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A closer look at right ventricular 3D volume quantification by transthoracic echocardiography and cardiac MRI

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AIM: To compare right ventricular (RV) volumetry using state-of-the-art three-dimensional (3D) transthoracic echocardiography (3DE) and cardiac magnetic resonance imaging (CMR) near-simultaneously in a clinical setting.

MATERIALS AND METHODS: Forty-seven consecutive patients received comprehensive echocardiography including 3DE within 30 minutes of CMR. RV volumetry was performed offline with semi-automated 3D endocardial border tracing as well as manual delineation of the compacted myocardium in short-axis views by CMR.

RESULTS: Forty-two examinations (89%) could be analysed offline by 3D RV reconstruction. Mean RV volumes assessed by CMR and 3DE were 215±63 and 127±42 ml for end-diastole (RV-EDV), as well as 110±43 and 62±27 ml for end-systole (RV-ESV). RV-EDV, RV-ESV, and RV stroke volume measured by 3DE were significantly lower than RV volumetry by CMR. Mean bias were −88, −48, and −41 ml, respectively. Mean RV ejection fraction (-EF) showed a non-significant deviation of +2% between 3DE and CMR and the correlation coefficient was r=0.58 for RV-EF.

CONCLUSION: RV-EF can be assessed reliably using transthoracic 3DE in patients with good image quality; however, absolute RV volumes measured by 3DE show a systematic deviation to CMR volumetry that has been previously neglected and requires careful interpretation regarding anatomical cardiac imaging.

Introduction

The association of right ventricular (RV) dysfunction to morbidity and mortality in patients with cardiopulmonary disease started to gain particular interest more than a decade ago.[1] Similar to the left ventricle, RV ejection fraction (-EF) is defined as a reference parameter for systolic RV function. First studies used invasive RV angiography for estimation of RV-EF.[2] Radionuclide ventriculography of the

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RV was subsequently introduced as a non-invasive alternative. These methods have been abandoned for the assessment of RV volumes and have been replaced predominantly by cardiac magnetic resonance imaging (CMR) as the reliable quantification of RV-EF affords three-dimensional (3D) volumetry due to the complex anatomy of the RV.[3–7] In the last 10 years, 3D transthoracic echocardiography (3DE) has proven to be technically feasible with commercially available ultrasound systems, allowing the bedside acquisition of whole-heart 3D datasets and the offline quantification of RV volumes by semi-automated endocardial border tracing software.[8–11] In 2011, 3D matrix array transducers with increased temporal and spatial resolution were introduced. Pilot studies comparing RV-EF measurements using CMR and 3DE showed very good correlations of RV-EF values, as well as for absolute end-diastolic and end-systolic RV volumes.[12–14] Based on nine pooled studies with 596 patients that were examined using 3DE, the comprehensive guidelines for the echocardiographic assessment of the right heart in adults in 2010 suggested RV-EF cut-off values <45% for 3DE similar to CMR studies.[2] This recommendation was continued by the updated guidelines for cardiac chamber quantification of the American Society of Echocardiography (ASE) in 2015.[15] Detailed reviews on 3DE assessed RV volumetry discuss its technical and practical challenges, describe reasonable limits of agreement compared to CMR measurements in meta-analyses, and propose RV-EF by 3DE in parallel to RV volumetry by CMR as a more broadly used functional measure than in the past.[16–21]

Since 2018, the acquisition of 3D datasets, as well as RV volumetry, can be conducted bedside with commercially available echocardiography systems; however, in 2012, a single study indicated controversial results with systemic underestimation of RV volumes by 3DE compared to CMR.[22] Therefore, the aim of the present study was to compare RV volumetry of up-to-date high-resolution 3DE to near-simultaneous CMR in a clinical setting.

Materials and methods

Study design and population

This study is registered at clinicaltrails.gov and was conducted within the “N4 branch” including patients with CMR for reference and methodical evaluation of new echocardiographic RV parameters. Patients receiving a clinically indicated CMR examination were invited to participate. The study was carried out prospectively after approval by the ethics committee (S-275/2010) and in concordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before conducting the CMR and 3DE examinations.

Forty-seven patients underwent comprehensive echocardiography following the CMR examination. Clinical characteristics are shown in Table 1. The patient population consisted of 15 patients with normal myocardial function without significant coronary artery disease, 10 patients with coronary artery disease (2 one-vessel, 2 two-vessel and 6 three-vessel disease), 14 patients with cardiomyopathy (10 dilated, two hypertrophic, two cardiac amyloidosis), four patients with different forms of cardiac arrhythmia, two patients after heart transplantation, one patient with an atrial septal defect, and one patient with systemic vasculitis were included. All patients had sinus rhythm during both examinations. According to the study protocol, patients with suboptimal image quality at transthoracic echocardiography were not excluded from the examination in order to represent a clinical setting.

Table 1
Clinical characteristics of the study population.

Parameter	n=47
Age, years	53 ± 19
Gender, % male	69
Height, cm	176 ± 10
Weight, kg	80 ± 13
BMI, kg/m^2	26 ± 4
BSA, m^2	2.0 ± 0.2
Heart rate, /min	68 ± 12
NYHA I, *n* (%)	26 (55)
II, *n* (%)	15 (32)
III, *n* (%)	6 (13)
IV, *n* (%)	0 (0)
NT-proBNP, ng/l	238 (116; 1246)

Values are given as mean ± standard deviation, in case of non-normality as median (25th and 75th percentiles).
BMI, body mass index; BSA, body surface area; NYHA, New York Heart Association functional classification; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Echocardiography

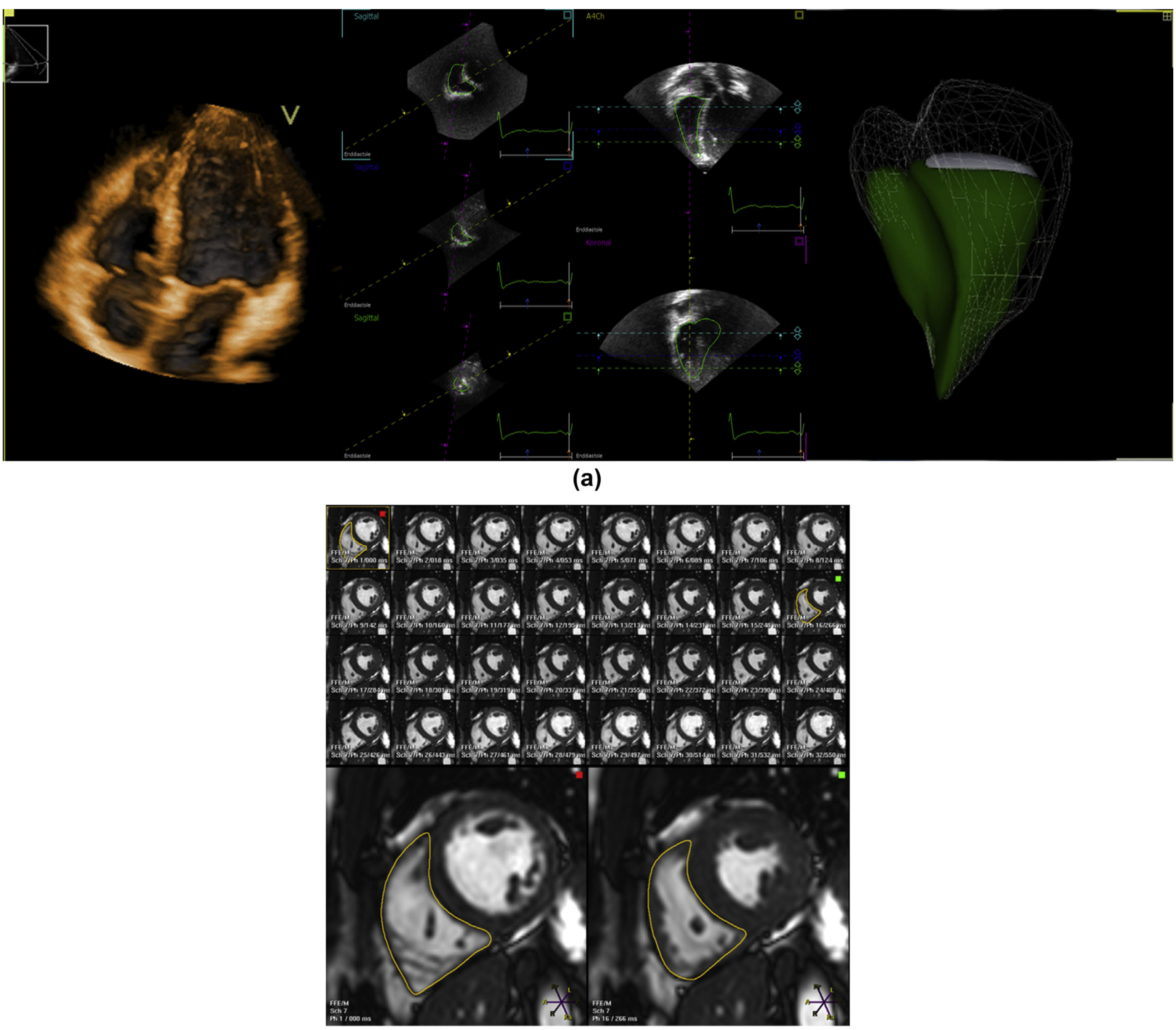
To minimise changes in RV preload and further haemodynamic changes, echocardiography was started within 30 minutes after CMR. All echocardiographic examinations were performed on a commercially available ultrasound machine (Vivid E9 BT 11, GE Healthcare Vingmed, Trondheim, Norway) according to the guidelines of the American Society of Echocardiography, using a 1.5–4.6 MHz phased array probe (M5S-D) and an active matrix four-dimensional volume phased array probe (4V-D).[2,15]

Three-dimensional echocardiography (3DE) was conducted in a multi-beat mode with at least 30 volumes per heart cycle to achieve adequate temporal resolution of less than 35 ms volume to volume, as described in detail previously.[23] Images were acquired during a breath-hold after passive end-expiration over at least four consecutive heart cycles. Special care was taken to include the whole RV as well as the RV outflow tract (RVOT) within the 3D pyramid, so that the patients received an additional 3DE acquisition focused on the RV. All data were transferred to a PACS server and was analysed offline with commercially available software (EchoPAC workstation BT11, GE Healthcare, Trondheim, Norway) by experienced examiners blinded to patients’ clinical history. 3D RV volumetry was carried out offline with commercially available, semi-automated endocardial border tracing software (4D-RV function, TomTec Imaging Systems, Unterschleissheim, Germany) embedded in the EchoPAC workstation as commonly used in previous studies.[8–14] Based on this software, a 3D model with temporal resolution of more than 30 volumes per cardiac cycle was reconstructed (Fig 1a).

Further parameters of RV function were assessed by two-dimensional (2D) echocardiography as advised by the ASE guidelines[2,15]: RV basal diameter (RV-EDD), RV fractional area change (RV-FAC), tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic velocity (TASV), and LV eccentricity index. Additionally, the RV automated systolic index (RV-ASI) and the RV 2D strain were assessed as previously described.[24,25] Although 3DE datasets of the RV could be acquired in all patients, exact analysis of the reconstructed RV 3D model showed persistent inadequate endocardial delineation in five cases, so that examinations of 42 patients (89%) were judged as technically feasible for offline RV 3D volumetry and were included in the statistical analysis.

CMR

A whole-body CMR system (1.5 T Achieva, Philips, Best, The Netherlands) was used for image acquisition applying a short-axis multi-section cine steady-state free-procession (SSFP) sequence with parallel imaging (8–12 sections, 8 mm thickness, 2 mm gap; balanced FFE; repetition time (TR)/echo time (TE)=2.9/1.45 ms; reconstructed voxel-size=1.5×1.5×8 mm acquisition; SENSE-factor=2). A complete cardiac cycle with 35 phases for up to 12 sections, respectively, was obtained by multi-beat acquisition within 7–10 seconds in breath-hold. According to the patients'



(a)

(b)

Figure 1 Examples of RV volumetry by 3DE with semi-automatic endocardial border tracing of the 3D dataset (a) and CMR with manual delineation of compacted myocardium for 3D reconstruction (b).

heart frequency a temporal resolution ranging from 28 to 38 ms can be calculated for comparison. The RV cavity, defined as the border between compacted and non-compacted myocardium, was traced semi-automatically in each short axis section in end-systole and end-diastole including visual control at the base of the RV in particular. 3D reconstruction of the RV volume by stacking of the marked layers was performed with a commercially available software package (Extended MR Workspace 2.6.3.4, Philips, Best, The Netherlands; Fig 1b). Finally, EDV, ESV, SV, and EF were calculated. The examinations by CMR allowed secondary RV volumetry in all 47 patients.

Statistical analysis

Statistical analyses of RV volumetry were based on measurable datasets (n=42) and were carried out with SPSS Statistics version 21.0 (IBM, Armonk, NY, USA). Graphs were plotted with GraphPad Prism Version 5 (GraphPad Software, La Jolla, CA, USA). The Kolmogorov–Smirnov test was used to identify normal distribution. With normal distribution approved, group differences were tested for significance using Student's *t*-test (unpaired, two-tailed). A *p*-value $<$0.05 was considered to indicate statistical significance. The association of measurements was examined by correlation analyses and deviations were visualised by Bland–Altman plots. Pearson's correlation coefficient was calculated. Ten randomly chosen datasets where re-analysed blinded to the former analysis by the same, as well as by a second experienced examiner to assess intra- and interobserver variability of echocardiographic as well as CMR measurements. These values are expressed as coefficients of variation and were calculated by the standard deviation of the differences between the two measurements, divided by their mean value and expressed as a percentage.

Results

Forty-seven patients were included in the present study. The 3DE examinations of five patients had to be excluded *a posteriori* for offline RV volume quantification due to inadequate offline endocardial border delineation accentuated in the RVOT, hindering the reliable reconstruction of a 3D RV model. Echocardiography image quality remained suboptimal in 11 (26%) patients, but endocardial delineation with manual correction was feasible nonetheless. All CMR images of the RV were of good quality and could be used for RV quantification. The characteristics of the study population are presented in Table 1.

Mean RV volumes measured by CMR and 3DE were 215±63 versus 127±42 ml for end-diastole (RV-EDV, $p<0.0001$), 110±43 versus 62±27 ml for end-systole (RV-ESV, $p<0.0001$) and 105±30 versus 64±22 ml for RV stroke volume (RV-SV, $p<0.01$) (Table 2, Fig 2). Mean left ventricular stroke volume by CMR was 95±25 ml. A highly significant difference between RV volumes measured by CMR and 3DE could be detected and mean biases for RV-EDV, RV-ESV, and RV-SV were −88 ml, −48 ml and −41 ml, respectively ($p<0.0001$ each). Mean RV-EF by 3DE showed no significant difference and a bias of +2% compared to CMR. Distribution of measurements and Bland–Altman analyses are visualised in Figs 3 and 4 and are summarised in Table 3. Person's correlation coefficients were r=0.68 for RV-EDV (SEE ±47 ml, $p<0.0001$), r=0.81 for RV-ESV (SEE ±26 ml, $p<0.0001$), r=0.43 for RV-SV (SEE ±27 ml, $p<0.01$) and r=0.58 for RV-EF (SEE ±7 %, $p<0.0001$). Coefficients for intra- and interobserver variability of RV-EF were 4% and 8% for 3DE and 4% and 6% for CMR.

In a subgroup analysis the echocardiography results of RV volumes and RV-EF were compared to CMR in patients with good (n=31) and with suboptimal (n=11) ultrasound image quality. Pearson's correlation coefficient for RV-EF increased to r=0.67 ($p<0.001$) when image quality of 3DE was rated good, but no correlation was found in examinations with suboptimal image quality (r=0.08, *p* not significant).

Table 2
Right ventricular parameters measured by cardiac magnetic resonance imaging and echocardiography.

Modality, Parameter	
CMR	
RV-EDD, mm	46±6
TAPSE, cm	1.8±0.5
RV-EDV, ml	215±63
RV-ESV, ml	110±43
RV-SV, ml	105±30
RV-EF, %	50±8
2D echocardiography	
RV-EDD, mm	33±7
TAPSE, cm	2.1±0.7
RV-FAC, %	41±13
RV 2D strain, −%	21±7
RV-ASI, %	53±9
3D-Echocardiography	
RV-EDV, ml	127±42
RV-ESV, ml	62±26
RV-SV, ml	64±22
RV-EF, %	52±9

CMR, cardiac magnetic resonance imaging; RV-EDD, right ventricular end-diastolic diameter; TAPSE, tricuspid annular plane systolic excursion; RV-EDV, right ventricular end-diastolic volume; RV-ESV, right ventricular end-diastolic volume; RV-SV, right ventricular stroke volume; RV-EF, right ventricular ejection fraction. RV-FAC, right ventricular fractional area change; RV-ASI, right ventricular automated systolic index; 3DE, three-dimensional echocardiography.

Discussion

In this clinical study on 3D volumetry, a significant underestimation of absolute RV volumes as measured using technical up-to-date 3DE compared to near-simultaneously CMR was identified. RV-EF derived from 3DE with optimal image quality showed statistically good correlation to values obtained by CMR, as well as stable re-measurements. Assessment of RV volumes by 3DE is a promising tool as it overcomes the limitations of 2D echocardiography in regard to the complex RV anatomy, and is applicable at the bedside.[26,27] Compared to standard 2D transthoracic echocardiography, the development of transthoracic 3D matrix

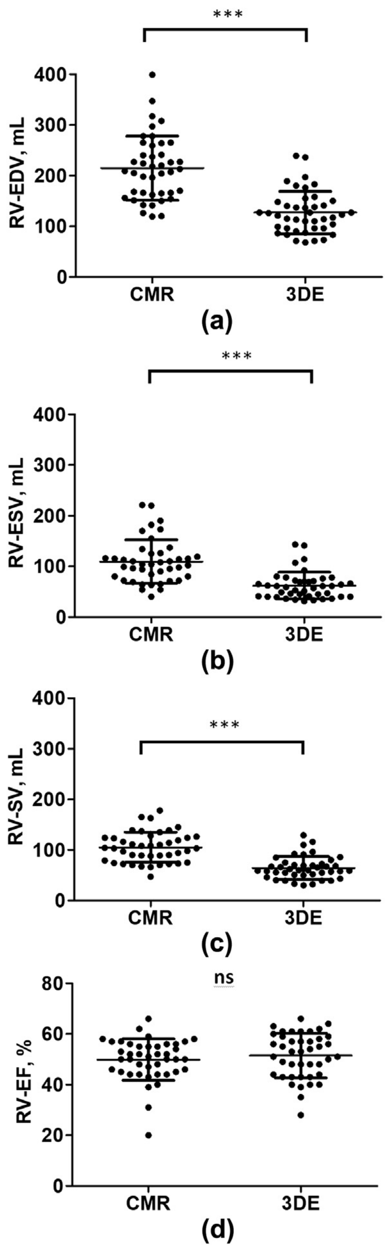


Figure 2 Scatter plots with mean values and standard deviations of RV volumes and RV ejection fraction measured by CMR and 3DE. RV-EDV, right ventricular end-diastolic volume; RV-ESV, right ventricular end-diastolic volume; RV-SV, right ventricular stroke volume; RV-EF, right ventricular ejection fraction.

array transducers including tests in animal models reached clinical availability rapidly.[28–32] More consistent results compared to other echocardiographic parameters for RV function are achievable, mainly due to the semi-automatic approach of the measurements.[10–13]

Before discussion of the results and the technical details of RV volumetry, the selection of patients for this study during clinical routine has to be clarified: for the CMR examination, patients were selected according to guidelines as they received a clinically indicated examination. Consequently, patients with claustrophobia, a CMR-incompatible pacemaker, or significant tachycardia were not accessible for this study. Although RV assessment by 2D echocardiography according to current guidelines was possible in all 47 patients, the exclusion of five 3D datasets for the statistical analysis highlights the technical challenges of RV volumetry by 3DE, although all examinations were conducted by sonographers with comprehensive experience in 3DE acquisition. Comparable to CMR or other imaging methods, preconditions for the standardised use of 3DE have to be defined for good diagnostic accuracy.[16,33] After exclusion of the five 3DE examinations that were inadequate for secondary RV volumetry, the remaining 42 datasets reflect a balanced selection based on clinical and technical requirements for both, CMR and 3DE, in order to compare RV volumetry in daily routine clinical practice in a tertiary cardiological centre.

Limitations of 3DE based on RV volume quantification were discussed in 2010 with a focus technical issues including time-consuming offline analysis.[2] In 2011, the next generation of 3D matrix array transducers with increased temporal resolution became available. The following studies with direct comparison of 3DE to CMR included from 29 up to 100 patients, and described persistent good correlations for RV-EDV (r=0.84–0.93), RV-ESV (r=0.83–0.91), RV-SV (r=0.74–0.81), and RV-EF (r=0.72–0.89). A detailed look at the reported data of these studies shows a trend for underestimation of absolute RV volumes by 3DE with mean biases of −17 to −34 ml for RV-EDV, −3 to −11 ml for RV-ESV, and −6 ml for RV-SV, but the reasons for the disparities were not discussed.[8–13] Even the results of studies, which intend to define normal ranges, as well as a recent study with detailed 3DE analyses of RV assessment, report low values of absolute RV volumes very similar to the mean values and standard deviation of RV-EDV, RV-ESV of the present study.[14,27] Until now, only a single centre study published in 2012 describes a significant underestimation of RV volumetry by 3DE compared to CMR measurements using the former 3D transducers with low temporal resolution. This study of Crean *et al.* reports even larger deviations of absolute RV volumes between CMR and 3DE in patients with dilated RV.[22] In parallel, a study of the present group showed systematic deviations of LV volumes by 3DE compared to CMR, including verification *in vitro*.[23] Unfortunately, advanced *in vitro* models for the evaluation of the complex RV anatomy including functional changes caused by RV impairment that could be applied similarly to CMR and to 3DE are lacking; however, RV volume quantification was evaluated thoroughly in this study by intra- and interobserver measurements, as well as analysis of deviations grouped by image quality. Image quality was rated as optimal, suboptimal, or insufficient for offline RV 3D volumetry. The 3DE datasets of five patients (11%) showed insufficient endocardial delineation for reliable offline 3D reconstruction, so that the method was not applicable in these patients. This technical failure rate is little lower than that reported in a former study including 118 patients without direct comparison to CMR volumetry (15% not feasible).[25] Furthermore, insufficient semi-automatic endocardial delineation of the anterior wall of the RVOT was frequently recognised during RV volumetry of

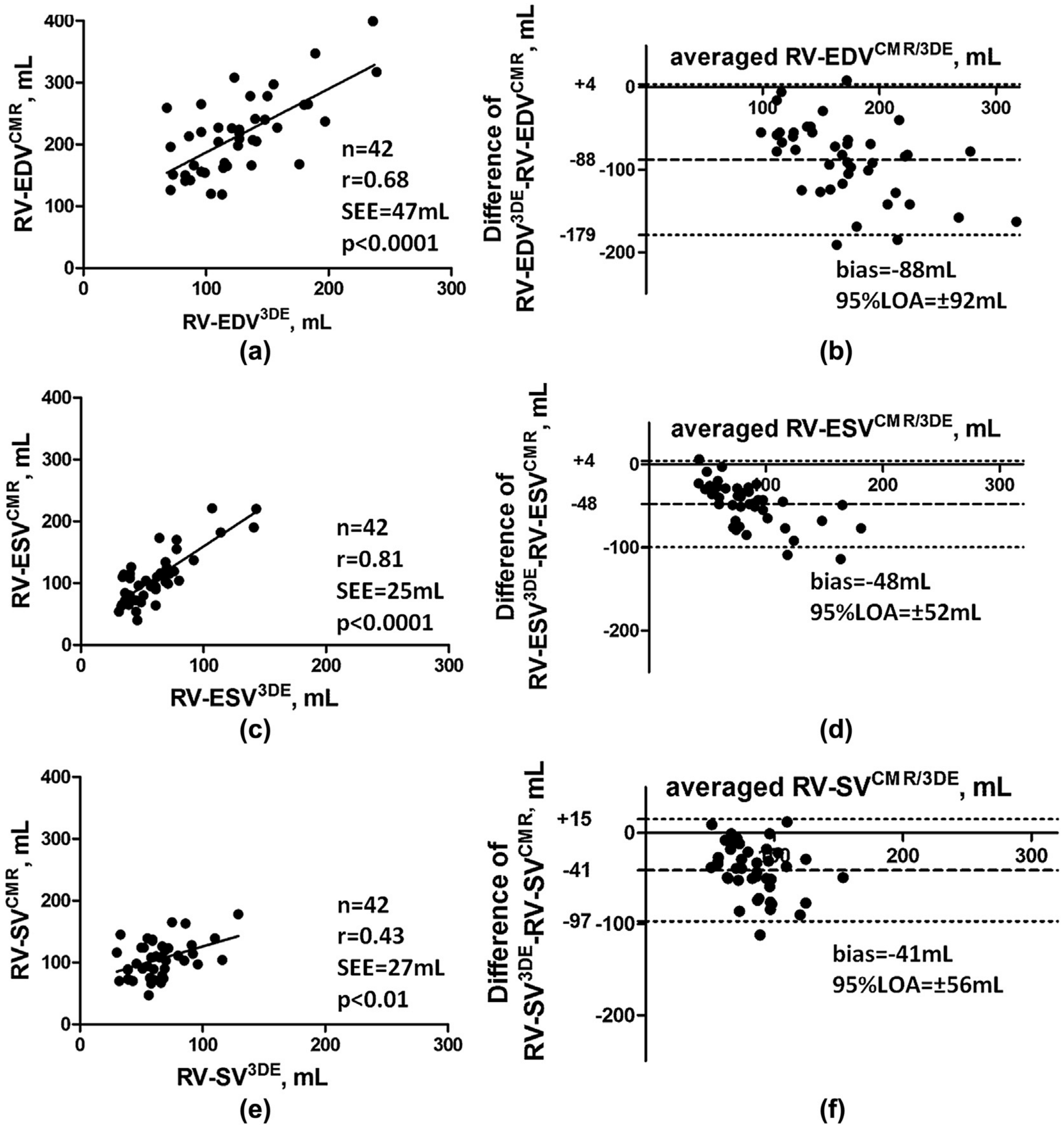


Figure 3 (a,c,e) Scatter plots of RV volumes measured by CMR and 3DE (panels A,C,E) as well as corresponding Bland–Altman plots (b,d,f). RV-EDV, right ventricular end-diastolic volume; RV-ESV, right ventricular end-diastolic volume; RV-SV, right ventricular stroke volume; RV-EF, right ventricular ejection fraction.

the remaining examinations, so that manual correction was mandatory. Reconstructed RV 3D models should be checked additionally with a focus on longitudinal contractility as well as the contraction pattern of the RVOT, if necessary in a standard 2D view, as regional impairment may originate from RV dysfunction or falsely by missed endocardial border tracing. In cases of normal RV function, a *peristaltic* contraction of the RV with a short delay in contraction of

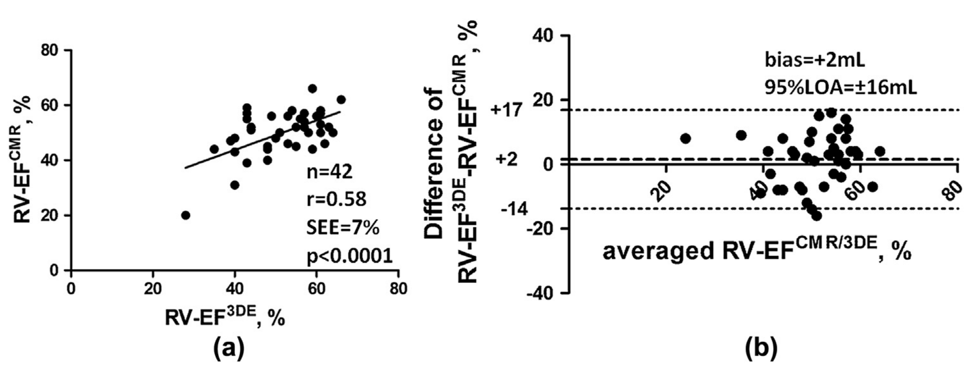


Figure 4 (a) Scatter plot of RV-EF measured by CMR and 3DE and corresponding Bland–Altman plot (b).

Table 3
Correlation analyses (Pearson's correlation coefficient) and Bland–Altman analyses for RV volumetry by 3DE compared to CMR.

	n	*r*	*p*-Value	Bias	95% LOA
RV-EDV, ml	42	0.68	<0.0001	−88	±92
RV-ESV, ml	42	0.81	<0.0001	−48	±52
RV-SV, ml	42	0.43	<0.01	−41	±56
RV-EF, %	42	0.58	<0.0001	+2	±16
RV-EF/RV-ASI, %	39	0.62	<0.0001	+2	±14

3DE, three dimensional echocardiography; CMR, cardiac magnetic resonance imaging; r, Pearson's correlation coefficient; LOA, limits of agreement; RV-EDV, right ventricular end-diastolic volume; RV-ESV, right ventricular end-diastolic volume; RV-SV, right ventricular stroke volume; RV-EF, right ventricular ejection fraction.

the RVOT can be observed.[34] Technical feasibility of endocardial border delineation is the basis for reliable RV volumetry and has to be checked precisely. In contrast to widely used semi-automatic software tools for left ventricular EF assessment or strain imaging, the currently available software for offline RV 3D reconstruction does not hinder analysis in cases with suboptimal endocardial tracing. Even if endocardial borders can be interpolated manually, the present data indicate a remarkable loss of information, resulting in a moderate correlation of RV-EF by 3DE to CMR if 3DE image quality is not considered. In parallel, good image quality has proven to be the most important factor for accuracy of left ventricular 3D volume quantification,[23] so that volumetry of the whole RV by 3DE requires optimal or "excellent"[16] acoustic windows.

Additionally, methodical aspects inherent to CMR and 3DE may explain differences in measured RV volumes and raise questions. To give an overview, significant deviations of absolute RV volumes measured by 3DE and CMR may result from the following aspects[1]: the very thin myocardium of the RVOT can be hard to trace, especially in suboptimal image quality as described above (Fig 1a)[2]; marked trabecula, especially of the RV apex, may influence semi-automatic border tracing and require manual correction. This point may have an increased influence in patients with impaired RV function due to enlarged and hypertrophic RVs[3]; absolute RV volumes calculated by CMR may be considered slightly overestimated with a mean cardiac output of about 7 l/min in the present study population (only one patient with an intracardiac shunt; 10 patients (24%) showing impaired RV function). This phenomenon can be observed in previous studies if RV stroke volume and heart rate are analysed.[11] A trend for overestimation in CMR-based RV volumetry may be caused by section width and difficulties in border definition at the base of the RV with its predominant longitudinal function and an oblique assessment of the tricuspid valve by cross-sectional imaging. In particular, the inclusion of right atrial parts in the reconstructed 3D volume of the RV has to be avoided by visual control and deselection of the corresponding sections before conducting 3D volumetry[4]; the adapted position of the ultrasound transducer to include the anterior segments of the RV in the 3D pyramid as advised by early RV 3D studies[10,13] may result in deviations of offline volumetry that are difficult to verify after 3D reconstruction. Although an independence of geometric assumptions is presumed for 3DE generally,[15] to the authors' knowledge, until now there have been no data for validation or calibration of RV volumetry by 3DE[5]; regarding the literature available, it remains unclear if the software algorithms for offline RV volume quantification of 3DE datasets incorporate RV shape assumptions beyond the defined anchor points to generate a valid 3D model of the RV, comparable to semi-automatic software tools used for LV endocardial border delineation and strain imaging.[24,25] Those algorithms could limit anatomical assessment of the highly volume-adaptive RV, especially in regard to the deviation of RV-EDV measurements.

With a focus on patients with cardiopulmonary disease who cannot receive CMR as described above, the clinical availability of 3DE seems a promising technique for cardiac imaging, including RV volumetry; however, detailed analyses of the data available, as well as the results of the present study, indicate that absolute RV volumes derived by these important imaging techniques should not be equalised due to methodical reasons.

Limitations

This study is a single-centre report with <50 patients; however, the results are consistent with independent and larger studies on 3DE after a detailed review of the reported data. The patients in the present study were not selected for pulmonary hypertension or congestive heart failure, although reliable quantification of RV function is of focused interest in these patients. The study protocol does not include haemodynamic measurements by right heart catheterisation as a reference. Invasively measured cardiac output and stroke volumes may have helped in the interpretation of the discrepancies between RV volumes by CMR and 3DE, although near-simultaneous measurements of all three techniques with corresponding haemodynamic circumstances seem hard to achieve.

Conclusion

In conclusion, although measured near-simultaneously, absolute RV volumes assessed by 3DE are considerably lower than those acquired by CMR; however, assessment of RV-EF by 3DE is feasible in patients with good image quality and shows an adequate correlation to CMR volumetry. In regard to anatomical imaging and absolute RV volumes, methodical differences between CMR and 3DE require critical interpretation to minimise systematic deviations in RV volume quantification.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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