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Usefulness of three-dimensional echocardiography for the assessment of ventricular function in children: Comparison with cardiac magnetic resonance, with a focus on patients with arrhythmia

Running title: 3D-ECHO in children: Focused on arrhythmia

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Abstract

Background: Focusing on patients with arrhythmia, the aims of this study was to assess ventricular function in children using three-dimensional echocardiography (3D-ECHO) and to compare the results to those obtained with cardiac magnetic resonance (CMR).

Methods: The study group consisted of 43 children in whom 3D-ECHO and CMR were performed. Twenty-five patients had a ventricular arrhythmia, 7 left ventricular cardiomyopathies, 9 proved to be healthy. In all children, 3D-ECHO (offline analysis) was used to assess ventricular ejection fraction (EF). The results were compared to CMR using the Bland-Altman analysis and linear regression. The Student paired T-test was used to compare of means between both modalities.

Results: The relation between the results derived from both methods is linear (for left ventricle: estimated slope = 1.031, $p < 0.0001$, R-squared = 0.998; for right ventricle: estimated slope = 0.993, $p < 0.0001$, R-squared = 0.998). In spite of minimal mean differences between results for both ventricles and narrow 95% confidence intervals, the paired t-test proved those differences not to be significant ($p > 0.05$) for the right ventricle but statistically significant ($p < 0.05$) for the left ventricle, for which the left ventricular EF calculated in 3D-ECHO was systematically underestimated with a mean difference of –1.8% ± 2.6% ($p < 0.0001$).

Conclusions: Three-dimensional echocardiography assessment of both left and right ventricular EF in children showed high significant correlation and agreement with CMR. 3D-ECHO could be a valuable tool in follow-up of children with arrhythmic disorders requiring regular assessment of ventricular function.

Key words: three-dimensional echocardiography, cardiac magnetic resonance, ventricular ejection fraction, children, arrhythmia

Introduction

Arrhythmias are considered one of the most significant problems of modern pediatric cardiology. As in the majority of children, no connection to specific structural or functional cardiac abnormality can be found, those cases often are defined as idiopathic. The use of three-dimensional-echocardiography (3D-ECHO) for non-invasive assessment of ventricular function is at present widespread and universal, especially in adult patients. In pediatric cardiology the method was embraced much later and its exploit is still noncompliant with potential benefits. Being close in accuracy although more feasible and less expensive than cardiac magnetic resonance (CMR) 3D-ECHO may be valuable diagnostic tool especially in groups of children demanding regular assessment of ventricular function.

The aim of the study was to assess ventricular function in children using 3D-ECHO and compare the results to those obtained with CMR, focusing especially on patients with arrhythmia.

Methods

The prospective study included 43 consecutive children hospitalised in the Pediatric Cardiology Department, aged 4 months to 17 years, average 13.7 ± 3.8 years, in whom both 3D-ECHO and CMR were performed due to clinical indications. In all the children electrocardiography (ECG) and 24-hours ECG Holter monitoring were used in diagnostics. In this group, 27 patients suffered from arrhythmia: two supraventricular (one with single extrasystolic beats, one with nodal rhythm), 25 ventricular arrhythmias (in all cases at least one of extrasystolic morphologies was left bundle branch block) classified as mild in 9 patients (single monomorphic beats, less than 20% of arrhythmia in 24-h Holter-ECG monitoring) and severe in 16 children (defined as complex with ventricular tachycardia (VT) or over 20% single beats during 24 h). Out of 25 children, in 20 ventricular arrhythmias were classified as idiopathic (no evident source in cardiac morphology or function was detected), three patients fulfilled the criteria of arrhythmogenic right ventricular cardiomyopathy (ARVC), one was diagnosed with Andersen-Tawill syndrome, and in one arrhythmia occurred after surgical repair of ventricular septal defect (VSD). Seven patients of the studied cohort were diagnosed with left ventricular cardiomyopathies, 9 patients proved to be healthy either in the course of diagnostics for suspected myocarditis (based on elevated plasma troponin level and/or abnormalities in ECG) or after completed healing process. The characteristics of the studied group are presented in Table 1.

In all patients 3D-ECHO and CMR were performed. In one child ejection fraction (EF) of both ventricles and in one — the right ventricle could not be calculated in CMR due to artefacts connected with excessive arrhythmia. Those patients were not included in the statistical analysis, leaving 42 children for the analysis of left and 41 — right ventricular function. The postprocessing (offline analysis) of echocardiography data was obtained without knowing the results of CMR.

Three-dimensional echocardiography (3D-ECHO): Image acquisition

All patients underwent standard echocardiography examination (Philips EPIQ system, Netherlands) during which the ECG-gated 3D full-volume data sets were recorded using a matrix X5-1/X7-2 transducer from an apical window in the patients' left lateral decubitus position, possibly while withholding breath. Four consecutive cardiac cycles were registered to obtain optimal resolution. In two patients with excessive arrhythmia we recorded only two cardiac cycles and the data proved adequate for further analysis. The left and right ventricles were addressed separately to assure that the data set would contain the whole chamber with its apical portion and the widest diameter of concordant atrioventricular valve. For the left ventricle standard 4-chamber view was used; for the right ventricle the probe was moved slightly to the left side with its tail tilted posteriorly and counter clockwise to open the apical part and include the full capacity of outflow track in the pyramidal data set. For both ventricles the probe's position and its spatial orientation was controlled by a simultaneous two-dimensional view of coronal and sagittal planes. At least three full-volume acquisitions for each ventricle were recorded in each patient; the one with the highest quality was assigned for later post processing. In patients with sinus rhythm the recording time approached 3 minutes, although in patients with arrhythmia it was considerably longer (mean 5 min) because recording of four consecutive sinus beats with no extrasystoly in real time was more challenging.

Postprocessing

Full-volume 3D digital data sets for both left and right ventricle were exported to an external server for offline analysis using dedicated software (TomTec Imaging Systems GMBH, Germany; Image Arena 4.6). For the left ventricle 4D LV-Analysis software was used and for the right ventricle — 4D RV-Function module. For each ventricle analysis, the user identified specific landmarks in end-diastolic and end-systolic views (apex, mitral, and aortic annulus for left ventricle, and additionally ventricular diameter in short axis view along with interventricular septum perimeters for the right ventricle). Based on the landmarks, semiautomatic tracing of endocardium was performed and corrected manually by the software operator. The analysis was performed using high-contrast monitor settings which, from experience, helps to define clearer line to track while manual correction of contour is made. Trabeculae and papillary muscles into ventricular cavity was included. For optimal quality of full-volume data sets the analysis of both ventricles was completed in a mean time of 4 minutes, and up to 9 minutes for images of poorer quality requiring more manual tracing. The results of the analysis being systolic function of both ventricles illustrated by EF were automatically calculated from end-diastolic volume (EDV), and end-systolic volume (ESV). A graphic presentation of the results is featured in Figure 1A, B.

Cardiac magnetic resonance

All CMR studies were acquired with a Siemens Magnetom Skyra 3 Tesla scanner (Siemens, Erlangen, Germany). Five patients who were unable to cooperate during the procedure (the youngest or hyperactive children) required general anaesthesia. A routinely used CMR protocol to assess left and right ventricular size and function included initial scout images followed by cine steady-state free precession (SSFP) breath hold sequences in 2-, 3-, and 4-chamber views to set up final imaging planes and a stack of short-axis images from the atrioventricular annulus to the apex. Imaging parameters were as follows: field of view 340 mm, matrix 208, repetition time approximately 39.24 ms, echo time 1.43 ms, flip angle 39 degrees, slice thickness 6–8 mm (depending on the child age), gap 2 mm, in-plane image resolution 1.6 × 1.6 × 6–8 mm, and temporal resolution 25 phases per cardiac cycle [1, 2]. Images were analysed with the use of a dedicated software. Initially, short-axis SSFP cine images were previewed from the base to the apex in a cinematic mode, then endocardial contours for end-diastole and end-systole of both ventricles were manually traced. Trabeculae and papillary muscles were considered as ventricle cavities. Delineated contours were used for the quantification of ventricular ejection fractions (left ventricular EF [LVEF], and right ventricular EF [RVEF]). The mean time of image acquisition was 40 minutes (longer in children requiring general anaesthesia — up to 1.5 h). The mean time of image analysis was 20 minutes.

Statistical analysis

Bland-Altman analysis and linear regression were used to compare results of LVEF and RVEF obtained with 3D-ECHO against CMR acknowledged as the method of reference. A p-value of less than 0.05 was considered statistically significant [3]. For the whole cohort and selected subgroups of patients with arrhythmia the mean differences between 3D-ECHO and CMR results were calculated and the 95% confidence intervals (CIs) determined. Because data were normally distributed (verified by the Shapiro-Wilk test), a paired Student t-test was used to compare means of LVEF and RVEF results obtained from 3D-ECHO and CMR, again using CMR as the method of reference.

All calculations and graphs were made in the R software version 3.3.1. (distributed under the terms of the GNU General Public License).

The study was approved by the Medical University's Ethics Committee. In all patients, written informed consent was obtained from parents and for children older than 16 years of age.

Results

Bland-Altman plot proved minor mean differences with narrow limits of agreement between the results obtained with 3D-ECHO and CMR for both LVEF and RVEF, marking very high significant correlation (for LVEF: $r = 0.903$, $p < 0.00001$; for RVEF: $r = 0.966$, $p < 0.00001$) and agreement (Fig. 2A, B). The relation between the results derived from both methods is linear, and it can be approximated by the identity function (Fig. 3A, B).

For LVEF, the estimated slope was 1.031, standard error = 0.007 ($p < 0.00001$), R-squared = 0.998; the average width of 95% prediction interval was 10.6% ± 5.3%). Comparing LVEF calculated with 3D-ECHO to reference CMR values — in 34% of patients the difference was lower than 1%, in 59% under 2%, in 68% under 3%, and in 78% below 4%. However, the paired Student t-test showed a statistically significant difference between means of LVEF calculated in 3D-ECHO and CMR — both for the whole cohort and in subgroups with arrhythmia ($p < 0.005$). 3D-ECHO results proved to be minimally underestimated comparing to CMR results with mean difference of –1.8 ± 2.6% ($p < 0.0001$) for the whole population, in the subgroup with arrhythmia –2.3 ± 2.5% ($p < 0.0001$), in children with severe ventricular arrhythmia –3.1 ± 2.7% ($p = 0.0006$), and in patients with severe idiopathic ventricular arrhythmia –2.6 ± 2.8% ($p = 0.0088$). At the same time the 95% CIs for the whole group studied and arrhythmic subgroups proved to be narrow, marking good consistency of both methods. Also, those underestimations are considered minimal and irrelevant for single patients in clinical practice. The results are presented in Table 2.

For RVEF the estimated slope was 0.993, standard error = 0.007 ($p < 0.00001$), R-squared = 0.998; average width of 95% prediction interval was 10.0 ± 5.0%. Comparison of RVEF from 3D-ECHO to CMR values in 39% of patients showed the difference below 1%, in 63% under 2%, in 78% under 3%, and in as much as 93% below 4%. Almost perfect agreement was obtained between results of 3D-ECHO and CMR with the paired Student t-test proving the lack of a statistically significant difference between mean values of RVEF calculated in 3D-ECHO and CMR marked by $p > 0.05$ for the whole cohort and in arrhythmic subgroups. The mean difference between 3D-ECHO and CMR results was 0.4 ± 2.4% for the whole cohort ($p = 0.29$), 0.3 ± 2.2% in the subgroup with arrhythmia ($p = 0.43$), 0.5 ± 2.3% in the subgroup with severe ventricular arrhythmia ($p = 0.46$) and 0.5 ± 2.4% for patients with severe ventricular arrhythmia classified as idiopathic ($p = 0.48$). The 95% CI for the whole group studied and arrhythmic subgroups proved to be narrow, again marking close agreement with CMR results. The data are presented in Table 3.

Discussion

Arrhythmias are considered one of the most prominent problems in pediatric cardiology [4]. Contrary to the adult population, most cases of arrhythmia in children are classified as idiopathic because no link to cardiac morphology or evident haemodynamic dysfunction can be found [5–8]. In most cases the risk is low and general prognosis is good, patients do not usually require pharmacotherapy, even if extrasystole is common. However, for some arrhythmias the risk of sudden cardiac death is much higher. In diagnostics of ARVC enlarged chamber and deteriorated function of the right ventricle are among the most prominent major criteria, providing in fact half of the definitive diagnosis [9, 10]. The progression of the disease, including deterioration of ventricular function, may be gradual and diffused in time [11–13]. For that reason, the accurate and regular assessment of ventricular function is crucial in patients with ventricular arrhythmia.

Unfortunately, widely accessible and inexpensive two-dimensional-echocardiography (2D-ECHO) offers very biased data because a single-plane view cannot illustrate the complex morphology of the right ventricle [14–17]. CMR is much more accurate in this assessment and is considered the gold standard in calculating ventricular volume and function. Additionally, it offers information about potential myocardial fibrosis or fatty infiltration (helpful in establishing the diagnosis of ARVC, although not included in diagnostic criteria). Unfortunately, its low accessibility and high cost prevent it from being a truly universal tool, especially in patients with severe arrhythmia in whom initially normal right ventricular parameters might yet evolve into cardiomyopathy with time and need to be measured regularly [14]. Furthermore, the use of CMR has significant limitations in a group of infants and small children as well as patients with hyperactivity or anxiety disorders. The procedure is lengthy (at least 40 min) and during that time the patient has to lie still and hold breath on demand; that alone creates a cooperative problem in the pediatric population. For this reason, many patients (5 in the present study cohort) required general anaesthesia with all its potential risks. Another group of patients in whom assessment of ventricular volume and function might be challenging is the population with excessive arrhythmia (especially with numerous extrasystolic beats), because the method is ECG-gated and requires 10 consecutive regular (sinus) beats to obtain optimal image resolution. Among the present study group, 2 children with multiple extrasystole, acquisition of optimal images was impossible.

Three-dimensional echocardiography, with its rapid evolution during the last three decades, seems to be an accessible and inexpensive tool for the assessment of cardiac function in clinical practice because it combines the accuracy of magnetic resonance imaging with the already high and constantly expanding accessibility and cost effectiveness of two-dimensional ultrasound systems [18–22]. The image acquisition is faster than CMR and requires fewer consecutive regular heart beats to produce data of adequate quality.

In the current study, focus was concentrated on evaluating the accuracy of 3D-ECHO in accessing ventricular function in children in comparison to CMR as the modality of reference.

In the group of children studied, results of both LVEF and RVEF calculated in 3D-ECHO proved to have a very high correlation and agreement with the data obtained in CMR. This consistency was proven both for the whole cohort and within extracted subgroups —

patients with arrhythmic disorders in general, severe ventricular arrhythmias, and among cases of arrhythmia classified as idiopathic.

The mean differences between values of ventricular systolic function (LVEF and RVEF) calculated in 3D-ECHO and CMR were minimal with narrow (< 4%) 95% CI. However, while for the right ventricle the consistency of results between both methods was proven to be almost perfect in the paired Student t-test ($p > 0.05$ interpreted in this case as a lack of significant difference), LVEF proved to be minimally underestimated by 3D-ECHO in the whole population and arrhythmic subgroups with the highest mean difference of –3.1 ± 2.7% in the group of patients with severe ventricular arrhythmia. That difference was proven to be statistically significant ($p < 0.05$) by the paired Student t-test although irrelevant in clinical practice. The small 95% confidence interval for mean difference pointed to close agreement with CMR results. This tendency is coherent with data published so far [23].

Published studies have shown good to excellent correlation between LVEF and RVEF measured in 3D-ECHO and CMR with a documented tendency towards minimal (although statistically significant) underestimation of 3D-ECHO results [23, 24]. Most of those studies concerned adults [25–29]. The literature comparing results of 3D-ECHO and CMR in children is much scarcer both in number and resources [27]. It usually addresses specific populations of patients: with congenital or acquired heart disease [30], after heart defect operations (prominently tetralogy of Fallot [31]) or with left ventricular cardiomyopathies [32]. No paper so far has offered data on the comparison between 3D-ECHO and CMR for ventricular function assessment in children with arrhythmia.

Whether impaired LVEF and RVEF are the source or the result of severe arrhythmia, and if ventricular function indeed deteriorates due to arrhythmic disorders, only further studies, especially within the pediatric population diagnosed with arrhythmia in morphologically healthy hearts, will show.

For this reason, systematic, regular, and accurate assessment of ventricular function in children with arrhythmia, even (or maybe especially) idiopathic, is crucial. 3D-ECHO appears to be the perfect tool for this purpose and a valuable alternative to CMR in this population [26–28, 33–36].

It is suggested herein, that after initial CMR children with arrhythmias and left ventricular cardiomyopathies can be monitored with 3D-ECHO. CMR can be repeated only in cases of deterioration of ventricular function observed in 3D-ECHO.

Limitations of the study

In the present study, attention concentrated on assessing the rank of agreement between 3D-ECHO and CMR results in a pediatric population, focusing prominently on arrhythmic patients in whom imaging was both necessary and technically difficult. Because the population analyzed was small, the problem calls for further study, especially in children with arrhythmia. Comparisons to a control group of healthy children would provide statistical clarity on the subject of potential ventricular dysfunction in patients with arrhythmia preliminarily classified as idiopathic, but it is difficult to gather a group of healthy children in whom CMR was used. One should also keep in mind that children with idiopathic arrhythmia might show a tendency towards deterioration of ventricular function in adulthood; therefore, follow-up assessment can be fruitful.

Conclusions

Three-dimensional-echocardiography assessment of both LVEF and RVEF in children shows a high significant correlation and agreement with CMR. 3D-ECHO could be a valuable tool in the follow-up of children with arrhythmic disorders requiring regular assessment of ventricular function.

Conflict of interest: None declared

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Table 1. Characteristics of the studied group

Patients' characteristics	**Details**				
Age [years]	13.7 ± 3.8				
Sex	Boys	26			
	Girls	17			
BSA [m^2]	0.56–2.04; mean 1.61 ± 0.34				
Diagnosis	Arrhythmia	Supraventricular	2		
		Ventricular	25		
			Severity	Mild	9

				(< 20%/24 h + no VT)	
				Severe (> 20%/24 h and/or VT)	16
			Cause	Idiopathic	20
				ARVC	3
				VSD (after operation)	1
				ATS	1
	LV cardiomyopathy	7			
		DCM	3		
		HCM	2		
		RCM	1		
		NCLV	1		
	Healthy subjects (initially suspected or successfully treated myocarditis)	9			

ARVC — arrhythmogenic right ventricular cardiomyopathy; ATS — Andersen-Tawill syndrome; BSA — body surface area; DCM — dilated cardiomyopathy; HCM — hypertrophied cardiomyopathy; NCLV — noncompacted left ventricle; RCM — restrictive cardiomyopathy; VSD — ventricular septal defect

Table 2. Results of left ventricular ejection fraction measurements in three-dimensional-echocardiography (3D-ECHO) and cardiac magnetic resonance (CMR) in subgroups of patients: ranges and mean values with standard deviations.

LVEF [%]	**3D-ECHO (n = 42)**	**CMR (n = 42)**	**95% CI***	**P**
Study group	Range: 46.6–69.1%	Range: 47.0–72.0%	[–2.6, –1.0]	< 0.0001
	Mean: 58.5 ± 5.4%	Mean: 60.3 ± 6.0%		
Arrhythmia (26)	Range: 49.2–69.1%	Range: 50.0–71.0%	[–3.3, –1.3]	< 0.0001
	Mean: 59.0 ± 4.7%	Mean: 61.2 ± 5.0%		
Severe ventricular arrhythmia (15)	Range: 49.2–68.0%	Range: 50.0–71.0%	[–4.6, –1.6]	0.0006
	Mean: 57.9 ± 4.5%	Mean: 60.7 ± 5.2%		
Severe idiopathic ventricular arrhythmia (12)	Range: 49.2–68.0%	Range: 50.0–71.0%	[–4.4, –0.8]	0.0088
	Mean: 58.4 ± 4.8%	Mean: 60.7 ± 5.8%		
ARVC (3)	Range: 53.5–58.7%	Range: 58.0–63.0%	Too small sample for statistical testing	

*Difference = ejection fraction [%] measured by 3D-ECHO – ejection fraction [%] measured by CMR; ARVC – arrhythmogenic right ventricular cardiomyopathy; CI — confidence interval; LVEF — left ventricular ejection fraction

Table 3. Results of right ventricular ejection fraction measurements in three-dimensional-echocardiography (3D-ECHO) and cardiac magnetic resonance (CMR) in subgroups of patients: ranges and mean values with standard deviations.

RVEF [%]	3D-ECHO (n = 41)	CMR (n = 41)	95%CI*	P
Study group	Range: 22.9–70.3%	Range: 25.0–70.0%	[–0.3, +1.2]	0.29
	Mean: 54.5 ± 8.8%	Mean: 53.6 ± 9.4%		
Arrhythmia (25)	Range: 22.9–70.3%	Range: 25.0–70.0%	[–0.5, +1.2]	0.43
	Mean: 52.8 ± 9.8%	Mean: 52.0 ± 10.1%		
Severe ventricular arrhythmia (14)	Range: 22.9–70.3%	Range: 25.0–70.0%	[–0.8, +1.7]	0.46
	Mean: 50.5 ± 11.9%	Mean: 49.1 ±11.9%		
Severe idiopathic ventricular arrhythmia (12)	Range: 48.5–70.3%	Range: 44.0–70.0%	[–1.0, +2.0]	0.48
	Mean: 55.2 ± 6.4%	Mean: 53.9 ± 7.1%		
ARVC (3)	Range: 22.9–39.0%	Range: 25.0–36.0%	Too small sample for statistical testing	

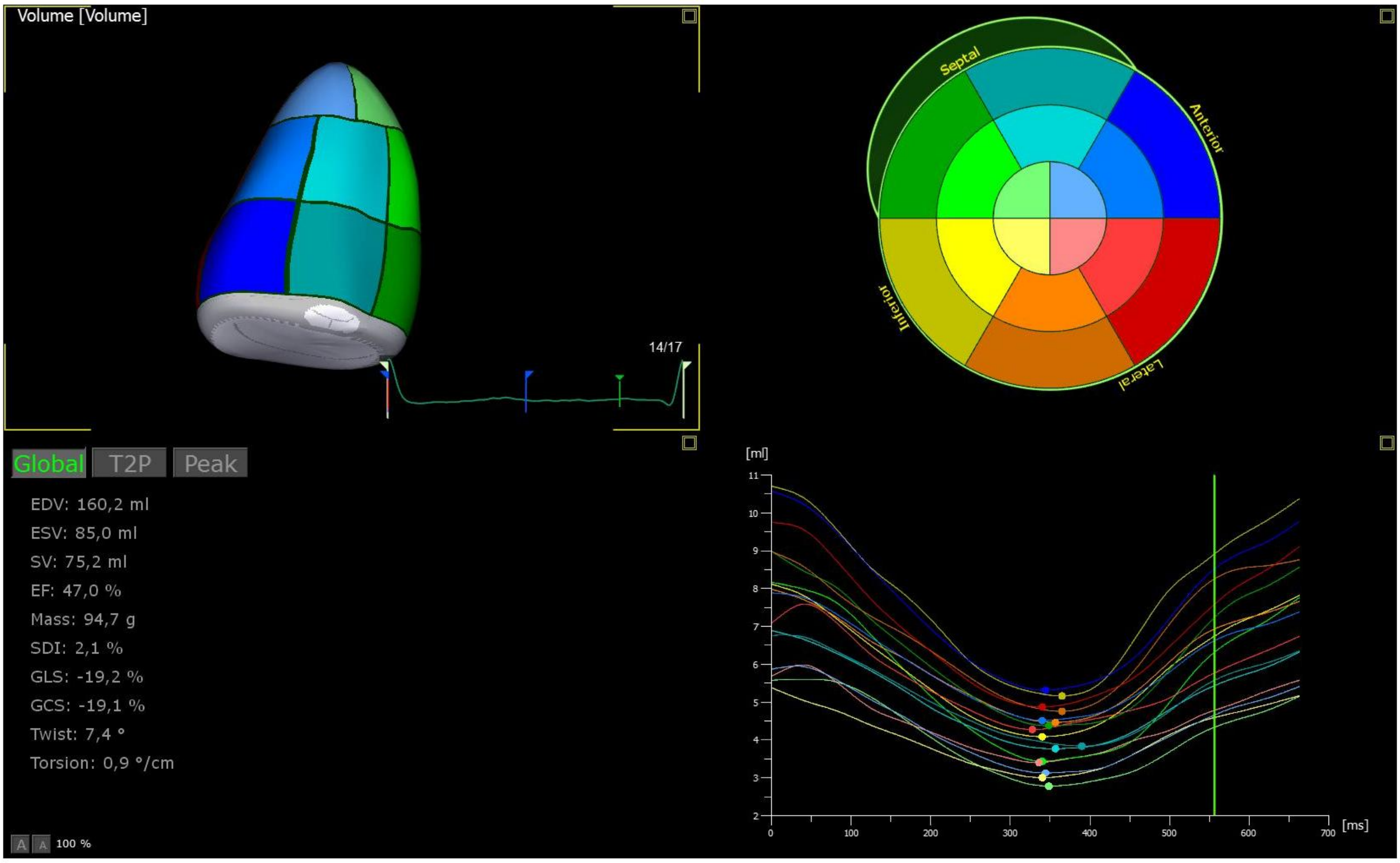
*Difference = ejection fraction [%] measured by 3D-ECHO – ejection fraction [%] measured by CMR; ARVC — arrhythmogenic right ventricular cardiomyopathy; CI — confidence interval; RVEF — right ventricular ejection fraction

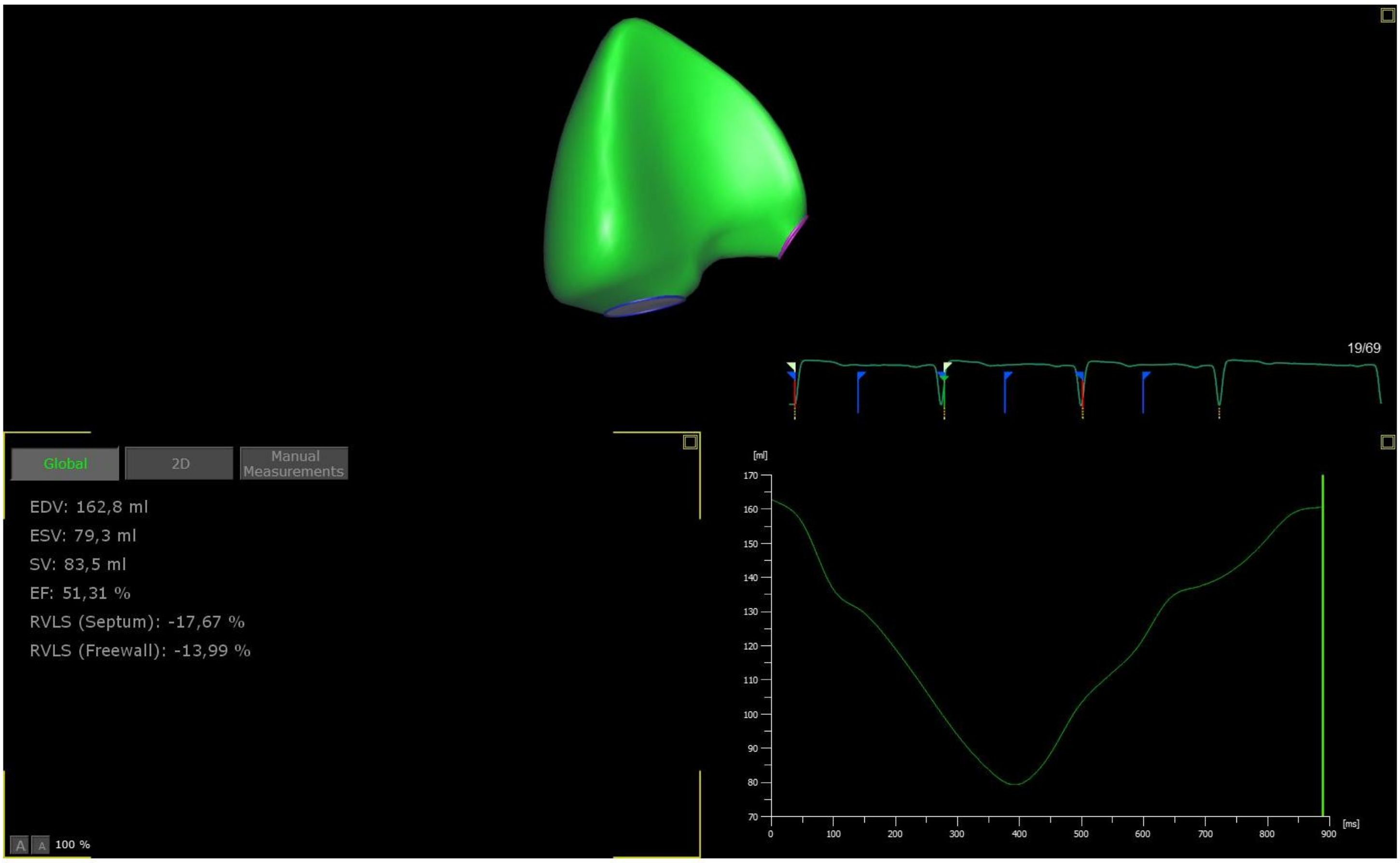
FIGURES LEGENDS

Figure 1. Three-dimensional echocardiography offline analysis; **A.** Left ventricular model with calculated ejection fraction; **B.** Right ventricular analysis results.

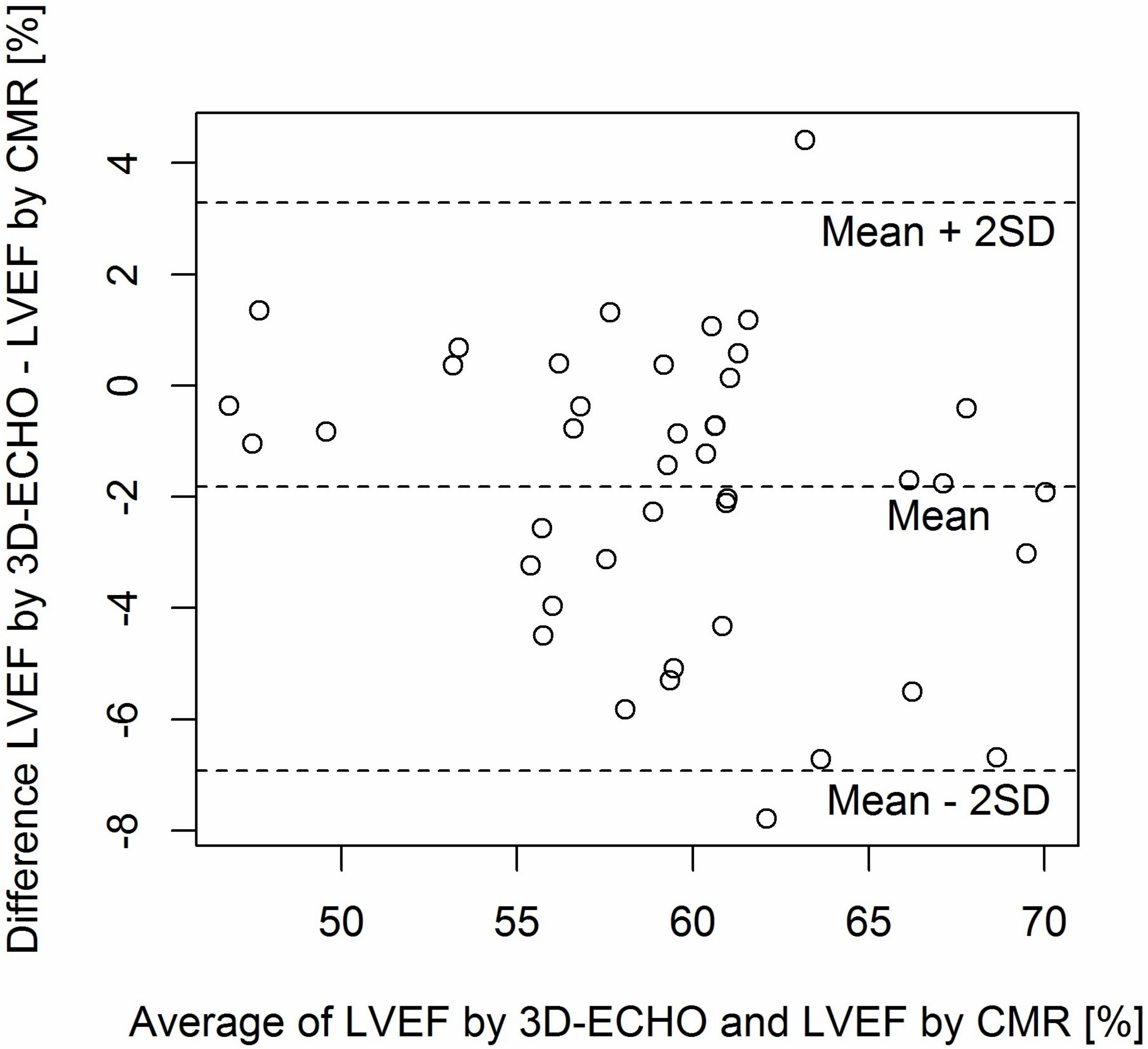
Figure 2. Bland-Altman analysis. Left (**A**) and right (**B**) ventricular ejection fraction (LVEF, RVEF, respectively): mean differences between results of three-dimensional-echocardiography (3D-ECHO) and cardiac magnetic resonance (CMR) with limits of agreement.

Figure 3. Identity function comparing results of left (**A**) and right (**B**) ventricular ejection fraction (LVEF, RVEF, respectively) between three-dimensional-echocardiography (3D-ECHO) and cardiac magnetic resonance (CMR). Regression of Y (CMR) on X (3D-ECHO), with prediction limits. **A.** The average width of prediction interval = 10.6 ± 5.3%; **B.** The average width of prediction interval = 10.0 ± 5.0%.

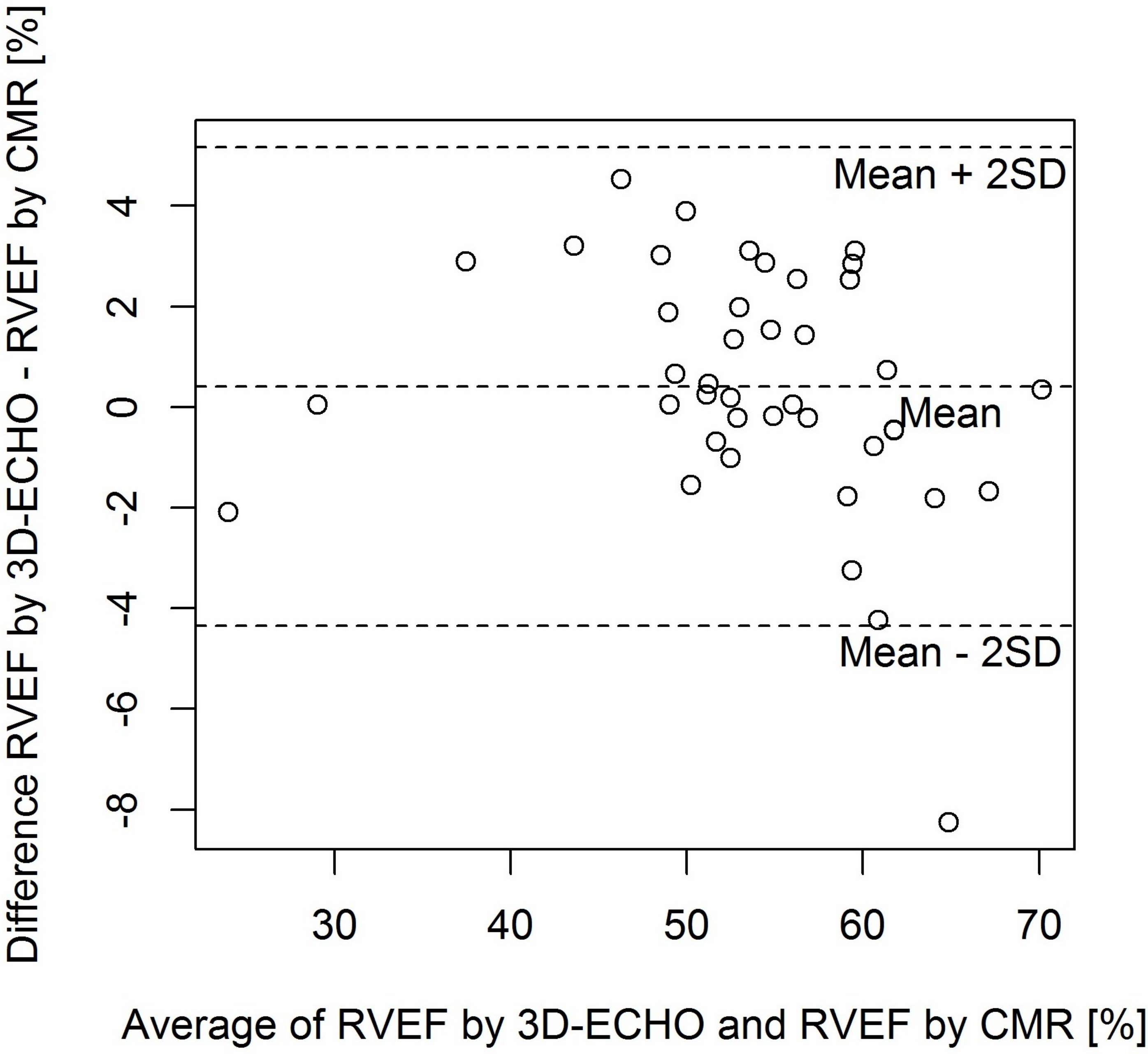

Volume [Volume]
14/17
Septal
Anterior
Inferior
Lateral
Global
T2P
Peak
EDV: 160,2 ml
ESV: 85,0 ml
SV: 75,2 ml
EF: 47,0 %
Mass: 94,7 g
SDI: 2,1 %
GLS: -19,2 %
GCS: -19,1 %
Twist: 7,4 °
Torsion: 0,9 °/cm
100 %
[ml]
[ms]



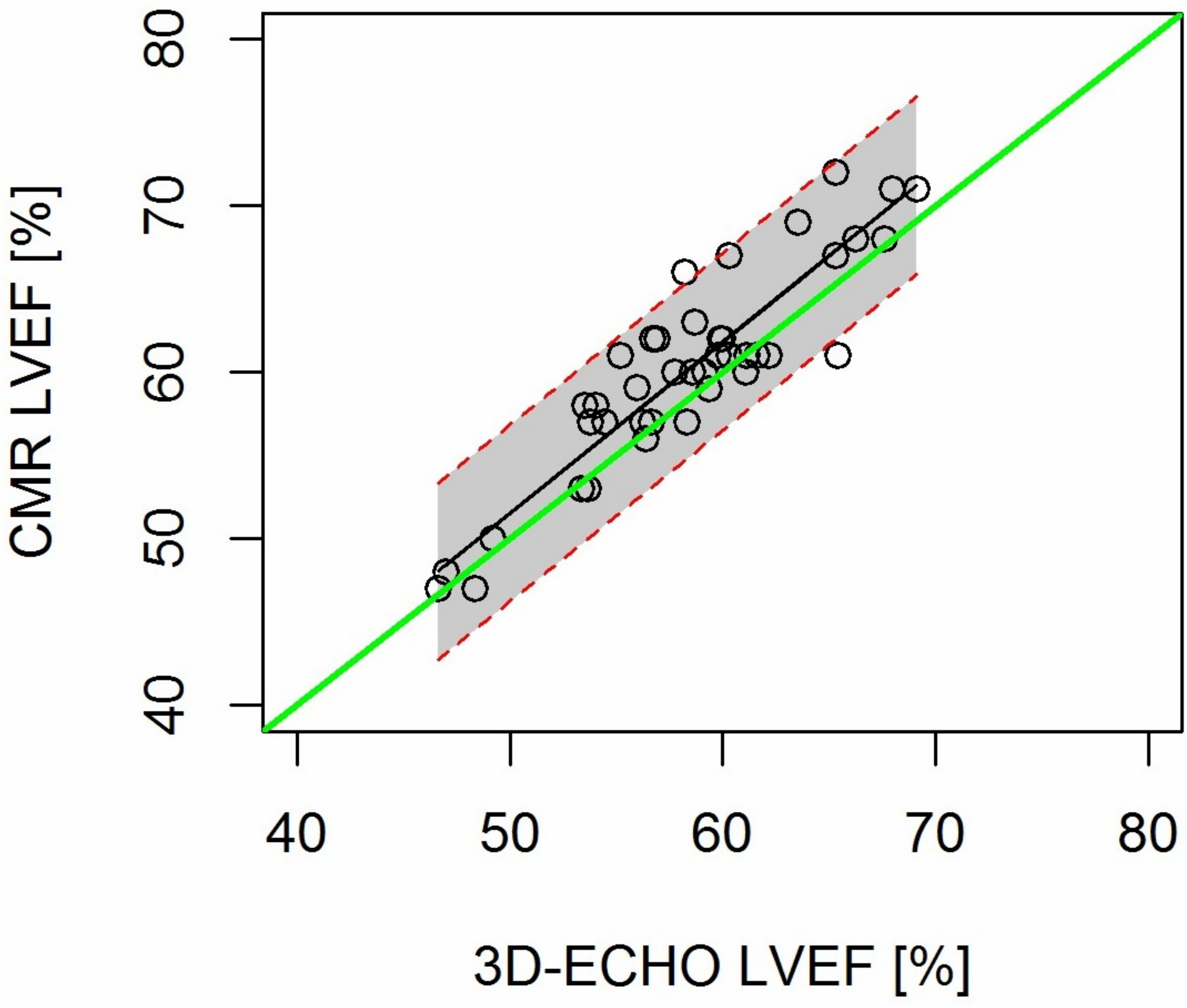
Global
2D
Manual Measurements
EDV: 162,8 ml
ESV: 79,3 ml
SV: 83,5 ml
EF: 51,31 %
RVLS (Septum): -17,67 %
RVLS (Freewall): -13,99 %
100 %
19/69
[ml]
[ms]



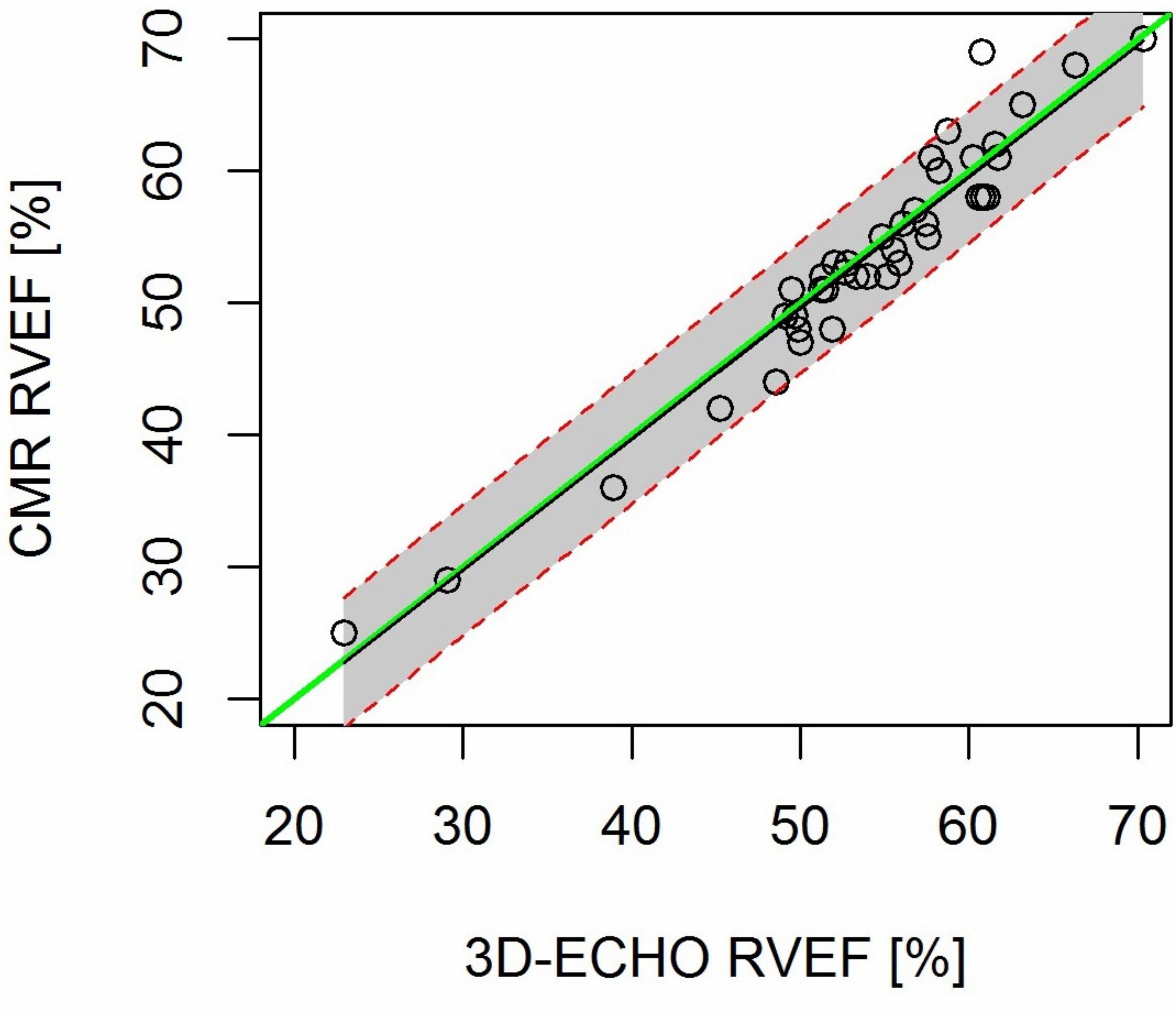
Difference LVEF by 3D-ECHO - LVEF by CMR [%]
4
2
0
-2
-4
-6
-8
Mean + 2SD
Mean
Mean - 2SD
50
55
60
65
70
Average of LVEF by 3D-ECHO and LVEF by CMR [%]



Difference RVEF by 3D-ECHO - RVEF by CMR [%]
Mean + 2SD
Mean
Mean - 2SD
4
2
0
-2
-4
-6
-8
30
40
50
60
70
Average of RVEF by 3D-ECHO and RVEF by CMR [%]



CMR LVEF [%]
80
70
60
50
40
40
50
60
70
80
3D-ECHO LVEF [%]



CMR RVEF [%]
20
30
40
50
60
70
3D-ECHO RVEF [%]