

# Validation of a novel automated border-detection algorithm for rapid and accurate quantitation of left ventricular volumes based on three-dimensional echocardiography

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## Aims

To assess the accuracy and reproducibility of a novel automated software for left ventricular (LV) volumes and ejection fraction (EF) measurements using real-time three-dimensional echocardiography (3DE).

## Methods and results

A total of 103 patients with a wide range of LV volumes were analyzed with both 4D AutoLVQ<sup>TM</sup> and 4D TomTec<sup>TM</sup> software. In 23 patients, a side-by-side comparison of LV volume and EF measurements was done between 3DE, 2DE, and cardiac magnetic resonance (CMR). Excellent correlation was found between 4D AutoLVQ and 4D TomTec [ $r = 0.98$  for end-diastolic volume (EDV),  $0.99$  for end-systolic volume (ESV), and  $0.97$  for EF,  $P < 0.0001$ ], with small biases and narrow limits of agreement: EDV  $5.2$  mL ( $-14$  to  $25$  mL), ESV  $2.9$  mL ( $-10$  to  $16$  mL), EF  $-0.2\%$  ( $-7$  to  $6\%$ ). Time of analysis was halved using 4D AutoLVQ with manual correction ( $1$  min  $52$  s  $\pm$   $30$  s) in comparison with 4D TomTec software ( $3$  min  $46$  s  $\pm$   $1$  min  $24$  s). Both softwares showed similar accuracy in comparison with CMR (4D AutoLVQ biases  $-11.0$  mL,  $-9.1$  mL, and  $2.9\%$ ; 4D TomTec biases  $-8.3$  mL,  $-7.4$  mL, and  $2.8\%$  for EDV, ESV, and EF, respectively,  $P = \text{NS}$  for all) and good reproducibility.

## Conclusion

Novel 4D AutoLVQ software showed very good agreement with more time-consuming 4D TomTec software, having similar accuracy against CMR.

## Keywords

Three-dimensional echocardiography • Cardiac magnetic resonance • Left ventricular volumes • Left ventricular function • Left ventricle • Automated border detection

## Introduction

Non-invasive quantitation of left ventricular (LV) size and function is critically important for clinical decision-making and represents the most frequent indication for an echocardiographic study.<sup>1</sup> Conventionally, LV volumes are calculated applying the biplane disc-summation algorithm to LV four- and two-chamber apical views obtained using two-dimensional echocardiography (2DE).

However, quantitative analysis of 2DE is highly experience-dependent and uses only partial information about cardiac anatomy and function contained in pre-defined cross-sectional

views. Therefore, it may be subject to substantial measurement errors, particularly in patients with regional wall-motion abnormalities and/or distorted LV geometry.<sup>2,3</sup> The advent of real-time three-dimensional modality (RT3DE) has significantly improved the accuracy and reproducibility of LV volume, mass, and ejection fraction (EF) measurements.<sup>3–7</sup>

Recent advancements in transducer and ultrasound computer technology allow good-quality wide-angle RT3DE acquisitions to be completed with good feasibility and acceptable temporal resolution. Real-time three-dimensional echocardiography data set analysis can now be performed using computerized automated

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or semi-automated surface detection software with only minimal human intervention throughout the cardiac cycle. The fully automated measurement of LV volumes and EF would be particularly attractive, but previous attempts have been confounded by endocardial border-tracking difficulties<sup>8</sup> or proved to be deceptively inaccurate.<sup>9</sup>

The present study aims to assess the accuracy and reproducibility of the novel 4D AutoLVQ™ software for automated measurement of LV volumes and EF from RT3DE data sets.

## Methods

### Study population

A total of 103 patients referred for routine echocardiography and LV function assessment as main indication for examination were prospectively enrolled in the study. Patients were selected for acceptable image quality, excluding patients with two or more segments not visualized by conventional 2DE and requiring contrast enhancement of endocardial border.<sup>10</sup> Other exclusion criteria included severely dilated LV (those impossible to be completely encompassed in the 3D data set), other than sinus rhythm or significant R-R variability, and unstable clinical conditions that prevent patients from cooperating for breathholding during 3D acquisition. Among the enrolled patients, a subset of 23 patients with clinical indication to cardiac magnetic resonance (CMR) and no exclusion criteria for CMR served as validation subgroup.

All patients gave their informed consent in agreement with the local Ethics Committee of the University Hospital.

### Image acquisition

#### Standard transthoracic two-dimensional echocardiography

Complete routine echocardiographic studies, including four- and two-chamber apical view recordings for LVEF measurement according to current guidelines,<sup>11</sup> were acquired by an experienced sonographer (L.D.M.), using a commercially available Vivid E9 ultrasound machine (GE Healthcare, Horten, Norway) equipped with M5S probe. All patients were examined in the left lateral position using greyscale second-harmonic 2D imaging technique, with the adjustment of image contrast, frequency, depth, and sector size for adequate frame rate and optimal LV border visualization. Care was taken to avoid LV foreshortening in both apical views, and image acquisition was done during breathhold to minimize respiratory movements.

#### Transthoracic real-time three-dimensional echocardiography imaging

Real-time three-dimensional echocardiography data set acquisition of the LV was performed by the same examiner at the end of the standard 2DE examination using a 3V matrix-array transducer (GE Healthcare). A full-volume scan was acquired using second-harmonic imaging from apical approach, and care was taken to encompass the entire LV cavity in the data set. Consecutive four-beat ECG-gated subvolumes were acquired during an end-expiratory apnoea to generate the full-volume data set. The quality of the acquisition was then verified in each patient by selecting nine-slice display mode available on the machine to ensure that the entire LV cavity is included in the RT3DE full volume, and, if unsatisfactory, the data set was re-acquired. Data sets were stored digitally in raw-data format and exported to a separate workstation equipped with commercially available software for offline analysis of LV volumes and EF from 2DE (EchoPAC PC

108.1.4, GE Healthcare) and RT3DE data sets: 4D AutoLVQ™ (GE Healthcare) and TomTec 4D LV function™ (version 2.6, TomTec Imaging Systems, GmbH, Unterschleissheim, Germany).

### Cardiac magnetic resonance

CMR was performed <1 h apart from the echocardiographic examination with a 1.5 T system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) using a previously published protocol<sup>12</sup> based on stacks of 8–12 short-axis slices. Acquisitions were analysed offline using commercially available software (Argus, Siemens Medical Systems) on a standard postprocessing workstation (Leonardo, Siemens Medical Systems).

### Image analysis

Each method used for the off-line LV quantitation (2DE, 4D TomTec, 4D AutoLVQ) was applied independently in all patients, on the digitally stored echocardiographic LV acquisitions analysed in random order. The analysis was done by the same observer (D.M.) blinded to the results obtained with the other methods. In the validation subgroup, CMR offline analysis was done by a different observer (G.P.), independently from the 2DE and RT3DE quantitation performed by the first observer (D.M.).

#### Two-dimensional echocardiography volume measurements

End-diastole and end-systole were identified from 2DE cine-loops using frame-by-frame analysis of the apical four- and two-chamber LV views as the largest and smallest cavity during the cardiac cycle, respectively. Then, tracing of endocardial border was manually done in both frames, paying attention to include the papillary muscles within the LV cavity. Left ventricular ejection fraction was automatically calculated by the software using the biplane disc-summation algorithm (modified Simpson's rule).<sup>11</sup>

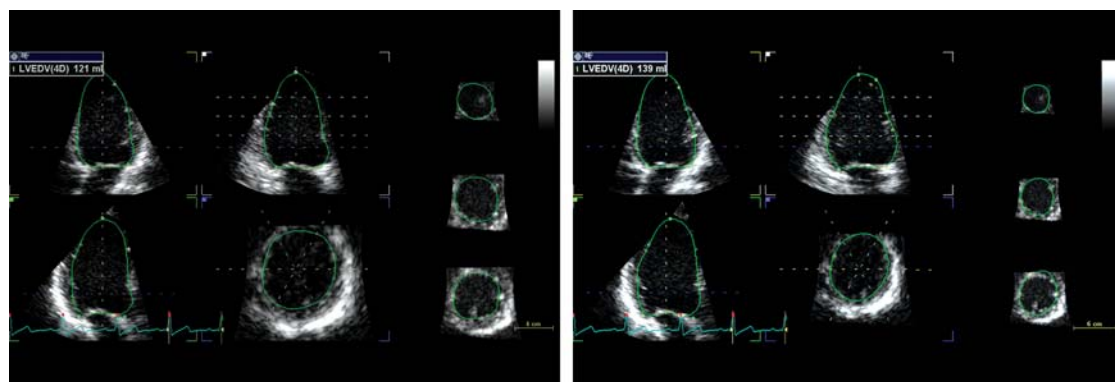
### Real-time three-dimensional echocardiography volume measurements

#### TomTec 4D LV function

Initially, on the basis of manual identification of endocardial border by placing a minimum of five points in each view, LV volume analysis with TomTec software was computed by dynamic semi-automated border detection, as described previously.<sup>13</sup> Border tracing during initialization was done carefully in order to reduce the need of cumbersome and time-consuming frame-by-frame manual contour editing.<sup>14</sup> However, checking border-tracking quality subsequently showed that further adjustments were necessary in most patients. This was done first by varying border-detection sensitivity and, if still necessary, frame-by-frame manual correction of border tracking for each view. Care was taken to trace the endocardial border just outside the apparent blood-tissue interface and to adjust the contour detection sensitivity so that papillary muscles and most endocardial trabeculae were included in the LV cavity. This approach has been demonstrated previously to produce volume measurements, which were better correlated with values obtained by CMR.<sup>15</sup> LV end-diastolic (EDV), end-systolic (ESV) volumes, and EF were derived and recorded for further comparative analysis.

#### 4D AutoLVQ

Left ventricular analysis was performed in random order on the same RT3DE data sets used for volume quantitation by 4D TomTec by completing the following steps.



**Figure 1** Example of fully automated (left) vs. manually corrected (right) endocardial contour on end-diastolic frame in the same patient, using 4D AutoLVQ software. After automatic slicing of real-time three-dimensional echocardiography data set and manual alignment, manual input of apical and mitral annulus reference points is followed by automatic detection of endocardial surface in three dimensions. In this example, manual adjustment by adding a total of four points in order to include most trabeculae in left ventricular cavity increased the volume by 15% automatically measured by the software.

- (i) *Automatic slicing of LV full-volume data set.* The end-diastolic frames needed for contour detection were automatically displayed in quad-view: apical four-, two-chamber, long-axis views and LV short-axis plane (Figure 1). Each longitudinal view was colour-coded and indicated on the short-axis image at 60° between each plane. Both reference frames in the end-systole and end-diastole could be also manually selected, if necessary.
- (ii) *Alignment.* Rapid manual alignment by pivoting and translating the four-chamber plane was first performed in order that the corresponding intersection line of all planes was placed in the middle of the LV cavity, crossing the LV apex and the centre of mitral valve opening in each view. Aligning one plane automatically changed the others. Once LV central longitudinal axis was identified, accurate orientation of LV views was ensured by manual refinement of the angles between the LV planes on the LV short-axis view, in order to correspond to the defining anatomical landmarks of each view.
- (iii) *Left ventricular reference point identification.* To subsequently identify a fitting geometric model, the software required manual input of only three single points for each of the three LV apical planes (two points at mitral annulus borders, and one at the apex) first in end-diastolic frames, and then for corresponding end-systolic frames. Manual positioning of the points was simultaneously shown on the LV short-axis view for guidance in LV endocardial border identification. Furthermore, the apex reference point previously identified on LV longitudinal planes was displayed before adding the apical landmark into the next plane.
- (iv) *Automated identification of endocardial border.* The software automatically detected LV cavity endocardial border in 3D and provided the measured EDV. Three additional short-axis views at different levels were displayed in order to facilitate verification of the accuracy of endocardial surface detection both in cross-section and in long-axis by rotating and translating active view plane (Figure 1). At this stage, LV borders could be manually adjusted, if unsatisfactory, by (dis)placing as many additional points as needed (manually corrected AutoLVQ), with secondary immediate automated refinement of boundary detection accordingly. This could be done on each of the six simultaneously

displayed LV views (Figure 1), but also possible in between reference planes for LV with distorted shape. After completing steps 1–4 for end-diastolic views, only 3–4 sequence was required for end-systolic frames, since adjustments done in steps 1–2 were automatically carried out subsequently in end-systolic views.

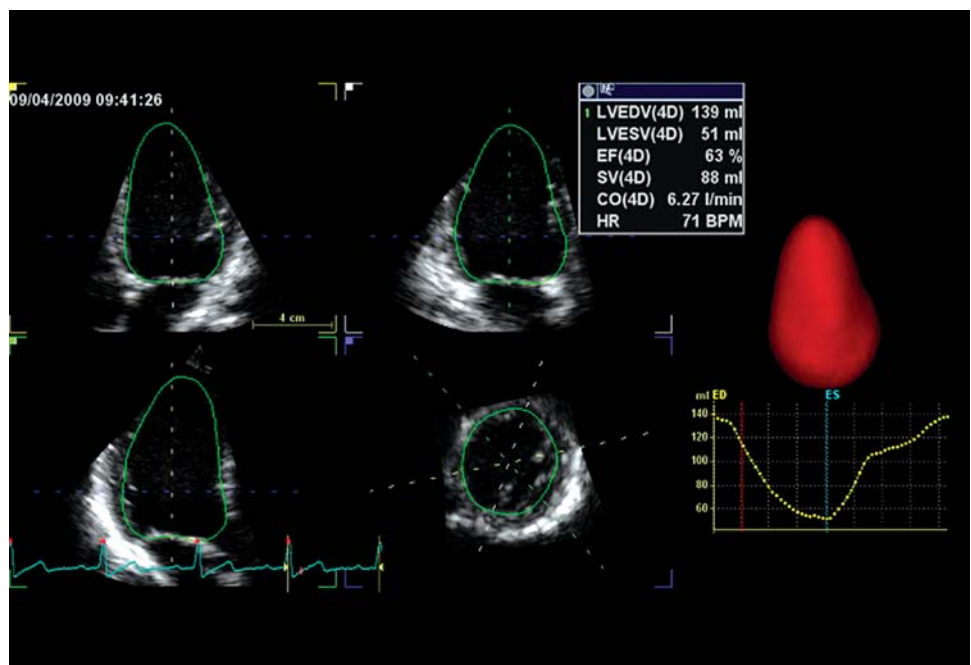
(v) *Final quantitative analysis and data display.* Using the initial contours in both end-systole and end-diastole, a corresponding dynamic surface-rendered LV cast was derived. Final data panel automatically displayed LVEDV, LVESV, LVEF, stroke volume, cardiac output, and heart rate values. A volume–time plot was also provided (Figure 2).

Time consumed to display LVEF of both 4D AutoLVQ and 4D TomTec was measured with a digital stopwatch.

## Statistical analysis

In the whole study population, LV parameters obtained by 4D AutoLVQ were compared with the data derived using 4D TomTec software. In the validation subgroup, head-to-head comparison was done among the various methods: 4D AutoLVQ (manually corrected), fully automated 4D AutoLVQ (with no manual correction), 4D TomTec, 2DE, and CMR.

Data were summarized as the mean  $\pm$  SD. Linear regression analysis was performed, and Pearson correlation coefficients were calculated for the comparison of EDV, ESV, and EF obtained with 4D AutoLVQ, with corresponding values derived by 4D TomTec software, CMR, and 2DE. Bland–Altman analysis<sup>16</sup> was performed to determine the systematic bias and limits of agreement (LA) of LV volumes and LVEF between the various imaging modalities tested. *t*-Test was used to compare time needed to calculate the EF by each method, and to compare mean values for statistical significance. To assess the reproducibility of the volumes measured using 4D AutoLVQ and 4D TomTec algorithms, the data of 23 CMR patients were re-analysed by the same observer (D.M.) at least 1 month after the first measurement, as well as by a second observer (L.P.B.) blinded to the results of the first observer. Both observers were experienced with 4D AutoLVQ and 4D TomTec software. The agreement between repeated measurements was analysed using Pearson correlation coefficient and



**Figure 2** Example of left ventricular endocardial surface reconstruction using 4D AutoLVQ software based on automatically detected endocardial border in three dimensions throughout the cardiac cycle (Supplementary data, Video). Quantitative analysis panel and volume–time plot are provided.

Bland–Altman analysis. Intra-observer and inter-observer reproducibility were also reported as the absolute difference of the corresponding pair of repeated measurements normalized to their average value in each patient and expressed as mean  $\pm$  SD for the entire subgroup. To compare the variability of the LV volumes and EF obtained using 4D AutoLVQ and 4D TomTec software, coefficient of variation was used by computing SD as per cent of the mean value for each technique in the validation subgroup.<sup>17</sup> *P*-value  $<0.05$  was considered statistically significant. Data analysis was performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA) and MedCalc for Windows, 8.1.1.0 release (Mariakerke, Belgium) statistical software.

Results

A total of 103 patients with various heart diseases and a wide range of LV volumes and LVEF at 2DE were enrolled in the study (Table 1). Average image frame-rate for 2DE was  $63 \pm 14$  fps (frames per second), whereas four-beat RT3DE data sets were acquired at a mean temporal resolution of  $52 \pm 16$  vps (volumes per second) in the entire study population and  $60 \pm 11$  vps in the CMR subgroup. There were 63 patients ( $54 \pm 18$  years old, 44% men) with normal LVEF ( $\geq 50\%$ ) assessed by 2DE, and 40 patients ( $66 \pm 12$  years, 63% men) with various degrees of LV dysfunction. Manual border initialization of LV endocardial surfaces and subsequent automated endocardial border tracking throughout the cardiac cycle were successful for all RT3DE data sets.

**Table 1** Clinical and echocardiographic characteristics of the study population

	<i>n</i> = 103
Age (years)	58 $\pm$ 17
Males (%)	52
BSA (m <sup>2</sup> )	1.79 $\pm$ 0.27
BMI (kg/m <sup>2</sup> )	25 $\pm$ 4
HR (bpm)	68 $\pm$ 11
LV parameters	
EDV (mL)	116 $\pm$ 49 (range 57–336)
ESV (mL)	61 $\pm$ 44 (range 19–278)
EF (%)	51 $\pm$ 14 (range 17–69)
Indication for echo study (%)	
Ischaemic heart disease	23
Hypertensive heart disease	15
Non-ischaemic dilated cardiomyopathy	14
Valvular heart disease	10
Aortic pathology	10
Anthracycline toxicity monitoring	9
Transplanted heart	4
Other	15

BSA, body surface area; BMI, body mass index; HR, heart rate; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.

The means  $\pm$  SD for LV volumes and EF obtained with each method in the validation subgroup are presented in Table 2.

## Time of analysis

Time from beginning the offline data set analysis (excluding time required for uploading images from server to workstation, which depends on computer performance, number and type of digitally stored recordings within one examination, and number of examinations per selected patient) was significantly shorter using 4D AutoLVQ than 4D TomTec software (1 min 52 s  $\pm$  30 s vs. 3 min 46 s  $\pm$  1 min 24 s,  $P < 0.0001$ ). Manual optimization of boundary detection with 4D AutoLVQ required the addition of a mean of nine points (range 3–14) after automatic processing. Manual adjustments slightly increased the analysis time in comparison with fully automated 4D AutoLVQ (requiring only 48  $\pm$  24 s) but significantly added in measurement accuracy (see what follows).

CMR measurements were obtained by manual endocardial border tracing on LV short-axis slices and required a mean time of 10 min (range 7–13).

## Comparison of fully automated AutoLVQ with other methods

In the subgroup of 23 patients who underwent clinically indicated CMR, mean LV volumes and LVEF at 2DE were similar to those averaged over the remaining 80 patients (108  $\pm$  31 vs. 105  $\pm$  49 mL for EDV; 48  $\pm$  17 vs. 45  $\pm$  43 mL for ESV; and 56  $\pm$  9 vs. 56  $\pm$  14% for EF;  $P = \text{NS}$  for all).

Pearson correlation coefficients and LA between 4D AutoLVQ with no manual editing of automated endocardial detection (fully automated 4D AutoLVQ) and the other methods are shown in Table 3. Fully automated 4D AutoLVQ analysis of RT3DE data sets produced a systematic underestimation of LV volumes and EF. Correlations between fully automated and manually corrected 4D AutoLVQ were less closer than expected ( $r < 0.90$  for all LV parameters), indicating a non-systematic bias between the two. Bland–Altman analysis showed a significantly higher bias for EDV and wider LA with CMR for ESV ( $P < 0.001$  for both) obtained with fully automated 4D AutoLVQ in comparison with those obtained with manually corrected 4D AutoLVQ. The correlation of LV volumes obtained with fully automated 4D AutoLVQ and CMR was significantly weaker than the correlation between manually corrected 4D AutoLVQ and CMR (Tables 3 and 4). Fully automated 4D AutoLVQ approach also showed a lower agreement with 4D TomTec and 2DE values than manually corrected 4D AutoLVQ ( $P < 0.05$  for all).

Therefore, all further results are related to LV volumes, and EF was obtained with manually corrected 4D AutoLVQ analysis.

## Comparison of 4D AutoLVQ and other methods with cardiac magnetic resonance

Table 4 summarizes the head-to-head comparison of 4D AutoLVQ measurements with those obtained from 2DE, 4D TomTec, and CMR. 4D AutoLVQ measurements showed a close correlation with CMR measurements, despite a small systematic

**Table 2** Comparison of left ventricular volumes and ejection fraction of the 23 patients in the validation group with the results of cardiac magnetic resonance (means  $\pm$  SD)

<i>n</i> = 23	2DE	Corrected 4D AutoLVQ	Fully automated 4D AutoLVQ	4D TomTec	CMR
EDV (mL)	110 $\pm$ 30*	126 $\pm$ 34	104 $\pm$ 30*	129 $\pm$ 34	137 $\pm$ 36
ESV (mL)	49 $\pm$ 17*	56 $\pm$ 20	51 $\pm$ 17*	58 $\pm$ 21	65 $\pm$ 20
EF (%)	55 $\pm$ 9	56 $\pm$ 8	52 $\pm$ 7	56 $\pm$ 8	53 $\pm$ 8

EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; 2DE, two-dimensional echocardiography; CMR, cardiac magnetic resonance.

\* $P \leq 0.01$ , paired *t*-test compared with CMR values.

**Table 3** Linear regression and Bland–Altman analyses for left ventricular volumes and ejection fraction obtained using fully automated 4D AutoLVQ in comparison with manually corrected 4D AutoLVQ and the other methods in the validation group

<i>n</i> = 23	2DE		Corrected 4D AutoLVQ		4D TomTec		CMR	
	<i>r</i>	Bias (LA)	<i>r</i>	Bias (LA)	<i>r</i>	Bias (LA)	<i>r</i>	Bias (LA)
EDV (mL)	0.91	−10.2 (−35 + 15)	0.89	−21.3 (−53 + 10)	0.88	−24 (−57 + 9)	0.77	−32.3 (−75 + 10)
ESV (mL)	0.93	−0.7 (−15 + 13)	0.83	−4.8 (−28 + 18)	0.82	−6.5 (−31 + 18)	0.72	−13.9 (−44 + 16)
EF (%)	0.80	−3.8 (−15 + 7)	0.75	−4.4 (−15 + 6)	0.75	−4.3 (−15 + 6)	0.64*	−1.5 (−14 + 11)

EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; 2DE, two-dimensional echocardiography; CMR, cardiac magnetic resonance; LA, limits of agreement; *r*, Pearson correlation coefficient.

$P < 0.0001$  for all, except \* $P = 0.001$ .



**Table 4** Linear regression and Bland–Altman analyses for left ventricular volumes and ejection fraction obtained using manually corrected 4D AutoLVQ in comparison with the other methods in the 23 patients of the validation group

<i>n</i> = 23	2DE		4D TomTec		CMR	
	<i>r</i>	Bias (LA)	<i>r</i>	Bias (LA)	<i>r</i>	Bias (LA)
EDV (mL)	0.89	13.8 (−15.4 + 43)	0.98	−2.7 (−14.9 + 9.5)	0.93	−11.0 (−34.7 + 12.7)
ESV (mL)	0.87	6.8 (−11.6 + 25.3)	0.98	−1.7 (−9.8 + 6.4)	0.95	−9.1 (−23.0 + 4.8)
EF (%)	0.93	−0.5 (−7.4 + 6.4)	0.95	−0.1 (−4.8 + 5.1)	0.85	2.9 (−5.2 + 11.1)

Abbreviations as in Table 3.  
*P* < 0.0001 for all.

**Table 5** Relative standard deviation (coefficient of variation) of left ventricular volumes and ejection fraction measured with the various methods in the 23 patients of the validation group

<i>n</i> = 23	2DE	Corrected 4D AutoLVQ	Fully automated 4D AutoLVQ	4D TomTec	CMR
EDV (mL)	27	27	29	26	26
ESV (mL)	35	36	33	36	31
EF (%)	16	14	13	14	15

Abbreviations as in Table 3.

**Table 6** Linear regression and Bland–Altman analyses for left ventricular volumes and ejection fraction using cardiac magnetic resonance as reference for comparison of 2DE, manually corrected 4D AutoLVQ, and 4D TomTec values in the validation group

<i>n</i> = 23	2DE		Corrected 4D AutoLVQ		4D TomTec	
	<i>r</i>	Bias (LA)	<i>r</i>	Bias (LA)	<i>r</i>	Bias (LA)
EDV (mL)	0.88	−26 (−61 + 9)	0.93	−11 (−35 + 13)	0.96	−8 (−27 + 11)
ESV (mL)	0.86	−17 (−42 + 8)	0.95	−9 (−23 + 5)	0.94	−7 (−20 + 6)
EF (%)	0.83	4.3 (−7 + 14)	0.85	2.9 (−5 + 11)	0.85	2.8 (−6 + 11)

Abbreviations as in Table 3.  
*P* < 0.0001 for all correlations.

underestimation of both volumes and a small overestimation of EF (Table 4). Calculated coefficients of variation for each method used to assess LV volumes and EF are displayed in Table 5.

The correlation coefficients and LA of 4D AutoLVQ with CMR were similar to those derived from the comparison of 4D TomTec analysis against CMR (Table 6).

### Comparison of 4D AutoLVQ with 4D TomTec

In the entire study population, 4D AutoLVQ and 4D TomTec software yielded similar results for LV parameters derived from RT3DE data sets: 124 ± 54 vs. 119 ± 54 mL for EDV, 65 ± 47 vs. 62 ± 46 mL for ESV, and 51 ± 13 vs. 51 ± 13%, respectively (*P* = NS for all).

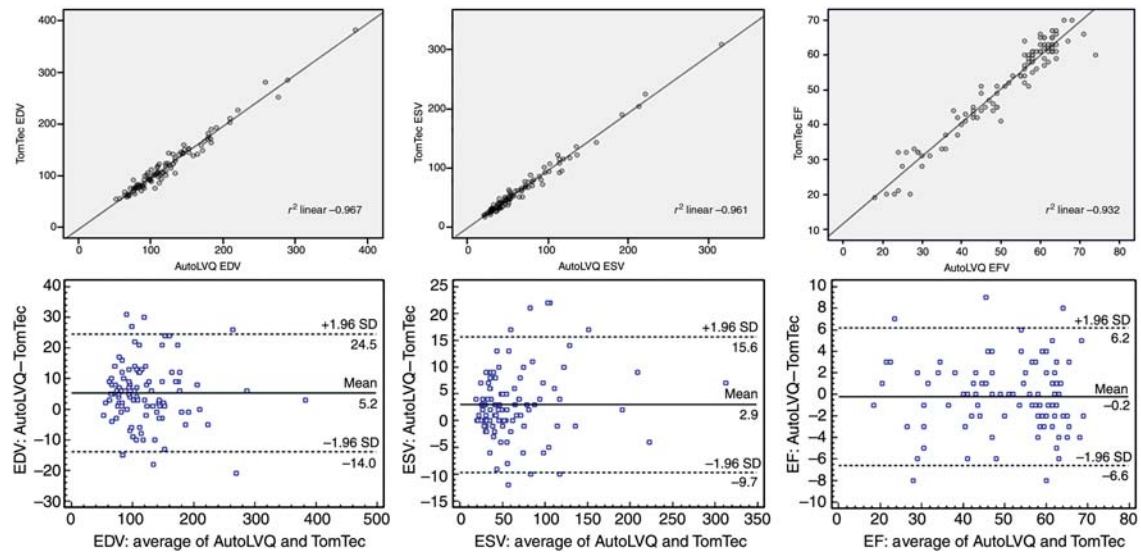
Linear regression analysis showed that there was an excellent correlation between 4D AutoLVQ and 4D TomTec for all LV

parameters: *r* = 0.98 for EDV, *r* = 0.99 for ESV, and *r* = 0.97 for EF (*P* < 0.0001 for all). Bland–Altman analysis resulted in a close agreement of LV volumes and EF measurements obtained using the two software, with small biases and narrow LA (Figure 3).

### Reproducibility

Intra-observer and inter-observer variability for 4D AutoLVQ measurements in comparison with other methods are displayed in Table 7.

In Bland–Altman analysis, the intra-observer and inter-observer agreements, expressed in terms of the mean difference ± 2 SD (upper and lower LA) for 4D AutoLVQ were: 1.3% (−10 to 12%) and 3.4% (−12 to 19%) for EDV, 0.8% (−13 to 15%) and 0.7% (−31 to 30%) for ESV, 1.4% (−10 to 8%) and 5.3% (−19 to 9%) for EF, respectively.



**Figure 3** Linear regression (top) and Bland–Altman analysis plots (bottom) for comparison between measurements of end-diastolic volume (EDV) (left), ESV (middle), and left ventricular ejection fraction (LVEF) (right) obtained with manually corrected 4D AutoLVQ and 4D TomTec software. In upper panels, scatter plots with regression line illustrating the close correlation of the two software measurements. In lower panels, the solid horizontal line in each plot represents the mean systematic difference (bias) between the two methods, whereas the dashed lines indicate the limits of agreement (95% confidence interval of differences).

**Table 7** Inter- and intra-observer variability in left ventricular volumes and ejection fraction obtained with 4D AutoLVQ and 4D TomTec

n = 23	Corrected 4D AutoLVQ			4D TomTec		
	r	Mean ± SD (%)	Range (%)	r	Mean ± SD (%)	Range (%)
EDV (mL)						
Intra-observer	0.99	3.6 ± 2.8	1.5–9	0.99	3.0 ± 2.5	0–10
Inter-observer	0.99	6.1 ± 5.9	0.3–20	0.99	10.3 ± 8.3	1.3–25
ESV (mL)						
Intra-observer	0.99	5.7 ± 3.2	0–14	0.99	4.9 ± 3.5	0–15
Inter-observer	0.99	9.7 ± 11.8	0–30	0.99	11.6 ± 8.3	1.3–26
EF (%)						
Intra-observer	0.95	3.8 ± 2.8	0–10	0.96	2.5 ± 2.6	0–9
Inter-observer	0.98	6.5 ± 6.0	0–18	0.98	4.6 ± 4.3	0–15

Abbreviations as in Table 3.  
P < 0.0001 for all correlations.

4D TomTec limits of intra-observer and inter-observer agreements for EDV, ESV, and EF between repeated measurements were: 1.4% (–8 to 6%) and 7.5% (–30 to 15%), 0.2% (–12 to 12%) and 7% (–32 to 18%), 0.1 (–7 to 7%) and 1.1% (–11 to 14%), respectively. Both intra- and inter-observer agreements of the LV measurements were not statistically different (P = NS for all) with 4D AutoLVQ and 4D TomTec, except for a higher inter-observer reproducibility of EF for 4D TomTec (P = 0.033).

Discussion

The results of our study demonstrate that: (i) automated quantification of LV volumes using 4D AutoLVQ is feasible with high concordance with those measured using the well-validated 4D TomTec software,<sup>7,13,18,19</sup> and similar accuracy of both software in comparison with CMR; (ii) measurements of LV volumes using 4D AutoLVQ are significantly faster and with similar reproducibility in comparison with 4D TomTec; (iii) fully automated

measurements with no manual correction of LV volumes using 4D AutoLVQ produce an underestimation of LV volumes in comparison with manually corrected 4D AutoLVQ and CMR.

4D AutoLVQ software is a high-performance recently developed computer algorithm that relies on artificial intelligence and pattern recognition. Therefore, it is supposed to require minimal human interaction for time-saving and reproducible processing of 3D LV full-volume data sets. The background assumption is that in apical views, when the ultrasound beam is parallel with LV walls, the apex and insertion points of the mitral valve are the only good reflector points and may represent key point references for automated cardiac silhouette delineation.<sup>20</sup> This principle is exploited by the tested software and contributes to the good reproducibility of the measurements, although the identification is done on still frames.

Recently, Hansegård et al.<sup>14</sup> have also demonstrated high agreement between 4D AutoLVQ and 4D TomTec software for LV volume quantitation in a small population of 35 patients. Our results corresponding to a larger population study expand their observation showing a non-significant systematic bias of LV volumes obtained with 4D AutoLVQ when compared with 4D TomTec, but with narrower LA than those found by Hansegård et al.<sup>14</sup> The latter may be explained by the fact that we applied the sensitivity-tracking adjustments and contour manual editing when using 4D TomTec software. In addition, we compared the accuracy of both software against current CMR reference standard and found similarly good accuracy for both. Finally, we have also demonstrated that 4D AutoLVQ software provides a rapid LV analysis with superior accuracy in comparison with conventional 2DE approach.

In our study, fully automated use of 4D AutoLVQ (i.e. with no manual correction of automatic endocardial border tracking) proved to be significantly less accurate than the manually corrected one, especially when compared against methods with demonstrated high accuracy for LV quantitation, like CMR and 4D TomTec. Despite the low biases between fully automated and manually corrected 4D AutoLVQ for EF and ESV measurements, the significantly wide LA for all LV parameters stand for a less systematic measurement error of the fully automated approach. Human border verification and subsequent manual correction of endocardial contours lowered the bias for LV volumes and significantly narrowed the LA with CMR and 4D TomTec for all LV parameters. Automatic algorithms tend to be more reproducible than those requiring various manual interventions from the operator, however at the expense of a significantly lower accuracy of the former.

Present study results support the previously demonstrated underestimation of LV volumes with both 2DE and 3DE in comparison with CMR.<sup>13,17,21</sup> Unfortunately, no imaging modality for measuring LV volumes in humans is error-free, which leaves us no ideal alternative. Although CMR is considered the reference standard for this purpose because of its higher image quality and reproducibility, several sources of error and variability raise questions about its role as 'gold standard'<sup>22</sup>: (i) by using discrete fixed slices, it disregards through-plane motion due to LV systolic shortening; (ii) the poor endocardial definition near the apex due to partial-volume artefacts affects the inter-measurement

reproducibility<sup>18</sup>; and (iii) it relies solely on operator's manual tracing<sup>17</sup> or choice criteria for inclusion of basal slices. Although CMR has a higher reproducibility than RT3DE, Mor-Avi et al.<sup>15</sup> recently reported practically no difference between 3DE and CMR values for LV volumes when the same software analysis is applied for quantitation and trabeculae are excluded from CMR volume cavity.

The issue of whether to include or not the trabeculae and the papillary muscles in the LV cavity is still open for debate. Even if it would be reasonable not to do so in order not to overestimate blood volume, the inclusion approach with CMR proved to be more reproducible both for LV volume and mass,<sup>23</sup> and we adopted this convention for a consistent analysis with all methods. Moreover, LV volume analysis with both 4D AutoLVQ and 4D TomTec was done so that in both initialization and manual editing steps the LV cavity delineation was outward the black-white (blood-trabecular) interface. This was necessary because the insufficient spatial resolution of the 3D data sets in comparison with CMR precluded the accurate discrimination between true endocardium and trabeculations. This approach has been reported to improve the agreement of RT3DE quantification of LV volumes with CMR.<sup>15</sup> Lowering border-detection sensitivity with 4D TomTec software was also applied for the same purpose.

Previous studies have shown that combination of RT3DE with semi-automated border detection is time-saving in comparison with manual tracing of 3DE, although providing a significant underestimation of LV volumes with respect to CMR.<sup>24</sup> We found that analysis time using manually corrected 4D AutoLVQ is halved in comparison with 4D TomTec software, with no significant difference in accuracy and reproducibility. This finding, along with the good agreement with CMR and high reproducibility, implies that this automated novel software may become a clinically useful method for LV assessment from RT3DE data sets whether on board or on workstation. Time-saving approaches for LV quantitation will eventually become a prerequisite in busy echocardiographic laboratories for an increased efficiency and quality of patient care. This will hopefully improve also the agreement between the data from core laboratories with the ones provided by local investigators sites in large-scale clinical trials.<sup>20</sup>

The fully automatic approach for LV quantitation would be an ultimate goal. However, our results demonstrated that the fully automated use of 4D AutoLVQ produced substantial, clinically meaningful error, especially since it does not adequately or predictably include trabeculae or papillary muscles. Similarly with the low agreement reported for the fully automated 2DE measurement of LV parameters in comparison with CMR,<sup>9</sup> we found that despite a non-significant difference of EF between fully automated AutoLVQ and CMR when overall mean values were compared, the correlation between the two measurements was only modest. Moreover, both EDV and ESV volumes were markedly underestimated, although in a lower extent than previously reported with 2D-based automatic approach.<sup>9</sup> From our experience, the relative error is higher in small hypertrophied or distorted-shape ventricles. Therefore, although a fully automated processing for LV quantitation may be allowed by current RT3DE software, present evidence supports that one should not



'skip' the border-tracking verification step required for quality checking and manual adjustment.

Previously reported data on RT3DE reproducibility covered a wide range, from as low as  $0 \pm 3.8$  and  $0.7 \pm 9.6\%$  for intra- and inter-observer ESV variability<sup>25</sup> to  $6 \pm 7.3$  and  $15 \pm 8.8\%$ .<sup>14</sup> In our sample group, we found evidence for an acceptable inter-observer reproducibility for both 4D AutoLVQ and 4D TomTec software, with no statistically significant variability difference in LV volume measurement between the two software. Yet, it is worth noting that, in individual patients, variability levels were quite high for both RT3DE software (particularly for inter-observer reproducibility, wide ranges up to 30%), possibly affecting the reported results of this study. However, significantly larger values (range 0–70% for inter-observer and 0–62% for intra-observer variability) were reported previously in a study specifically designed to investigate sources of error for RT3DE quantitation.<sup>15</sup> Since no relation with different expertise level was demonstrated, further studies addressing other possible confounders are warranted before the implementation of RT3DE for clinical decision making in the single patient.

## Limitations

Patients were selected for good image quality and sinus rhythm, as well as cooperation for breathholding. Selection criteria bias is inherent to RT3DE method itself, yet our results may not apply to the common unselected population. Confirmation of our results in a larger cohort of patients is warranted.

In the present study, data comparison with standard reference method was available in a limited subset of patients (22%) who had clinical indication of CMR study. However, there was no significant difference for LV dimensions and functions assessed by 2DE in the CMR subgroup in comparison with the corresponding values of the study population. Therefore, the CMR patients served as sample group for validation, method comparison, and reproducibility assessment.

High image quality is a prerequisite for any border-detection method and no less dependent on the operator's expertise in image acquisition. Both acquisitions and data set analysis were done by experienced operators after completing the corresponding learning curve for RT3DE data set recording and post-processing and after becoming familiarized with all software facilities. A superior reproducibility for inexperienced readers of the automated vs. manually measured LVEF by Simpson's method was demonstrated previously,<sup>26</sup> yet the impact of operator's experience with 4D AutoLVQ software analysis was beyond the scope of our study.

## Conclusions

The results of this study indicate that novel 4D AutoLVQ software based on automated border detection represents an accurate and rapid method to quantitate LV volumes and EF from RT3DE data sets when compared with CMR and previously validated 4D TomTec software. In patients who fulfil the criteria of being good candidates for an RT3DE study based on image quality, cooperation, and rhythm regularity, on-board 4D AutoLVQ may be an attractive alternative to more time-consuming offline analysis modalities. However, human verification and manual adjustments

are highly important for a reliable LV quantitation with available automated or semi-automated border-tracking algorithms designed for RT3DE.

## Supplementary data

Supplementary data are available at European Journal of Echocardiography online.

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