on a PACS server (Intellispace CV, Philips Medical Systems, Andover, MA, USA). [AQ4] Two-dimensional greyscale harmonic images were acquired in the three standard apical views (two-, three-, and four chambers) and the three standard short-axis views (at the basal, mid-, and apical ventricular level) during breath-hold (three heartbeats each). The average frame rate of the clips was 59 ± 9 frames per second. Care was taken to avoid foreshortening and to image the true apex in apical views. Data were anonymized and analysed offline by one single experienced observer (L.H.).

LV volumes were calculated according to the biplane modified Simpson's rule after semi-automatically tracing end-diastolic and end-systolic endocardial boundaries in the apical two- and four-chamber views. LVEF, TAPSE, FAC were also performed according to the latest guidelines.[10] LV and RV-STE were assessed using Tomtec Software (4.6 Version; Tomtec Imaging Systems, Germany) as previously reported.[7] Endocardial borders of the RV and LV were automatically tracked throughout the cardiac cycle by the software, with manual corrections if necessary. STE-LV-end-systolic-global longitudinal strain (GLS) was computed by averaging two-, three-, and four-chamber views. For the RV, we evaluated both peak systolic GLS and RV-free wall longitudinal strain. LVEF and GLS were both performed automatically with manual correction if necessary.

Cardiac magnetic resonance

All subjects underwent a standardized cMR myocardial function study on a 3T scanner (Achieva, Philips Medical Systems, Best, The Netherlands). Ten to 12 consecutive short-axis images covering the entire LV, and, respectively, one two-, three-, and four-chamber long-axis cine single shot fast precession (SSFP) images were acquired for assessment of myocardial function. [AQ5] Imaging parameters were as follow: field of view: 320 mm, imaging matrix 160 × 154 resulting in spatial resolution of 2 × 2.1 mm, slice thickness 8 mm with 2 mm gap, flip angle 60º, repetition time 3.6 ms, echo time 1.7 ms using SENSE acceleration factor 2.The frame rate was 25 cycles/heartbeat. Acquisitions were performed with retrospective gating and three slices were acquired per breathhold. cMR RV and LV volumes and ejection fraction were computed using the freely available software Segment version 2.2 (http://segment.heiberg.se)[13] from short-axis cine images by tracing the endo- and epicardial contours in the end-diastolic and end-systolic phases. [AQ6] LV and RV endocardial and epicardial contours were detected automatically with manual corrections if needed. Values were indexed to the body surface area. FT-LV and RV-GLS was computed using CVI-42 software (Circle CV, Montreal, Canada). Mid-ventricular global circumferential strain (GCS) was obtained from consecutive short-axis views, FT-LV-GLS by averaging measurements of two-, three-, and four-longitudinal views and FT-RV-GLS on a four-chamber view.

Statistical analysis

Statistical analyses were performed using SPSS 21 and R software (version 3.3.2). The power of our study was computed using R package ~~intraclass correlation coefficient (ICC)~~*ICC-power* indicating a power of 0.8 to distinguish difference of Intraclass correlation (ICCP) of 0.79 from a null hypothesis of 0.9 and with an of alpha 0.05.

Continuous variables were expressed as mean ± one standard deviation (SD), categorical variables as counts and percentages. All cMR and echocardiographic measurements were normally distributed as determined by the Kolmogorov–Smirnov test.

To investigate test–retest reliability we performed Bland–Altman analysis with computation of within-subject coefficient of variation (CV) and single measures two-way mixed ICC with interaction for the absolute agreement. Differences in CV were compared using an asymptotic test according to Feltz and Miller using the routine *cvequality* ~~(Version 0.1.3; Marwick and Krishnamoorthy 2019)~~. [AQ7] Differences in ICC were compared using *F*-test according to the method described by Feldt, and *P* values were adjusted for multiple comparison by Hochman's method. Standard error of measurement was assessed as $\sigma_i \sqrt{1 - \mathrm{ICC}}$, where σ is SD. The smallest detectable change repre-

senting the minimal difference between the measurements that must be overcome to ascertain a true change or difference with a <5% chance of error was computed as $1.96 \times \sqrt{2} \times \text{SEM}$. We also estimated sample sizes to demonstrate clinical change for the different parameters studied using typical cut-off values used in the literature (i.e. >5% LVEF, >2% strain), but also 5% and 10% of relative normal values in healthy volunteers. These sample size computations were made assuming a power of 90% and an α error of 0.05. These computations were performed using the *pwr.t.test* function in R.

Finally, intra- and interobserver reproducibility of the measurement studied was evaluated in 20 randomly selected patients using, respectively, single measures two-way mixed-effect ICC and two-way random effect ICC with absolute agreement. All tests were two-sided and *P* value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

Table 1 illustrates the baseline characteristics of the study population. The mean age was 46 ± 19 years with 69% of men. The population had a wide range of LVEF and RVEF.

Table 1 Clinical characteristics

	All (*n* = 50)	HV (*n* = 30)	Heart-failure pts (*n* = 20)
Age (years)	46 ± 19	35 ± 11	63 ± 17
Female sex (*n*, %)	15 (31%)	10 (33%)	2 (26%)
BMI (kg/m^2)	23 ± 3	22 ± 2	25 ± 4
BSA (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.9 ± 0.2
ATHT (*n*, %)	9 (18)	0 (0)	6 (24)
Diabetes (*n*, %)	6 (12)	0 (0)	6 (30)
History of CAD (*n*, %)	6 (12)	0 (0)	6 (30)
Echocardiography			
LVEDVi (mL/m^2)	91 ± 38	80 ± 18	108 ± 53
LVESVi (mL/m^2)	39 ± 5	30 ± 7	74 ± 40
LVEF (%)	51 ± 16	63 ± 4	33 ± 8
STE-LV-GLS (%)	−19 ± 6	−24 ± 3	−12 ± 3
STE-RV-FWLS (%)	−25 ± 7	−28 ± 6	−21 ± 6
STE-RV-GLS (%)	−24 ± 5	−27 ± 3	−19 ± 4
TAPSE (mm)	22 ± 5	24 ± 4	19 ± 5
FAC (%)	45 ± 10	48 ± 5	40 ± 14
cMR			
LVEDVi (mL/m^2)	110 ± 65	85 ± 15	146 ± 90
LVESVi (mL/m^2)	61 ± 58	32 ± 7	103 ± 92
LVEF (%)	50 ± 17	62 ± 54	31 ± 10
FT-LV-GLS	−11 ± 4	−14 ± 2	−7 ± 3
FT-LV-GCS	−13 ± 5	−17 ± 2	−8 ± 3
RVEDVi (mL/m^2)	85 ± 22	87 ± 18	81 ± 26
RVESVi (mL/m^2)	41 ± 19	38 ± 11	45 ± 25
RVEF (%)	51 ± 11	55 ± 6	43 ± 13

	All ($n = 50$)	HV ($n = 30$)	Heart-failure pts ($n = 20$)
FT-RV-GLS (%)	−14 ± 6	−16 ± 6	−11 ± 6

AHT, arterial hypertension; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; cMR, cardiac magnetic resonance; FAC, fractional area change; FT, feature tracking; HV, healthy volunteers; LVEDVI, left ventricular end-diastolic volume indexed; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume indexed; LV-GCS, left ventricular global circumferential strain; RVEDVI, right ventricular end-diastolic volume indexed; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume indexed; RV-FWLS, right ventricular-free wall longitudinal strain; RV-GLS, right ventricular-global longitudinal strain; STE-LV-GLS, speckle-tracking echocardiography-left ventricular-global longitudinal strain; TAPSE, tricuspid annular systolic excursion.

Table 2 shows haemodynamic measurements between the two acquisitions. There was no statistical difference in blood pressure or heart rate between study 1 and 2 neither between echocardiography nor cMR studies on the same day. Example of STE and FT measurement from a healthy volunteer and a patient are shown in *Figure 1A and B*. For the LV, STE-LV-GLS (r=−0.94, $P < 0.001$), cMR-FT-LV-GLS (r=−0.91, $P < 0.001$), cMR-FT-LV-GCS (r =−0.93, $P < 0.001$) were highly correlated to cMR-LVEF. Also, STE-LV-GLS was highly correlated to FT-LV-GLS ($r = 0.90$, $P < 0.001$) and echocardiography-LVEF to cMR-LVEF ($r = 0.96$, $P < 0.001$). However, STE-LV-GLS provided significantly greater values than FT-GLS (−19 ± 6 vs. −11 ± 4, $P < 0.001$). There were no significant differences in LVEF between cMR and Echo ($P = 0.23$). For the RV, FAC ($r = 0.60$, $P < 0.001$), TAPSE (0.54, $P < 0.001$), STE-RV-GLS (r = −0.66, $P < 0.001$), FT-RV-GLS (r = −0.58, $P < 0.001$), and FT-RV-GLS (r=−0.56, $P < 0.001$) were moderately correlated with RVEF. STE-RV-GLS was moderately correlated to FT-RV-GLS ($r = 0.67$, $P < 0.001$), but STE-RV-GLS values were significantly greater than FT-RV-GLS (−24 ± 5 vs. −14 ± 4%, $P < 0.001$).

Figure 1 Example of (*A*) speckle-tracking echocardiography and (*B*) cardiac magnetic feature-tracking assessment. Graphs are not scaled to same data range.

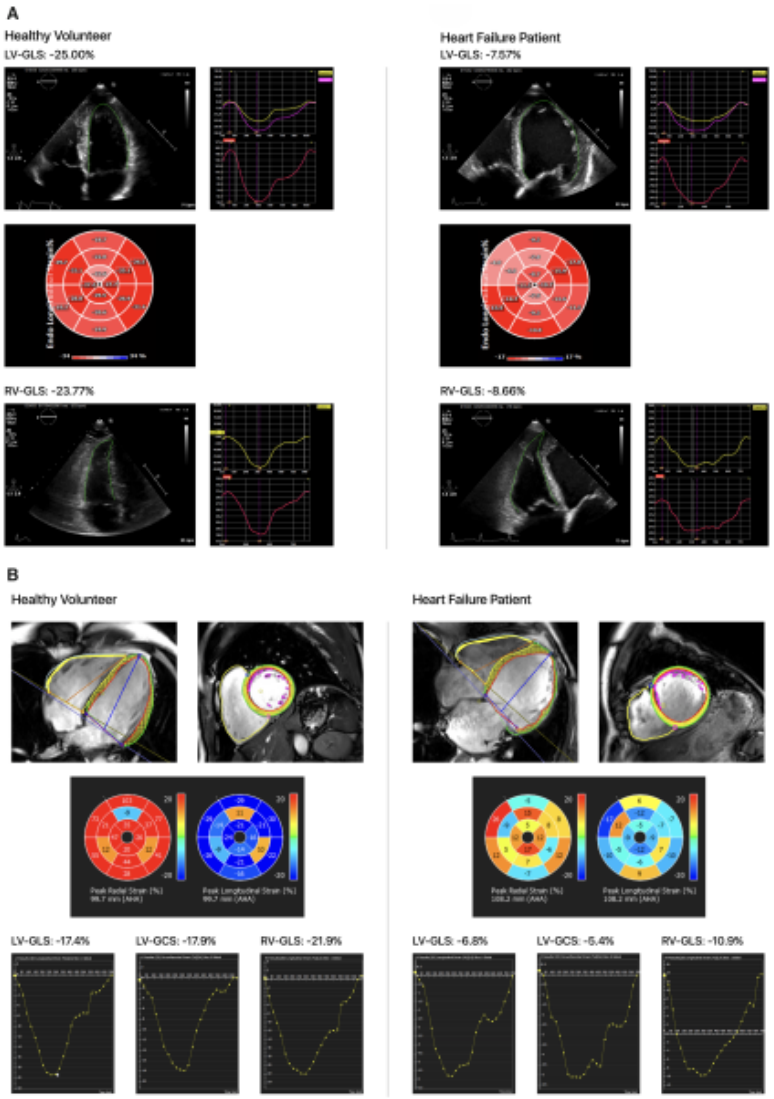


Table 2 Haemodynamic measurements

	Day 1	Day 2	*P* value
cMR			
HR (bpm)	67 ± 11	66 ± 12	0.79
SBP (mmHg)	118 ± 17	120 ± 13	0.28
DBP (mmHg)	75 ± 11	75 ± 8	1
MAP (mmHg)	89 ± 12	90 ± 9	0.63
Echo			
HR (bpm)	64 ± 10	64 ± 10	0.87
SBP (mmHg)	118 ± 17	120 ± 13	0.28
DBP (mmHg)	75 ± 11	75 ± 8	1
MAP (mmHg)	89 ± 12	90 ± 9	0.63

cMR, cardiac magnetic resonance; DBP, diastolic blood pressure; Echo, echocardiography; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

Interstudy reproducibility data

Average values of LV measurements on Day 1 and 2, their difference, CV, limits of agreement, ICC, and smallest detectable difference are shown in *Table 3*, while Bland–Altmann graphs are shown in *Figure 2*.

Figure 2 Bland–Altmann analysis with mean differences and limits of agreement of paired measurements of the studied parameters to assess LV systolic function. The blue dots represent asymptomatic volunteers and the red dots heart failure patients. To allow comparisons all graphs are scaled to same data range.

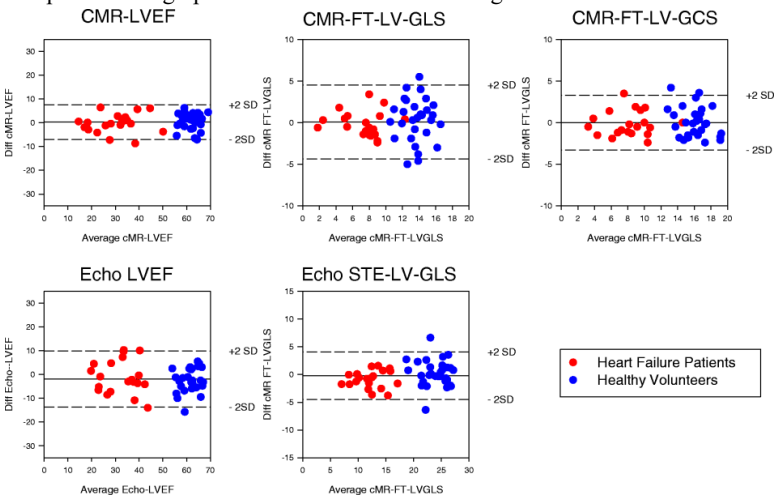


Table 3 Test–retest reproducibility and smallest detectable difference

	Measurement day 1	Measurement day 2	Mean difference ± SD	*P* value	CV	ICC	SDC95 abs. (%)	SCD95 rel. (%)
LV parameters								
cMR								
LVEF (%)	49.2 ± 17.3	49.0 ± 16.8	0.23 ± 3.65	0.66	6.7[b]	0.98 (0.96–0.99)[b]	1.5	3.1
FT-LV-GLS (%)	−11.1 ± 3.8	−11.1 ± 3.9	0.08 ± 2.22	0.8	15.1[a]	0.84 (0.73–0.90)[a]	2.5	22.2
FT-LV-GCS (%)	−13.1 ± 4.7	−13.1 ± 4.8	0.00 ± 1.64	0.99	11.5[a]	0.94 (0.90–0.97)[a,b]	1.1	8.5
Echo								
LVEF (%)	48.9 ± 15.5	50.9 ± 16.1	−1.89 ± 5.88	<0.03	11.3[a]	0.93 (0.87–0.96)[a,b]	4.4	8.7
STE-LV-GLS (%)	−19.4 ± 6.1	−19.1 ± 6.6	−0.21 ± 2.14	0.47	8.9[b]	0.94 (0.91–0.97)[a,b]	1.4	7.2
RV parameters								
CMR								
RVEF (%)	50.7 ± 11.3	50.2 ± 13.1	0.46 ± 7.55	0.66	13.0[c,d]	0.82 (0.69–0.89)[c]	9.1	18

	Measurement day 1	Measurement day 2	Mean difference ± SD	*P* value	CV	ICC	SDC95 abs. (%)	SCD95 rel. (%)
FT-RV-GLS (%)	−13.6 ± 5.2	−14.8 ± 4.8	1.14 ± 5.77	0.17	42.9[d]	0.39 (0.13–0.59)[d]	12.5	88
Echo								
STE-RV-GLS (%)	−24.1 ± 4.9	−24.3 ± 5.2	0.20 ± 2.14	0.51	7.3[c]	0.91 (0.85–0.95)[c]	1.7	7.2
STE-RV-FWS (%)	−26.0 ± 5.8	−25.6 ± 6.5	0.72 ± 3.81	0.19	12.8[c,d]	0.81 (0.69–0.88)[c]	5.8	22.6
TAPSE (mm)	22.3 ± 5.6	22.2 ± 5.1	0.13 ± 3.61	0.62	16.5[c,d]	0.78 (0.63–0.87)[d]	4.7	21.2
FAC (%)	44.4 ± 9	45 ± 11	−0.64 ± 9.06	0.79	12.1[c,d]	0.60 (0.39–0.75)[d]	15.8	35.5

abs, absolute; cMR, cardiac magnetic resonance; CV, coefficient of variation; Echo, echocardiography; ICC, intra-class correlation; LV, left ventricular; RV, right ventricular; SD, standard deviation; SDC, small detectable change; rel, relative.

The SDC represents the minimal difference between the measurements that must overcome to ascertain a true change or difference with a <5% chance of error.

LV parameter comparisons: [a]$P < 0.05$ vs. cMR-LVEF; [b]$P < 0.05$ vs. cMR-FT-LV-GLS.

RV parameter comparisons: [c]$P < 0.05$ cMR-FT-RV-GLS; [d]$P < 0.05$ vs. STE-RV-GLS.

Overall, there were no significant difference in LV measurements between Day 1 and 2, except for a small difference of LVEF by echocardiography Simpson's method, which was slightly ($P < 0.03$) higher on Day 2. For all LV parameters, the coefficient of variability was good, and all ICC were high (>0.75) indicating good reproducibility. cMR-LVEF had the highest reproducibility of all LV parameters, with a significantly ($P < 0.05$) higher ICC than the other modalities and a significantly lower CV ($P < 0.005$) than cMR-FT-LV-GLS, cMR-FT-LV-GCS, and echocardiography-LVEF. STE-LV-GLS was the second most reproducible parameter. Interestingly, the CV of STE-LV-GLS was significantly ($P < 0.005$) better than the CV of cMR-FT-LV-GLS. Also, the ICC of cMR-FT-LV-GCS, echocardiography-LVEF, and STE-LV-GLS were significantly ($P < 0.05$) better than cMR-FT-GLS. *Figure 3* illustrates the temporal variability of the LV parameters studied.

Figure 3 Temporal variability of LV parameters. *$P < 0.05$ CV vs. cMR-LV-GLS, cMR-LV-GCS and LV-Echo EF; [#]$P < 0.05$ CV vs. cMR-FT-LV-GLS.

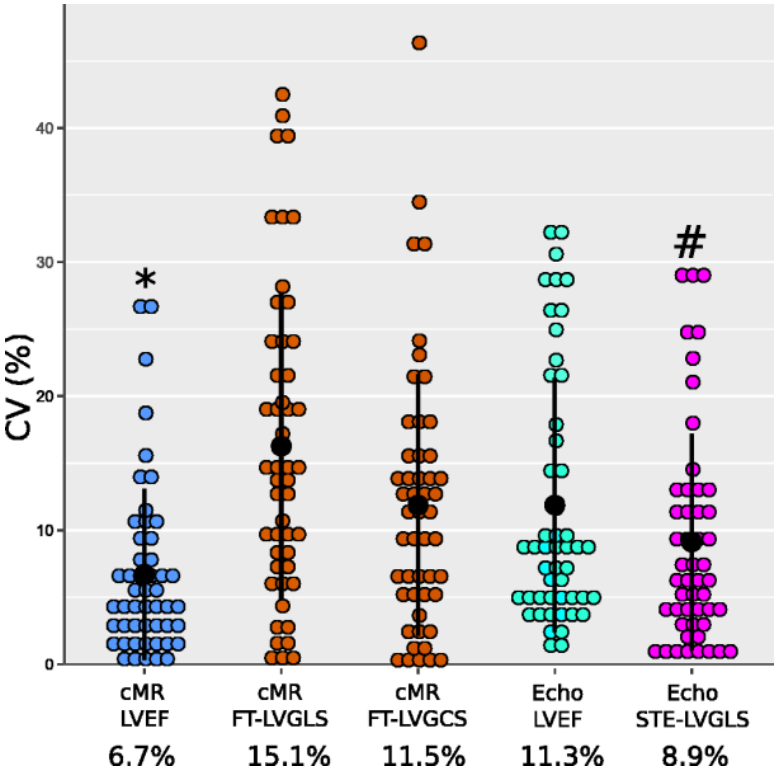


Table 3 shows the average values of RV measurements on Day 1 and 2, their difference, CV, limits of agreement, ICC, and their smallest detectable difference, while Bland–Altmann graphs are illustrated in *Figure 4*. All parameters had acceptable reproducibility with CVs <20% and ICCs >0.75, except FAC who had an ICC of 0.60 and cMR-FT-RV-GLS which had poor day-to-day reproducibility (CV 43% and ICC 0.39). Among RV parameters, STE-RV-GLS was the most reproducible parameter with a significantly ($P < 0.005$) lower CV than all other parameters and a significantly ($P < 0.005$) higher ICC than cMR-FT-RV-GLS, TAPSE, and FAC. On the other hand, cMR-FT-RV-GLS was the least reproducible parameter with significantly ($P < 0.001$) worse CV than all other parameters and significantly ($P < 0.001$) lower ICC than cMR-RVEF, STE-RV-GLS, and FW-RV-GLS. *Figure 5* illustrates the temporal variability of the RV parameters studied.

Figure 4 Bland–Altmann analysis with mean differences and limits of agreement of paired measurements of the studied parameters to assess right ventricular systolic function. The blue dots represent the asymptomatic volunteers and the red dots the heart failure patients. To allow comparisons all graphs are scaled to same data range.

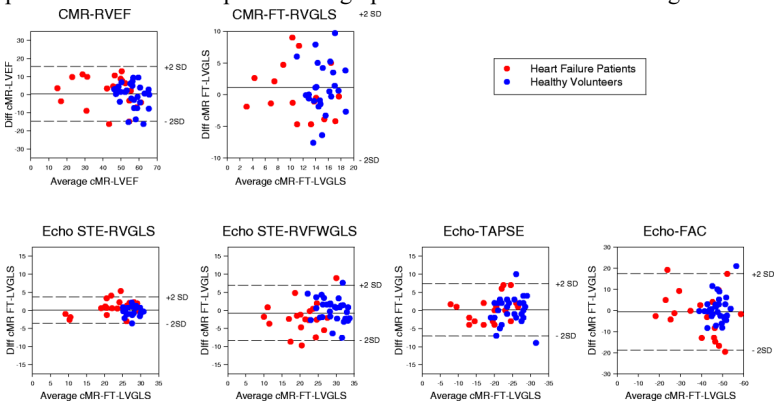
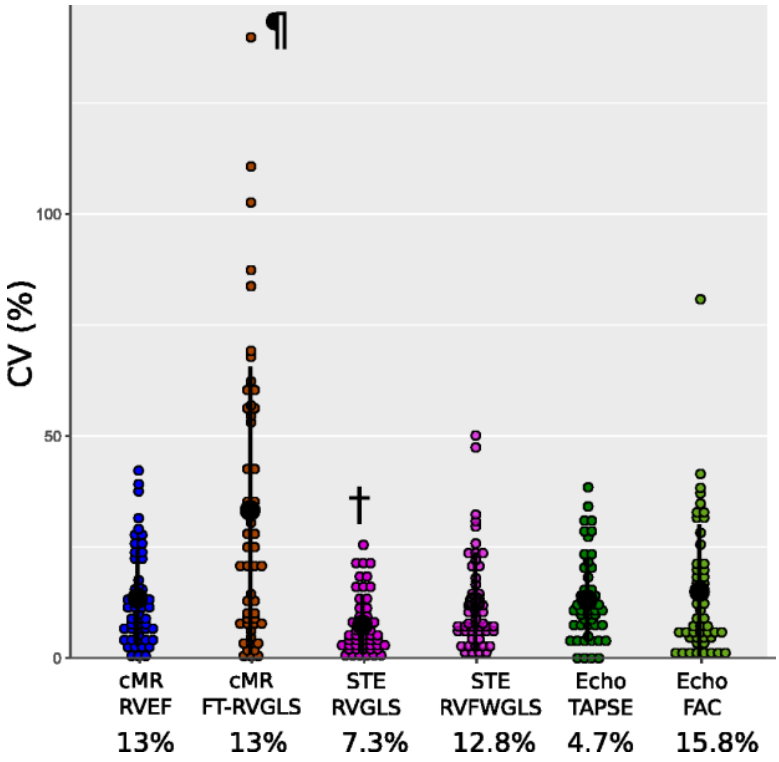


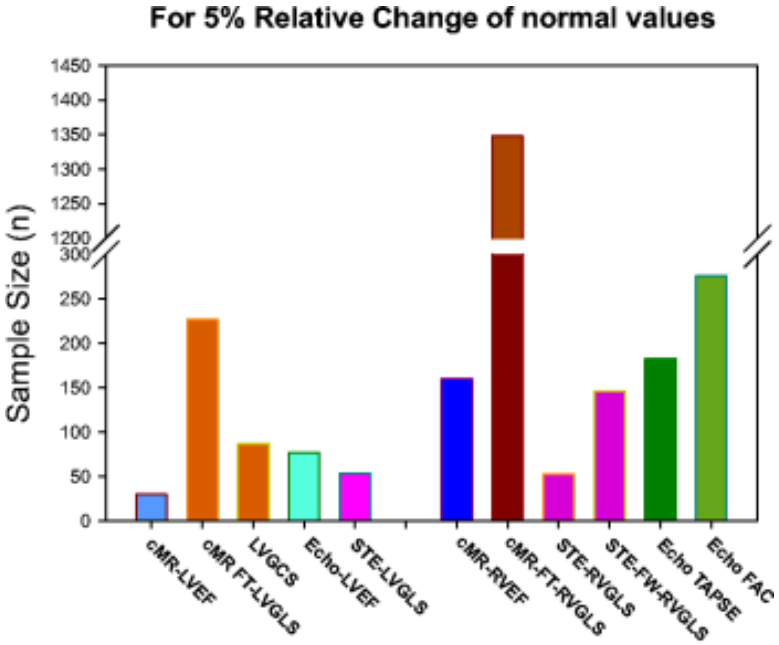
Figure 5 Temporal variability of right ventricular parameters. ¶$P < 0.05$ CV cMR-FT-RV-GLS vs. all other groups; †$P < 0.05$ CV STE-RV-GLS vs. all other groups.



Sample size computation

Table 4 and *Figure 6* reveal the sample size computations for different changes in LV and RV functional parameters.

Figure 6 Estimated sample sizes to demonstrate 5% and 10% relative change of normal values in healthy volunteers for different LV and RV parameters. [AQ10]



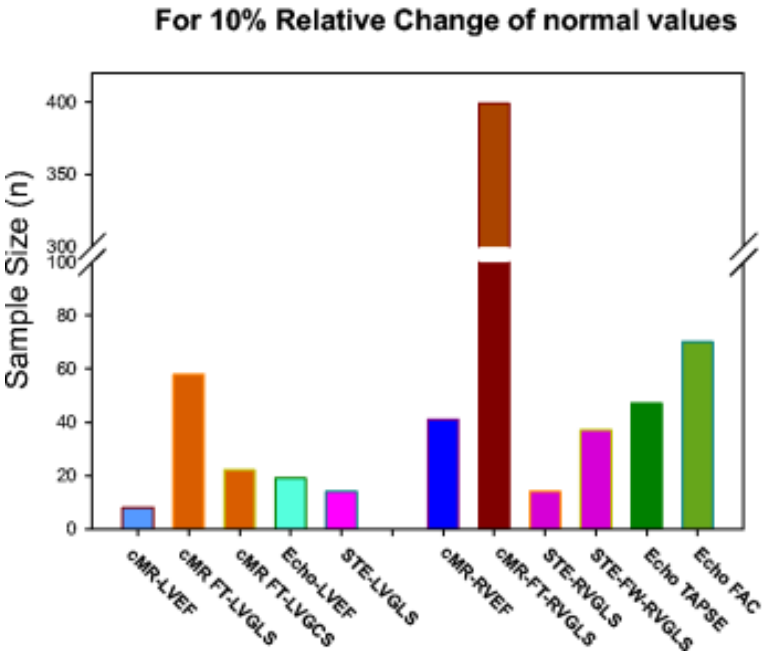


Table 4 Sample sizes required to detect a clinically significant change in LV and RV function (with 90% power and an α error of 0.05) using two-tailed t-test

	Absolute changes		Relative changes			
			Change in >5% normal value in HV		Change in >10% normal value of HV	
	Cut-off value	Sample size	Cut-off value	Sample size	Cut-off value	Sample size
LV parameters						

	Absolute changes		Relative changes			
			Change in >5% normal value in HV		Change in >10% normal value of HV	
	Cut-off value	Sample size	Cut-off value	Sample size	Cut-off value	Sample size
cMR						
LVEF	>5%	12	>3.1%	30	>6.1%	12
FT-LV-GLS	>2%	27	>0.7%	227	>1.4%	56
FT-LV-GCS	>2%	15	>0.8%	86	>1.6%	22
Echo						
LVEF	>5%	30	>3.1%	76	>6.2%	19
STE-LV-GLS	>2%	25	>1.4%	54	>2.7%	14
RV parameters						
CMR						
RVEF	>5%	48	>2.75%	160	>5.5%	41
FT-RV-GLS	>2%	148	>0.7	1348	>1.5%	399
Echo						
STE-RV-GLS	>2%	25	>1.4%	53	>2.7%	14
STE-RV-FWS	>2%	77	>1.4%	146	>2.9%	37
TAPSE	>2 mm	70	>1.25 mm	184	>2.5 mm	47
FAC	>7%	36	>2.5%	276	>5%	70

cMR, cardiac magnetic resonance; Echo, echocardiography; HV, healthy volunteer; LV left ventricular; RV, right ventricular.

Among LV parameters, given its highest interstudy reproducibility, cMR-LVEF required the smallest sample size to demonstrate a clinical change using the 5% and 10% cut-off of relative normal value in healthy volunteers (i.e. $n = 30$ and $n = 12$). To demonstrate a similar change using Echocardiography-LVEF, a sample size of $n = 76$ and $n = 19$ would have been required. cMR-FT-LV-GLS and FT-LV-GCS did not allow to reduce sample sizes relative to cMR-LVEF. STE-LV-GLS, however, allowed smaller sample sizes to demonstrate a clinical change than echocardiographic LVEF. Interestingly, projected sample sizes for STE-LV-GLS were also smaller than those for cMR-FT-LV-GLS and FT-LV-GCS.

For the RV, demonstration of absolute and relative changes of cMR-RVEF using the same cut-off required larger sample sizes than absolute and relative changes of cMR-LVEF. Among all RV parameters, STE-RV-GLS allowed the smallest sample size to demonstrate a change in 5% and 10% of relative normal values. The sample sizes needed to demonstrate changes in RV function by STE-RV-FWLS, TAPSE, and FAC were larger. Given the observed low reproducibility, cMR-FT-RV-GLS would have required the largest sample size to evaluate significant statistical relative changes in normal RV function.

Inter- and intraobserver variability data

The reproducibility of the studied measurements is shown in *Table 5*. All measurements had good intra- and interobserver reproducibility except cMR-FT-RV-GLS.

Table 5 Intra- and interobserver reproducibility data

	Intraobserver reproducibility		Interobserver reproducibility	
	CV % (95% CI)	ICC	CV % (95% CI)	ICC
LVEF Simpson	7.9	0.97	4.7	0.96

	Intraobserver reproducibility		Interobserver reproducibility	
	CV % (95% CI)	ICC	CV % (95% CI)	ICC
FAC	9.5	0.98	13.9	0.79
TAPSE	7.9	0.97	8.5	0.88
STE-LV-GLS	10.2	0.86	11.8	0.9
STE-RV-GLS	9.2	0.92	10.3	0.83
STE-RV-FWLS	13.3	0.93	10.8	0.85
cMR-LVEF	5.2	0.99	8.1	0.98
cMR-RVEF	7.3	0.98	13.9	0.92
cMR-FT-LV-GCS	11.1	0.99	10.9	0.97
cMR-FT-LV-GLS	12.9	0.94	21.5	0.90
cMR-FTE-RV-GLS	39.6	0.63	38.6	0.24

CI, confidence interval; cMR-FT-LV-GCS, cardiac magnetic resonance-feature tracking-left ventricular-global circumferential strain; cMR-FT-LV-GLS, cardiac magnetic resonance-feature tracking-left ventricular-global longitudinal strain; cMR-LVEF, cardiac magnetic resonance-left ventricular ejection fraction; cMR-RVEF, cardiac magnetic resonance-right ventricular ejection fraction; FAC, fractional area change; FT-cMR-RV-GLS, feature tracking-cardiac magnetic resonance-right ventricular-global longitudinal strain; ICC, Intraclass correlation coefficient; LVEF Simpson, left ventricular ejection fraction calculated according to the biplane modified Simpson's rule; RV-FWLS, right ventricular -free wall longitudinal strain; RV-GLS, right ventricular-global longitudinal strain; STE-LV-GLS, speckle-tracking echocardiography-left ventricular-global longitudinal strain; TAPSE, tricuspid annular systolic excursion.

Discussion

Our study is to our knowledge the first head-to-head comparison of test-to-test reproducibility of not only LV and RV STE but also cMR-FT techniques vs. conventional echocardiography and cMR. The salient findings of our study were: (i) among LV parameters, LVEF by cMR had the highest reproducibility followed by STE-LV-GLS. Both had better test–retest reliability than LVEF by 2D echocardiography. cMR-FT-GLS was less reproducible than cMR-LVEF and STE-GLS. (ii) Among parameters of RV function, STE-RV-GLS had the highest test–retest reliability to assess RV systolic function. In contrast, cMR-FT-RV-GLS performed poorly. (iii) Due to their better reproducibility, cMR-LVEF, RVEF, and STE-LV-GLS and STE-RV-GLS were the parameters allowing the lowest calculated sample sizes to detect significant change in LV or RV systolic function when planning research studies.

The observation that cMR-LVEF is the most reproducible parameter for evaluation of LV systolic function was expected in accordance with earlier works.[14–17] cMR-LVEF was also confirmed to be more reproducible than LVEF by 2D biplane echocardiography Simpson's method, which may be restricted by echocardiographic windows, geometrical assumptions, difficult endocardial definition, and foreshortening. Nevertheless, the reproducibility of 2D-LVEF in our study was satisfactory and somewhat better than in prior studies,[14,18–20] possibly reflecting improvements in imaging technology. In agreement with earlier reports for 2D[21] and 3D STE[22] but in contrast to the study by Baron *et al.*,[20] we showed that STE strain is a highly reproducible method for assessment of systolic function by echocardiography with better test–retest reproducibility than echocardiography-LVEF. This could be easily explained by the fact that strain analysis is more automated and thus less user-dependent[12] than LVEF analysis. Surprisingly, however, this was not the case for cMR deformation techniques, since both cMR-FT-GLS or FT-GCS were less reproducible than cMR-LVEF. Also, cMR-FT-GLS had lower reproducibility than STE-LV-GLS. While other studies reported comparable measurements of cMR-FT and STE strains,[23,24] no such comparison of test–retest reproducibility between STE and cMR-FT has been performed until now. cMR-FT reproducibility in our study was consistent with other reports,[25–27] ruling out methodological issues. Therefore in our opinion, the most likely explanation of why STE allows more accurate estimates of strain than cMR-FT, is mainly due to the presence of physical markers (speckles) and much higher spatial and temporal resolution.[12] Indeed, STE evaluates speckle motion, while cMR-FT does not distinguish intramyocardial features, as the grey-level distribution in cine SSFP images is relatively homogenous. Finally, cMR-FT showed significantly lower strain value than STE. This fact is in accordance with our previous

works comparing STE to tagging.[28] The most likely explanation for this is that STE software provide more endocardial strain estimates than cMR-FT software which provide mid-ventricular strain. Also, the lower frame rate of FT-cMR could also explain lower strain values than STE.[12]

The comparison of test–retest reproducibility of RV functional parameters is also novel. To the best of our knowledge, our study is the first to directly compare test–retest variability of RV echocardiographic and cMR parameters. Reproducibility of cMR-RVEF was similar to earlier works.[14] The main source of errors in evaluation of volumes by cMR Simpson's method are the demarcation of the basal slice near the atrioventricular valves and outflow tracts, and the large motion of the base through the plane of the short axis (slice thickness are typically 8–10 mm), giving rise to significant partial volume effects at the base and apex. Because of its smaller wall thickness demarcation of the basal extent of the RV is more challenging than for the LV,[29] probably explaining the larger test–retest variability of cMR-RVEF than cMR-LVEF. For echocardiographic assessment of RV systolic function, current guidelines[10] recommend mainly the use of FAC and TAPSE. In our study, these parameters had excellent inter- and intraobserver variability, but poor test–retest variability compared with the other parameters studied. This is probably related to the fact that they are not only strongly geometry dependent with difficulties reproducing similar views in repeat studies, but also operator dependent. In contrast, in line with our observations for STE-LV analysis, STE-RV-GLS presented much more robust reproducibility. This is probably again explained by automated analysis of STE benefitting from physical markers, but also translates the fact that RV function is mainly dependent on longitudinal shortening. Unexpectedly, however, cMR-FT-RV-GLS performed very poorly in terms of reproducibility. This was probably because the FT-tracking algorithm used track less well the RV than the LV. Indeed, cMR-FT-RV-GLS often failed to adequately track the base of the RV especially in subjects with relatively vigorous annular motion or in presence of flow artefacts.

Clinical implications

We have demonstrated that STE deformation techniques were the most accurate echocardiographic approach for detecting small changes in LV and RV function. For the LV, they performed nearly as well as cMR, and for the RV they even surpassed the reproducibility of cMR-RVEF. This suggests that these STE techniques could be used clinically to reliably follow patients for development of subclinical dysfunction in different conditions, for example, to monitor cardiotoxic effects of cancer therapy[30,31] or to detect afterload mismatch in aortic stenosis.[32] Obvious advantages of using STE over cMR are wider availability and lower costs. Nevertheless, STE has potential limitations such as the need of high-quality image and the lack of uniformity in software algorithms[12] and intervendor differences, despite efforts to standardize STE measurements.[33]

The second clinical implication of our study applies to the design of clinical studies. Given the high reproducibility and low variability, cMR is often used to reduce sample size[11] of prospective studies evaluating changes in LV or RV function. Our study suggests that sample sizes for studies may be nearly as low when using STE. This suggests that, when taking precautions for uniformity of acquisitions and analysis, STE could also be useful for evaluation of LV and RV systolic function in longitudinal studies with potentially lower cost than cMR. In contrast, we did not observe advantages of FT over conventional cMR, for reproducibility of LV or RV function assessment. Therefore, we cannot currently recommend these techniques to limit sample sizes in research studies. The reproducibility of FT-cMR strains could be theoretically improved by higher temporal and spatial resolution, either through parallel imaging or iterative reconstruction techniques. Nevertheless, with the compromise of decreasing signal-to-noise ratio leading to more artefacts and consequently to a less good tracking.

Limitations

Our study was limited by being single-center observational study of limited sample size. Nevertheless, we had enough statistical power to detect small differences between different cardiac techniques. Atrial fibrillation/flutter, acute heart failure, and poor image quality were exclusion criteria and therefore our study findings may not apply to these populations. Systolic cardiac function is load dependent, and all evaluations of cardiac deformations are preload and afterload dependent, whether they are based on visualization of either wall deformation (strain) or cavity deformation (EF). Importantly, systolic cardiac function evaluates only shortening and never contractility. In our study, we wanted to include the physiological effects of variable loading conditions and evaluated true day-to-day variability of

the different cardiac imaging techniques rather than test–retest on the same day. Haemodynamic conditions were stable with no significant difference in the heart rate and the blood pressure between the 2 days, since we included only stable euvolemic patients and we performed the two acquisitions with a short delay. However, the evaluation of cardiac function over a longer delay or in different population might result in larger physiological variations of loading conditions and, consequently larger variability of EF. Additionally, 2D echocardiography may suffer from incomplete reproducibility of imaging planes, foreshortening and through-plane motion. Indeed, 3D echocardiography may have better reproducibility[34,35] and test–retest variability[19] by allowing more reproducible views and less geometric assumptions. Nonetheless, this technique was not tested in our study since its feasibility is still extremely dependent on high-image quality, regular rhythm, and patient cooperation. Finally, STE and FT strain analysis were performed with one single vendor so they may not apply to other software.

Conclusion

In head-to-head comparison with cMR, STE-LV-GLS, and STE-RV-GLS measurement showed high test–retest reliability, performing more accurately with smaller detectable changes than other echocardiographic measurements of LV and RV function. This suggests that these techniques might be useful for longitudinal follow-up of LV and RV function. Furthermore, computed sample sizes to demonstrate clinically significant changes of LV and RV function by these approaches were low, permitting potential use for longitudinal follow-up in research studies.

Funding

This work was supported by the Fondation Nationale de la Recherche Scientifique of the Belgian Government (FRSM CDR 31243249). [AQ8]

Conflict of interest: none declared. [AQ9]

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