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Three-dimensional echocardiographic quantification of the left-heart chambers using an automated adaptive analytics algorithm: multicentre validation study

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Aims Although recommended by current guidelines, adoption of three-dimensional echocardiographic (3DE) chamber quantification in clinical practice has lagged because of time-consuming analysis. We recently validated an automated algorithm that measures left atrial (LA) and left ventricular (LV) volumes and ejection fraction (EF). This study aimed to determine the accuracy and reproducibility of these measurements in a multicentre setting.

Methods and results 180 patients underwent 3DE imaging (Philips) at six sites. Images were analysed using automated HeartModel (HM) software with endocardial border correction when necessary and by manual tracing. Measurements were performed by each site and by the Core Laboratory (CL) as the reference. Inter-technique comparisons included HM measurements by the sites against manual tracing by CL, and showed strong correlations (*r*-values: LVEDV: 0.97, LVESV: 0.97, LVEF: 0.88, LAV: 0.96), with the automated technique slightly underestimating LV volumes (biases: LVEDV: -14 ± 20 ml, LVESV: -6 ± 20 ml), LVEF (-2 ± 7%) and LAV (-9 ± 10 ml). Intra-technique comparisons included HM measurements by the sites against CL, with and without corrections. Corrections were unnecessary or minimal in most patients, and improved the measurements only modestly. Comparisons without corrections showed perfect agreement for all parameters. With corrections, correlations were better (*r*-values: LVEDV: 0.99, LVESV: 0.99, LVEF: 0.94, LAV: 0.99) and biases (LVEDV: -8 ± 12 ml, LVESV: -6 ± 12 ml, LVEF: 1 ± 5%, LAV: -10 ± 6 ml) smaller than in inter-technique comparison. All automated measurements with corrections were more reproducible than manual measurements.

Conclusion Automated 3DE analysis of left-heart chambers is an accurate alternative to conventional manual methodology, which yields almost the same values across laboratories and is more reproducible. This technique may contribute towards full integration of 3DE quantification into clinical routine.

Keywords 3D echocardiography • cardiac chamber quantification • automated analysis • multicentre study

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Introduction

Over the past decade, real-time three-dimensional (3D) imaging has become an integral part of the echocardiography landscape because of its proven advantages over two-dimensional (2D) imaging in multiple areas. With the wide availability of 3D echocardiography (3DE) equipment and analysis software and the rapidly growing body of knowledge, this novel methodology is earning its place as the new standard in many areas. One area where its advantages over 2D echocardiography (2DE) are particularly well established is the quantification of cardiac chambers' size and function, with benefits of increased accuracy and improved clinical prognostic significance. This is because the 3DE approach does not rely on geometric assumptions and thus avoids the risk of underestimating chamber volumes because of the use of foreshortened views,[1–3] which are common with 2DE. Because the use of the additional dimension translates into improved accuracy and reproducibility, recently published guidelines recommend the use of 3DE quantification of left-heart chambers when possible.[4] However, the current software implementation of this approach relies on extensive user input, making it time consuming, which adversely affects the workflow of a busy clinical laboratory. As a result, this methodology has not been widely embraced nor fully integrated into the routine clinical work in most centres,[1,5,6] which continue to rely on traditional, frequently qualitative 2DE assessment of cardiac function.

To bridge this gap between available technology and routine clinical work, we recently tested the feasibility of a new automated approach for left-heart chamber quantification based on an adaptive analytics algorithm, which was trained on a large number of 3DE datasets obtained in patients with a variety of normal and abnormal hearts, including common asymmetric left ventricular (LV) shapes, but excluding aneurysms (*Figure 1*). In a single-centre study, we showed good accuracy and reproducibility, and improved speed of analysis, compared with the conventional 3DE methodology.[7] As the development of the algorithm continued, multiple refinements were made, resulting in improved endocardial boundary detection that requires minimal to no manual corrections, as well as improved ability to analyse a larger percentage of the patient population. We hypothesized that in its current form, the automated 3DE analysis that simultaneously quantifies LV and left atrial (LA) volumes and LV ejection fraction (EF) would universally provide accurate and reproducible measurements, and would therefore be suitable for widespread clinical use. To test this hypothesis, we designed a prospective validation study with a standardized protocol in a multicentre setting. The validation included comparisons of the automated measurements made by the participating sites with and without corrections against two sets of reference values, both generated by trained personnel at a highly experienced Core Laboratory (CL): (i) conventional 3DE chamber quantification methodology (inter-technique comparisons), and (ii) the new automated measurements (intra-technique comparisons).

Methods

Population and study design

We studied patients referred for clinically indicated echocardiograms for a wide range of suspected cardiovascular conditions, who underwent transthoracic 2DE and 3DE imaging at six institutions. Participating sites underwent brief training by the developers of the new software in both 3DE image acquisition and analysis. The protocol was approved by the institutional review board of each participating institution. Written informed consent was obtained from each patient.

Each institution enrolled 30 patients into four groups defined according to the biplane 2DE LVEF (group 1 ≤20%, group 2 = 21–40%, group 3 = 41–55%, group 4 >55%), to ensure a wide range of chamber size and function. Exclusion criteria were: complex congenital heart disease, history of mechanical valve replacement, pacemaker or defibrillator leads, arrhythmia during acquisition, moderate or severe right ventricular enlargement, LV aneurysm, and poor quality images, defined as poor endocardial visualization on 2DE or 3DE in >2 contiguous segments using a 17-segment model. Patients with common asymmetric ventricular shapes were not excluded from the study. All images were submitted to the CL at the University of Chicago for quality approval. Studies with incomplete acquisitions, corrupt files, missing images, or studies not fully compliant with the inclusion criteria were rejected, and the site was asked to enrol another patient into the same slot.

3DE images of patients approved by the CL ($N = 180$, age 57 ± 18 years, 66% men and 34% women, body surface area 1.80 ± 0.29 m^2, see *Table 1* for clinical characteristics) were analysed by both the enrolling site and the CL to measure LV volumes and EF and LA volume (LAV) using two 3DE techniques: the conventional manual analysis and the new automated analysis. These measurements were used for the aforementioned inter- and intra-technique comparisons. In addition, to determine the effects of the choice of a cardiac cycle for analysis, we analysed two different cardiac cycles in a randomly selected subgroup of 60 patients using the fully automated approach without any manual corrections. Finally, reproducibility of both the new technique and the conventional methodology in our study population was assessed using blinded repeated measurements.

Echocardiographic imaging

Imaging was performed using the EPIQ system (version 1.3 or greater, Philips Medical Systems, Andover, MA, USA) and an X5-1 phased-array transducer with the patient in the left lateral decubitus position. Before each acquisition, images were optimized for endocardial visualization by modifying the gain, compress, and time gain-compensation controls. Image acquisition included: (i) 2DE images in the apical 2- and 4-chamber views containing six cardiac cycles in each view, and (ii) a wide-angled 'full-volume' 3DE datasets of one cardiac cycle each from the apical position during a single breath-hold (HM ACQ key on EPIQ 7C). Care was taken to include the entire LV and LA cavity within the 2DE and 3DE images. Images were optimized to obtain the highest possible frame rate.

2DE image analysis

2DE images collected at all sites were initially analysed by each site using standard methodology. In each view (apical 2- and 4-chamber), the LV end-diastolic (ED) and end-systolic (ES) frames were chosen with the corresponding largest (the first frame after mitral valve closure) and smallest (the frame after aortic valve closure) LV cavity, respectively. In these frames, LV boundaries were manually traced in both views to obtain ED and ES volumes (EDV, ESV) and EF was calculated using the biplane method of disks. These EF values were used to enrol patients into particular slots in the four groups described above.

3DE image analysis

All 3DE images were reviewed by the enrolling site to select the best dataset, which was analysed by both the site and the CL. Measurements were performed by independent experienced

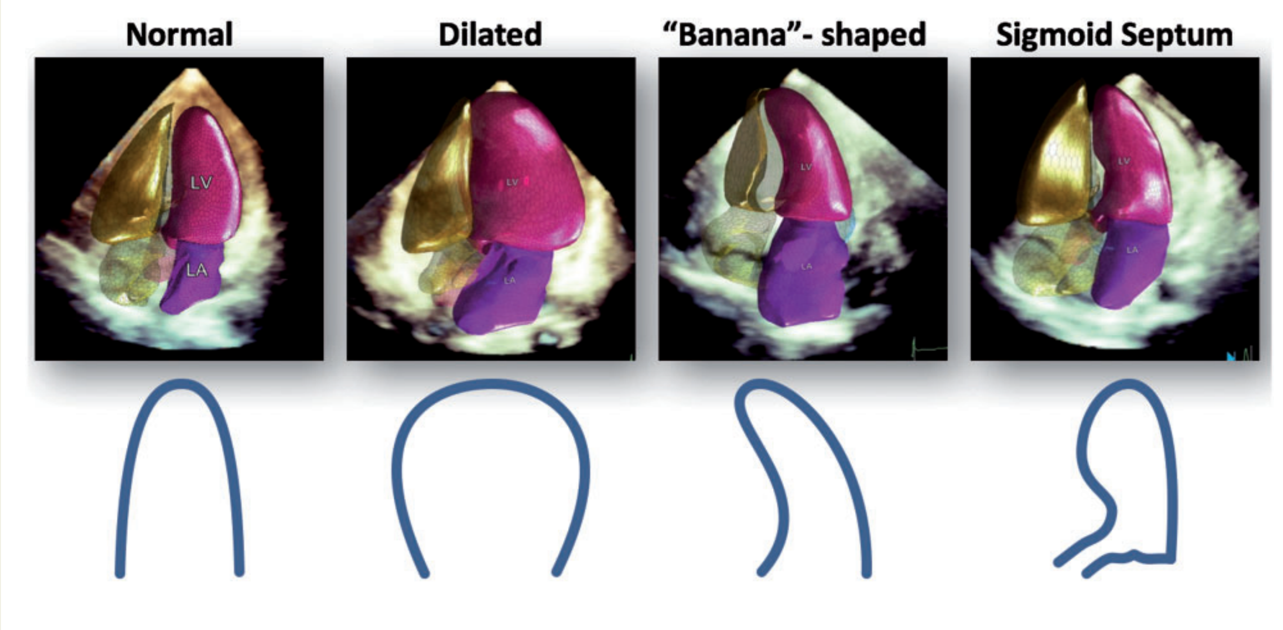

Figure 1 Different left ventricular shapes that the automated software was trained to recognize. In addition to normal ventricles, the training set included a number of common abnormal/asymmetrical ventricular shapes. (Note that the program displays RV and RA casts but no volume values are provided because they have not been validated).

Table 1 Clinical characteristics of the 180 study patients

	Hypertension (0 = no, 1 = yes)		Coronary artery disease (0 = no, 1 = yes)		Cardiomyopathy (0 = no, 1 = Ischemic, 2 = Idiopathic)		Valvular heart disease (0 = no, 1 = yes)		Congenital heart disease (0 = no, 1 = yes)		Arrhythmia (0 = no, 1 = yes)	
	#	%	#	%	#	%	#	%	#	%	#	%
0	86	48%	120	67%	66	37%	160	89%	176	98%	151	84%
1	94	52%	60	33%	54	30%	20	11%	4	2%	29	16%
2					60	33%						

investigators and included: LV EDV, ESV, EF, and LAV at end-ventricular systole by two 3DE techniques: the new automated analysis (Philips, HeartModel (HM)) and the conventional manual analysis (Philips, 3DQ). In each case, the reader was blinded to the results of all previous analyses.

A: Automated 3DE LV and LAV measurements

The automated 3DE software was described in our recent publication.[7] Briefly, the software simultaneously detects LV and LA endocardial surfaces using an adaptive analytics algorithm, which uses knowledge-based identification to orient and locate chambers and patient specific adaptation of endocardial borders. The algorithm automatically identifies the ED and ES phases of the cardiac cycle, and creates ED and ES 3D casts of the LV cavity and an ES cast of the LA cavity, from which LV and LAVs are derived directly without geometric assumptions. Because of the fully automated nature of the algorithm, it has a deterministic convergence response, thus yielding the exact same result when repeating the analysis on the same dataset. However, manual corrections of the resultant LV and LA endocardial surfaces are possible, when the operator judges the automatically detected surface as inadequate. This is achieved by displaying the LA and LV contours on ED and ES 4-, 3- and 2-chamber cutplanes extracted from the 3DE datasets using the same default setting for all patients (74 for ED and 68 for ES), optimized in the training set by maximizing the agreement between automated and manual measurements performed by three readers.[7] The user has the option to edit the contours in order to optimize the match between the detected and the perceived endocardial boundary in the corresponding focused views (*Figure 2*). The LV casts can be edited by either changing the entire border globally (dilating or contracting the entire surface uniformly by the same distance) or by editing it regionally. In contrast, the LA cast can be edited only regionally. The readers were instructed to include endocardial trabeculae in the LV volume.

B: Manual 3DE LV and LA measurements

Manual 3DE measurements of LV EDV, ESV, and LAV were performed using commercial software (3DQ, QLAB, Philips). The ED and ES frames used for analysis were the same ones chosen by the automated

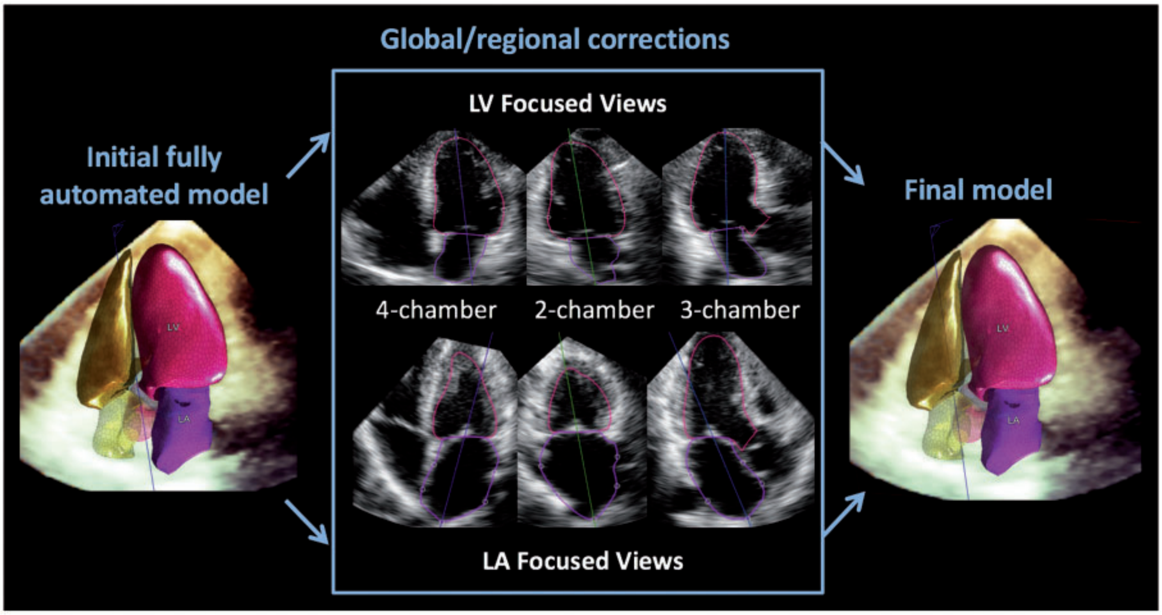

Figure 2 Automated technique for left-heart 3D chamber quantification. Following initial fully-automated detection of left ventricular and left atrial endocardial surfaces (left), the software allows the user to perform manual corrections of the endocardial boundaries when needed (centre), resulting in final 3D casts of the cardiac chambers. The optional correction are performed in anatomically correct non-foreshortened 2D planes showing focused long-axis views of the left ventricle (top) and left atrium (bottom), both automatically extracted from the 3D dataset.

technique. Users were asked whether they agreed or not with the choice made by the automated software, based on their visual identification of valve closures/openings, and their responses were recorded. The following steps were performed on the ED and ES frames. First, the user selected from the 3DE dataset the anatomically correct, non-foreshortened apical 2- and 4-chamber views focused on the relevant chamber (LV or LA), in which the long-axis dimension of the respective chamber was maximized. Then, four mitral annular points were marked in each of the views, and an additional point was placed to mark either the LV apex for LV analysis, or the most distal point on the LA roof for the LA analysis. The endocardial border was automatically generated and then manually edited to optimize its position. Finally, LV EDV, ESV, and LAV were obtained and LVEF calculated.

Reproducibility assessment

The reproducibility of the LV and LAV measurements using the two 3DE techniques (manual and automated) was tested in a randomly selected subgroup of 90 patients. One week after the initial analysis, the same loops of the original 3DE datasets were re-analysed using both programs, at the enrolling site by the same investigator who was blinded to all prior measurements. These repeated measurements were used to determine the intra-observer variability. Inter-observer variability was assessed by comparing measurements performed by the enrolling sites and the CL on the same 90 patients.

In addition, test–retest variability of the automated technique was assessed in a subgroup of 72 patients (randomly chosen three patients from each LVEF subgroup at each site, total of 12 patients per site). After the initial 3DE dataset was obtained, the sonographer removed the probe from the patient's chest, and 5 min later repositioned the transducer to obtain a second dataset.

Inter-measurement variability (inter-observer, intra-observer and test–retest) of each parameter was expressed as an absolute difference between the corresponding pair of repeated measurements in percent of their mean in each patient and then averaged over the relevant subgroup.

Comparison with conventional four-beat full-volume images

In order to determine how the automated analysis of the HM ACQ single-beat acquisitions compares with conventional manual analysis of four-beat acquisitions, we analysed 30 patients enrolled by one of the sites that had both types of images acquired. The four-beat acquisitions were analysed using the conventional methodology (3DQ software, QLAB, Philips), and the results were compared with the automated measurements.

Statistics

For each parameter, the aforementioned intra- and inter-technique comparisons included linear regression with Pearson correlation coefficients and Bland–Altman analyses to assess the bias and limits of agreement (defined as 2 SD around the mean). In addition, biases were expressed in percent of the mean measured value of each parameter, to put the biases in perspective of the absolute value of the relevant parameter. Paired *t*-tests were used to verify the significance of the biases. Values of $P < 0.05$ were considered significant.

Results

Average frame rate for the 3D volume sets was 17 ± 4 Hz. Manual 3DE derived maximal LVEDV ranged between 53 and 524 ml (median 190 ml), LVESV ranged between 17 and 453 ml (median 110 ml), LVEF ranged between 10% and 72% (median 39%), LAV ranged between 23 and 170 ml (median 80 ml). Despite the initial exclusion of patients with inadequate image quality, of the images submitted by the sites to the CL, 10% were rejected, and their slots were repopulated with new patients.

Inter-technique comparisons against conventional Core Lab measurements

Automated choices of frames for analysis were in agreement with visual assessment of the phases of the cardiac cycle in 71% of the cases for ED and 64% for ES. In the remaining patients, the difference in the number of frames was one. Inter-technique comparisons showed excellent agreement between the automated 3DE volume measurements performed by the sites without boundary corrections and the CL manual 3DE measurements, with measured values being similar between the two techniques (*Table 2*, rows 1 and 2). The correlations for the volumes were excellent ($r = 0.97$, 0.97, and 0.96 for LVEDV, LVESV, and LAV, respectively), while that for LV EF was lower ($r = 0.88$) (*Figures 3–6A*, top). Volumes were underestimated with small biases (-14 ± 20 ml for LVEDV, -6 ± 20 ml for LVESV, and -9 ± 10 ml for LAV), and the bias in LVEF was also minimal (-2 ± 7%) (*Figures 3–6A*, bottom).

Manual contour corrections of the automatically detected boundaries resulted in minimal changes in the measurements as a percent of the mean measured value (*Table 2*, row 4) and in the correlations: $r = 0.97$, 0.98, 0.90, 0.96 for LVEDV, LVESV, LVEF, and LAV, respectively (*Figures 3–6B*, top). The biases became smaller, with the exception of LAV, and a minimal decrease was noted in the limits of agreement (*Figures 3–6B*, bottom). When expressed as percent of the mean measured value, the biases were 3–7% for the LV volumes and only 2% for LV EF, and were not significant for LV parameters; however, LAV was significantly underestimated by 11% (*Table 2*, rows 3). These biases were not clearly affected by contour corrections (*Table 2*, rows 5).

One observation from the Bland–Altman plots was that the limits of agreement in LV and LAV measurements were wider in patients with larger volumes, as reflected by the bigger spread of the data points in the higher end of the scale (*Figures 3, 4* and *6A* and *B*, bottom). In contrast, the limits of agreement in LV EF were independent of EF magnitude (*Figure 5A* and *B*, bottom).

Intra-technique comparisons against automated Core Lab measurements

Intra-technique comparisons showed perfect agreement between all automated measurements made by the sites against those made by the CL, when no contour corrections were made by either the sites or the CL. This perfect agreement was reflected by volumes and EF that were identical (*Table 3*, rows 1 and 2), correlations that were all $r = 1.0$ and biases all zero (*Figures 3–6C*).

With contour corrections made by both the sites and the CL, intra-technique comparisons showed excellent agreement with volumes and EF values being similar (*Table 3*, rows 4 and 5) and the correlations being: $r = 0.99$, 0.99, 0.94, 0.99 for LVEDV, LVESV, LVEF, and LAV, respectively (*Figures 3–6D*, top). These correlations were all higher than in the inter-technique comparisons with contour corrections (*Figures 3–6B*, top). In contrast, biases were similar to those noted in the inter-technique comparisons with contour corrections, but importantly the limits of agreement were considerably narrower (*Figures 3–6D*, bottom compared with *B*, bottom). The biases were 5–6% of the measured values for the LV volumes and only 3% for LV EF, and 12% for LAV, which remained the only significant bias (*Table 3*, rows 6).

Effects of contour corrections on volume measurements

Overall, readers determined that no contour corrections were needed in 35 (19%) patients for EDV, in 40 (22%) patients for ESV, and in 72 (40%) patients for LAV, while some contour correction was performed in the remaining patients. Of note, in the majority of the patients only global contour corrections were performed for LV volumes: 98 patients for EDV (54%) and 90 patients for ESV (50%), while no global editing is available for LAV. Importantly, the relative changes in volumes caused by contour corrections were ≤4% (*Table 4*).

Effects of heartbeat selection on the automated measurements

The results of the comparisons between two cardiac cycles measured using the fully automated approach are shown in *Figure 7*. The correlation between the two measurements for LV EDV, and ESV was $r = 1.00$, while those for LV EF, and LAV were slightly lower (upper panels). The biases between these measurements have not exceeded a single measurement unit (1 ml for volumes or 1% for EF), and the limits of agreement were reasonably narrow relative to the mean measured value of each parameter. As expected, these comparisons showed lower levels of agreement than the intra-technique comparisons of the fully-automated measurements performed on the same beat (*Figures 3–6C*), but better agreement than those performed using manual corrections (*Figures 3–6D*).

Effects of acquisition modes

The results of the comparisons between the automated analysis of the HM ACQ single-beat acquisitions and conventional manual analysis of four-beat acquisitions in a subgroup of 30 patients are shown in *Figure 8*. We found very good agreement between the two techniques, which was similar to that between measurements performed using the automated analysis on two different cardiac cycles acquired in the HM ACQ mode (*Figure 7*).

Reproducibility

Reproducibility results are presented in *Table 5*. Not surprisingly, for all four parameters measured by both techniques, the inter-observer variability was higher than the intra-observer variability. Importantly, both the inter- and intra-observer variability levels were lower for the automated measurements than for conventional manual technique for all four parameters. Variability in LV volume measurements

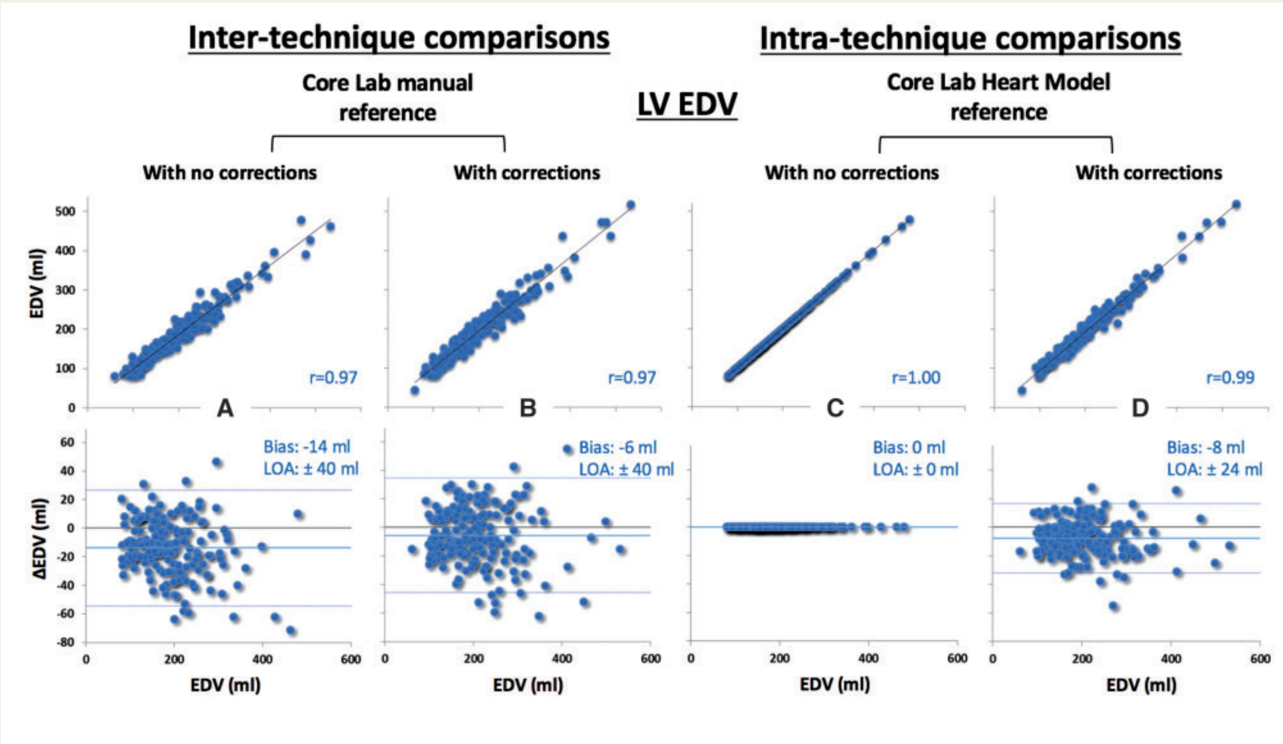

Figure 3 Inter- and intra-technique comparisons for left ventricular end-diastolic volume. Correlation and Bland–Altman analysis for the automated measurements by the sites without and with contour correction against the conventional manual technique by the Core Lab (*A* and *B*, respectively), as well as against the corresponding automated technique by the Core Lab (*C* and *D*, respectively).

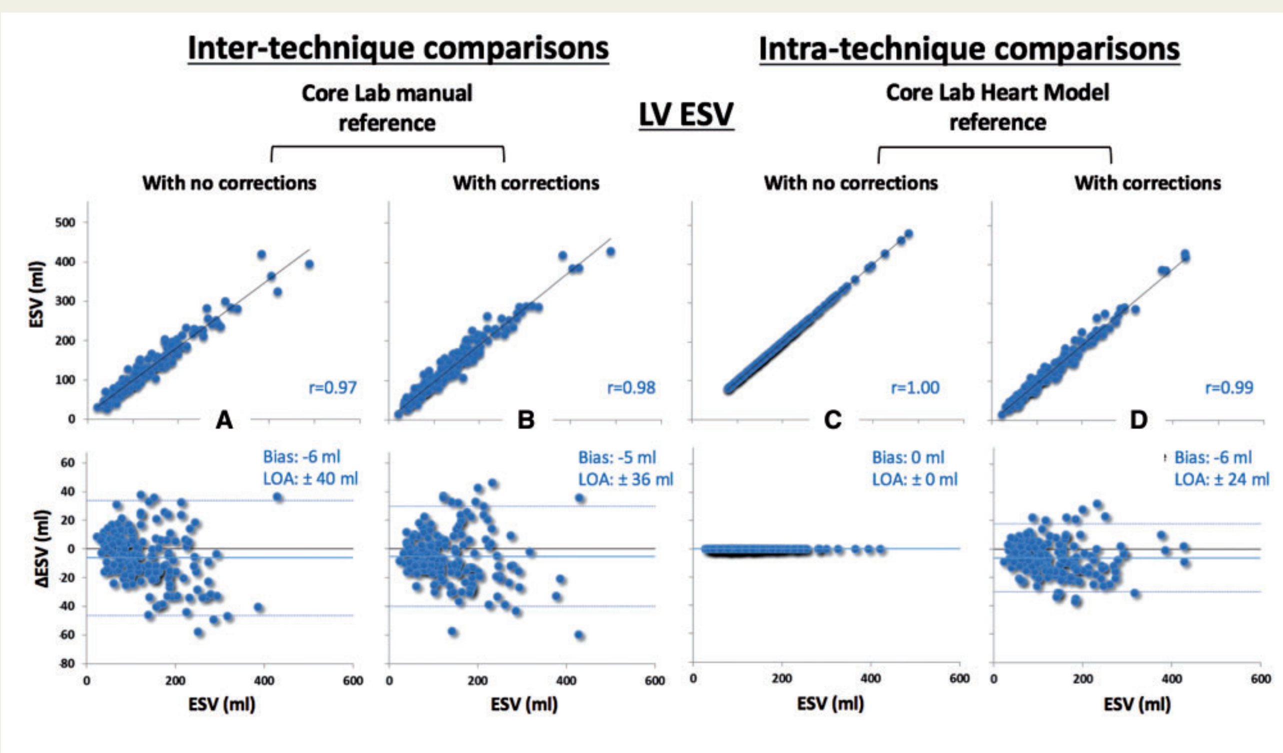

Figure 4 Inter- and intra-technique comparisons for left ventricular end-systolic volumes. Data are presented in the same format as in *Figure 3*.

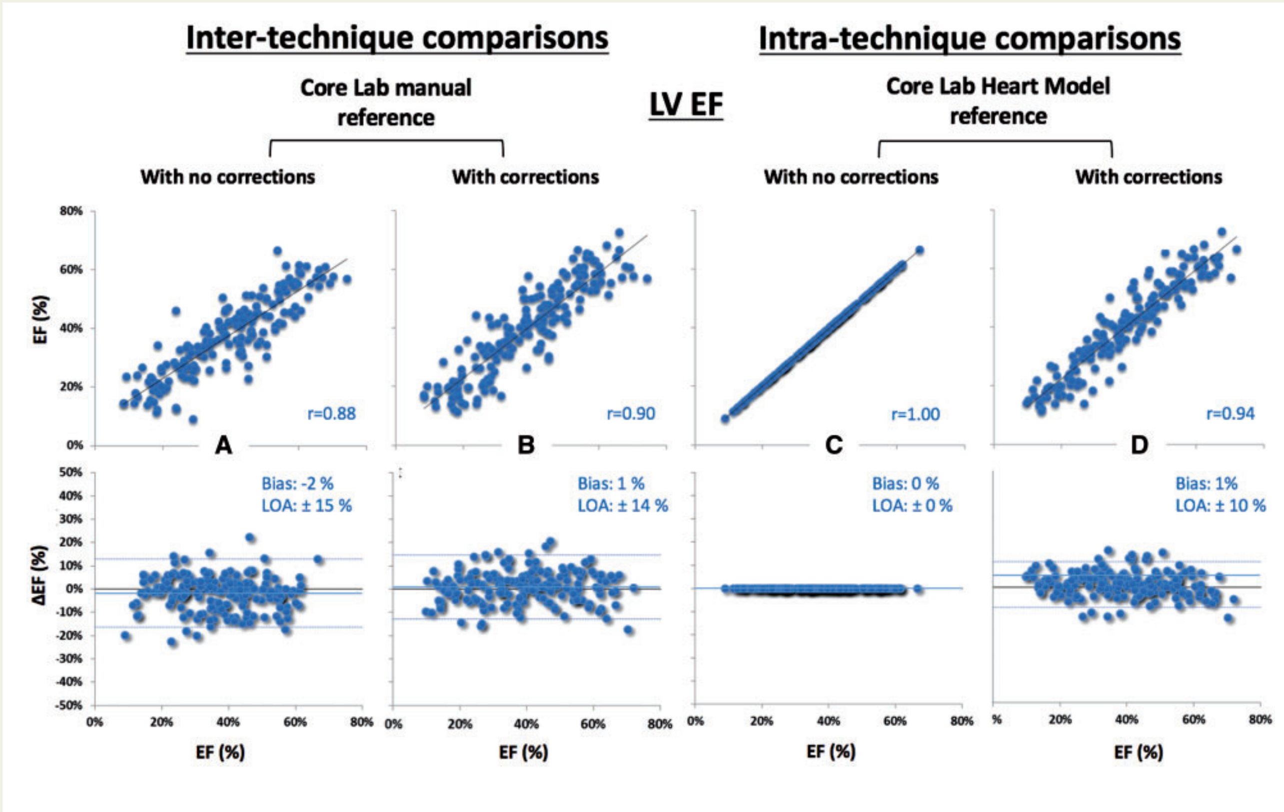

Figure 5 Inter- and intra-technique comparisons for left ventricular ejection fraction. Data are presented in the same format as in *Figure 3*.

was always <10%, while that in LAV and EF reached slightly higher levels.

Figure 9 shows the intra- and inter-observer variability analyses of the automated measurements with a break-up by level of contour corrections. For LV EDV, ESV, and EF, most variability was caused by global editing, while the addition of regional editing resulted in only minimal increase in variability. No clear differences were found in the reproducibility of the automated analysis between subgroups of patients with low and normal EF.

The test–retest variability of the automated program was similar to that when the automated measurements were performed twice on the same datasets: for LV EDV, ESV, EF, and LAV it was 4 ± 4%, 4 ± 4%, 9 ± 11%, and 7 ± 7%, respectively, without contour corrections, and, 6 ± 5%, 10 ± 9%, 14 ± 9%, and 9 ± 8% with contour correction (compare with data in *Table 5*).

Differences between sites

No clear differences were noted in the agreement between the measurements performed by the six participating sites and the CL reference values in either the inter- or intra-technique comparisons. Of note, reproducibility of the automated technique was better than that of the conventional manual analysis for each individual site.

Discussion

Left-heart chamber quantification is critical for both clinical management and clinical trials. The recent guidelines emphasize that 3DE measurements should be preferred over 2DE. However, 3DE has not been widely incorporated into the routine practice because of the workflow constraints, including the fact that it is currently time consuming and requires special expertise. The new automated technique evaluated in this international multicentre study is able to overcome the current workflow limitations associated with conventional 3DE chamber quantification, resulting in significant time savings, as shown in our previous study.[7] Because of its simplicity, minimal training is needed, in contrast to the conventional manual 3DE methodology.[8,9]

Although most previously published reports have endorsed earlier automated techniques for 3DE evaluation of LV volumes for clinical use, their conclusions were based on single centre studies, in which data were acquired and measured by highly trained personnel.[10–13] To the best of our knowledge, this is the first multicentre study to test the new automated 3DE approach for simultaneous LV and LAVs, and LV function assessment based on an adaptive analytics algorithm. This study shows that experienced readers in different parts of the world can obtain accurate and reproducible automated measurements of LVEDV, LVESV, and LVEF with clinically non-significant

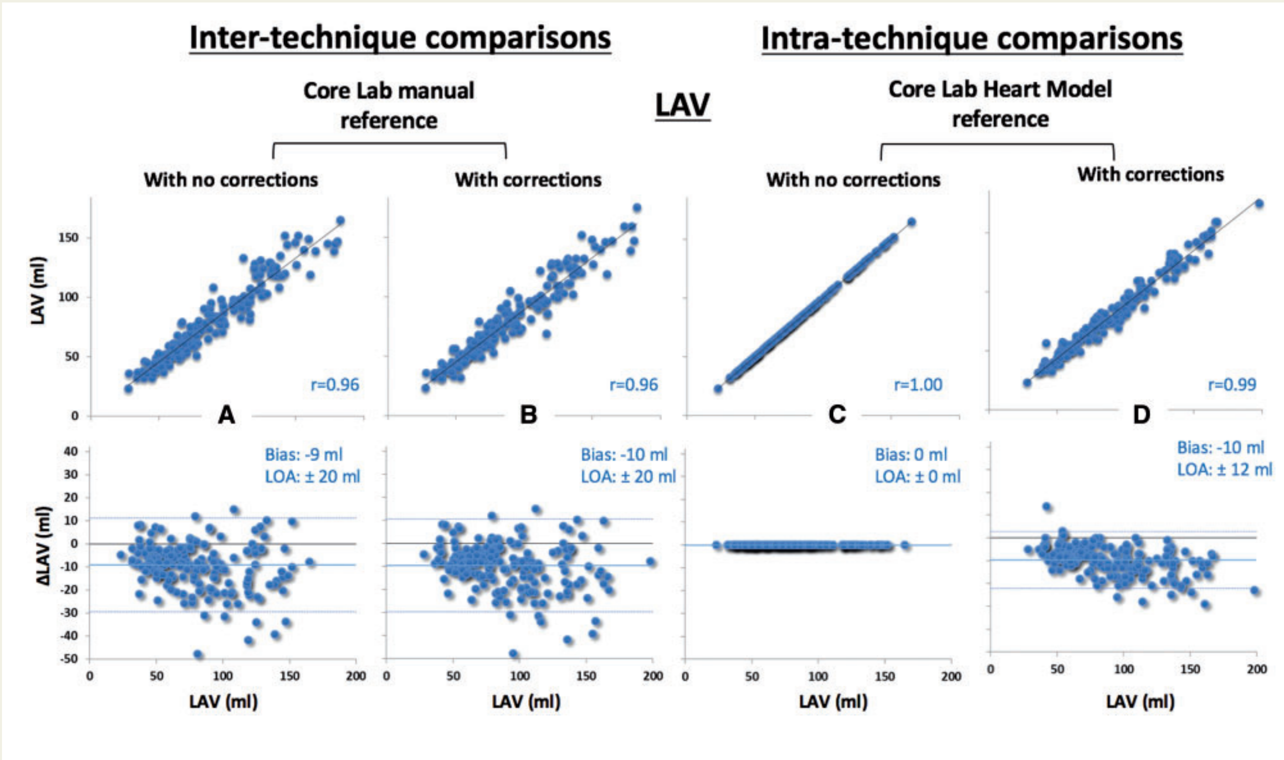

Figure 6 Inter- and intra-technique comparisons for left atrial volume. Data are presented in the same format as in *Figure 3*.

Table 2 Comparison of the Sites' HeartMode measurements to the Core Lab's manual measurements ($N = 180$)

	EDV (ml)	ESV (ml)	EF (%)	LAV (ml)
Core Lab's Manual values	203 ± 83	132 ± 80	39 ± 15	89 ± 36
Sites' HeartModel values without corrections	190 ± 75	126 ± 71	37 ± 13	80 ± 32
Bias (% mean) ± SD	-7 ± 10	-3 ± 16	-2 ± 24	-11 ± 11*
Sites' HeartModel values with corrections	198 ± 80	127 ± 77	40 ± 15	79 ± 32
Bias (% mean) ± SD	-3 ± 11	-5 ± 15	3 ± 23	-12 ± 12*

EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; LAV, left atrial volume.
*$P < 0.05$.

Table 3 Comparison of the Sites' HeartModel measurements to the Core Lab's HeartModel measurements ($N = 180$)

	EDV (ml)	ESV (ml)	EF (%)	LAV (ml)
Core Lab's HeartModel values without corrections	190 ± 75	126 ± 71	37 ± 13	80 ± 32
Sites' HeartModel values without corrections	190 ± 75	126 ± 71	37 ± 13	80 ± 32
Bias (% mean) ± SD	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Core Lab's HeartModel values with corrections	206 ± 80	133 ± 78	39 ± 15	89 ± 35
Sites' HeartModel values with corrections	198 ± 80	127 ± 77	40 ± 15	79 ± 32
Bias (% mean) ± SD	-5 ± 7	-6 ± 12	3 ± 17	-12 ± 8*

EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; LAV, left atrial volume.
*$P < 0.05$.

Table 4 Frequency of contour corrections and their effects on the measured volumes ($N = 180$)

		EDV	ESV	LAV
No correction needed	# of patients (%)	35 (19%)	40 (22%)	72 (40%)
Global only correction	# of patients (%)	98 (54%)	90 (50%)	N/A
	Change in volume, ml (%)	3 ± 13 (2 ± 8%)	-2 ± 12 (-4 ± 13%)	
Regional correction (may or may not include global correction)	# of patients (%)	145 (81%)	140 (78%)	108 (60%)
	Change in volume, ml (%)	8 ± 18 (4 ± 9%)	1 ± 16 (-2 ± 14%)	-1±6 (-1 ± 7%)

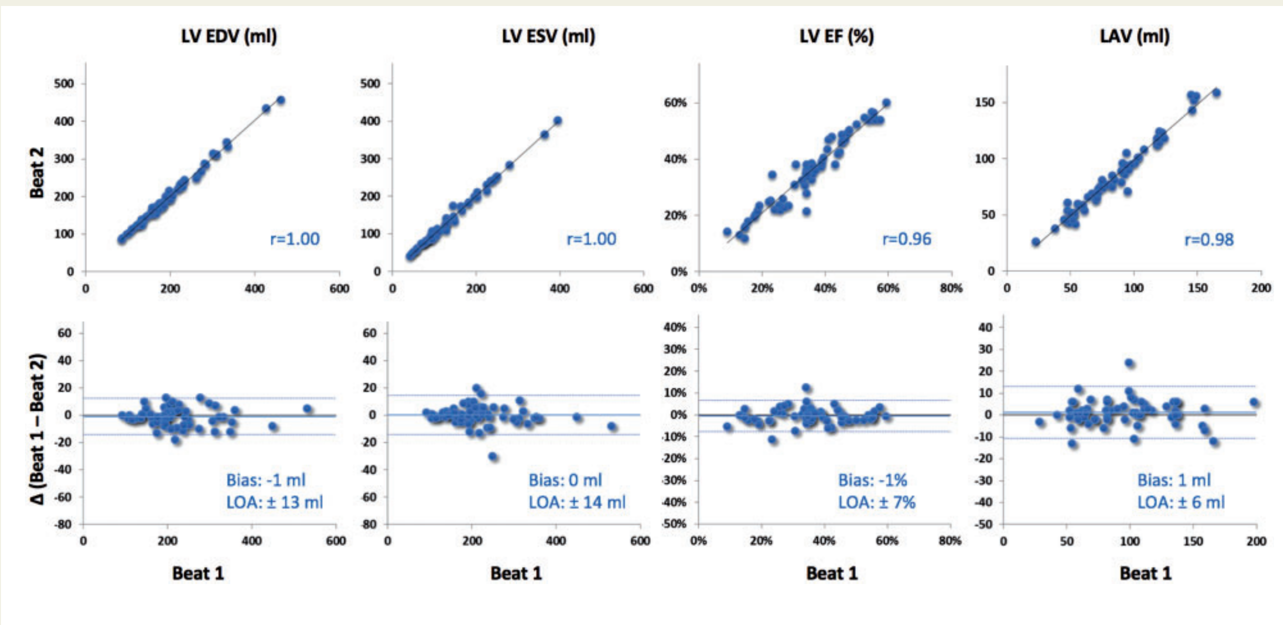

Figure 7 Effects of heartbeat selection on volume measurements. Results of regression and Bland–Altman analyses for left ventricular end-diastolic and end-systolic volumes (EDV, ESV), ejection fraction (EF) and left atrial volume (LAV) for measurements performed on two different cardiac cycles using the fully automated analysis in a subgroup of 60 patients (see text for details).

differences, contrary to previous studies that tested other automated algorithms.[14–16] Moreover, in the current study, the new software was more accurate than its previous version tested in our recent study,[7] as reflected by smaller biases and tighter limits of agreement with the conventional manual tracing based reference values.

This new automated software has the option to perform rapid global and/or regional corrections, as needed. Such border correction was deemed necessary in the majority of patients in this study. Importantly, however, the fully automated analysis was accurate and with endocardial border editing, the accuracy improved only slightly on the average. Nevertheless, one should not disregard the importance of boundary corrections in individual patients, when judged necessary, especially in patients with enlarged chambers. Moreover, with border corrections, the reproducibility was better than that of the conventional manual measurements.

On top of these advantages in terms of LV quantification, the new automated 3DE algorithm also simultaneously measures LAV without additional time or effort involved. Also, unlike 2DE, where dedicated LA focused views are needed to perform accurate bi-plane measurements, with 3DE, the LA is included in the pyramidal dataset and no additional image acquisition is needed either. Similar to LV endocardial contour editing, the new software allows correction of the LA borders, albeit on a regional basis only. These corrections are also performed on three anatomically correct non-foreshortened LA-focused views, which are also automatically extracted from the 3DE dataset, and displayed similar to that used for LV border editing (*Figure 2*, bottom). With this approach, automated reasonably accurate and reproducible LAV measurements were obtained in this multicentre study.

Furthermore, in contrast to the conventional manual 3DE analysis, in the automated software, the endocardial borders of both the LV and LA can be easily followed through the entire chamber both in ED and ES by changing the view angle. This feature may prove especially useful in patients with LV aneurysms, who were not included in this

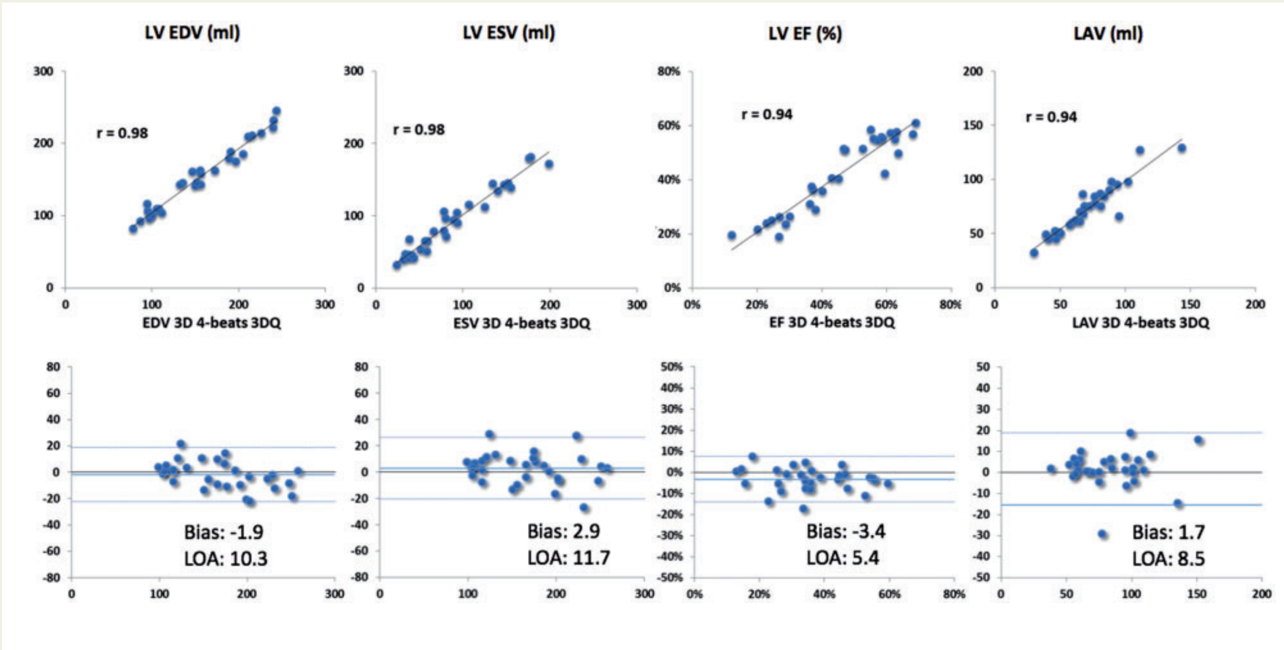

Figure 8 Effects of acquisition mode on volume measurements. Results of comparisons between the automated analysis of the HM ACQ single-beat acquisitions and conventional manual analysis of four-beat acquisitions in a subgroup of 30 patients. Data are presented in the same format as in *Figure 7*.

Table 5 **Intra- and inter-observer variability data (*N* = 90)**

% **Variability**	**HeartModel (with corrections when needed)**				**Conventional manual**			
	EDV	**ESV**	**EF**	**LAV**	**EDV**	**ESV**	**EF**	**LAV**
Intra-observer	3 ± 3	5 ± 5	7 ± 9	7 ± 6	7 ± 6	8 ± 9	12 ± 13	9 ± 7
Inter-observer	6 ± 5	9 ± 9	13 ± 12	11 ± 6	11 ± 8	13 ± 11	17 ± 14	15 ± 12

study, because in these patients, border corrections are truly needed and would have bigger effects on volume measurements.

The inter- and intra-technique comparisons between the automated analyses by the sites against the different reference standards generated by the CL showed that the new methodology can be used universally and provide similar results. An unexpected finding of these analyses is that contour editing, although judged as necessary by the readers in the majority of patients, had only limited effects on the measurements on the average in the entire cohort. One might suggest that these differences would not be clinically significant, because the largest bias we found in LV EF was 3% of the measured value, which, with a median EF value of 39% in our patients, translates to an actual difference of only 1.2% (in actual EF units), which is below the accuracy of any cardiac imaging technique that measures EF. However, boundary corrections are likely to be important in individual patients, where they can result in considerably larger volume and EF differences that may have important clinical implications.

Another interesting finding was that the automated technique with corrections was more reproducible than the conventional manual technique for all four parameters, in terms of both inter- and intra-observer variability. This may be related to the fact that the automated software starts from endocardial border position that is based on algorithm settings that were optimized on images obtained in thousands of patients. In contrast, the manual analysis starts with no pre-determined endocardial border, and the user determines the border position according to their personal preferences. This is likely to cause inter-measurement variability that may be larger than when the same reader has to decide how much a reasonable default position needs to be adjusted.

Another potential source of variability of the conventional technique is the need to visually identify the non-foreshortened apical views. In addition, the automated software identifies the ED and ES frames which are analysed, unlike the manual analysis, wherein the user needs to select the correct frames, which would in itself result in inter-measurement variability. In this study, the readers were instructed to use for their manual analyses the same frames chosen by the automated software, in order to eliminate this source of variability. Also, both inter- and

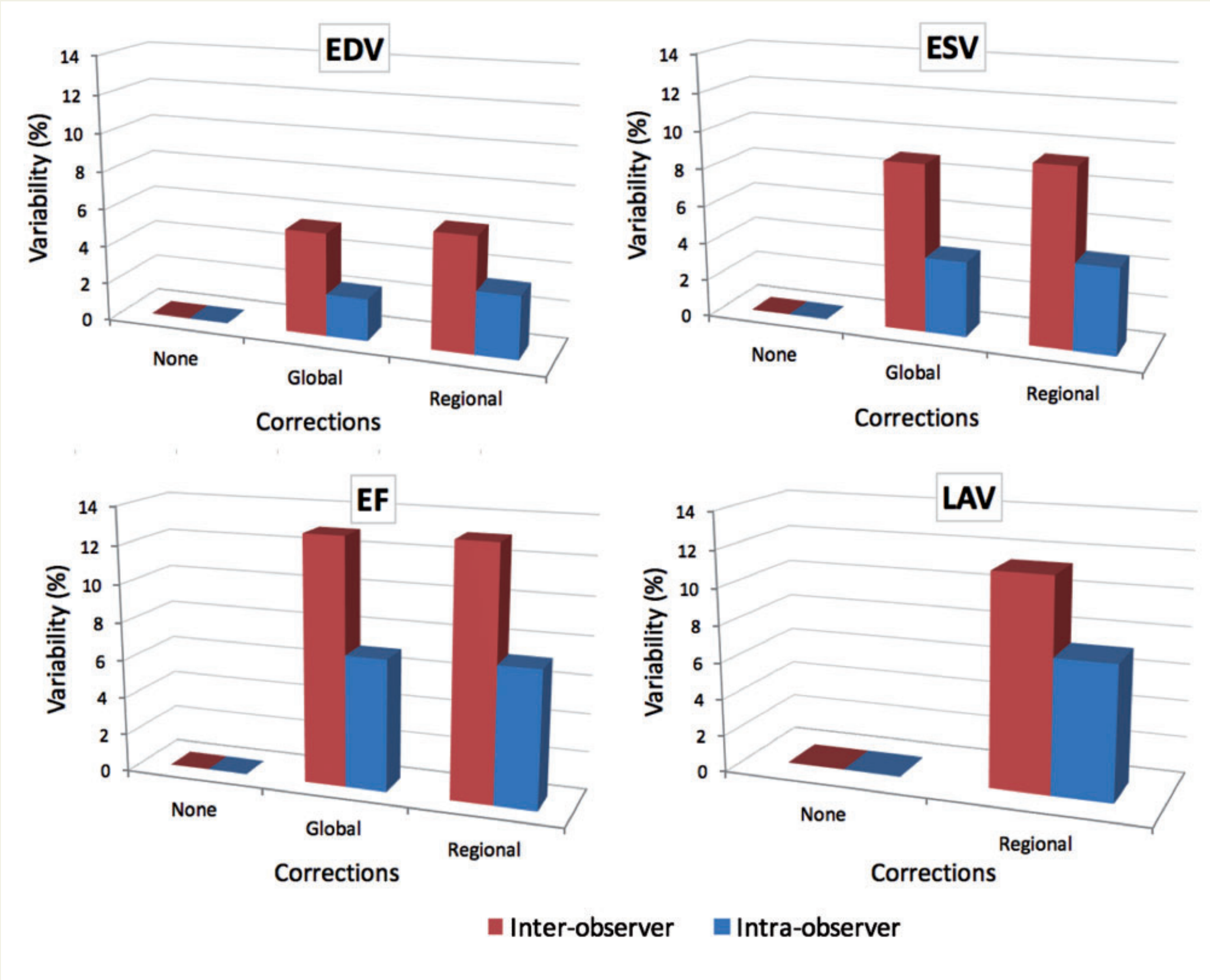

Figure 9 Intra and inter observer variability of the automated 3DE left heart chamber quantification. Percent variability is shown for left ventricular end-diastolic and end systolic volumes (EDV, ESV), ejection fraction (EF) and left atrial volume (LAV). Inter- and intra-observer variability was calculated with no contour corrections, with global correction only (for EDV, ESV and EF) and with additional regional adjustments (for all four parameters), as deemed necessary by the readers.

intra-technique comparisons were performed using the same heartbeat. Our analysis of the different beats showed the level of variability this source may account for. Therefore, our study underestimated the true real-world variability of the conventional manual methodology, which further underscores the value of the new automated approach. This is because by reducing measurement variability, this new software may allow true changes in LV and LAVs or LV function to be detected with more confidence. In addition, comparisons between imaging modes (HM ACQ vs. conventional four-beat) showed differences of the same order of magnitude as those resulting from using the algorithm on different cardiac cycles.

Study limitations

First, one of the inclusion criteria was the need for sufficiently good image quality to allow automated measurements. Therefore, our results cannot be extrapolated to consecutive patients, and future studies are needed to determine the feasibility of this automated approach in the general patient population. However, no technique, either automated or manual can be expected to accurately measure cardiac chambers on images of substandard quality. On the basis of our experience with the new software, we estimate that it is likely to provide accurate and reproducible measurements in ∼2/3 of consecutive patients.

Secondly, all six participating sites were selected for the study based on their expertise with 3DE imaging and analysis, which again limits the generalizability of our results that involve user input. However, one of our main findings is that the need for user input in the automated analysis is questionable.

Low frame rates are a known limitation of 3DE imaging, especially of the single-beat acquisition, because low frame-rate datasets may miss the true end of systole. However, in this study, both inter- and intra-technique comparisons were always performed on the same ED and ES frames. As a result, the low frame rates could not have affected our findings.

Finally, this study only analysed patients in sinus rhythm, without pacemaker or ICD leads, dilated RV or severely abnormal LV shapes. Thus these results cannot be extrapolated to patients with atrial fibrillation or ectopic rhythm, or patients with exclusion criteria for this study. The applicability and accuracy in these populations remains to be determined in future studies.

It is worthwhile noting that the automated algorithm is currently available from a single vendor. Therefore, it cannot be applied retrospectively to images obtained using other formats.

Conclusions

In summary, automated volumetric analysis of left-heart chambers is an accurate and robust alternative to conventional manual methodology, which yields almost the same values across laboratories and is more reproducible. This technique may contribute towards full integration of 3DE quantification into clinical routine, when such algorithms become universally available.

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