

Volumetric Quantification of Global and Regional Left Ventricular Function From Real-Time Three-Dimensional Echocardiographic Images

Cristiana Corsi, PhD; Roberto M. Lang, MD; Federico Veronesi, MS; Lynn Weinert, BS; Enrico G. Caiani, PhD; Peter MacEneaney, MD; Claudio Lamberti, MS; Victor Mor-Avi, PhD

Background—Real-time 3D echocardiographic (RT3DE) data sets contain dynamic volumetric information on cardiac function. However, quantification of left ventricular (LV) function from 3D echocardiographic data is performed on cut-planes extracted from the 3D data sets and thus does not fully exploit the volumetric information. Accordingly, we developed a volumetric analysis technique aimed at quantification of global and regional LV function.

Methods and Results—RT3DE images obtained in 30 patients (Philips 7500) were analyzed by use of custom software based on the level-set approach for semiautomated detection of LV endocardial surface throughout the cardiac cycle, from which global and regional LV volume (LVV)–time and wall motion (WM)–time curves were obtained. The study design included 3 protocols. In protocol 1, time curves obtained in 16 patients were compared point-by-point with MRI data (linear regression and Bland-Altman analyses). Global LVV correlated highly with MRI ($r=0.98$; $y=0.99x+2.3$) with minimal bias (1.4 mL) and narrow limits of agreement (± 20 mL). WM correlated highly only in basal and midventricular segments ($r=0.88$; $y=0.85x+0.7$). In protocol 2, we tested the ability of this technique to differentiate populations with known differences in LV function by studying 9 patients with dilated cardiomyopathy and 9 normal subjects. All calculated indices of global and regional systolic and diastolic LV function were significantly different between the groups. In protocol 3, we tested the feasibility of automated detection of regional WM abnormalities in 11 patients. In each segment, abnormality was detected when regional shortening fraction was below a threshold obtained in normal subjects. The automated detection agreed with expert interpretation of 2D WM in 86% of segments.

Conclusions—Volumetric analysis of RT3DE data is clinically feasible and allows fast, semiautomated, dynamic measurement of LVV and automated detection of regional WM abnormalities. (*Circulation*. 2005;112:1161-1170.)

Key Words: imaging ■ echocardiography ■ magnetic resonance imaging ■ ventricles ■ endocardium

Echocardiography is the most widely used imaging modality for the evaluation of global and regional left ventricular (LV) function. The conventional visual interpretation of 2D echocardiographic (2DE) images aimed at the evaluation of LV function relies on the reader's experience and ability to effectively integrate spatial and temporal information. More objective approaches aimed at quantitative analysis of dynamic images are based primarily on frame-by-frame manual or semiautomated tracing of endocardial boundaries. Other alternative approaches, such as acoustic quantification,^{1,2} color kinesis,^{3,4} and Doppler tissue imaging,^{5,6} designed to avoid manual tracing, have not gained widespread clinical use. Nevertheless, both visual interpretation and quantitative analysis of 2DE images use only partial information about cardiac anatomy and function contained in specific cross-sectional planes.

Over the past decade, multiple studies have demonstrated the ability of 3D imaging based on offline multiplane reconstruction to overcome some of the limitations of the 2DE methodology and provide more accurate measurements,⁷⁻⁹ because it uses more complete information. Real-time 3D echocardiographic (RT3DE) technology, which has recently become widely available, allows fast acquisition from a single acoustic window of dynamic pyramidal data structures that encompass the entire heart. Several recent studies have demonstrated the potential improvements in the evaluation of global LV function from RT3DE data.^{10,11} However, analysis procedures applied to 3D data did not fully exploit the volumetric information, because they were still based on tracing of endocardial boundaries on selected planes and on geometric modeling.¹² Because modeling may be inaccurate under certain conditions, the use of information limited to 2

Received October 11, 2004; revision received April 18, 2005; accepted May 10, 2005.

From the University of Chicago Medical Center, Chicago, Ill (C.C., R.M.L., L.W., P.M., V.M.-A); the Department of Electronics, Computer Science and Systems, University of Bologna, Bologna, Italy (C.C., F.V., C.L.); and the Dipartimento di Bioingegneria, Politecnico di Milano, Milan, Italy (E.G.C.).

Correspondence to Victor Mor-Avi, PhD, University of Chicago MC5084, 5841 S Maryland Ave, Chicago, IL 60637. E-mail vmoravi@medicine.bsd.uchicago.edu

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/CIRCULATIONAHA.104.513689

dimensions renders this procedure subject to many of the same limitations as the techniques used to analyze 2DE images. Moreover, the information on regional wall motion contained in 3D data sets has thus far been studied only by use of visual interpretation of selected planes^{13,14} or by quantification of model-based, interpolated endocardial surfaces,¹⁵ rather than by quantifying the displacement of the true endocardial surface detected in 3D space. These approaches are again fundamentally 2D and can be inaccurate, because small areas of abnormality can be overlooked. It is likely that direct 3D quantification of the displacement of endocardial surface segments could aid in accurate determination of the extent of wall motion abnormalities.

We hypothesized that our recently developed technique for direct 3D detection of the endocardial surface¹⁶ could be applied to RT3DE data sets throughout the cardiac cycle and thus lead to an alternative approach for fast, easy, and objective dynamic quantification of global and regional LV function. Our hypothesis was that this approach, which fully exploits the volumetric information contained in RT3DE data sets without the need for either plane selection or geometric modeling, could allow accurate evaluation of not only the magnitude but also the temporal aspects of LV function and would thus create new opportunities for objective detection of wall motion abnormalities, quantification of LV systolic asynchrony, and assessment of regional LV diastolic properties. Accordingly, our goal was to test the clinical feasibility of this approach and validate it against cardiac MRI on a global and regional basis.

Methods

Study Design

The study design included 3 protocols, which were performed in 30 subjects (19 men, 11 women; age, 58 ± 19 years), including 6 normal volunteers, 11 patients with coronary artery disease (CAD), 9 with dilated cardiomyopathy (DCM), 2 with valvular disease, 1 with aortic coarctation, and 1 with a right atrial mass. Protocol 1 was designed to test and validate the RT3DE-based continuous measurements of global LV volume, partial volumes at the basal, mid, and apical levels, and regional wall motion–time curves against cardiac MRI reference values. In protocol 2, we tested the ability of this technique to differentiate populations with known differences in LV performance by comparing global and regional indices of systolic and diastolic LV function obtained in a group of patients with DCM with those obtained in a group of normal subjects. In protocol 3, we tested the feasibility of automated detection of regional wall motion abnormalities in a group of patients with CAD by comparing the results of automated interpretation against expert interpretation of 2D wall motion.

MRI and Analysis

Cardiac MRI scans were obtained by use of a 1.5-T scanner (General Electric) with a phased-array cardiac coil. ECG-gated localizing spin-echo sequences were used to identify the long axis of the heart. The steady-state free precession (FIESTA) dynamic gradient-echo mode was then used to acquire images during 12-second breath-holds. Cine loops were obtained in 6 to 10 short-axis slices, from the atrioventricular ring to the apex (9-mm slice thickness, no gaps) with a temporal resolution of 20 frames per cardiac cycle.

Images were analyzed on a Sun workstation by use of commercial software (General Electric, MASS Analysis). Initially, LV slices were selected for analysis beginning with the highest basal slice in which the LV outflow tract was not visible and ending with the lowest apical slice in which the LV cavity was visualized. In every

slice, LV endocardial contours were traced semiautomatically frame by frame, with the papillary muscles included in the LV cavity, and manually corrected when necessary to optimize the boundary position, resulting in LV cross-sectional area for each slice over time. Global LV volume was computed throughout the cardiac cycle by use of a disk-area summation method (modified Simpson's rule),¹⁷ resulting in volume-time curves, from which end-systolic and end-diastolic volumes (EDV and ESV) were obtained and ejection fraction (EF) was calculated. These data were used as a reference for comparisons with RT3DE time curves. In addition, a standard segmentation procedure was used to obtain regional wall motion over time (in millimeters, relative to end-diastolic endocardial boundary position) for anteroseptal, anterior, lateral, posterior, inferior, and septal segments in each slice.

To obtain MRI references for partial volume–time curves at 3 different levels of the LV¹⁸ and regional wall motion–time curves, the number of slices covering the LV from base to apex, which was different in each patient, was divided by 3. The resultant number was used to create weight coefficients that reflected the contribution of each slice toward the calculation of basal, mid, and apical partial volumes on the basis of slice area and thickness information. The same weight coefficients were used to determine the contribution of wall motion in each slice toward the calculation of regional wall motion for each endocardial surface segment at each level.

RT3DE Imaging and Analysis

RT3DE imaging was performed from the apical window with the patient in the left lateral decubitus position in the harmonic mode by use of a commercial scanner (SONOS 7500, Philips Medical Systems) equipped with a fully sampled matrix array transducer ($\times 4$). Care was taken to include the entire LV cavity within the pyramidal scan volume. RT3DE data sets were acquired by use of the wide-angled acquisition mode, wherein 4 wedge-shaped subvolumes ($93 \times 21^\circ$) were acquired over 8 consecutive cardiac cycles during a breath-hold. Acquisition of each subvolume was triggered to the ECG R wave of every other heartbeat (total of 4 heartbeats) to allow sufficient time for the probe to be recalibrated and each subvolume stored.¹¹ RT3DE data sets were stored digitally for offline analysis. In addition to RT3DE acquisition, 2D images were acquired in apical 2-, 3-, and 4-chamber views.

Analysis of RT3DE images was implemented in Matlab software (MathWorks). The RT3DE data sets were analyzed by use of custom software for semiautomated endocardial surface detection on the basis of the level set approach.^{19,20} This method uses an implicit representation of curves as a partial differential equation to track boundaries, without geometrical assumptions or a priori shape knowledge.¹⁹ Four planes rotated around the LV long axis at 45° steps were selected from the 3D data set, and a small number of endocardial boundary points (6 to 12) were manually initialized in each plane. To be consistent with the cardiac MRI reference, papillary muscles were included within the LV cavity, and the aortic outflow tract was excluded. The selected points were connected to define a set of polygons. For each polygon, a signed distance function was calculated,¹⁶ and a rough surface corresponding to the endocardium was computed by use of linear interpolation of the signed distance functions. This surface was then used as the initial condition for the level-set partial differential equation, which guided surface evolution within the volumetric data set toward the endocardium under the constraints of 2 forces: (1) an interface tension force that depends on the curvature of the evolving surface and has a regulating effect and (2) a force that attracts this surface toward the image boundaries. When the 2 forces balance each other, the evolution reaches a steady state, and the resultant surface was used to represent the endocardium.

The endocardial surface detected from the first frame was then used as the initial condition for the second frame, and so on throughout the cardiac cycle. Thus, manual interaction was necessary only for the first frame analyzed. For each frame throughout the cardiac cycle, global LV volume (in milliliters) was calculated by multiplying the total number of voxels inside the detected surface by the volume of a single voxel, resulting in global LV volume–time

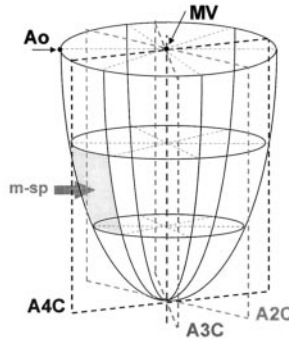
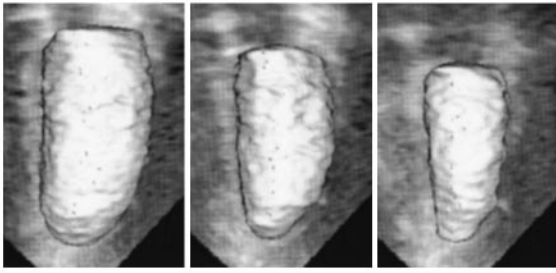


Figure 1. Example of LV endocardial surfaces detected from a RT3DE data set at 3 different phases of cardiac cycle: (A) end diastole, (B) mid systole, and (C) end systole, superimposed on cross-sectional long-axis planes of original data. Schematic representation of 3D segmentation model (right): A2C, A3C, and A4C, apical 2-, 3- and 4-chamber planes; MV, central point of mitral valve; Ao, central point of aortic annulus (see text for details). Shaded area is an example of an LV endocardial surface segment representing midseptal (m-sp) wall.

curves. From these time curves, EDV and ESV were obtained and EF was calculated.

Subsequently, each detected LV endocardial surface was segmented as follows (Figure 1, right). Twelve cross-sectional views of the first frame, 15° apart, were displayed to allow the operator to select 2 planes: (1) the plane in which the mitral annulus was best visualized (Figure 2A) and (2) the plane that contained the central portion of the aortic valve (Figure 2B). In plane 1, the operator selected 2 points in which the anterior and posterior mitral leaflets were attached to the annulus and then 2 additional mitral annulus points in the perpendicular plane passing through the center of the line connecting the first 2 points. From these 4 points, the center of the mitral annulus was calculated and the apical tip of the detected surface automatically identified. The straight line connecting these 2 points was used as the long axis of the ventricle for this particular time frame. Subsequently, in every frame throughout the cardiac cycle, the 4 mitral points were identified by use of 3D optical flow^{21,22} and region matching techniques,²¹ and the apex was automatically identified, allowing independent calculation of the long axis of the ventricle for each consecutive frame. Then, for each frame, the long axis was automatically divided into 3 equal parts, and the detected endocardial surface was divided accordingly into 3 parts: basal, mid, and apical. For each part, the partial volume inside the endocardial surface was calculated for each consecutive frame throughout the cardiac cycle, resulting in partial volume–time curves.

In plane 2, the same procedure was applied to identify the center of the aortic annulus for each consecutive frame. For each frame, a plane defined by this point and the apex was used as the origin of rotational segmentation, dividing the entire ventricle into 6 equal-size walls corresponding to the MRI segmentation, thus resulting in 6 wedge-shaped 60° segments at each of the 3 above-described LV levels (Figure 1, right), or a total of 18 segments.¹⁷ In each segment, regional volume was calculated throughout the cardiac cycle. Regional volume–time curves were used to calculate for each segment the time interval between the ECG R wave (beginning of ejection) and the time at which the smallest regional LV volume was reached

(end of regional ejection). The SD of these time intervals calculated for the 18 segments was used as an index of LV systolic asynchrony (ISA) in each patient.

In addition, in each segment, the distance between the long axis and each surface voxel was computed and averaged for all surface voxels, resulting in the mean regional endocardial distance from the long axis, or regional radial dimension. This procedure was also applied to all consecutive frames throughout the cardiac cycle. In each segment, to allow comparisons with the MRI values, wall motion was calculated for each frame as the difference between end-diastolic and current regional radial dimension, resulting in 18 regional wall motion–time curves. According to this definition, regional wall motion equals zero at end diastole, as for the MRI analysis. In addition, for each endocardial surface segment at each level of the LV, wall motion from end diastole to end systole (peak wall motion) was divided by regional end-diastolic radial dimension to obtain regional shortening fraction (RSF). RSF was computed¹⁷ for each surface segment and averaged for each subject.

To allow point-by-point comparisons between techniques and subjects, RT3DE-derived time curves reflecting global LV volume as well as basal, mid, and apical volumes and regional wall motion in 18 segments were resampled at 20 frames per cardiac cycle by use of cubic spline interpolation, resulting in a data point every 5% of the RR interval, irrespective of heart rate.

Protocols

Protocol 1

This protocol was designed to test and validate RT3DE-based continuous measurements of global LV volume, partial volumes at the basal, mid, and apical levels, and regional wall motion–time curves against cardiac MRI reference values. Sixteen patients who had adequate transthoracic 2D acoustic windows that allowed visualization of at least 85% of the endocardium were included in the study. Exclusion criteria included dyspnea precluding a 10- to 15-second breath-hold, atrial fibrillation, pacemaker or defibrillator implantation, claustrophobia, and other known contraindications to MRI. RT3DE data acquisition was performed on the same day as the MRI study.

Protocol 2

This protocol was designed to test the ability of our RT3DE technique to differentiate 2 populations with known differences in LV performance by comparing global and regional indices of systolic and diastolic function obtained in a group of 9 patients with DCM (6 men, 3 women; age, 58 ± 14 years) with those obtained in a group of 9 age-matched subjects with normal global LV function (5 men, 4 women; age, 51 ± 17 years). For each subject, global ESV and EDV were extracted from the global LV volume–curves as the minimum and maximum values, respectively, and used to calculate the EF. Peak ejection rate and peak rapid and atrial filling rates were calculated from the time derivative of the global LV volume curve¹² and normalized by end-diastolic volume. In addition, ISA and RSF were computed for each subject.

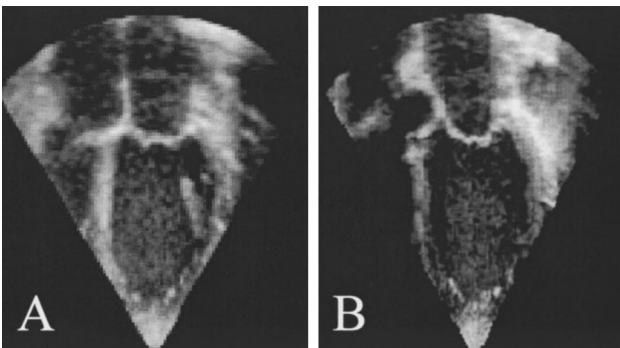


Figure 2. Example of 2 cross-sectional views extracted from RT3DE data set in which mitral annulus (A) and central portion of aortic valve (B) were best visualized.

Protocol 3

This protocol was designed to test the feasibility of automated detection of regional wall motion abnormalities by use of quantitative analysis of RT3DE data and included 18 subjects: 11 patients (6 men, 5 women; age, 70 ± 16 years) with CAD and 7 subjects (4 men, 3 women; age, 40 ± 16 years) with no history of cardiac disease and no evidence of LV dysfunction, who were used as a reference group. Apical 2-, 3-, and 4-chamber 2D images obtained in the 11 patients with CAD were reviewed by an experienced echocardiographer who graded wall motion in each segment as normal or abnormal. The mean RSF minus 1 SD of the normal group was used as a threshold for automated classification of each segment as normal or abnormal in these 11 patients.

Statistical Analysis

In all protocols, statistical analyses were performed by use of Matlab software (MathWorks). Probability values of $P < 0.05$ were considered significant.

In protocol 1, the significance of differences between RT3DE and MRI measurements of LV volume was tested by use of 2-way ANOVA with repeated measures on both factors (imaging modality and time)²³ to account for the fact that the same subjects were measured twice (RT3DE and MRI) and that multiple measurements were performed in each subject over time (20 time points throughout the cardiac cycle). The comparisons between RT3DE and MRI also included linear regression and Bland-Altman analyses of EDV, ESV, EF (16 patients \times 1 point = 16 points for each parameter) and volume-time curves (16 patients \times 20 time points for each curve = total of 320 data points), as well as concordance correlation coefficients (CCC).²⁴ In addition, the percent discordance between the 2 techniques was calculated for each pair of MRI and RT3DE curves as the point-by-point sum of absolute differences between RT3DE and MRI values, normalized by the point-by-point sum of MRI values. For wall motion curves, comparisons were performed for peak systolic values only, resulting in 288 comparisons (16 patients \times 18 segments). Furthermore, segments at each LV level were grouped together and analyzed separately (96 points = 16 patients \times 6 segments for each level). The significance of differences between RT3DE and MRI measurements of wall motion was tested by use of 2-way ANOVA with repeated measures on both factors (imaging modality and segment or level)²³ to account for the fact that the same subjects were measured twice (RT3DE and MRI) and that multiple segments or levels were measured in the same subject. In addition, because the comparisons between RT3DE and MRI included multiple measurements for each study subject, we performed regression analysis with dummy variables as described by Glantz and Slinker²³ to test the possible effects of data clustering by patient.

In protocol 2, all calculated indices of global and regional LV function, including EDV, ESV, EF, peak ejection rate, peak rapid filling rate, peak atrial filling rate, ISA and RSF, were compared between the patients with DCM and their age-matched normal counterparts by use of paired *t* test. In protocol 3, the performance of our algorithm for detecting wall motion abnormalities was tested by calculating the percentage of segments in which the automated classification agreed with the expert interpretation of 2D images, as well as the percentage of false-positive and false-negative detections. These data were obtained for different RSF thresholds to construct the receiver operating characteristic (ROC) curve.²⁵ To this effect, RSF thresholds for automated detection (1 for each of the 18 segments) were varied one at a time in the range of mean RSF \pm 6 SD. For each set of thresholds, the sensitivity and specificity of the automated detection in individual patients was calculated for the entire group. The ROC curve was then constructed as a plot of sensitivity versus (1 - specificity), and the area under the curve and the confidence interval were calculated to evaluate the performance of the automated detection of wall motion abnormalities.

Results

RT3DE imaging and analysis were feasible in all study subjects. The average time required to analyze the first frame,

including data retrieval, frame selection, surface detection and segmentation, and computation of volumes and regional wall motion, was approximately 5 minutes on a personal computer (Pentium II, 755 MHz, 512 MB RAM), of which only 30 seconds was required for the computations once user interaction was complete. Analysis of all phases of the cardiac cycle added 30 seconds times the number of frames, ie, < 10 minutes, resulting in a total analysis time of < 15 minutes. Figure 1 (left) shows an example of LV endocardial surface detected from RT3DE data at different phases of the cardiac cycle. The analysis of MRI data representing 1 cardiac cycle by use of the standard methodology required from 40 to 60 minutes, primarily for manual contour corrections.

Protocol 1

Linear regression analysis of RT3DE and MRI values resulted in high correlation coefficients and regression slopes near 1.0 for both EDV (CCC = 0.99, $r = 0.99$, $y = 1.03x + 1.9$) and ESV (CCC = 0.99, $r = 0.99$, $y = 1.06x - 1.2$) and EF (CCC = 0.97, $r = 0.98$, $y = 1.02x - 0.02$). Bland-Altman analysis showed no significant biases between the 2 techniques for EDV, ESV, and EF (bias: 2.9 mL, 2.8 mL, and -1.01% , respectively). These biases reflected systematic errors of 2.1%, 4.3%, and -1.8% of the corresponding mean values. The 95% limits of agreement were relatively narrow (EDV, 12 mL; ESV, 7 mL; EF, 5%), providing additional support to the close agreement between the 2 techniques. RT3DE underestimated the LV long axis by 12.9% at end diastole and overestimated it by 1.4% at end systole compared with MRI.

Figure 3 shows an example of time curves reflecting global and partial LV volumes and regional wall motion obtained in 1 patient from RT3DE and MRI data. All curves showed good agreement between the 2 modalities. This high level of agreement was confirmed by statistical analysis of the point-by-point data obtained in the entire group enrolled in this protocol. ANOVA showed no significant differences between RT3DE and MRI measurements for either volumes or wall motion. Global LV volume (Figure 4) showed excellent correlation and a negligible bias of 1.4 mL (1.3% of mean MRI value) with narrow 95% limits of agreement at ± 20 mL (18.7% of mean MRI value). The CCC was 0.97, and percent discordance was only $6 \pm 3\%$.

The correlation between RT3DE and MRI for the partial volumes ranged between good and excellent but showed pronounced differences between the different LV levels, with markedly lower rates of agreement at the apical level (Figure 5, right) compared with those at the basal and midventricular levels (Figure 5, left and middle). The CCC reflected this trend: 0.96 for basal, 0.97 for mid, and 0.80 for apical volumes. Bland-Altman analysis showed only small biases of -0.5 , 1.7, and 1.1 mL for the basal, mid, and apical levels, respectively (-1% , 4%, and 6% of the corresponding mean MRI partial volume) and narrow limits of agreement at 11, 8, and 10 mL. The calculated percent discordance values were $9 \pm 6\%$, $8 \pm 4\%$, and $21 \pm 12\%$ for the basal, mid, and apical partial volumes, respectively, confirming the lower rates of agreement at the apical level.

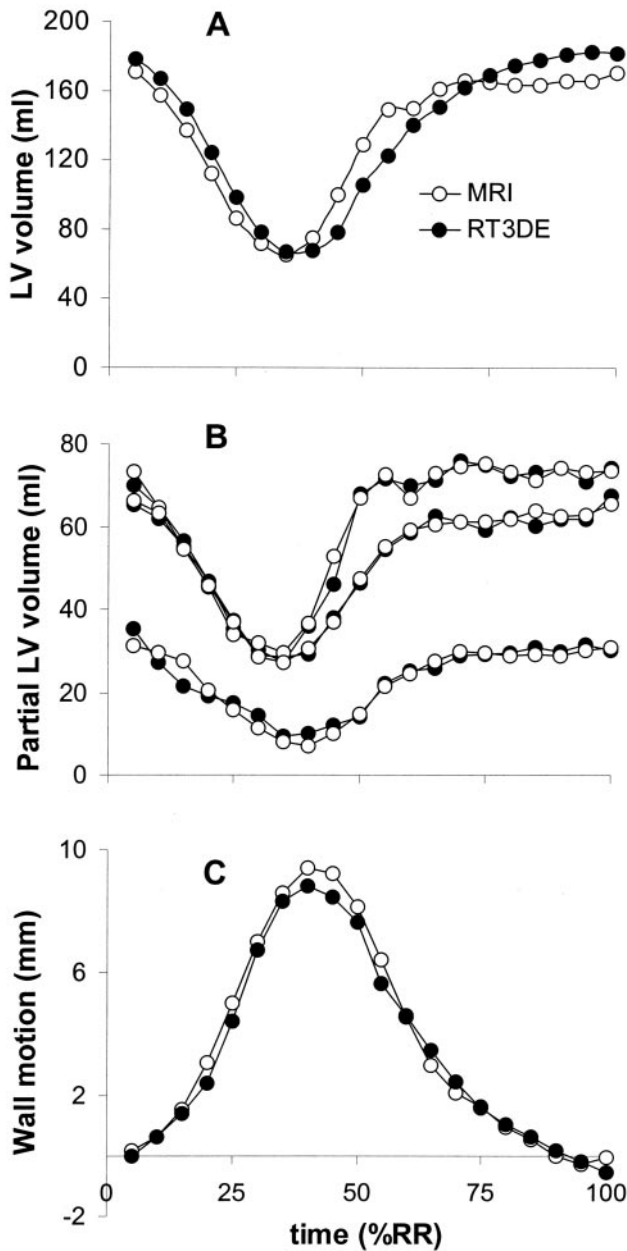


Figure 3. Example of time curves obtained in 1 patient from RT3DE (solid dots) and MRI data (open dots): (A) global LV volume, (B) partial LV volumes (from top to bottom: basal mid and apical), and (C) regional wall motion measured in 1 endocardial surface segment (mid anteroseptal).

The correlation between MRI- and RT3DE-derived peak systolic wall motion values was modest ($r=0.69$, $CCC=0.64$) when calculated for all LV segments combined, with a bias of -1.3 mm (-15% of the mean MRI value) and 95% limits of agreement at ± 4.6 mm. With the apical segments excluded, the agreement with MRI was markedly improved ($r=0.89$, $CCC=0.87$), with only a minimal bias of -0.5 mm (only -6% of the mean MRI value) and 95% limits of agreement at ± 2.6 mm. The calculated percent discordance was $22 \pm 25\%$ for all segments combined, $40 \pm 34\%$ for apical segments, and only $13 \pm 12\%$ for the basal and midventricular segments.

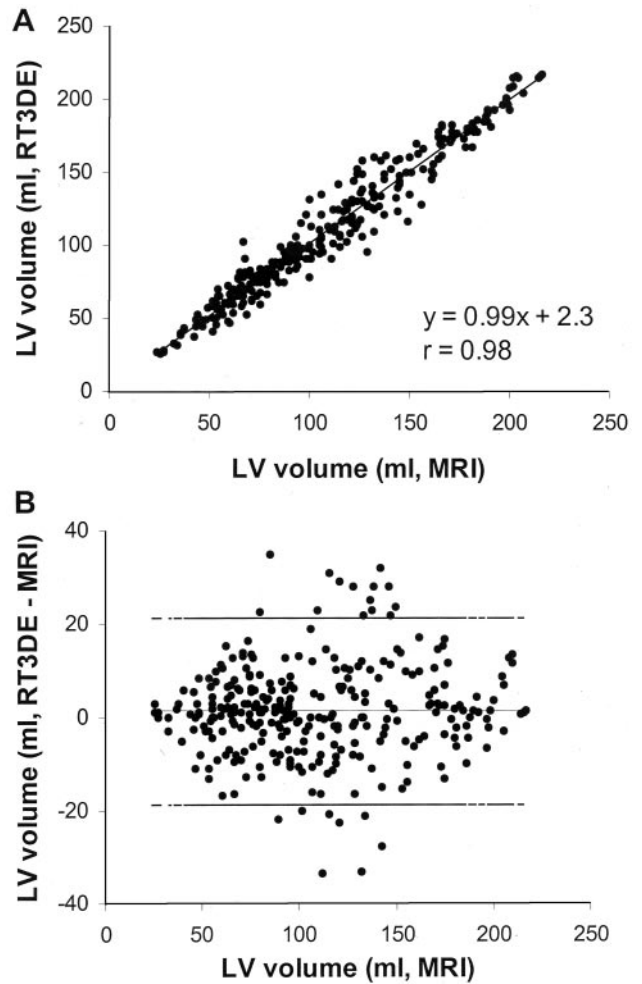


Figure 4. Results of linear regression (A) and Bland-Altman (B) analyses of point-by-point measurements of global LV volume obtained from RT3DE vs MRI values (see text for details).

Importantly, the 320 points shown in each panel in Figures 4 and 5 were obtained in 16 subjects throughout the 20 phases of the cardiac cycle. Thus, these points do not represent 320 independent measurements and could theoretically be clustered by patient. Regression analysis with dummy variables revealed that adding the dummy variable did not significantly reduce the residual sum of squares.²³ Therefore, clustering did not significantly affect these data, and the data could indeed be fitted to a single regression line.

Protocol 2

Figure 6 (left) shows an example of global LV volume–time curves obtained in a patient with DCM and an age-matched normal subject, reflecting the expected differences in LV dimensions (note scale differences), despite the similar morphology of the curves. In both cases, the peaks in the time derivatives of these curves clearly reflected the different phases of the cardiac cycle, including ejection, rapid filling, and atrial contraction, and demonstrated the reduced LV function in the patient with DCM. Figure 6 (right) shows the group composite LV volume–time curves with the respective SD bars, which were bigger in the DCM group, reflecting the

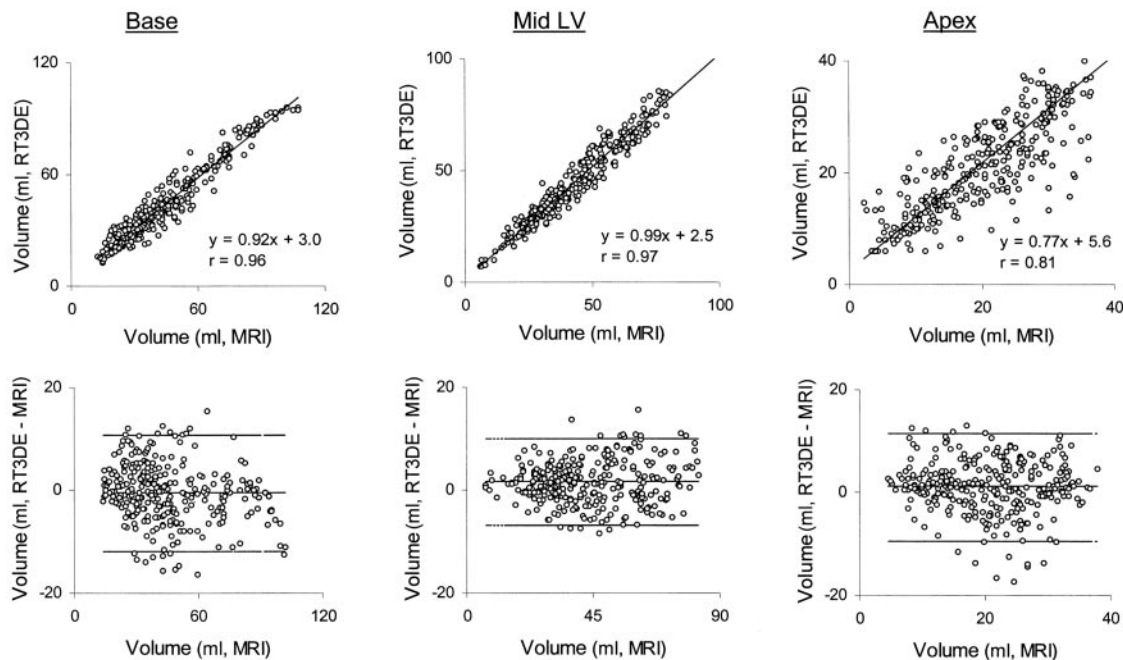


Figure 5. Results of linear regression (top) and Bland-Altman (bottom) analyses of point-by-point measurements of partial LV volume at basal (left), midventricular (middle), and apical (right) levels obtained from RT3DE compared with corresponding MRI reference values (see text for details).

variable severity of the disease in these patients. These composite curves demonstrated the intergroup differences in LV volume, with no overlap at any phase of the cardiac cycle. Figure 7 shows an example of regional volume and wall motion-time curves and RSF obtained in a normal subject (left) and a patient with DCM (middle). As expected, regional volumes in the patient with DCM were markedly increased compared with the normal subject. Also, both regional volume and wall motion curves showed a less synchronous pattern of contraction in the patient with DCM than in the normal subject. Despite the common morphological features between the wall motion curves in these 2 subjects, RSF was smaller in all segments, demonstrating on a regional basis the reduced LV function observed in patients with DCM. The

results of statistical analysis showed that all parameters of global and regional LV systolic and diastolic function calculated from volume and wall motion-time curves were significantly different between the 2 groups (Table).

Protocol 3

In the 11 patients with CAD, regional wall motion was graded visually by an expert reader as normal in 95 of 198 segments (48%) and abnormal in 103 of 198 segments (52%), including 65 of 198 hypokinetic segments (33%) and 38 of 198 akinetic or dyskinetic segments (19%). Figure 7 (right) shows data obtained in a patient with CAD and a regional wall motion abnormality in the apicolateral segment, as reflected by the low amplitude and asynchronous motion noted in both regional volume and wall

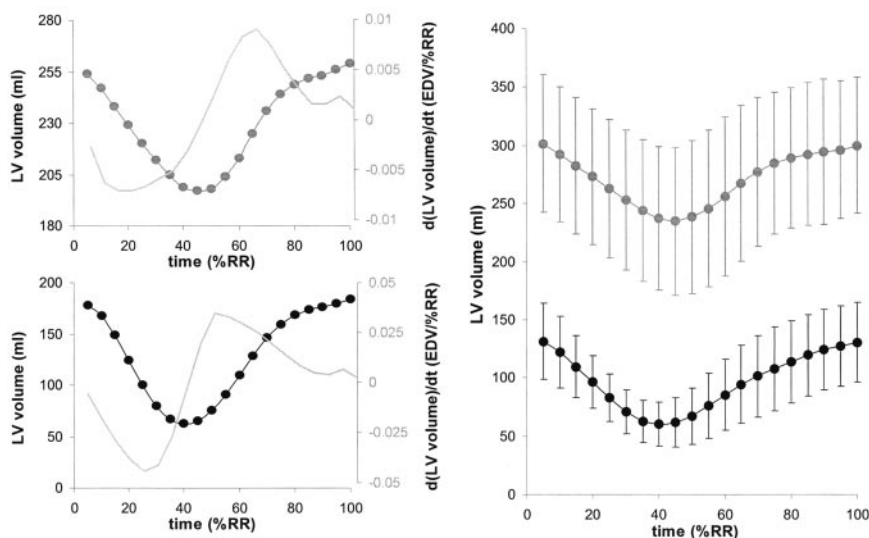


Figure 6. Example of global LV volume-time curves obtained in a patient with DCM (top, left) and an age-matched normal subject (bottom, left), shown with time-derivatives (solid lines without symbols, secondary y axes). Group composite LV volume-time curves (right) clearly differentiated between groups with no overlap at any phase of cardiac cycle.

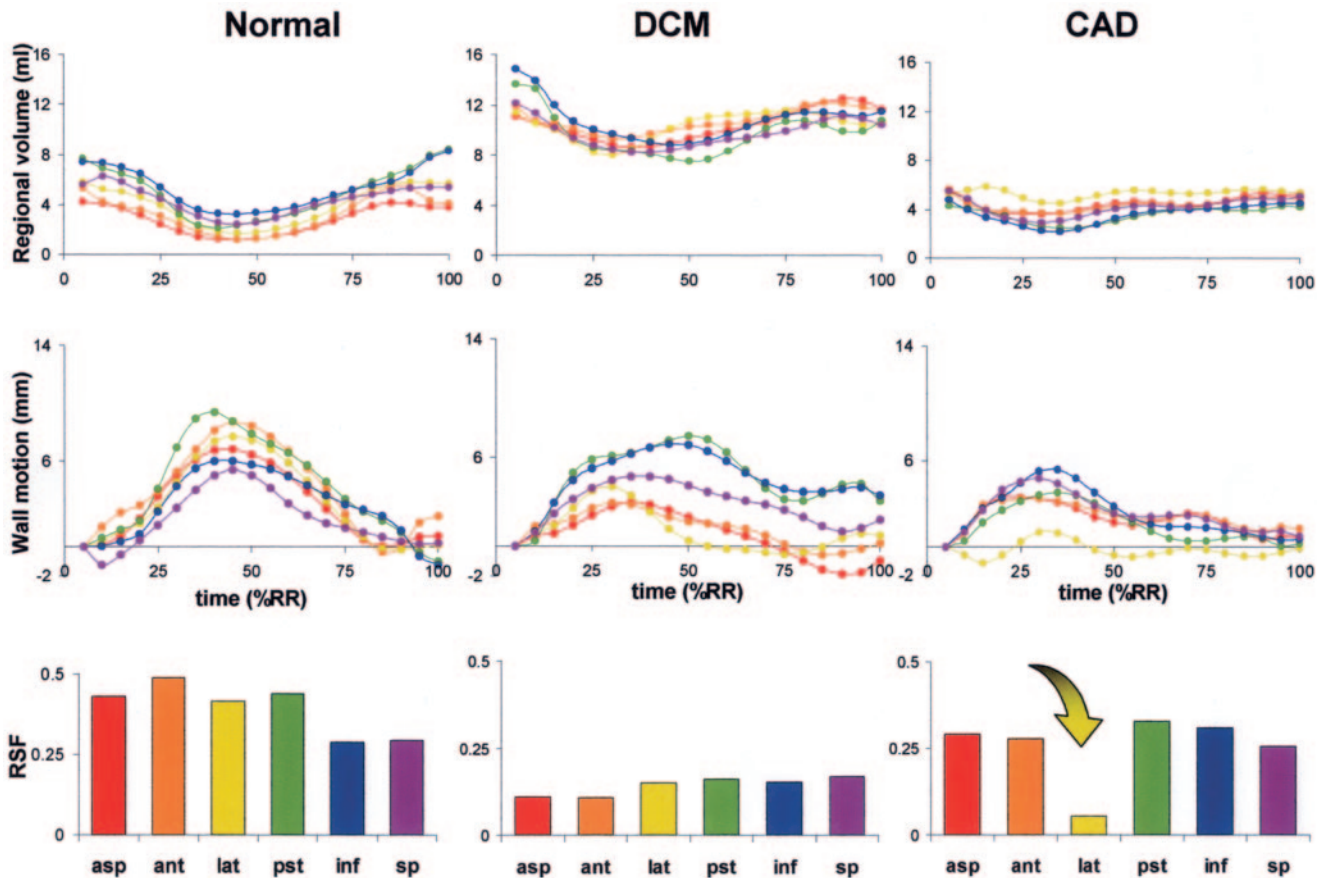


Figure 7. Example of regional volume (top) and wall motion (center) –time curves and RSF (bottom) in 6 apical segments, obtained in a normal subject (left), a patient with DCM (middle), and a patient with CAD (right) in lateral wall (arrow; see text for details).

motion–time curves. The RSF value was markedly reduced in the apicolateral segment. The RFS values obtained in the normal group (Figure 8, left) allowed correct automated classification of 170 of 198 segments (86%) as normal or abnormal in the CAD group, in agreement with the expert wall motion scores based on visual interpretation of 2D apical 2-, 3-, and 4-chamber views. Eighteen of 198 segments (9.1%) were misclassified as abnormal, and only 10 of 198 segments (5.1%) were falsely graded as

normal. Figure 8 (right) shows the rate of agreement with the expert grades for each individual endocardial surface segment. The area under the ROC curve was 0.85, and the 95% confidence interval was 0.74 to 0.89.

Parameters of Global LV Systolic and Diastolic Function Obtained in a Group of Normal Subjects (n=9) and a Group of Patients With DCM (n=9)

	Normal	DCM
EDV, mL	143±30	302±59*
ESV, mL	59±18	230±62*
EF, %	59±9	24±10*
PER, EDV/RR	-4.1±1.2	-0.9±0.3*
PRFR, EDV/RR	2.9±0.6	1.1±0.4*
PAFR, EDV/RR	1.02±0.84	0.29±0.19*
ISA	5.8±1.5	16.6±7.5*
RSF	0.39±0.07	0.16±0.08*

PER indicates peak ejection rate; PRFR, peak rapid filling rate; PAFR, peak atrial filling rate; RSF averaged in each subject over 18 endocardial surface segments.

*P<0.05 by paired t test between patients with DCM and their age-matched normal controls.

Discussion

The recent development of 3D echocardiographic imaging has resolved many of the limitations associated with the evaluation of LV volume from 2D images and significantly improved the accuracy of these measurements. However, analysis of 3D echocardiographic data described in previous studies was largely 2D, because it relied on model-based calculations of LV volume by interpolating endocardial contours detected on 2D planes extracted from the 3D data sets.^{7-9,14} Although some previous investigators described this methodology as accurate,²⁶ others found it to be limited in the presence of asymmetrical ventricles or wall motion abnormalities.²⁷ Moreover, the clinical assessment of regional LV function remains completely subjective, because even for 2D images, there is no widely accepted technique for quantitative analysis of regional wall motion. Our present study is the first to test the hypothesis that direct detection of the endocardial surface in the 3D domain could allow accurate continuous measurement of global and regional LV volumes throughout the cardiac cycle. Compared with a previous study by Zeidan and colleagues,¹² who studied LV volume–time

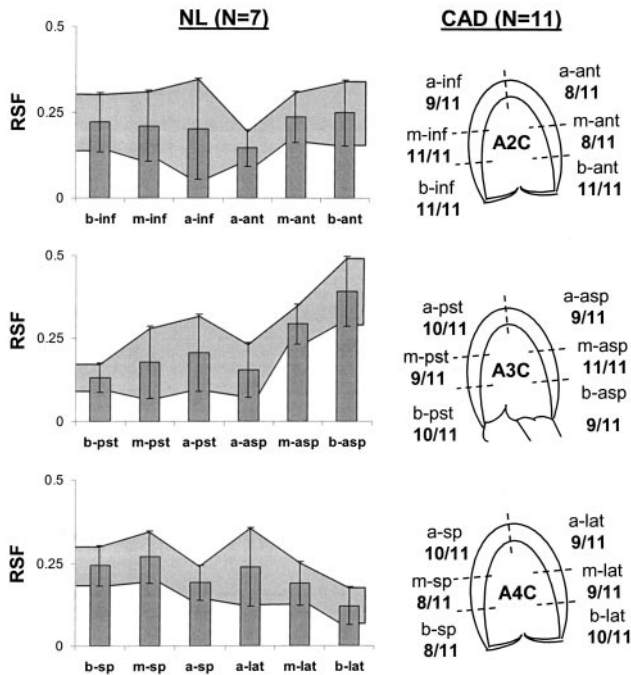


Figure 8. RSF calculated for 18 endocardial surface segments, averaged over a group of 7 subjects with normal wall motion (left), with error bars denoting ± 1 SD. For each segment, lower limit of normal RFS range (shaded areas) was used as a threshold for automated detection of hypokinetic segments and resulted in agreement rates with expert wall motion scores (right).

curves obtained by manual frame-by-frame tracing of endocardial contours in multiple slices, our approach offers the important advantage of being largely automated. The LV volume–time curves could be used for the objective assessment of LV systolic and diastolic function and provide the basis for automated interpretation of regional wall motion from RT3DE data sets.

The detection of the endocardial surface in the 3D domain was performed by use of level set models, which have been used previously in medical imaging for shape recovery and recognition.^{19,28,29} Our approach is based on the use of an implicit function without a priori morphological knowledge and is thus capable of detecting any complex shape in the 3D space without modeling.¹⁶ This is a clear advantage, because ventricular shape can be affected by disease. The time requirements of this procedure are likely to decrease as computational power continues to grow. An additional important advantage of our analysis procedure is that the use of a floating reference frame as a built-in feature of our segmentation addresses the problems associated with cardiac translation.

The hypothesis of this study was tested in 3 separate protocols. In protocol 1, we validated multiple variables that could be compared with data provided by the commercial MRI analysis package: EDV, ESV, EF, point-by-point estimates of global and partial LV volumes, and regional wall motion. Regional volume–time curves could not be directly validated, because these data are not calculated by the MRI analysis package. Partial volumes were relatively easily

obtained from the slice area data by use of the same standard model as used by the MRI package to calculate global volumes and allowed us to determine the effects of volume subdivision on the accuracy of our measurements. EDV, ESV, EF, and direct point-by-point comparisons of global LV volumes showed excellent concordance with MRI, as reflected by the excellent correlation, minimal biases, and low percent discordance between the RT3DE data and MRI data, in agreement with previous reports.^{12,14} Our results also showed that there was essentially no decrease in levels of agreement as a result of volume subdivision. Moreover, the high levels of agreement for wall motion measurements proved the ability of our technique to access information about regional LV function as readily as the current standard reference MRI technique.

The relatively low correlation and high percent discordance for the apical partial volumes and wall motion can be explained by several factors. First, near the apex, endocardial boundary is less well defined than at higher levels of the LV for both RT3DE and MRI, which is likely to affect the accuracy of its detection by both techniques. Second, whereas the use of a fixed number of slices of fixed thickness by MRI disregards systolic longitudinal shortening, the segmentation scheme of our volumetric analysis is based on true anatomic information. Although this feature of our analysis may partially explain the discrepancy between the 2 techniques in this study, it seems logical that this approach better reflects the true patterns of regional LV function than the current MRI-based techniques. In this regard, despite the superior endocardial definition, MRI cannot provide perfectly accurate measurements. Because these measurements are derived from discrete slices by geometrical modeling and rely on the operator's subjective tracing, MRI may not be the perfect "gold standard" for comparisons. Nevertheless, our choice of MRI as such stemmed from the fact that its use as the standard reference technique is common and well established.^{15,30–32}

Protocol 2 was designed as a first step for clinical testing of our technique. Importantly, this protocol is the first successful attempt to quantify regional LV wall motion from RT3DE data. It also confirmed the ability of RT3DE to assess LV asynchrony from clinical data as recently described by Krenning et al.¹⁵ We studied 2 groups of patients with well-known differences in global LV function to establish whether our technique is sufficiently sensitive to accurately detect these differences. In this regard, our choice of patients with DCM and age-matched normal subjects was natural, and the use of paired *t* tests allowed fair comparisons that were not affected by age. This choice also allowed us to test our technique on a regional basis knowing that every single segment in these patients would be hypokinetic without the need to corroborate regional LV dysfunction by other means, as would be necessary in patients with regional abnormalities. The availability of regional volume curves gave us access to regional timing information, which was used to successfully diagnose LV systolic asynchrony, known to be prevalent in patients with DCM.³³ This information could be extremely useful in strategizing resynchronization therapy.^{15,34} In summary, the results of this protocol proved the ability of our

technique to accurately detect LV dysfunction not only on a global but also on a regional basis and to diagnose asynchrony in the temporal patterns of LV contraction.

The ability to detect regional wall motion abnormalities was then further tested in protocol 3, which was aimed at establishing the clinical usefulness of segmental analysis of RT3DE data in patients with CAD, who are the ultimate target population of this methodology. The results of this protocol demonstrated the clinical feasibility of this approach, albeit in a small group of patients. However, the goal of this protocol was feasibility testing, which was achieved, as reflected by the high levels of agreement with the expert interpretation of regional wall motion.

Limitations

A limitation of our technique is that LV volume measurements obtained by apical imaging are known to be underestimated because of the inadvertent use of tangential scan planes,³⁵ especially in the presence of anterior and apical wall motion abnormalities.³⁶ Although recent studies have demonstrated the advantages of 3D imaging in this context, this issue requires further investigation. The use of cardiac MRI as a reference could be viewed as a limitation of this study, because MRI cannot provide perfectly accurate LV volume measurements, despite its superior endocardial definition, because these measurements are derived from manually traced discrete slices. Nevertheless, MRI is widely used as the standard, albeit an imperfect one, for LV volume measurements. Also, one might suggest that subjective visual interpretation of wall motion in protocol 3 is not the ideal standard for comparison and that other quantitative measurements of regional LV function could have been used. Indeed, in protocol 1, our measurements were validated against an MRI reference on different levels, including global and partial LV volumes and regional wall motion. Having these measurements validated, we designed the ensuing protocols to test the feasibility of the use of our technique in the clinical setting. In particular, we compared this technique with the most widely used clinical standard for echocardiographic assessment of wall motion, ie, visual interpretation of 2D images, despite the subjective nature of this methodology. In addition, the relatively small number of normal subjects used as controls in protocol 3 could also be viewed as a limitation. However, LV volume curves obtained in these normal subjects were very similar to those obtained in a larger group of normal subjects by Zeidan et al.¹²

With these limitations in mind, it is important to remember that this study constitutes the first attempt to objectively interpret LV wall motion from RT3DE data by use of a technique that is fully automated once the endocardial surface and segmentation are complete. Our results warrant future studies aimed at clinical testing in larger patient populations and further validation.

Summary

This is the first study to develop, validate, and test in the clinical setting a new technique aimed at fast quantification of global and regional LV function from RT3DE data. The results of this study proved that true volumetric analysis of RT3DE data for quantitative assessment of LV function

without the limitations of 2D imaging or 2D-based analysis of 3D data is feasible. This approach allows the quantification of not only global but also regional LV function, including the magnitude and timing of regional wall motion. This analysis holds promise for multiple clinical applications, such as objective diagnosis of regional wall motion abnormalities, guidance of resynchronization therapy, and evaluation of regional diastolic performance in a variety of disease states affecting myocardial relaxation properties. Witnessing how the RT3DE technology is gaining widespread use and anticipating the development of commercial software for true volumetric analysis, we believe that this combination will become routine in clinical practice in the near future.

Acknowledgments

Dr Corsi is a recipient of a grant from the Marco Polo Program at the University of Bologna, Italy. This study was supported by a Grant-in-Aid from the American Heart Association (Dr Mor-Avi, principal investigator).

References

1. Gorcsan J III, Morita S, Mandarino WA, Deneault LG, Kawai A, Kormos RL, Griffith BP, Pinsky MR. Two dimensional echocardiographic automated border detection accurately reflects changes in left ventricular volume. *J Am Soc Echocardiogr.* 1993;6:482–489.
2. Marcus RH, Bednarz J, Coulden R, Shroff S, Lipton M, Lang RM. Ultrasonic backscatter system for automated on-line endocardial boundary detection: evaluation by ultrafast computed tomography. *J Am Coll Cardiol.* 1993;22:839–847.
3. Lang R, Vignon P, Weinert L, Bednarz J, Korcarz C, Sandelski J, Koch R, Prater D, Mor-Avi V. Echocardiographic quantification of regional left ventricular wall motion using color kinesis. *Circulation.* 1996;93:1877–1885.
4. Mor-Avi V, Vignon P, Koch R, Weinert L, Spencer KT, Lang RM. Segmental analysis of color kinesis images: new method for quantitative assessment of left ventricular contraction and relaxation. *Circulation.* 1997;95:2082–2097.
5. Sutherland G, Stewart M, Groundstroem K, Moran C, Fleming A, Guell-Peris F, Riemersma R, Fenn L, Fox KAA, McDicken W. Color Doppler myocardial imaging: a new technique for the assessment of myocardial function. *J Am Soc Echocardiogr.* 1994;7:441–458.
6. Erbel R, Wallbridge DR, Zamorano J, Drozd J, Nesser HJ. Tissue Doppler echocardiography. *Heart.* 1996;76:193–196.
7. Hozumi T, Yoshikawa J, Yoshida K, Akasaka T, Takagi T, Yamamuro A. Three-dimensional echocardiographic measurement of left ventricular volumes and ejection fraction using a multiplane transesophageal probe in patients. *Am J Cardiol.* 1996;78:1077–1080.
8. Gopal AS, Schnellbaecher MJ, Shen Z, Boxt LM, Katz J, King DL. Freehand three-dimensional echocardiography for determination of left ventricular volume and mass in patients with abnormal ventricles: comparison with magnetic resonance imaging. *J Am Soc Echocardiogr.* 1997;10:853–861.
9. Mele D, Maehle J, Pedini I, Alboni P, Levine RA. Three-dimensional echocardiographic reconstruction: description and applications of a simplified technique for quantitative assessment of left ventricular size and function. *Am J Cardiol.* 1998;81:107G–110G.
10. Shiota T, Jones M, Chikada M, Fleishman CE, Castellucci JB, Cotter B, DeMaria AN, von Ramm OT, Kisslo J, Ryan T, Sahn DJ. Real-time three-dimensional echocardiography for determining right ventricular stroke volume in an animal model of chronic right ventricular volume overload. *Circulation.* 1998;97:1897–1900.
11. Sugeng L, Weinert L, Lang RM. Left ventricular assessment using real time three dimensional echocardiography. *Heart.* 2003;89(suppl 3):iii29–iii36.
12. Zeidan Z, Erbel R, Barkhausen J, Hunold P, Bartel T, Buck T. Analysis of global systolic and diastolic left ventricular performance using volume-time curves by real-time three-dimensional echocardiography. *J Am Soc Echocardiogr.* 2003;16:29–37.
13. Collins M, Hsieh A, Ohazama CJ, Ota T, Stetten G, Donovan CL, Kisslo J, Ryan T. Assessment of regional wall motion abnormalities with

- real-time 3-dimensional echocardiography. *J Am Soc Echocardiogr*. 1999;12:7-14.
14. Kuhl HP, Schreckenber M, Rulands D, Katoh M, Schafer W, Schummers G, Bucker A, Hanrath P, Franke A. High-resolution trans-thoracic real-time three-dimensional echocardiography: Quantitation of cardiac volumes and function using semi-automated border detection and comparison with cardiac magnetic resonance imaging. *J Am Coll Cardiol*. 2004;43:2083-2090.
 15. Krenning BJ, Szili-Torok T, Voormolen MM, Theuns DA, Jordaens LJ, Lancee CT, De JN, Van Der Steen AF, Ten Cate FJ, Roelandt JR. Guiding and optimization of resynchronization therapy with dynamic three-dimensional echocardiography and segmental volume-time curves: a feasibility study. *Eur J Heart Fail*. 2004;6:619-625.
 16. Corsi C, Saracino G, Sarti A, Lamberti C. Left ventricular volume estimation for real-time three-dimensional echocardiography. *IEEE Trans Med Imaging*. 2002;21:1202-1208.
 17. Schiller NB. Two-dimensional echocardiographic determination of left ventricular volume, systolic function, and mass: summary and discussion of the 1989 recommendations of the American Society of Echocardiography. *Circulation*. 1991;84(suppl 1):I-280-I-287.
 18. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539-542.
 19. Malladi R, Sethian JA, Vemuri BC. Shape modeling with front propagation: a level set approach. *IEEE Trans Pattern Analysis Machine Intelligence*. 1995;17:158-175.
 20. Sethian JA. *Level Set Methods and Fast Marching Methods*. Cambridge, UK: Cambridge University Press; 1999.
 21. Lucas BD, Kanade T. An iterative image registration technique with an application to stereo vision. *Proceedings of the DARPA Image Understanding Workshop*. 1981;121-130.
 22. Barron JL, Fleet DJ, Beauchemin SS. Performance of optical-flow techniques. *Int J Comput Vision*. 1994;12:43-77.
 23. Glantz S, Slinker BK. Repeated measures. *Primer of Applied Regression and Analysis of Variance*. New York, NY: McGraw-Hill; 1990:381-463.
 24. Lin LI. A concordance correlation coefficient to evaluate reproducibility. *Biometrics*. 1989;45:255-268.
 25. Metz CE. Basic principles of ROC analysis. *Semin Nucl Med*. 1978;8:283-298.
 26. Buck T, Schon F, Baumgart D, Leischik R, Schappert T, Kupferwasser I, Meyer J, Gorge G, Haude M, Erbel R. Tomographic left ventricular volume determination in the presence of aneurysm by three-dimensional echocardiographic imaging. I: asymmetric model hearts. *J Am Soc Echocardiogr*. 1996;9:488-500.
 27. Wyatt HL, Meerbaum S, Heng MK, Gueret P, Corday E. Cross-sectional echocardiography, III: analysis of mathematic models for quantifying volume of symmetric and asymmetric left ventricles. *Am Heart J*. 1980;100:821-828.
 28. Chen YM, Huang F, Tagare HD, Rao M, Wilson D, Geiser EA. Using prior shape and intensity profile in medical image segmentation. *Proceedings of the 9th International Conference on Computer Vision*. 2003; 1117-1125.
 29. Paragios N. A level set approach for shape-driven segmentation and tracking of the left ventricle. *IEEE Trans Med Imaging*. 2003;22:773-776.
 30. Malm S, Frigstad S, Sagberg E, Larsson H, Skjaerpe T. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography: a comparison with magnetic resonance imaging. *J Am Coll Cardiol*. 2004;44:1030-1035.
 31. Alfakih K, Reid S, Jones T, Sivananthan M. Assessment of ventricular function and mass by cardiac magnetic resonance imaging. *Eur Radiol*. 2004;14:1813-1822.
 32. Spuentrup E, Schroeder J, Mahnken AH, Schaeffter T, Botnar RM, Kuhl HP, Hanrath P, Gunther RW, Buecker A. Quantitative assessment of left ventricular function with interactive real-time spiral and radial MR imaging. *Radiology*. 2003;227:870-876.
 33. Godoy I, Mor-Avi V, Weinert L, Vignon P, Korcarz C, Spencer KT, Lang RM. Use of color kinesis for evaluation of left ventricular filling in patients with dilated cardiomyopathy and mitral regurgitation. *J Am Coll Cardiol*. 1998;31:1598-1606.
 34. Hong TE, Sugeng L, Weinert L, Mor-Avi V, DeSai A, Lang RM, Knight BP. Use of real-time three-dimensional echocardiography to measure ventricular dyssynchrony and assess cardiac resynchronization in heart failure patients. *J Am Coll Cardiol*. 2004;43:309A.
 35. Erbel R, Schweizer P, Lambertz H, Henn G, Meyer J, Krebs W, Effert S. Echoventriculography: a simultaneous analysis of 2D echocardiography and cineventriculography. *Circulation*. 1983;67:205-215.
 36. Muller S, Bartel T, Katz MA, Pachinger O, Erbel R. Partial cut-off of the left ventricle: determinants and effects on volume parameters assessed by real-time 3-D echocardiography. *Ultrasound Med Biol*. 2003;29:25-30.

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