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Echocardiography

High-Resolution Transthoracic Real-Time Three-Dimensional Echocardiography

Quantitation of Cardiac Volumes and Function Using Semi-Automatic Border Detection and Comparison With Cardiac Magnetic Resonance Imaging

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OBJECTIVES We sought to validate high-resolution transthoracic real-time (RT) three-dimensional echocardiography (3DE), in combination with a novel semi-automatic contour detection algorithm, for the assessment of left ventricular (LV) volumes and function in patients.

BACKGROUND Quantitative RT-3DE has been limited by impaired image quality and time-consuming manual data analysis.

METHODS Twenty-four subjects with abnormal (n = 14) or normal (n = 10) LVs were investigated. The results for end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) obtained by manual tracing were compared with the results determined by the semi-automatic border detection algorithm. Moreover, the results of the semi-automatic method were compared with volumes and EF obtained by cardiac magnetic resonance imaging (CMRI).

RESULTS Excellent correlation coefficients (r = 0.98 to 0.99) and low variability (EDV −1.3 ± 8.6 ml; ESV −0.2 ± 5.4 ml; EF −0.1 ± 2.7%; p = NS) were observed between the semi-automatically and manually assessed data. The RT-3DE data correlated highly with CMRI (r = 0.98). However, LV volumes were underestimated by RT-3DE compared with CMRI (EDV −13.6 ± 18.9 ml, p = 0.002; ESV −12.8 ± 20.5 ml, p = 0.005). The difference for EF was not significant between the two methods (EF 0.9 ± 4.4%, p = NS). Observer variability was acceptable, and repeatability of the method was excellent.

CONCLUSIONS The RT-3DE, in combination with a semi-automatic contour tracing algorithm, allows accurate determination of cardiac volumes and function compared with both manual tracing and CMRI. High repeatability suggests applicability of the method for the serial follow-up of patients with cardiac disease. (J Am Coll Cardiol 2004;43:2083–90) © 2004 by the American College of Cardiology Foundation

Assessment of left ventricular (LV) volumes and function conveys important prognostic information in patients with heart disease (1,2). Moreover, these parameters yield important information for the timing of surgery in patients with valvular heart disease (3,4) and for the choice of pharmacologic (5) or nonpharmacologic (6) treatment of patients with heart failure. Therefore, a robust method that allows reliable estimation of volumes and function in serial studies is required. Cardiac magnetic resonance imaging (CMRI) is generally considered to meet these needs, but the technique is costly, not widely available, and not applicable to patients with pacemakers and defibrillators, who constitute an increasing proportion of patients with heart failure.

Echocardiography is regarded as the technique of first choice for the serial follow-up of patients with structural heart disease (7). Although it has been shown that three-dimensional echocardiography (3DE) using reconstructive (8–11) or real-time (RT) image acquisition (12) techniques is superior to two-dimensional echocardiography for the quantitation of LV volumes and function, the method has not gained widespread access to routine clinical use. The main obstacles include difficult image acquisition using the reconstruction techniques, limited image quality provided by the first-generation RT scanners, and laborious manual data analysis in a number of selected cross sections of the LV. Recent technical development has permitted construction of a high-resolution RT-3DE transducer that allows facilitated acquisition of 3DE datasets with high image quality from a single acoustic window. Moreover, a computerized contour tracking algorithm has been developed that enables semi-automated data analysis with only minimal interaction by the investigator. Thus, the premise for fast, accurate, and less observer-dependent quantitation of

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Abbreviations and Acronyms

CMRI	= cardiac magnetic resonance imaging
3DE	= three-dimensional echocardiography
EDV	= end-diastolic volume
EF	= ejection fraction
ESV	= end-systolic volume
LV	= left ventricular/ventricle
RT	= real-time

LV volumes and function using RT-3DE may now be fulfilled.

Therefore, the aims of the study were to assess: 1) the feasibility of RT-3DE data acquisition in patients with and without heart disease; and 2) the usefulness of the semi-automatic border detection algorithm for quantitation of LV volumes and function, comparing the results obtained by the algorithm with the results obtained by both manual tracing and high-resolution CMRI.

METHODS

Patients. A total of 24 patients scheduled for routine echocardiography were included into the study. There were 14 patients (65 ± 12 years old) with heart disease due to dilated (n = 4) or ischemic (n = 10) cardiomyopathy and 10 subjects (42 ± 8 years of age) without apparent heart disease, as assessed by two-dimensional echocardiography, showing normal dimensions as well as normal global and regional function. Patients were selected for acceptable imaging quality, excluding patients with two or more segments not visualized by conventional echocardiography. Other exclusion criteria included an unstable clinical condition, severe dyspnea due to either pulmonary disease or congestive heart failure precluding breath-holding for at least 10 s, atrial fibrillation, pacemaker or defibrillator implantation, and claustrophobia. Each patient gave written, informed consent, in agreement with the local Ethics Committee of the University Hospital.

Transthoracic RT-3DE. Data acquisition was performed by using a commercial ultrasound scanner equipped with a special transducer and dedicated software for RT-3DE (Sonos 7500, Philips, Andover, Massachusetts). The transducer is a matrix array with almost 3,000 active elements (X4, Philips), which is connected to the ultrasound machine. The RT-3DE data acquisition is accomplished in a limited conical volume of 58° × 29° (azimuth and elevation directions, respectively). In order to encompass the complete LV into the 3DE dataset, a larger scan volume needs to be acquired. For this purpose, a pyramidal volume of 93° × 84° is scanned, which is divided into four conical subvolumes of approximately 93° × 20° each. Acquisition of the subvolumes is steered electronically by the ultrasound system, with the transducer kept in a stable position. The acquisition is trigged to the R wave of the electrocardiogram of every second heartbeat to allow acquisition of a full cardiac cycle for each subvolume. In order to accomplish correct spatial registration of each subvolume, the acquisition is performed in an end-expiratory breath-hold lasting 6 to 8 s (depending on the heart rate). The resultant 3DE dataset is stored on CD-ROM and transferred to a separate workstation for off-line data analysis. The temporal resolution of the system depends on the depth of the imaging sector and is between 40 and 50 ms. Data acquisition was performed using the fundamental imaging mode in the majority of the recordings (85%).

Magnetic resonance imaging. Imaging was performed on a 1.5-T scanner (Intera, Philips, Best, the Netherlands). A steady-state free precession imaging sequence was used (echo time/repetition time of 1.6/3.2 ms, flip angle of 55°, matrix 128 × 256), in combination with the parallel imaging technique called SENSE (13). After acquiring scout images and SENSE reference scans, a stack of contiguous, double-oblique, short-axis slices (slice thickness 8 mm, 2-mm gap) covering the LV from base to apex was acquired in repeated breath-holds lasting 6 to 8 s. Temporal resolution was set to 40 frames per RR interval. The CMRI and RT-3DE studies were performed on the same day to ensure comparable hemodynamic conditions between the different examinations.

Data analysis. Two experienced observers (H.P.K. and D.R.) performed the analysis of the RT-3DE datasets independently from each other and blinded to both the patient data and results of CMRI. Observer 1 (H.P.K.) analyzed all datasets using manual contour tracing, whereas Observer 2 (D.R.) analyzed all datasets using the semi-automatic contour tracing algorithm. A third independent observer (M.K.) analyzed the MRI data blinded to the patient data and results of RT-3DE.

Manual analysis. The 3DE raw data were analyzed off-line using commercially available software (CardioView RT, TomTec, Unterschleissheim, Germany). A detailed description of the algorithm and the measurement procedure has been published previously (14). After definition of the long-axis of the LV in the 3DE dataset, eight evenly rotated long-axis image planes were automatically generated by the system. Endocardial borders were traced manually at end systole (smallest cavity area) and end diastole (largest cavity area) in each of the eight cross sections. For tracing, a spline algorithm was applied, allowing the definition of a smooth, closed contour by setting points on the endocardial border. End-diastolic volume (EDV) and end-systolic volume (ESV) were then computed by the system using the "Rotaplane" algorithm (14). Ejection fraction (EF) was assessed as: (EDV − ESV)/EDV·100.

Automated border detection and volume computation algorithm. Data analysis was performed using the original raw data for all 3DE datasets. Generation of the eight image planes used for analysis was performed as described earlier. In each of eight cut-planes, the mitral valve annulus was earmarked with points in the end-diastolic and end-systolic images. These points were subsequently used by the semi-automatic algorithm for definition of the mitral valve plane.

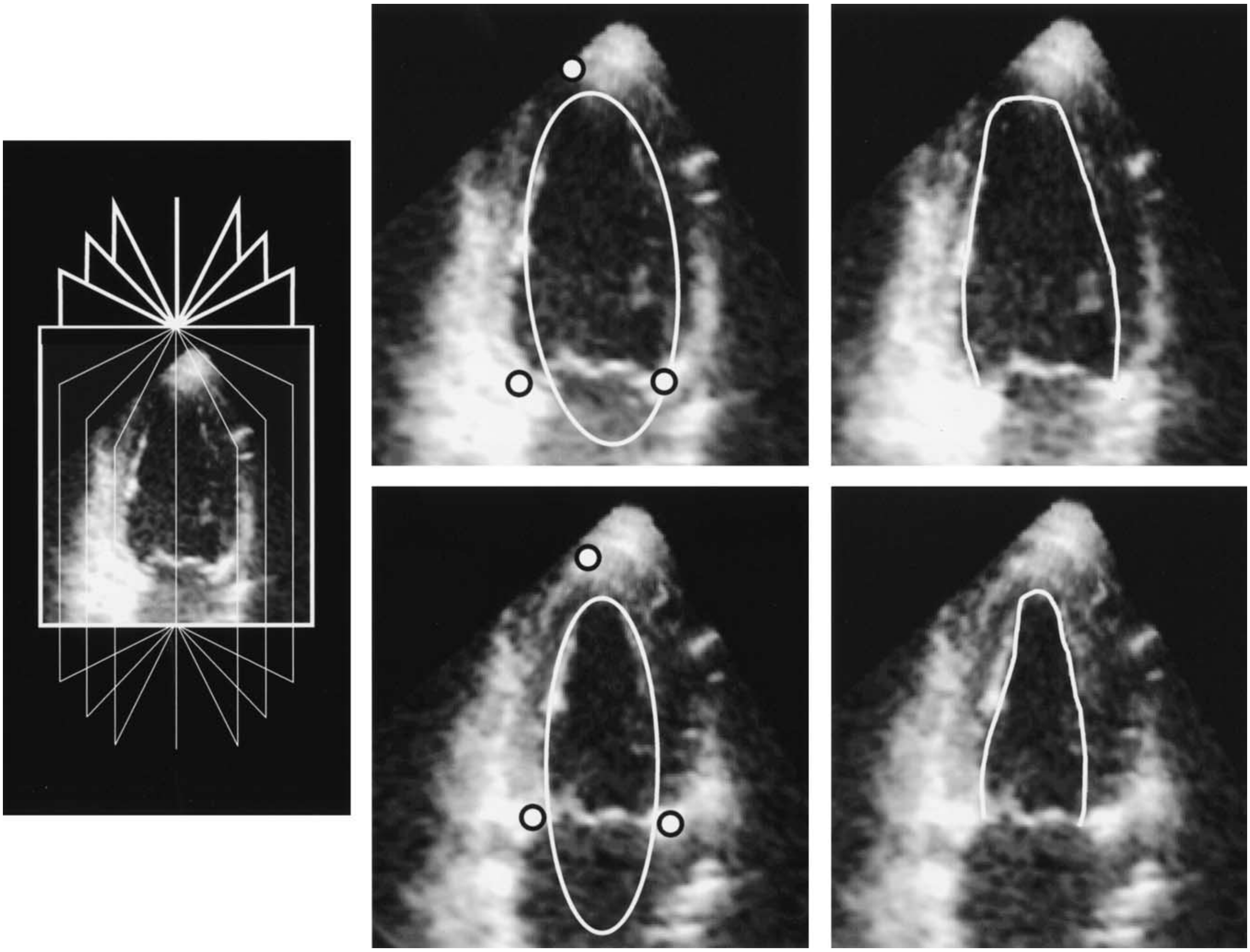

Figure 1. Method of semi-automatic contour detection using real-time three-dimensional echocardiography (3DE): a stack of eight rotated long-axis images is automatically selected from the 3DE dataset **(left panel)**. In each of these long-axis cross sections (only one shown), the left ventricular (LV) apex and mitral annulus are earmarked in an end-diastolic **(middle upper panel)** and end-systolic **(middle lower panel)** stop frame. The markers at the mitral annulus are subsequently used by the algorithm to set the mitral valve plane and to truncate the contours of the LV cavity. Thereafter, an **ellipse** is placed in each of the end-diastolic and end-systolic stop frames for initiation of the model. This **ellipse** is manually adapted (length, width, and rotation angle) to fit as closely to the endocardial border as possible. The contours are subsequently detected automatically by the algorithm (**right upper and lower panels** for end-diastolic and end-systolic stop frames, respectively, with detected contour). See text for further details.

An ellipse was then placed in the end-diastolic and end-systolic images in each of the eight selected long-axis cross sections (Fig. 1). These ellipses served for initiation of the semi-automatic algorithm. The shape and angular position of the ellipse were adapted manually to fit as close as possible to the endocardial border. The semi-automatic algorithm was then used to process the image data as follows:

1. Based on the manually defined ellipses, a spatio-temporal spline model based on thin-plate splines is initialized (15). This model ensures both smooth contours in the spatial domain and continuous motion in the temporal domain.
2. Perpendicular to the model's contours, the algorithm seeks those image points which most likely define the endocardium. This is done by finite impulse response and morphologic filtering of gray-scale profiles perpendicular to the current contour estimate. Filter response and distance to the current contour are used to yield a likelihood estimate for each detected image point.
3. All detected image points are now approximated by the same spline model as used in step 1. The approximation considers the derived likelihood measures.
4. If the approximation step 3 yields a significant change, another iteration is started with step 2.
5. Using the manually set mitral annulus points, a periodic spline is computed to track the mitral annulus over time. The detected contours of the endocardium are cut at this spline.

After contour detection, contours for each cross section and all temporal phases are available. Using the cine mode, the correct alignment of the contours with the endocardium during the cardiac cycle is controlled (Fig. 2). If gross deviations are noticed, the procedure is repeated after adapting the initial ellipse closer to the endocardial border. Moreover, interactive adaptation of the stiffness of the

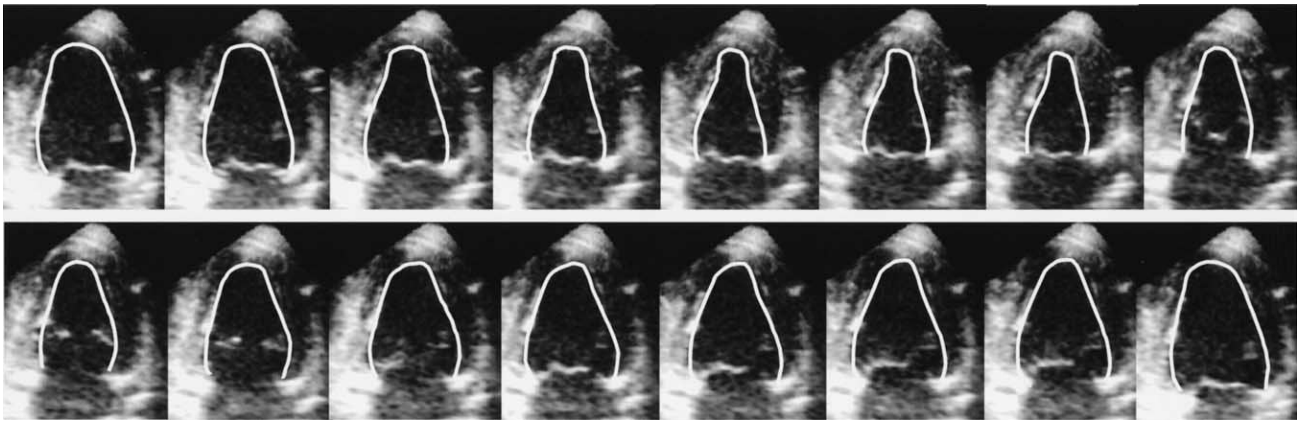

Figure 2. Example of semi-automatic contour detection in a patient with normal left ventricular function. In each of the 17 time frames of each of eight long-axis cut-planes, the endocardial border was detected by the semi-automatic algorithm.

contours allows for optimized alignment of the detected contours with the endocardium. For each phase, contours of the eight different cross sections are then reconstructed as a wire-frame model in three-dimensional space. Thereafter, this wire frame (one per phase) is approximated by a smooth spline model (16). The thereby generated surface is still open—the boundary of the orifice representing the mitral annulus, which is now closed by a curvature minimizing spline surface. The entire surface model is discretized as polyhedron, and the enclosed volume is computed using gaussian quadrature formulas (17).

Analysis of CMRI data. Manual data analysis was performed using the contiguous short-axis slices acquired from base to apex. End diastole was defined as the image with the largest cavity area, and end systole as the image with the smallest cavity area. Endocardial contours were outlined manually on each end-diastolic and end-systolic short-axis frame in each short-axis slice. The papillary muscles were excluded from LV volume when they were contiguous with the LV wall and included when they were within the LV cavity. Because echocardiographic tracing of the endocardium in long-axis cut-planes is accomplished excluding trabeculae from the cavity volume, the trabeculae were also excluded from the LV volume using CMRI. Both EDV and ESV were calculated after summing all subvolumes of all short-axis slices, and EF was determined as described previously.

Statistics. All data are expressed as the mean ± SD. Linear regression analysis was performed, and Pearson correlation coefficients were calculated. Agreement was assessed using the method proposed by Altman and Bland (18). To assess the robustness of the algorithm, the data of 15 randomly selected patients were reanalyzed by the same observer at least one week after the first investigation, as well as by a second observer blinded to the results of the first observer. Variability was expressed as mean difference ± SD of the mean difference between two observations. Moreover, the repeatability of RT-3DE and semi-automatic border detection was assessed in 10 randomly selected patients. For this purpose, patients were asked to stand up and lie back down again on the examination bed before acquisition of a second dataset. The interval between acquisitions of two separate datasets was at least 5 min.

RESULTS

Acquisition of RT-3DE datasets was feasible in all patients. The duration of data acquisition averaged 6.8 ± 2.4 s. The

Table 1. Comparison of RT-3DE Using the Semi-Automatic Algorithm With Manual Tracing and With Results Obtained by CMRI

	Mean Difference ± SD	p Value versus 0	95% CI	Regression Equation	r	SEE
Comparison of the Semi-Automatic Algorithm With Manual Tracing Using RT-3DE						
EDV (ml)	−1.3 ± 8.6	NS	−18.5 to 15.9	y = 1.0x − 1.6	0.99	8.8
ESV (ml)	−0.2 ± 5.4	NS	−11.0 to 10.6	y = 1.0x − 1.3	0.99	5.2
EF (%)	−0.1 ± 2.7	NS	−5.5 to 5.3	y = 0.98x + 0.5	0.98	2.8
Comparison of RT-3DE and Semi-Automatic Border Detection With CMRI						
EDV (ml)	−13.6 ± 18.9	0.002	−51.4 to 24.2	y = 0.93x + 1.3	0.98	17.8
ESV (ml)	−12.8 ± 20.5	0.005	−53.8 to 28.8	y = 0.90x + 0.4	0.98	18.3
EF (%)	0.9 ± 4.4	NS	−9.7 to 7.9	y = 0.91x + 4.7	0.98	4.0

CI = confidence interval; CMRI = cardiac magnetic resonance imaging; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; NS = not significant; RT-3DE = real-time three-dimensional echocardiography; SD = standard deviation; SEE = standard error of the estimate.

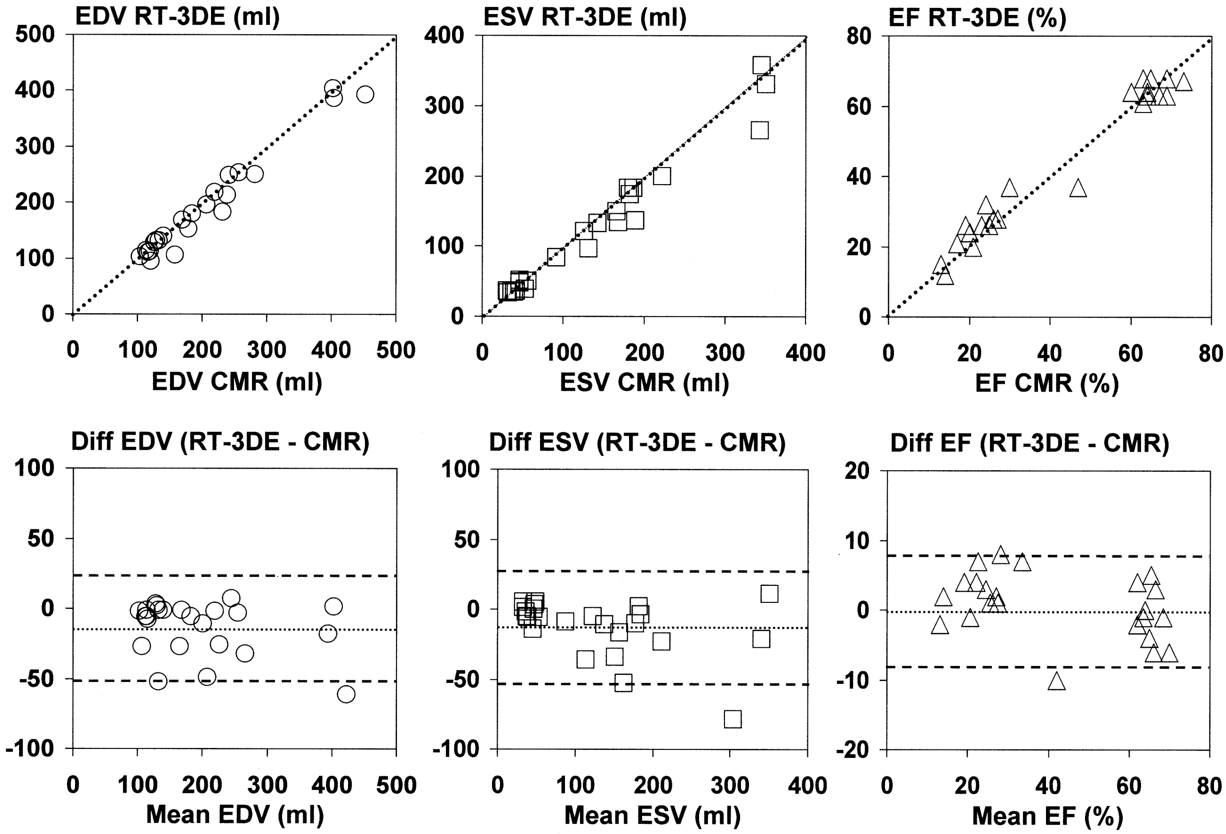

Figure 3. Linear regression plots and Bland-Altman plots for end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF), as assessed with real-time three-dimensional echocardiography (RT-3DE), as compared with cardiovascular magnetic resonance (CMR) imaging as the reference standard.

duration of a complete RT-3DE examination was shorter (5 min on average, including patient preparation), compared with CMRI data acquisition (25 min on average, including patient preparation and acquisition of scout images, reference scans for SENSE technique, as well as planning and acquisition of the stack of short-axis images).

Comparison of the semi-automatic algorithm with manual contour tracing. Results for the comparison between the semi-automatic algorithm and manual contour tracing are summarized in Table 1. Excellent correlation coefficients and acceptable limits of agreement for EDV, ESV, and EF were observed over a wide range of volumes and EF. The time for data analysis averaged 12 ± 5 min for the semi-automatic method and 4 ± 1 min for manual tracing ($p < 0.001$).

Comparison of RT-3DE with semi-automatic border detection and CMRI. Results are summarized in Table 1 and Figure 3. High correlation coefficients and acceptable limits of agreement were observed for volumes and EF. However, RT-3DE significantly underestimated EDV (−13.6 ± 18.9 ml, $p = 0.002$) and ESV (−12.8 ± 20.5 ml, $p = 0.005$), compared with CMRI. In contrast, no bias was noted for EF calculation (0.9 ± 4.4%; p = NS). The analysis time was similar between the two methods (12 ± 5 min for RT-3DE and 14 ± 4 min for CMRI, p = NS).

Observer variability. Results of intra- and inter-observer variability for the semi-automatic algorithm and manual tracing are summarized in Table 2. There were high correlation coefficients and low variability for the results of the same observer and for the results of two different observers. Moreover, variability was comparable between manual border tracing and semi-automatic border detection.

Table 2. Observer Variability for the Semi-Automatic Algorithm and Manual Tracing

	Intra-Observer Variability		Inter-Observer Variability	
	Mean Difference ± SD	r	Mean Difference ± SD	r
Semi-Automatic Algorithm (n = 15)				
EDV (ml)	0.2 ± 6.6	0.99	0.9 ± 6.9	0.98
ESV (ml)	−0.0 ± 3.8	0.98	0.7 ± 9.6	0.97
EF (%)	−0.6 ± 4.1	0.93	−1.5 ± 7.0	0.81
Manual Tracing (n = 15)				
EDV (ml)	1.9 ± 3.9	0.99	2.3 ± 5.3	0.99
ESV (ml)	1.3 ± 4.1	0.98	1.2 ± 6.1	0.97
EF (%)	−0.2 ± 3.5	0.93	−0.4 ± 4.2	0.93

Abbreviations as in Table 1.

Repeatability. Correlation coefficients were high for assessment of volumes and EF between two separate acquisitions (r = 0.99). Moreover, the standard deviations of the differences were similar to those obtained for interobserver variability (EDV ±8.4 ml; ESV ±6.7 ml; EF ±2.7%).

DISCUSSION

The results of this study demonstrate that: 1) acquisition of RT-3DE datasets for volumetric analysis is feasible in patients; 2) there is high concordance between manual and semi-automatic analysis of RT-3DE datasets; and 3) there is good agreement between RT-3DE using semi-automatic border detection and CMRI for the assessment of LV volumes and function. Variability for the semi-automatic border detection algorithm was low and comparable with that by manual tracing. Furthermore, repeatability was excellent, making the method potentially suitable for the serial investigation of patients.

In the last decade, 3DE has been extensively validated in patients for the assessment of volumes and function, using angiography, radionuclide angiography, or CMRI as reference standards (8,9,11,19). Moreover, its superiority over conventional echocardiographic techniques has been convincingly demonstrated (8–11). More recently, the high accuracy of RT-3DE for volumetric analysis of the LV using first-generation, low-resolution matrix arrays has been reported in comparison with CMRI (12,20,21). However, this technology was limited by impaired image quality. Furthermore, the need for laborious manual data analysis still precluded widespread clinical use of the method (22).

The recent introduction of high-resolution RT-3DE using novel, sophisticated matrix array transducer technology has permitted acquisition of RT-3DE datasets with improved image quality. Thus, fast acquisition of high-quality RT-3DE datasets is now possible. Furthermore, a semi-automatic border detection algorithm has been developed that enables data analysis with only minimal interaction by the investigator. The present study demonstrates that RT-3DE, in combination with semi-automatic data analysis, is feasible and accurate for the assessment of LV volumes and function. The results of the present study are in agreement with the results of previous studies using RT-3DE and manual data analysis in patients for the assessment of volumes and function (12,21). Compared with the results obtained by CMRI, underestimation of volumes was observed with RT-3DE and semi-automatic border detection. The main reasons for this finding may be explained by differences in the applied tracing techniques (tracing of long-axis cross sections vs. short-axis cut-planes for RT-3DE and MRI, respectively), variable inclusion of trabeculae with CMRI due to limited spatial resolution and a partial volume effect, and inclusion of the most basal slice in the CMRI analysis, which may lead to inclusion of the atrial volume contained within the funnel formed by the mitral valve leaflets. Moreover, in two patients with severely dilated LVs, the apex was not fully incorporated into the conical imaging sector, which might have contributed to the underestimation of volumes observed with RT-3DE. Underestimation of volumes using RT-3DE compared with CMRI has also been reported by others (12,20,21).

A potential advantage of the semi-automatic algorithm is the fact that volumes are calculated for each acquired time point during the cardiac cycle. This allows for generation of three-dimensional volume-time curves, representing true volume changes over time and which may provide additional quantitative information on systolic and diastolic function of the LV (23). However, this was not the primary focus of the study, and further validation is needed to ensure accuracy of volumes for each time point. Moreover, semi-automatic border detection may allow comprehensive assessment of regional myocardial function, which might be useful to better characterize the extent of ischemically jeopardized or dysfunctional myocardium (24) or to assess regional asynchronicity (25).

Automatic RT endocardial edge detection using echocardiography has been an important goal (26). Previous investigators have used a different approach for semi-automatic border detection, based on acoustic quantification of integrated backscatter combined with three-dimensional reconstruction (27). However, this approach resulted in gross underestimation of volumes, as compared with CMRI. Other investigators have used a different semi-automatic algorithm for the analysis of LV volumes and function (28). Although good agreement with CMRI was demonstrated, this algorithm was limited to the acquisition of three apical orthogonal views. Recently, Corsi et al. (29) reported a method for the semi-automatic analysis of RT-3DE datasets based on level set techniques. They reported an excellent correlation between semi-automatically calculated volumes and manually traced volumes (r = 0.992), which is in line with the results of the current study.

Study limitations. In order to acquire a full-volume dataset that encompasses the complete LV, four high-resolution subvolumes need to be acquired over consecutive heartbeats in a short breath-hold. These subvolumes are subsequently assembled by the computer to build a complete 3DE dataset. Thus, although RT-3DE data acquisition and display are fast (6 to 8 s in the present study), it is not intrinsically RT. Even though data acquisition is steered electronically with the transducer kept in a stable position, the acquisition process is sensitive to heart rate variability and patient compliance. Therefore, patients with arrhythmia (e.g., atrial fibrillation, frequent premature beats) or severe dyspnea, who are incapable of breath-holding, cannot be readily investigated using this technique. However, these patients are also difficult to study with CMRI.

Patients were selected for good image quality and for the presence of sinus rhythm, which must be considered in the interpretation of the results. Because this was a feasibility study, we deliberately excluded patients with poor image quality and arrhythmia. Although the patient population encompassed a wide range of pathologies, including normal hearts and severely dilated LV with poor function, only a limited number of patients were included. Thus, confirmation of our results in a larger cohort of patients is warranted.

Analysis time using the semi-automatic algorithm was longer compared with manual tracing. Yet, analysis was performed without manual interaction, and volumes were obtained for each time frame, potentially providing more information than with manual tracing of only end-diastolic and end-systolic frames. Manual tracing was used for analysis of CMRI data, although semi-automatic algorithms are available. However, as CMRI was considered as the reference standard, unequivocal endocardial contours were required.

Conclusions and clinical implications. The results of the study indicate that RT-3DE, in combination with semi-automatic border detection, allows robust and accurate quantitation of LV volumes and function, compared with both manual tracing and CMRI as the reference standard, over a wide range of volumes and EF. Data acquisition using RT-3DE is easy and faster than with CMRI. The semi-automatic contour detection algorithm allows data analysis with only minimal interaction by the investigator. Therefore, in patients with good image quality, RT-3DE may be an attractive alternative to CMRI for the rapid and accurate quantitation of LV function at the bedside. Moreover, this method might be clinically useful for the accurate quantitation of LV volumes and function in patients with contraindications for CMRI scanning (i.e., pacemakers, defibrillators, claustrophobia). Furthermore, it may be useful for the serial follow-up of patients with valvular heart disease, in whom reliable quantitation of LV function is of clinical importance for the timing of surgery and for patients with heart failure to guide pharmacologic or nonpharmacologic (i.e., biventricular pacing) therapy.

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