

**THREE-DIMENSIONAL ECHOCARDIOGRAPHY  
AN ACCURATE TECHNIQUE FOR CARDIAC  
QUANTIFICATION**

ISBN 90-73235-76-6

Printed by Optima Grafische Communicatie, Rotterdam.

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**Cover illustrations:**

Upper diagram shows the principle of precordial 3DE acquisition using 2° rotational intervals from the apical transducer position.

Middle figure shows the clinical application of paraplane analysis from 3DE data set to calculate the mitral valve area (upper left panel), left ventricular volume (upper right panel), Left atrial myxoma (lower left panel) and left ventricular mass (lower right panel).

Lower figure shows the principle of left ventricular volume measurement using the paraplane analysis with 8 parallel equidistant short axis slices spanning the ventricular cavity from the apex to the mitral annulus.

**Back illustrations:**

*Right photo.* Imhotep (2800 B.C.), advisor to Pharaoh Djoser, originator of the step pyramid at Saqqara and the first physician in history with a written records. Imhotep means literally "he who comes in peace".

*Left upper photo.* The step pyramid at Saqqara (2800 B.C.).

*Left lower photo.* The three pyramids of Kufu, Kafa and Menkaura at Giza (2500 B.C.).

**THREE-DIMENSIONAL ECHOCARDIOGRAPHY  
AN ACCURATE TECHNIQUE FOR CARDIAC  
QUANTIFICATION**

**Drie-dimensionale echocardiografie  
Een nauwkeurige techniek voor cardiale kwantificering**

*Erasmus Universiteit Rotterdam*

**PROEFSCHRIFT**

**Ter verkrijging van de graad van doctor  
aan de Erasmus Universiteit Rotterdam  
op gezag van de rector magnificus Prof. dr P.W.C. Akkermans M.A.  
en volgens besluit van het College voor Promoties**

**De openbare verdediging zal plaatsvinden  
op woensdag 13 Januari 1999 om 13.45 uur.**

**door**

**Youssef Fathy Mohamed Nosir**

**geboren te Cairo, Egypt**

**Promotiecommissie**

**Promotor:**

**Prof.dr. J.R.T.C. Roelandt**

**Overige Leden:**

**Prof.dr. M.M. Goma**

**Prof.dr. C.A. Visser**

**Prof.dr.Ir. N. Bom**

**Co-promotor:**

**Dr. F.J. ten Cate**

Financial support by the Netherlands Heart Foundation for publication of this thesis is gratefully acknowledged.

To The Soul of My Father and To My Mother  
To Ghada, Mahmoud and Ahmed

Whom I Love Very Much and Whom I Owe  
Much More Than That I Can Give

*Y.F.M. Nosir*



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## CHAPTER 1

### INTRODUCTION

#### BACKGROUND

Cardiac ultrasound has become the dominant imaging technology in clinical cardiology. Two-dimensional echocardiography (2DE) gained widespread use and allows rapid and comprehensive evaluation of anatomy and function by providing tomographic cardiac views recorded from transthoracic (TTE) or transesophageal (TEE) acoustic windows. However, the diagnosis of a cardiac disorder is based on a mental spatial reconstruction process of these views into their correct geometry. This process is not always easy and accurate particularly in complex congenital heart disease and in patients with coronary artery disease and distorted ventricles. Three-dimensional echocardiography (3DE) obviates these limitations and is able to provide more accurate quantitative and qualitative information in complex disorders. The first attempt to obtain 3DE images for cardiac diagnosis and quantification started two decades ago.<sup>1-4</sup> 3DEs were computed from a series of nonparallel echocardiographic images using either an articulated device or an acoustic ranging technique using multiple spark gaps for spatial registration. However, this approach was tedious and time consuming. In addition, cycle selection, border digitizing and tracing together with the computer analysis would take several days. With the revolutionary advances in the computer technology, 3DE acquisition is considerably shortened with optimal spatial and temporal registration by using computer controlled transducer systems.

Approaches to 3DE are:

- Random acquisition with external reference (mechanical, acoustic and electromagnetic).
- Predetermined acquisition with internal reference (linear, fan like and rotational).
- Real time acquisition (pyramidal volumetric scan).

Real time volumetric scan is by definition the ideal technique for 3DE.<sup>5</sup> Initial results are promising, but further improvement in image quality is needed for routine clinical application.

In practice the most commonly used methods are the random acquisition and the predetermined rotational acquisition technique.

#### *Random acquisition.*

In this method for left ventricular volume (LVV) measurement, the 3DE data set is acquired using free-hand scanning to obtain a series of non-parallel parasternal short-axis images (8 to 9 images in end-diastole and end-systole). A line-of-intersection display is used as a guide. The constructed line of intersection is derived from two temporally dispersed short axis views selected from two parasternal long axis views. Each acquired short axis is then readjusted by displaying this line of intersection several times. All images for ventricular reconstruction are acquired during suspended respiration. A polyhedral surface reconstruction algorithm has been adapted for LVV computation using the traced endocardial borders of the short axis image.<sup>6-8</sup> However, with the parasternal window it is often impossible to define the basal and apical landmarks for the LV long axis in a single cross section. Two different long axis views are necessary to avoid the possible error for alignment.

***Predetermined acquisition with rotational approach.***

Rotational acquisition software has been interfaced to commercially available ultrasound systems for both TTE and TEE. Rotational acquisition is performed usually with steps of 2° or 3°, controlled by an ECG and respiratory gating algorithm. The images are formatted in their correct rotational sequence according to their ECG phase in a volumetric data set. Each complete data set contains images recorded between 0° to 180° of rotation. The post-processing of the data set is performed off-line and a "trilinear cylindric interpolation" algorithm is used to fill the gaps in the far fields.<sup>9,10</sup> Images can be displayed from the 3DE data in the following modes: anyplane (obtaining countless cut planes at any direction independent from the point of origin of the sector scan), paraplane (parallel short-axis cuts along a defined long axis) and volume rendering (different algorithms are applied to maintain tissue grey level information and to give the perception of depth).

For quantitative purposes the paraplane mode is used to obtain multiple parallel equidistant cross-sectional views spanning the desired cardiac structure for area and volume measurements.

**ADVANTAGES**

3DE provides a unique tool to study patients with complex geometry. With the standardized examination procedure and objective display of the anatomy and the complex relationships among different structures, 3DE improves the accuracy of qualitative assessment and decreases the variability of interpretation among echocardiographers. En face views are uniquely 3D and allow qualitative and quantitative assessment of patients with atrial septal defect (ASD), ventricular septal defect (VSD) and valvular diseases. Paraplane analysis allows accurate and reproducible pixel (surface area) and voxel (volume) based quantification. The advantages, display modalities and the possible clinical applications of 3DE using the rotational acquisition technique are discussed in chapter 2.

**PRESENT LIMITATIONS**

Most currently available 3DE systems use ECG and respiration triggered image acquisition. This requires 3 to 5 minutes and in certain circumstances up to 10 minutes, depending on the rotational intervals and the variability in cardiac cycle length. Artefacts from inadvertent patient or operator movement are more likely when the procedure of image acquisition takes longer. This long acquisition time is a significant limitation in some clinical scenarios such as intra-operative studies, the interventional laboratory, stress echocardiography and contrast perfusion echocardiography. Real time 3DE would allow to overcome these limitations. 3DE using an ultrafast continuously rotating phased array transducer can be an alternative to real time imaging, as it will reduce the acquisition time to seconds. In addition, with the advances in computer technology, processing and analysis time has decreased from hours to minutes and is targeted to reach seconds in the near future.

With rotational acquisition systems the image accuracy in the 3D volumetric data set varies according to both the angular step and the width of the ultrasound beam. Since the beam width depends on the scan depth and scan angle, the image resolution will degrade at points further away from the transducer and at larger scan angle. This is important for the selection of anyplane images. Currently available experience suggests that, the best possible resolution is gained within the focal region along the central axis of the transducer.

Reconstructed images of cut planes far away from the rotational axis will have a reduced reliability although they may look acceptable because of computerized smoothing. In addition, 3DE image information depends on the 2DE scan plane density. At certain scan depth, increase of the intervals angle will reduce the acquisition time, but at the same time will increase the gaps between consecutive scan planes, resulting in lower sampling data of the volume. This allows for LVV studies, whereas anyplane studies for structure analysis require a much higher sampling rate.

At present most of the endocardial border tracing is done manually. This is laborious, time consuming and subjective. Automated border detection algorithms are available and initial results show that it reduces the analysis time and allows more accurate calculation of LVV and function. In addition, endocardial border delineation can be enhanced by using the second harmonic imaging or adding intravenous injections of contrast agents for endocardial border delineation.

The aim of the present thesis was to assess feasibility and to validate 3DE with rotational acquisition technique for accurate and reproducible quantification of cardiac function and valve orifice area.

Serial monitoring of LVV and derived parameters is important for clinical decision making, prediction of outcome in many cardiac disorders and following medical or surgical interventions.<sup>11,12</sup> Currently used imaging methods including angiography<sup>13-15</sup>, radionuclide angiography (RNA)<sup>16-17</sup>, and 2DE<sup>18-21</sup> require the use of geometric assumptions for LV shape. MRI produces accurate measurement of LVV<sup>22-23</sup>, but is not widely available. Since 3DE allows calculation of LVV and EF without geometric assumptions, the technique may be equally accurate and has practical advantages.<sup>7,8,10</sup>

Quantification of LV mass is important and has both therapeutic and prognostic implications in many cardiac diseases.<sup>24</sup> Measurement of myocardial mass has been performed by both M-mode and 2DE<sup>25-27</sup> but needs LV geometrical assumptions.<sup>28</sup> 3DE enables the analysis of complex anatomical structures in off-line reconstructed cutplanes from the dataset using Simpson's rule.<sup>29-31</sup> In addition, the suboptimal delineation of epicardial and endocardial contour could be overcome by intravenous injection of echocardiographic contrast agents.

Accurate measurement of the valve orifice area is essential in the evaluation of patients with valve stenosis. Measurement of valve orifice area using the formula of Gorlin and Gorlin<sup>32,33</sup> from hemodynamic data obtained at cardiac catheterization has been considered the reference method. However this method is invasive and influenced by valve geometry<sup>34</sup>, LV function, cardiac output,<sup>35</sup> pressure gradients<sup>36</sup> and severity of concomitant regurgitation.<sup>37</sup>

Two-dimensional and Doppler echocardiography are presently the principal noninvasive tools to obtain morphologic and hemodynamic information concerning the mitral and aortic valves. 2DE allows imaging of the stenotic orifice and its direct measurement by planimetry.<sup>38</sup> However, 2DE is highly dependent on the examination technique particularly in locating the stenotic orifice in its short-axis.<sup>39,40</sup> Mitral valve orifice area derived by pressure half-time using Doppler echocardiography is now an acceptable method and can be used in the presence of mild regurge.<sup>41,42</sup> Limitations of this method include concomitant moderate or severe aortic regurgitation and poor left ventricular compliance.<sup>43,44</sup>

Doppler evaluation of aortic valve flow allows quantification of transvalvular gradient and valve resistance. Valve area calculation is usually indirect, based upon the continuity equation.<sup>45</sup> 3DE allows accurate valve orifice area measurement by generating a series of equidistant parallel cross-sections through the long axis and identification of the smallest orifice area of mitral or aortic valve apparatus.<sup>39,40</sup>

## OUTLINE OF THIS THESIS

*Chapter 2.* Methodological description of precordial rotational 3DE technique was provided. In addition, an overview was given for its various display modalities with some examples.

*Chapter 3.* The feasibility and reproducibility of 3DE using Simpson's rule for calculating left ventricular ejection fraction, was studied and compared with RNA. Special attention was paid to determine the largest slice thickness that can be used for left ventricular volume and ejection fraction calculation without losing accuracy.

*Chapter 4.* Left ventricular ejection fraction calculation from 3DE using both Simpson's rule and biplane modified Simpson's method was calculated and compared with values obtained from RNA, in patients with normal and abnormally shaped ventricles. In addition, the accuracy of left ventricular ejection fraction calculated by 3DE methods with respect to each individual left ventricular site of regional dysfunction was studied.

*Chapter 5.* The spatial angle between both the apical two chamber and the apical long axis views relative to the apical four chamber view, was calculated. In addition, values of left ventricular volume and ejection fraction calculated with biplane ellipse method using the apical four chamber view with either the apical two chamber or the apical long axis view, were compared with the values obtained from 3DE.

*Chapter 6.* This study was designed to validate the paraplane analysis with 8 equidistant short axis slices for left ventricular volume and ejection fraction calculation with comparison to MRI.

*Chapter 7.* The day-to-day variability of left ventricular volume and ejection fraction calculation by 3DE using the paraplane analysis with 8 equidistant short axis slices was calculated. In addition, observer variability was studied and compared with values obtained from MRI.

*Chapter 8.* In this study we defined a faster method for precordial 3DE rotational acquisition by finding the largest 3DE rotational interval that can be used for left ventricular volume calculation without losing accuracy as compared with MRI.

*Chapter 9.* Review article for different 3DE techniques used for calculating left ventricular volume and ejection fraction.

*Chapter 10.* The feasibility, reproducibility and accuracy of 3DE for calculating mitral valve area in patients with native mitral stenosis were studied.

*Chapter 11.* The feasibility, reproducibility and accuracy of 3DE for calculating aortic valve area in patients with native aortic stenosis were studied. In addition, the errors resulting from planimetry in suboptimally selected cross-sectional images were calculated.

*Chapter 12.* This study was performed to analyse the alteration in size and geometry of left ventricular outflow tract in patients with hypertrophic cardiomyopathy.

*Chapter 13.* This study was aimed to determine whether myocardial enhancement with a novel contrast agent (Quantison Depot<sup>TM</sup>) could improve the reproducibility of mass quantification assessed with 3DE in a porcine model.

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## CHAPTER 2

### **PRECORDIAL MULTIPLANE ECHOCARDIOGRAPHY FOR DYNAMIC ANYPLANE, PARAPLANE AND THREE- DIMENSIONAL IMAGING OF THE HEART**

**Roelandt J, Salustri A, Vletter W, Nosir Y, Bruining N.**

*Thoraxcentre J 1994;6:4-13*

In two decades, cardiac ultrasound has become the most widely disseminated diagnostic imaging method in clinical cardiology. The method allows one to noninvasively look into the heart by providing serial tomographic views recorded from limited precordial and transesophageal acoustic windows. However, most of our diagnostic decision making is based on a mental reconstruction of these tomographic views into their three-dimensional geometry. Clearly, this is a difficult process requiring skill and experience. Thus, the availability of objective and more intelligible three-dimensional images would greatly facilitate the diagnosis of unknown and complex pathology and improve diagnostic accuracy in general. This also applies to other tomographic techniques such as computer tomography and magnetic resonance imaging.

The most practical approach to three-dimensional echocardiography is the acquisition of a consecutive series of tomographic views using standard available ultrasound equipment together with accurate spatial and temporal information and subsequent "off-line" reconstruction. Recently, computer technology became available allowing both precordial and transesophageal controlled image acquisition using parallel,<sup>1-3</sup> fan-like<sup>4-6</sup> and rotational scanning methods.<sup>7-9</sup> Data processing algorithms for volume rendered reconstruction with grey scale tissue imaging represented another major breakthrough.<sup>10</sup>

Three-dimensional reconstruction using transesophageal rotational acquisition with a commercially available multiplane imaging probe has been described.<sup>7,8</sup> In this approach, a computer-based steering logic which considers both heart cycle variation and the respiration phase controls a step motor which rotates the imaging plane in predetermined steps via the external control knob of the multiplane probe.

However, the rotational approach can also be used at a single pivot point over a small acoustic window. A transducer assembly has been constructed which can accommodate any commercially available transducer for precordial rotational image acquisition.<sup>9</sup> The transducer is centered in the inner cylindrical housing of a double walled cylindrical rotation mechanism and can be rotated around its center axis via a step-motor under control of the same steering logic as is used for transesophageal image acquisition. With this transducer assembly, controlled precordial multiplane echocardiography can be performed similar to multiplane transesophageal echocardiography. This approach is not only the basis for routine three-dimensional echocardiography but also for a more standardized semi-automated examination procedure.<sup>8-9</sup>

In this chapter we discuss various possibilities with this prototype transducer assembly demonstrating the feasibility of precordial three-dimensional echocardiography in adult patients.

## **REQUIREMENTS FOR THREE-DIMENSIONAL RECONSTRUCTION WITH ROTATIONAL APPROACH**

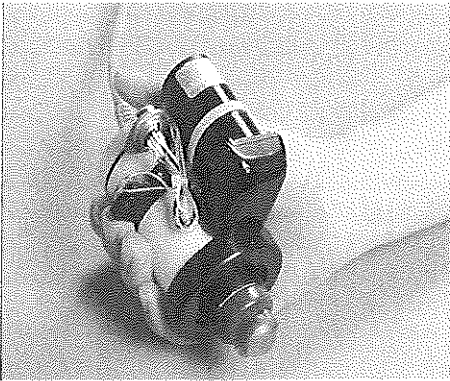
- (1) Acquisition (sequential rotational cardiac cross-sections with spatial and temporal information)
- (2) Processing (resampling and conversion from polar to Cartesian coordinates)
- (3) Interpolation (filling the space between individual cross-sections)
- (4) Enhancement (noise suppression)



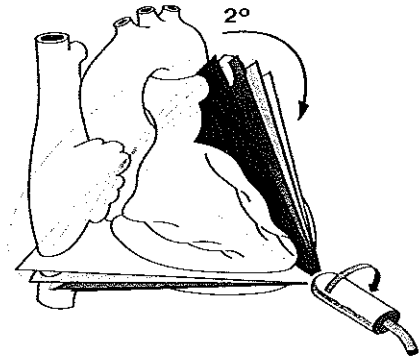
(5) Display (anyplane, paraplane echocardiography and volume rendered images).<sup>11</sup>

### THE PRECORDIAL TRANSDUCER ASSEMBLY AND ULTRASOUND SYSTEM

The inner components of the transducer assembly for precordial image acquisition consist of a cylindrical housing with a cog-wheel to which any standard precordial imaging transducer can be adapted. This cylindrical housing with the contained transducer fits into a cylindrical holder and can be rotated with a step-motor via a wheel-work interface (figure 1). The step-motor is commanded by a steering-logic for controlled image acquisition (Echo-scan, TomTec GmbH, Munich, Germany). The transducer assembly is hand-held and can be placed either over the parasternal, apical or subcostal window (figure 2). The probe can be aimed in any direction to find the center axis of the sector images encompassing the region or structure of interest. During acquisition, the probe is kept stationary while the transducer is rotated through 180° degrees around this center axis in predetermined steps by means of the step-motor. The sampled cardiac cross-sections encompass a conical image volume with the transducer positioned at its apex. The video output of the echocardiographic imaging system is interfaced with the TomTec Echo-scan system for three-dimensional reconstruction.<sup>11-13</sup>



**Figure 1.** The hand-held transducer assembly used for precordial image acquisition containing a Vingmed 3.5 MHz sector scanning transducer. The stepmotor is mounted on the cylindrical holder and rotates via a wheel-work interface, the transducer inside the holder. A cable which transmits the pulses from the computer algorithm to steer the step-motor for controlled acquisition is attached to the connector mounted next to the step-motor. There is a micro-switch to control the start at 0 degrees and the end at 178 degrees of the image acquisition. By adapting the size and shape of the inner housing any commercially available precordial transducer can be used.

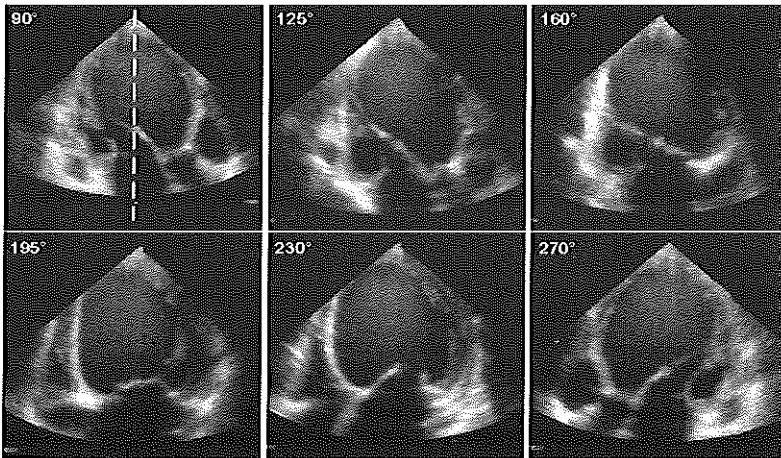


**Figure 2.** This diagram explains the principle of acquisition of sequential cross-sectional images at 2 degrees steps from the apical transducer position

### PRECORDIAL IMAGE ACQUISITION

The step-motor in the transducer assembly is commanded by a software-based steering

logic which controls the image acquisition in a given plane by an algorithm considering both heart cycle variation by ECG-gating and respiratory cycle phase by impedance measurement. These parameters are recorded prior to the actual image acquisition for a certain time period to select the average cardiac cycle and respiratory phase pattern. Based on this information, the step-motor is commanded by the steering logic to acquire cross-sections of cardiac cycles that fall within a selected range of cycle length and respiratory phase. This permits optimal temporal and spatial registration of the precordial images. After a cardiac cycle is selected by the steering logic, the cardiac images are sampled at 40 msec intervals (25 frames/sec), digitized and stored in the computer memory. Then, the step-motor is activated and rotates the transducer 2 degrees to the next scanning plane, where the same steering logic is followed. To fill the conical data volume, 90 sequential cross-sections from 0-178 degrees must be obtained each during a complete cardiac cycle. The transducer assembly can also be used for routine precordial multiplane echocardiography (figure 3) or semi-automated echocardiographic image acquisition for left ventricular function studies or stress-echocardiography. Respiration gated recording of cardiac cycles in a given plane reduces the influence and random error caused by extracardiac motion effects<sup>11-13</sup>



**Figure 3.** Apical (precordial) multiplane echocardiography of a patient with a dilated left ventricle. Under computer control, the imaging plane is rotated over 180° starting with a left ventricular long-axis plane and with steps of 35°. The axis of rotation is indicated in panel A. All images are recorded in the same phase of the respiratory cycle. Images A and F are mirror images. The images can be recorded on videotape or optical disc for further analysis. Increments of 2° during acquisition allow the completion of a rotational dataset for three-dimensional reconstruction.

## DATA PROCESSING

The recorded images are formatted in the correct sequence according to their ECG phase in volumetric data sets (256\*256\*256\* pixel/each 8 bit). To convert the rotated images into an isotropic cubic data set, a geometric transformation is necessary. To fill the gaps in the far fields, a "trilinear cylindric interpolation" is used. The size of the gaps is dependent on the distance from the rotation axis and the angle increment between two acquired images.

An oversampling is done near the rotation axis and an undersampling in the outer region. This phenomenon can be compared to a regular two-dimensional sector image. In such an image, the near field is over- and the far field is under-sampled as well. To reduce motion artifacts which can be created by patient movement, respiratory artifacts or probe movement, a dedicated image processing filter is used (ROSA filter: Reduction Of Spatial Artifacts).<sup>11-13</sup>

### CLINICAL PROCEDURE

Echocardiographic studies are performed with the transducer system in the parasternal or apical positions while the patient is comfortable lying in the 45-degree left recumbent position. The operator has to find the center axis around which the imaging plane is rotated to encompass the structure(s) or region of interest. Since the spatial coordinate system changes with transducer movement, motion of the transducer must be avoided. An experienced operator, after a learning period is able to keep the transducer stationary during the acquisition period. Inadvertent patient movement during the image acquisition can be largely prevented by thoroughly explaining the procedure before the study. The examination, including the calibration procedures, selection of the optimal gain settings and conical volume with a few test runs and the actual image acquisition, requires approximately 8-10 minutes in patients with sinus rhythm. In order to secure optimal image quality of individual regions of interest, different image acquisition sequences from different windows are performed. Calibration and storage of the data in the computer memory between acquisition sequences requires approximately 3 minutes. Off-line three-dimensional reconstruction of an area of interest requires 30-60 minutes depending how difficult it is to select the optimal cut planes to visualize a given structure in its three-dimensional perspective as there may be significant anatomical variability between patients. Guidelines to identify approximate cutting planes in various disease categories have been proposed.<sup>11-12</sup>

### DISPLAY MODALITIES OF THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Different displays from three-dimensional data sets can be produced.

#### (1) Two-dimensional display from:

(a) individual selected cut-planes (anyplane echocardiography):

Any desired cross-section of the heart or of a selected structure which is difficult or physically impossible to obtain from standard precordial or transesophageal acoustic windows can be computed from the data set and displayed in motion with zoom facility in cine-loop format at 25 frames/sec<sup>11,12</sup> (figure 4).

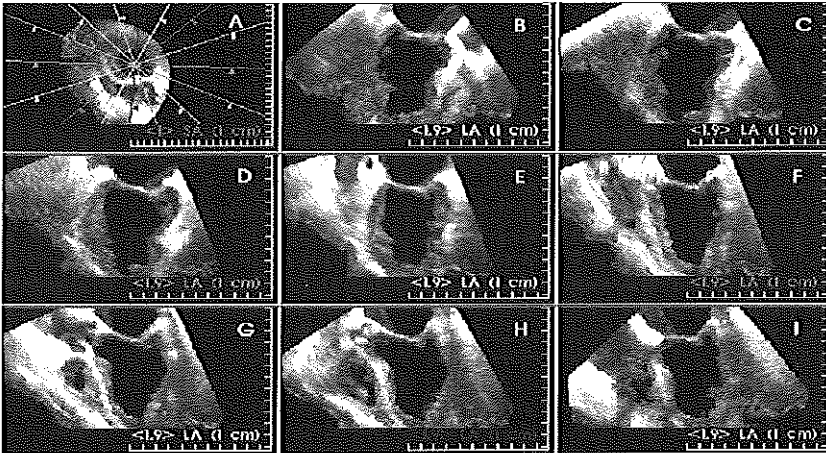
(b) parallel short-axis cuts along a defined long-axis (paraplane); Parallel slicing through the data set is possible and allows the generation of equidistant cross-sections at selected intervals in any plane through a region or structure of interest (figure 5). These computed cross-sections can be displayed in cine-loop format at 25 frames/sec.

(c) long-axis cuts (up to 8 different views at different angle increment)

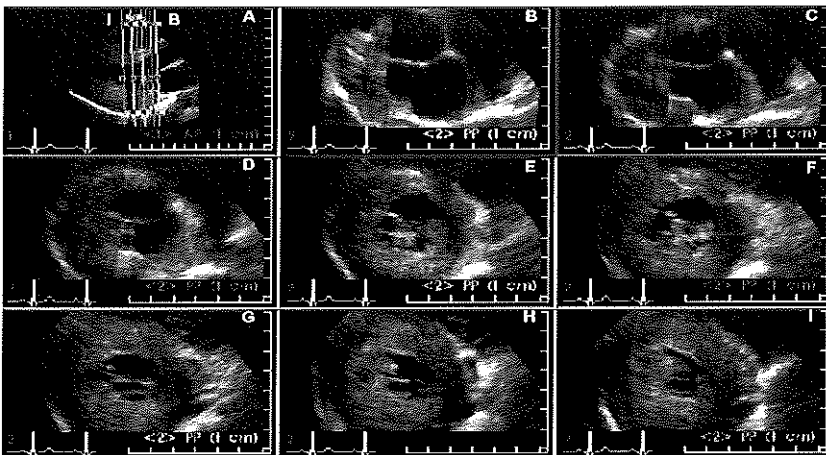
#### (2) Three-dimensional reconstruction (Volume rendered technique).

From any defined cut-plane, different algorithms are applied to represent the information in space. To distinguish between a structure of interest and the background image, a greylevel threshold is used. This difficult process is known as image segmentation.

A "hard" decision is somewhat relaxed by using a "fuzzy segmentation", where a probability is assigned to each greylevel, to decide whether it belongs to a structure or the background. A more or less subjective decision is always necessary (i.e. to adjust for the Time Gain Compensation used during acquisition of the original two-dimensional images).<sup>11,12</sup>



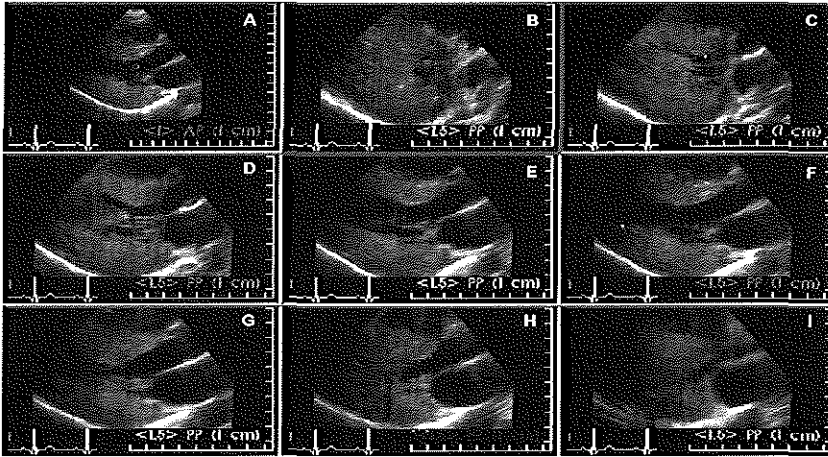
**Figure 4.** Anyplane echocardiography. From the three-dimensional data set up to 8 cut planes can be selected and reconstructed by computer. In this example left ventricular (LV) long-axis views are generated (panels B-I) and their orientation is shown in panel A. A comprehensive standardized analysis of the shape, size and wall motion of the left ventricle is possible.



**Figure 5.** Paraplane echocardiography using the three-dimensional data set of a patient with hypertrophic cardiomyopathy. The parasternal long-axis view is shown in panel A and the lines indicate the computer generated parallel short axis views of the left ventricle from B to I.

Since ultrasound images are noisy, algorithms for edge enhancement and noise reduction must be applied. The performance characteristics of these algorithms will have an effect on the overall quality of the three-dimensional image. Furthermore, the definition of a threshold

to recognize the interface between cardiac structures and the blood pool during the segmentation procedure is based on visual inspection. This introduces a subjective factor similar to the optimization of two-dimensional echocardiograms during standard examination procedures.



**Figure 6.** The same patient as in figure 6. The left ventricle is now sliced in planes parallel to the long axis view from interventricular septum to the lateral wall. Panel E corresponds to the standard parasternal long-axis view.

Different rendering algorithms are used and mixed with different weighting factors to create a three-dimensional shaded display.<sup>14</sup> These algorithms are: (a) distance shading; (b) transparent adaptive greylevel gradient shading; (c) texture shading and (d) maximum intensity projection.

The tissue display of the three-dimensional reconstructions has a close resemblance to the actual anatomy of the heart. This effect can be further enhanced by creating rotational sequences on the output screen.

## CLINICAL APPLICATIONS OF THREE-DIMENSIONAL ECHOCARDIOGRAPHY

The initial results of the application of three-dimensional echocardiography in humans are promising (8-10,15-19).

### (A) "ANYPLANE TWO-DIMENSIONAL IMAGING

The limitations of acoustic access and registration of individual two-dimensional images can potentially be overcome by three-dimensional echocardiography. From the original three-dimensional data set, new individually optimized otherwise unobtainable image planes can be computed and displayed in motion (dynamic anyplane echocardiography). Zoom facility allows visualization of detailed structures. Slicing of a given structure can be performed with parallel scanning in a way similar to computed tomography or magnetic resonance imaging. Up to 8 longitudinal cut planes with different angle interval can be simultaneously displayed for better spatial appreciation (Figure 2). Furthermore, the final assessment of cavity dimensions or the evaluation of a given structure will be more objective and less operator dependent.

## B) QUANTIFICATION

### *(1) Volumes measurements.*

Various two-dimensional approaches for measuring left ventricular volume have been proposed, but all make some assumption about cavity shape<sup>20</sup>. With standard two-dimensional echocardiography only a limited number of planes can be obtained, thus a theoretical geometrical model must be assumed which is often far from the reality. From the three-dimensional data set, orthogonal long-axis cut planes can be automatically selected, which partially compensates the geometric assumption for biplane methods.

The major advantage of three-dimensional echocardiography over standard two-dimensional imaging relies on more objective assessment of ventricular shape and size, since it does not rely on any specific transducer location or orientation plane. Thus, three-dimensional echocardiography should be able to define chamber volume in an accurate and reproducible manner. Manual tracings of endocardial borders from a series of parallel short-axis cut planes of the left ventricle at variable intervals allow computation of left ventricular volumes independent from theoretical models. Volumes of individual slices are calculated ( $V = A \times h$ , where  $A$  = area of the slice, and  $h$  = distance between adjacent cut planes) and summed to obtain the total<sup>13</sup> volume (figure 3). Serial studies with three-dimensional echocardiography will provide more insight into the natural history of complex cardiac pathology and in the rate of progression of its severity (e.g. ventricular remodeling).

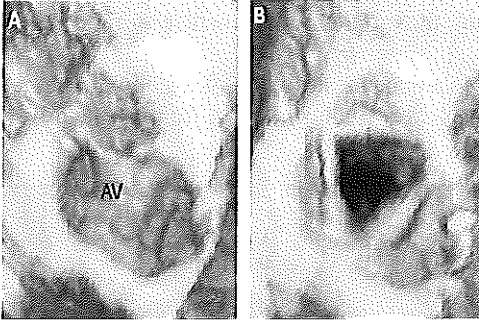
### *(2) Distance measurements.*

The different surface points of a three-dimensional reconstruction are not in one plane. Thus, a distance measurement must take always the depth into account. From the volume rendered display, the definition of a start and end point of the distance to be measured will result in the computation of the distance in the voxel space.

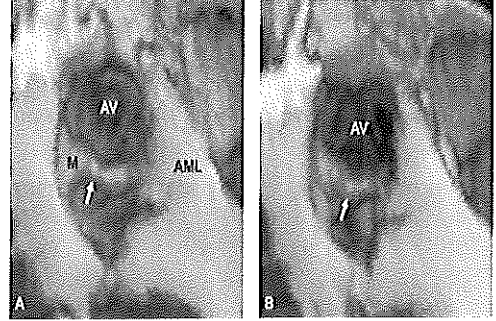
### *(3) Area measurements.*

Although area measurements can only be applied to two-dimensional images, three-dimensional echocardiography permits sectioning of the heart in any desired orientation. Thus, cut-planes can be selected which cross section the structure in the desired optimal orientation. This makes orifice area measurement more accurate.

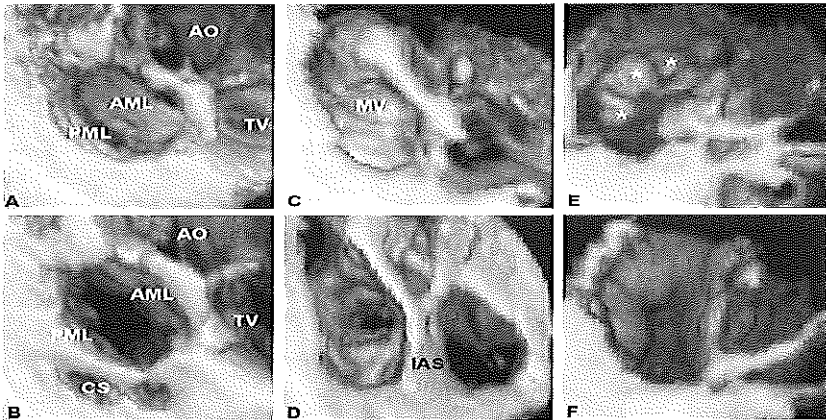
Preliminary study in Thoraxcenter<sup>12</sup> includes 97 patients (mean age  $32 \pm 9$  years) selected on the basis of good precordial image quality and sinus rhythm with a variety of cardiac disorders including myocardial disease (26), valvular heart disease (26), congenital heart disease (35) and normal subjects (10). In these patients, a total of 176 acquisition sequences, 78 with the transducer in the parasternal and 98 in the apical position, were performed. Adequate dynamic volume rendered display was possible in 77% of the patients. Three-dimensional image quality was considered adequate when there was complete visualization in depth of the structures of interest. Inadequate reconstructions may result from incomplete acquisition, poor image quality or inadequate gain settings during acquisition of the original data so that structures could not be detected by threshold changes during the volume rendered procedure. Dynamic anyplane and paraplane echocardiography were always possible and allowed the display of cut planes unobtainable from precordial windows of selected structures.



**Figure 7.** Three-dimensional reconstruction with volume rendered display of the aortic valve (AV). Electronic aortotomy is performed and the valve is visualized from above in the closed position during diastole (A) and open position during systole (B).



**Figure 8.** Three-dimensional volume rendered display of a subaortic membrane (M) seen from within the left ventricle. Note the aortic valve (AV) closed in diastole (A) and open in systole (B). AML: anterior mitral leaflet.



**Figure 9.** Examples of volume rendered three-dimensional reconstructions of normal, stenotic and prolapsing mitral valves. Electronic atriotomy is performed and the mitral valve leaflets are seen from an atrial viewpoint. Panel A shows a normal mitral valve in the closed position during systole and panel B in the open position during diastole (B). A stenotic mitral valve is shown closed in panel C and in the open position during diastole in panel D. Note the small stenotic orifice. The prolapsing scallops of both mitral leaflets are seen in panel E (see asterisks). Panel F shows the mitral valve open in diastole. Ao: aorta; AML and PML: anterior and posterior mitral valve leaflets; CS: coronary sinus; IAS: interatrial septum; MV: mitral valve; TV: tricuspid valve.

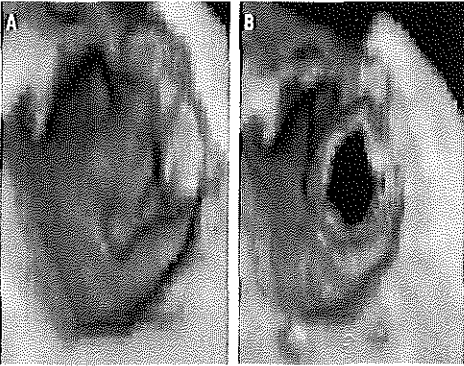
Three-dimensional reconstructions showing the aortic valve from the ascending aorta allow a direct qualitative evaluation (figure 7).

The left ventricular outflow can be visualized from a ventricular viewpoint and the nature of subaortic pathology is directly visualized (figure 8).

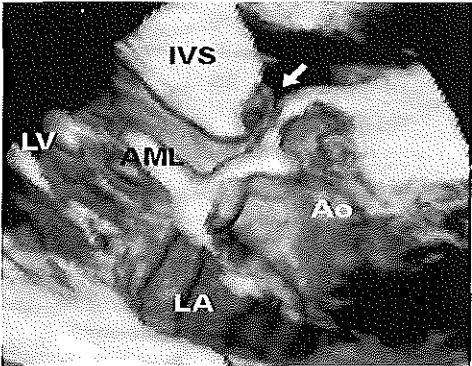
Imaging of the normal and pathologic mitral valve is possible from both atrial and ventricular viewpoints. Excellent delineation of the leaflets and qualitative analysis of the pathology is possible (figures 9 and 10).

Direct visualization of the ventricular septal defect and its structural relationships in a patient with tetralogy of Fallot is shown in figure 11. In these conditions the pathomorphology was better appreciated from the three-dimensional than from the standard two-dimensional images.

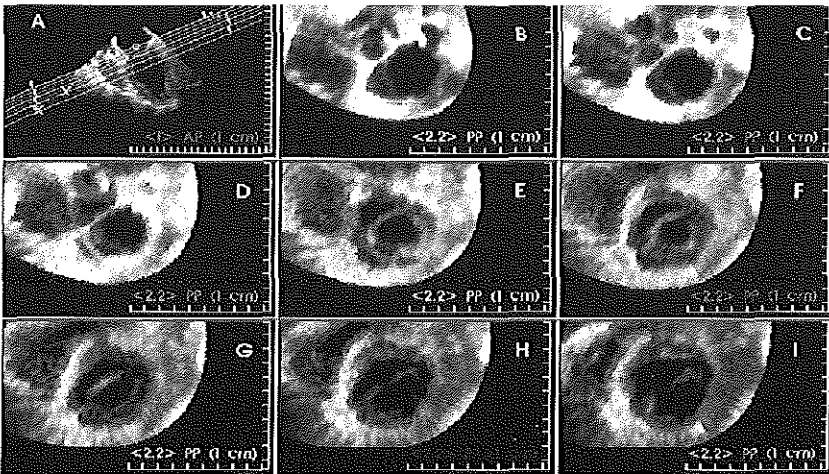
The potential of electronic anyplane and paraplane echocardiography for both qualitative and quantitative analysis of specific cardiac pathologies is illustrated in figures 4-6, 12 and 13.



**Figure 10.** Three-dimensional reconstructions of a stenotic mitral valve viewed from within the left ventricle in the closed position during systole (A) and open during diastole (B).

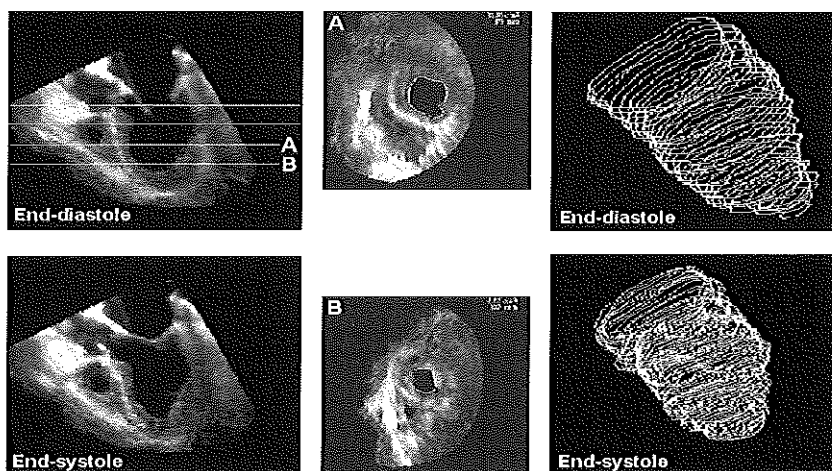


**Figure 11.** Three-dimensional reconstruction following a long-axis cut plane of the left ventricle in diastole of a patient with tetralogy of Fallot. The ventricular septal defect (arrow) and the overriding aorta are visualized.



**Figure 12.** Paraplane echocardiography in a patient with mitral stenosis. From the original three-dimensional data set (panel A), 8 parallel cut planes in the optimal orientation (anyplane capability) through the mitral valve are generated and the corresponding two-dimensional images are represented in panels B to I. This allows a slicing of the structure in a way similar to computed tomography or magnetic resonance imaging. The smallest orifice area is represented in panel F. This approach allows accurate planimetry of the mitral valve orifice.





**Figure 13.** The principle of left ventricular volume measurement using a three-dimensional data set. An end-diastolic long-axis view is selected as a reference view (panel A) and the left ventricle is sliced at equidistant intervals to generate a series of short axis views (paraplane capabilities). The surface area of each cross-section is measured by planimetry and the volume of each slice calculated. Adding up the volumes of all slices provides an accurate volume measurement of the left ventricle (Simpson's rule). This is performed for both end-diastolic and end-systolic data sets. The figure shows an end-diastolic long-axis view on which the two lines A and B correspond to the short-axis views shown in the middle panels A and B. Panel C shows reconstructions of the left ventricle using the planimetric contours of short axis views obtained at 3 mm intervals.

## DISCUSSION

Three-dimensional reconstruction of the heart has been an important research goal ever since the introduction of two-dimensional echocardiography. Several directions have been followed. Scanning in "real-time" of a pyramidal volume encompassing the whole heart is the most exciting development but progress is slow and clinical application remote.<sup>21</sup> Most approaches towards three-dimensional echocardiography are "off-line" and are based on the sequential acquisition of multiple cross-sectional images together with their spatial position and orientation using either external or internal coordinate reference systems. Mechanical articulated arm<sup>22</sup> and acoustical spark gap<sup>23,24</sup> location systems allow the continuous registration of the transducer position and the imaging plane with respect to an external reference point and have been used for precordial image acquisition. In most of these studies, static wire-frame or surface rendered displays have been generated. These displays do not contain the important grey scale information about tissue.<sup>25</sup>

Parallel, fan-like and rotational scanning methods are based on internal coordinate reference systems and have recently been successfully applied for precordial<sup>26-29</sup> acquisition in infants and small children.

However, it appears that small acoustic windows make rotational scanning the most effective precordial acquisition approach in children and certainly in adults since the basic images are obtained from a small and fixed pivot point.<sup>30</sup>

The possibility of generating three-dimensional reconstructions from standard precordial two-dimensional images will undoubtedly stimulate interest and expand the clinical application of three-dimensional echocardiography since information similar to that obtained

from other tomographic imaging techniques including radionuclide, computed tomography and magnetic resonance can be obtained with the additional advantages of better temporal resolution, portability, bedside application and relatively low cost. Three-dimensional echocardiography is still in its infancy and interest in this technique is growing.

From our experience we feel that three-dimensional reconstruction will facilitate the assessment of structures and pathology of unknown or complex geometry such as the right ventricle, aneurysmatic ventricles in coronary artery disease and complex congenital heart disease.<sup>31,32</sup> Topographic maps of elusive structures such as the mitral valve can be created helping to better understand its pathology.<sup>33</sup> The surgeon can now have a preview of what he will find during surgery (electronic cardiotomy) but with additional information on function. This will be of particular help in valve and congenital defect repair.

The acquisition time is at present short enough to consider three-dimensional imaging as part of a standard echocardiographic examination whenever is felt that it would provide incremental information for clinical decision-making. However, at this stage of its development the long reconstruction time and the need for a dedicated operator remain major limitations of its routine use. Although we have demonstrated the feasibility of precordial acquisition using rotational scanning, it should be emphasized that this study included only patients in sinus rhythm with good image quality. It thus remains an investigational tool with respect to clinical practicality and the independent additional information it provides in different clinical conditions and scenarios.

Perhaps the greatest advantage of acquiring a three-dimensional data-set is that now cross-sectional images can be computed in any desired plane independent from orientations dictated by the available acoustic windows and that parallel slicing of selected structures can be performed electronically.

These capabilities allow the selection of cut planes for optimal visualization of a cardiac structure and accurate quantitative measurement. By using a series of computer generated equidistant parallel cross-sections accurate measurement of specific structures can be made such as orifice areas of normal or pathologic valves (figure 12). Accurate volume calculation of the right or left ventricle is possible and the need for making geometric assumptions is eliminated (figure 13). Clearly, new complex parameters to define global and regional left ventricular function will become available in the future.<sup>34</sup>

The semi-automated and controlled registration of multiplane precordial with the hand-held transducer assembly will allow an easier and more standardized examination procedure for routine echocardiography in the future.<sup>29</sup> For example, the exact relationship between the apical views can be accurately documented rather than assuming an orthogonal relationship. Respiration gated cardiac cycles can be recorded during stress echocardiography thus avoiding random variability resulting from extracardiac motion in both interpretation and quantitative analysis.<sup>35</sup> Automatic endocardial border detection can be integrated to calculate left ventricular volumes on-line from a limited number of cross-sections. The echocardiographic examination will become less operator-dependent and more objective. Most of the performance variability will thus be avoided.

## ADVANTAGES AND LIMITATION OF THREE-DIMENSIONAL ECHOCARDIOGRAPHY

*Advantages of three-dimensional echocardiography are:*

- (1) Standardized examination procedure
- (2) Objective imaging
- (3) Improved accuracy of qualitative information
- (4) New quantitative parameters of cardiac function
- (5) Preoperative simulation of repair

*Present problems with three-dimensional echocardiography.*

- (1) Acquisition and processing time (storage space, computing power)
- (2) Transducer stability during acquisition
- (3) Limited resolution
- (4) Susceptibility for background noise artefacts
- (5) No on-line three-dimensional representation

## IN SUMMARY

We are entering an exciting new era in the development of cardiac ultrasound, which may ultimately have a greater impact on clinical cardiology than two-dimensional echocardiography. With further developments in computer technology both the image quality and display facilities will improve and the reconstruction time rapidly decrease. The semi-automated standardized examination procedure with the transducer assembly necessary for three-dimensional image acquisition will change the practice of echocardiography in the future by making the procedure less operator dependent. The computer generation of anyplane and paraplane images will further expand the range of clinical diagnostic problems that can be solved.

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## **CHAPTER 3**

# **ACCURATE MEASUREMENT OF LEFT VENTRICULAR EJECTION FRACTION BY THREE-DIMENSIONAL ECHOCARDIOGRAPHY A COMPARISON WITH RADIONUCLIDE ANGIOGRAPHY**

**Youssef FM Nosir MD, Paolo M Fioretti MD, Wim B Vletter BSc, Eric  
Boersma MSc, Alessandro Salustri MD, Joyce Tjoa Postma Bsc,  
Ambroos EM Reijs MSc, Folkert J Ten Cate MD,  
Jos RTC Roelandt MD.**

*Circulation 1996;94:460-66*

## ABSTRACT

**Background.** Three-dimensional echocardiography is a promising technique for left ventricular ejection fraction calculation, since it allows its measurement without geometric assumptions. However, few data exist studying its reproducibility and accuracy in patients.

**Methods.** 25 patients underwent radionuclide angiography and three-dimensional echocardiography using rotational technique (2-degree interval, ECG and respiratory gating). Left ventricular volume and ejection fraction were calculated using Simpson's rule at 3-mm slice thickness. Analyses were performed to define the largest slice thickness required for accurate left ventricular volume and ejection fraction calculation.

**Results.** Three-dimensional echocardiography had excellent correlation with radionuclide angiography for left ventricular ejection fraction calculation (mean $\pm$ SD = 38.9 $\pm$ 19.8 and 38.5 $\pm$ 18.0 respectively,  $r=0.99$ ), their mean difference was not significant ( $0.03 \pm 0.17$ ,  $p=0.3$ ). They had a close limit of agreement ( $-0.385$ ,  $+0.315$ ). Intraobserver variability for radionuclide angiography and three-dimensional echocardiography were 4.2% and 2.6% respectively, while interobserver variability were 6.2% and 5.3% respectively. There was no significant difference of left ventricular volume and ejection fraction calculated by 3-mm thickness and those calculated at different slice thickness up to 24-mm. However, the standard deviation of the mean difference showed stepwise increase, particularly above 15-mm slice thickness. At 15-mm slice thickness the probability of three-dimensional echocardiography to detect  $\geq 6\%$  difference in ejection fraction was 80%.

**Conclusions.** Three-dimensional echocardiography has excellent correlation and close limits of agreement with radionuclide angiography for calculating left ventricular ejection fraction in patients and has at least similar observer variability of radionuclide angiography. We recommend to use 15-mm slice thickness for accurate and rapid left ventricular volume and ejection fraction measurements.

## INTRODUCTION

Calculation of left ventricular ejection fraction has important diagnostic, prognostic and therapeutic implications and a rapid, accurate, reproducible and noninvasive method would be desirable.<sup>1-2</sup>

Radionuclide angiography is an accepted method for the measurement of left ventricular ejection fraction.<sup>3-4</sup> However, since it is rather expensive and necessitates the exposure of the patient to radiation, it is a suboptimal test when serial calculations of left ventricular ejection fraction are required.

Two-dimensional echocardiography is a widespread technique for clinical evaluation of left ventricular ejection fraction. However, assessment of left ventricular performance by two-dimensional echocardiographic techniques is based on geometric assumptions.<sup>5-6</sup> Accurate measurement of left ventricular volume and function requires the reconstruction of the true geometry of the heart, particularly in patients with distorted left ventricular geometry and impaired left ventricular function.<sup>7-8</sup>

Three-dimensional echocardiographic technique reduces the limitations of two-dimensional echocardiography and allows quantification of left ventricular volumes and ejection fraction without geometric assumptions.<sup>9</sup> Three-dimensional echocardiography was



shown to be highly accurate in determining volumes in vitro. In studies using phantoms and excised ventricles, left ventricular volumes calculated by three-dimensional echocardiography agreed closely with the actual volumes.<sup>10</sup> Few data have been published so far on the comparison between three-dimensional echocardiographic calculation of left ventricular volumes and ejection fraction with other techniques in humans.<sup>11-12</sup>

The aim of this study was to determine the feasibility and accuracy of three-dimensional echocardiography for calculating left ventricular ejection fraction in comparison with radionuclide angiography. Reproducibility of both techniques were compared in terms of intraobserver and interobserver variability. In addition, left ventricular volumes and ejection fraction were assessed using different slice distances to determine the largest slice thickness required for calculating left ventricular volumes and ejection fraction without losing accuracy.

## SUBJECTS AND METHODS

### *Study population.*

Three-dimensional echocardiography was performed in 25 patients undergoing multigated radionuclide angiography for evaluation of left ventricular ejection fraction. Patients were not selected clinically but for echocardiographic quality, patients in whom it was possible to visualise the whole left ventricle in all standard apical echocardiographic views were included in this study. Of the 25 patients 15 were men and 10 were women ranging in age from 25 to 82 years with a mean age of  $53 \pm 16$  years. Eleven patients had ischaemic heart disease (10 with previous myocardial infarction and 1 with angina pectoris), 5 patients had dilated cardiomyopathy, 8 patients were evaluated during chemotherapy for cancer and 1 normal volunteer was also studied.

### *Study protocol.*

Informed consent was taken from every patient after full explanation of the procedure. In each patient a multigated radionuclide angiogram for evaluation of left ventricular ejection fraction was performed. This was followed by a three-dimensional echocardiographic study on the same day in 17 patients and at an interval of 1 - 9 days (mean 3.5 days) in 8 patients. The clinical condition of the patient and medical therapy remained stable between the two studies.

## MULTIGATED RADIONUCLIDE ANGIOGRAPHY

Radionuclide angiography was performed in the 45° left anterior oblique view after in vivo labelling of the red blood cells with 15 mCi (540 MBq) of technetium-99m. Acquisition was performed during a six minute period with a Siemens (Orbiter) gamma camera equipped with a low energy all purpose collimator. The data were processed with standard software and background correction and the left ventricular ejection fraction was computed from the end systolic and end diastolic images.

## ECHOCARDIOGRAPHIC EXAMINATION

Echocardiographic studies were performed with a transducer system in the apical position, while the patient was comfortable lying in the 45-degree left recumbent position.

To acquire the cross-sectional images for reconstruction, the operator has to find the centre axis around which the imaging plane is rotated to encompass the whole left ventricular cavity. Since the spatial coordinate system changes with transducer movement, motion of the transducer must be avoided. Inadvertent patient movement during the image acquisition can be largely prevented by thoroughly explaining the procedure before the study. The examination, including the calibration procedures, selection of the optimal gain settings and conical volume with a few test runs and the actual image acquisition, requires approximately 8 -10 minutes in patients with sinus rhythm.

***The precordial transducer assembly and ultrasound system:***

We used a newly developed custom-build hand-held transducer assembly that can be rotated with a step motor via a wheel-work interface.<sup>13-14</sup> A commercially available 3.75 MHz sector scanning transducer (Toshiba Sonolayer SSH-140A system) is mounted in the probe assembly (figure 1). The step-motor is commanded by a steering-logic for controlled image acquisition (Echo-scan, Tom Tec GmbH, Munich, Germany).

**THREE-DIMENSIONAL ECHOCARDIOGRAPHY**

Reconstruction of the left ventricle by three-dimensional echocardiography requires three basic steps: image acquisition, image processing, and data analysis.

***Image acquisition:***

A software-based steering logic activates the step-motor in the transducer assembly that controls the image acquisition in a given plane by an algorithm considering both heart rate variations (ECG-gating) and respiratory phase by thoracic impedance measurement. Prior to the actual image acquisition the R-R intervals were predetermined with an acceptable variability of 150 msec or less and respiration was gated at the end-expiratory phase. Based on this information, the step-motor is commanded by the steering logic to acquire cross-sections of cardiac cycles that fall within the preset ranges. This allows optimal temporal and spatial registration of the cardiac images. After a cardiac cycle is selected by the steering logic, the cardiac images are sampled at 40 msec intervals (25 frames/sec), digitized, and stored in the computer memory. Then, the step motor is activated and rotates the transducer 2 degrees to the next scanning plane, where the same procedure is followed. Cycles that do not meet the preset ranges are rejected. To fill the conical data volume, 90 sequential cross-sections from 0 to 178 degrees must be obtained each during a complete cardiac cycle.

***Image processing:***

The recorded images are formatted in their correct rotational sequence according to their ECG phase in volumetric data sets (256x256x256 pixel/each 8 bit). The post-processing of the data sets is performed off-line using the analysis program of the system. To fill the gaps in the far fields, a "trilinear cylindric interpolation" algorithm is used.

***Trilinear cylindrical interpolation algorithm:***

When a rotational device is used to acquire an image, the rotation axis is assumed to be parallel to the vertical axis ( $= y - \text{axis}$ ) of each acquired image (the  $x$  position of the rotation

axis is defined as 'axpos'). Each voxel  $x, y$  in the acquired image 'n' of the rotational series may be then considered as a point in a cylindrical coordinate system with  $R = \{x - \text{axpos}\}$ ,  $\Phi = n * \text{angular stepwidth} + 0 \text{ or } + 180 \text{ degrees}$  (depending on the sign of  $x - \text{axpos}$ ) and  $Z = y$ . If the above parameters and a pixel resolution of 1mm for the acquired image are assumed, the maximal gap width will be approximately 6.7 mm. It is obvious that some kind of interpolation algorithm has to be applied to fill the gaps. A trilinear interpolation in the cylindrical space gives acceptable results. Each Cartesian voxel coordinate  $x, y, z$  of the volume to be reconstructed is transformed into a cylindrical coordinate  $R, \Phi, Z$ . The greyvalues of the eight points in the cylindrical coordinate system of the acquired images, That come closest to  $r, \Phi, z$  contribute to a weighted sum, that makes up the grey value at voxels  $x, y, z$ . Weights are inversely proportional to the distances of point  $r, \Phi, z$  to its neighbours  $R(i), \Phi(i), Z(i)$  ( $i=1 \dots 8$ ).

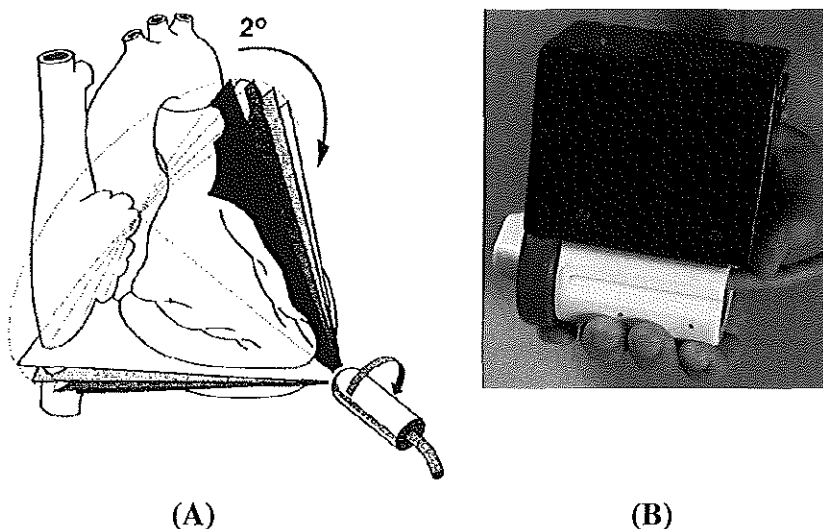


Figure 1. This diagram explains the principle of acquisition of sequential cross-sectional images at 2 degrees steps from the apical transducer position (panel A). The figure in (panel B) shows the hand-held transducer assembly used for precordial image acquisition containing a Toshiba 3.75 Mhz sector scanning transducer. The stepmotor is mounted on the cylindrical holder and rotates via a wheel-work interface, the transducer inside the holder. A cable which transmits the pulses from the computer algorithm to steer the step-motor for controlled acquisition is attached to the connector mounted next to the step-motor. There is a micro-switch to control the start at 0 degrees and the end at 178 degrees of the image acquisition.

### Image analysis:

Left ventricular ejection fraction was calculated from the three-dimensional data sets by using Simpson's method. By this method left ventricular volume is calculated by manual tracing of sequential short-axis views of the left ventricle from the apex to the mitral annulus. After selecting the long-axis view of the left ventricle, end-diastolic ( the first frame before closure of the mitral valve ) and then end-systolic ( the first frame before the opening of the mitral valve ) data sets are selected. Parallel slicing through the data sets was then

adjusted at 3-mm intervals. This resulted in generation of equidistant cross-sections of the left ventricle. The computer displays the corresponding short axis view in (1) a dynamic display for better identification of the endocardium in a digitized complete cardiac cycle, and (2) a static display for manual endocardial tracing. When manual tracing of the displayed short-axis is completed, the system calculates the volume by summing the Voxels included in the traced area in 3-mm slice thickness. Slice by slice, the system sums the corresponding subvolumes and finally calculates the end-diastolic and end-systolic left ventricular volumes. The system then calculates and displays the values of stroke volume and ejection fraction (figure 2).

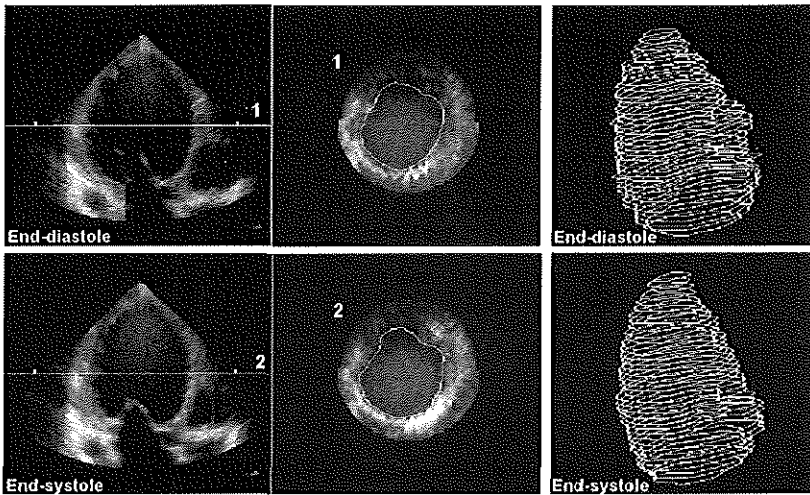


Figure 2. The principle of left ventricular volume measurement using a three-dimensional data set. An end-diastolic and end-systolic long-axis view is used as a reference view. The left ventricle is sliced at equidistant intervals to generate a series of short axis views. The surface area of each cross-section is measured by planimetry and the volume of each slice is calculated. Adding up the volumes of all slices provides the volume measurement of the whole left ventricle (Simpson's method). This is performed for both end-diastolic and end-systolic data sets. The figure shows an end-diastolic and end-systolic long axis views (panel A, upper and lower image respectively) on which the transverse sector 1 and 2 cut the left ventricular cavity at this level to give rise the corresponding short-axis views at end-diastole and end-systole (1 and 2) respectively, shown in the middle panel B. Panel C shows reconstruction of the left ventricle using the planimetered contours of short axis views obtained at 3-mm intervals at end-diastole (upper part) and end-systole (lower part).

## STATISTICAL ANALYSIS

For each technique the measurements of left ventricular ejection fraction were performed by two experienced blinded to each other's results. In addition, the first observer repeated the measurement after 7 days. Intraobserver variability was calculated, and expressed as the standard deviation of the difference of the two readings divided by the average value. For determining the interobserver variability the average value of the first observer was compared with the reading of the second. Observer variabilities were analysed by paired Student's t-test. Significance was stated at the 0.05 probability level. The p-value, the mean difference with 95% confidence interval (CI), and the limits of agreement<sup>15</sup> are reported.

A paired t-test was also performed to compare radionuclide angiography and three-dimensional echocardiography, using the average values of the first observer obtained at 3 mm slice distance. Pearson's correlation coefficients are presented.

In addition, left ventricular end-diastolic and end-systolic volumes, and ejection fraction were calculated by the first observer from three-dimensional echocardiography by using slice distances ranging from 6 to 24 mm, with stepwise increments of 3 mm. Repeated (7) comparisons were made with the value obtained at a slice distance of 3 mm by paired t-tests with Bonferroni's correction. Power analysis was performed to determine the possibilities of a beta error in the comparison with the 15-mm slice distance.

## RESULTS

### *Feasibility.*

Three-dimensional echocardiographic acquisition and reconstruction could be performed in all patients recruited in this study without difficulties. Three-dimensional echocardiographic acquisition was repeated in one patient due to an error in the calibration procedure of the rotational axis. All patients included in this study were in sinus rhythm, the difference between the mean  $\pm$  standard deviation of the patients heart rate during radionuclide angiography and three-dimensional echocardiography was not significant ( $82 \pm 11$  and  $81 \pm 10$  respectively,  $p=0.7$ ). Echocardiographic examination revealed that 10 patients had segmental wall motion abnormalities, 5 patients had global hypokinesia and 10 patients had normal wall motion. In each case the examination including the calibration procedures, selection of optimal gain setting and conical volume, and image acquisition required approximately 8-10 minutes. Calibration and storage of the data in the computer memory required approximately 3 minutes. Off-line image processing and analysis required on average 50 minutes.

Table 1. Mean  $\pm$  SD of left ventricular ejection fraction (LVEF) calculated by radionuclide angiography (RNA) and three-dimensional echocardiography Simpson's method (3DS), with intra- and interobserver variability, 95%CI and limits of agreement of each method.

Method	RNA	3DS
Obs. 1A (Mean $\pm$ SD)	39.0 $\pm$ 19.6	38.8 $\pm$ 18.7
Obs. 1B (Mean $\pm$ SD)	38.0 $\pm$ 20.0	38.3 $\pm$ 17.4
Average obs. 1 (Mean $\pm$ SD)	38.5 $\pm$ 19.8	38.6 $\pm$ 18.1
Obs. 2 (Mean $\pm$ SD)	38.3 $\pm$ 19.6	37.0 $\pm$ 16.1
Intraobserver variability	4.2%	2.6%
95% CI	-0.002, +0.062	-0.019, +0.021
Limit of agreement	-0.17, +0.23	-0.1, +0.1
Interobserver variability	6.2%	5.3%
95% CI	-0.034, ++0.046	-0.02, +0.06
Limit of agreement	-0.19, +0.21	-0.18, +0.22

Obs.1A= first reading of first observer, Obs.1B= second reading of first observer.

***Intraobserver and interobserver variability of radionuclide angiography (table 1).***

There was no significant difference in measurement of left ventricular ejection fraction obtained by the same observer in two different settings {mean difference (SD) = 0.03(0.016),  $p=0.07$ }, with an intraobserver variability of 4.2%. There was no significant difference in measurement of left ventricular ejection fraction obtained by the two independent observers {mean difference (SD) = 0.007(0.024),  $p=0.8$ }, with interobserver variability of 6.2%. In addition there were close limits of agreement and 95% CI between both intraobserver and interobserver measurements obtained by radionuclide angiography.

***Intraobserver and interobserver variability of three-dimensional echocardiography, Simpson's method (table 1).***

There was no significant difference in measurement of left ventricular ejection fraction obtained by the same observer in two different settings {mean difference (SD) = 0.001(0.01),  $p=0.9$ }, with intraobserver variability of 2.6%. There was no significant difference in measurement of left ventricular ejection fraction obtained by the two independent observers {mean difference (SD) = 0.02(0.02),  $p=0.3$ }, with interobserver variability of 5.3%. In addition there were close limits of agreement and 95% CI between both intraobserver and interobserver measurements obtained by three-dimensional echocardiography-true Simpson's method.

***Comparison of radionuclide angiography and three-dimensional echocardiography.***

The mean  $\pm$  SD values of left ventricular ejection fraction obtained by radionuclide angiography and three-dimensional echocardiography are presented in table 1. There was excellent correlation in the measurements of left ventricular ejection fraction obtained by radionuclide angiography and three-dimensional echocardiography ( $r$  value = 0.99) (figure 3). No significant difference existed in the mean difference between the average values of left ventricular ejection fraction obtained by radionuclide angiography and three-dimensional echocardiography (figure 4) (table 2). In addition, there were close limits of agreement and 95% CI between the measurements of radionuclide angiography and three-dimensional echocardiographic Simpson's method (table 2).

***Three-dimensional echocardiographic measurement of left ventricular volumes and ejection fraction at different slice distances.***

The mean values  $\pm$  standard deviation of left ventricular end-diastolic and end-systolic volumes and ejection fraction measurement using different slice distances are represented in table 3. There was no significant difference between the mean difference of left ventricular end-diastolic and end-systolic volume and ejection fraction calculated at a 3 mm slice distance and those calculated at different slice distances ranging from 6 to 24 mm, with stepwise increments of 3 mm (table 3, figure 5). The difference between left ventricular ejection fraction calculated by radionuclide angiography and that by three-dimensional echocardiography at different slice distances ranging from 3 to 24 mm with stepwise increments of 3mm, was not significant for the whole group of patients as well as in patients subgroups with normal and abnormal left ventricular wall motion (table 4, figure 6).

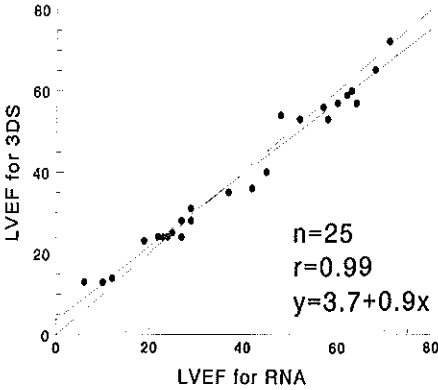


Figure 3. Linear regression of left ventricular ejection fraction (LVEF) in all patients, measured by three-dimensional echocardiographic Simpson's method (3DS) versus radionuclide angiography (RNA). n = number of patients, r = correlation coefficients. The dashed line represents the identity line.

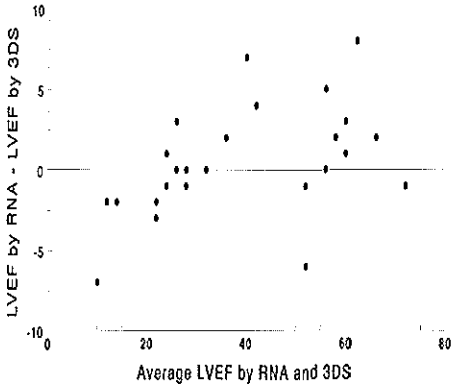


Figure 4. Difference of each pair of radionuclide angiography - three-dimensional echocardiographic left ventricular ejection fraction measurements plotted against the average value.

Table 2. Comparison between RNA and 3DE.

Method	Mean difference $\pm$ (SEE)	p value	95%CI	Limits of agreement
RNA-3DE	-0.035 $\pm$ 0.035	0.3	-0.11, +0.035	-0.385, +0.315

SEE = standard error of differences, other abbreviation as in table 1

Table 3. Mean values and mean differences of end-diastolic and end-systolic LVV and LVEF calculated at different slice thickness by 3DS.

	ESV (ml)		EDV (ml)		EF (%)	
	Mean $\pm$ SD	MD $\pm$ SD	Mean $\pm$ SD	MD $\pm$ SD	Mean $\pm$ SD	MD $\pm$ SD
3-mm	90.2 $\pm$ 63.3	----	135.6 $\pm$ 67.1	----	38.7 $\pm$ 18.4	----
6-mm	90.7 $\pm$ 63.8	0.8 $\pm$ 2.0	136.0 $\pm$ 67.8	0.3 $\pm$ 2.3	38.5 $\pm$ 18.5	0.13 $\pm$ 1.6
9-mm	90.8 $\pm$ 63.3	0.6 $\pm$ 3.2	136.1 $\pm$ 67.4	0.4 $\pm$ 3.5	38.6 $\pm$ 18.2	0.03 $\pm$ 2.2
12-mm	90.4 $\pm$ 64.2	0.2 $\pm$ 3.7	137.3 $\pm$ 68.5	1.7 $\pm$ 4.9	39.6 $\pm$ 18.6	0.88 $\pm$ 2.4
15-mm	92.5 $\pm$ 65.3	2.3 $\pm$ 4.4	136.4 $\pm$ 68.4	0.8 $\pm$ 7.1	38.3 $\pm$ 18.1	0.37 $\pm$ 3.3
18-mm	91.1 $\pm$ 65.6	0.9 $\pm$ 6.3	136.3 $\pm$ 67.3	0.6 $\pm$ 9.1	39.7 $\pm$ 19.5	0.98 $\pm$ 5.1
21-mm	89.2 $\pm$ 61.7	1.0 $\pm$ 12.0	133.3 $\pm$ 70.0	2.3 $\pm$ 12.7	37.6 $\pm$ 18.9	1.07 $\pm$ 8.48
24-mm	91.9 $\pm$ 68.1	1.6 $\pm$ 8.5	137.9 $\pm$ 70.8	2.3 $\pm$ 15.4	38.4 $\pm$ 22.9	0.23 $\pm$ 11.8

ESV=end-systolic volume, EDV=end-diastolic volume, MD $\pm$ SD= mean difference between values at 3 mm and values at 6, 9, 12, 15, 18, 21, 24 mm slice thickness respectively, all other abbreviations as in table 1.

Table 4. Mean difference  $\pm$  SD of LVEF calculated by RNA and 3DS at different slice thickness of the whole patients group (A), patients with normal LV wall motion (B) and patients with abnormal LV wall motion (C).

	MD $\pm$ SD ( A )	MD $\pm$ SD ( B )	MD $\pm$ SD ( C )
	MD $\pm$ SD	MD $\pm$ SD	MD $\pm$ SD
3-mm	-0.8 $\pm$ 3.2	-1.6 $\pm$ 4.0	-0.3 $\pm$ 2.5
6-mm	-0.9 $\pm$ 3.8	-1.6 $\pm$ 5.0	-0.5 $\pm$ 2.7
9-mm	-0.8 $\pm$ 3.7	-2.0 $\pm$ 3.9	-0.1 $\pm$ 3.4
12-mm	-0.1 $\pm$ 4.1	-0.4 $\pm$ 4.6	0.4 $\pm$ 3.9
15-mm	-1.2 $\pm$ 4.8	-3.0 $\pm$ 5.1	-0.01 $\pm$ 4.4
18-mm	0.2 $\pm$ 5.6	-0.7 $\pm$ 3.7	0.8 $\pm$ 6.7
21-mm	-1.9 $\pm$ 9.6	-3.5 $\pm$ 5.8	-0.8 $\pm$ 11.5
24-mm	-1.0 $\pm$ 11.9	1.0 $\pm$ 8.3	-2.4 $\pm$ 13.8

MD $\pm$ SD= mean difference between LVEF calculated by RNA and that by 3DS at 3, 6, 9, 12, 15, 18, 21, 24 mm slice thickness respectively, All abbreviations as in table 1.

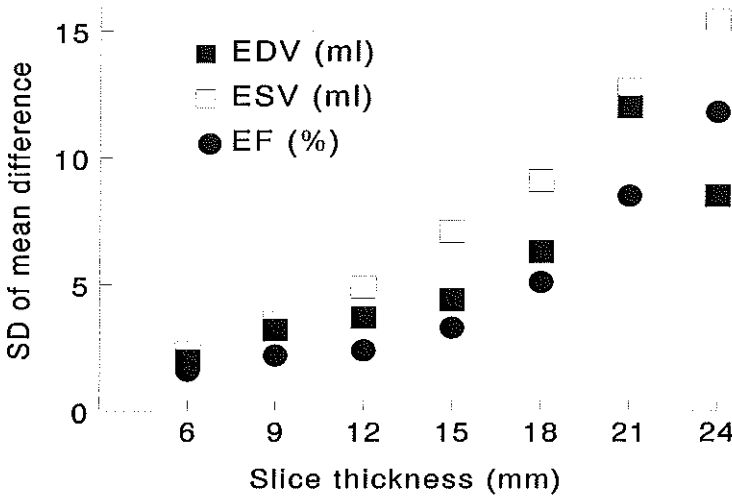


Figure 5. The standard deviation of the mean difference of left ventricular end-diastolic (EDV) and end-systolic (ESV) volumes and ejection fraction (EF) calculated by three-dimensional echocardiography at 3-mm slice thickness and values calculated at different slice thickness ( from 6 to 24 mm) plotted against the slice thickness, in the whole group of patients.

At a 15-mm slice distance with this number of patients, three-dimensional echocardiographic Simpson's method was able to detect a difference of 6% in left ventricular ejection fraction with a power of 80%, while this power was 99% for detecting a difference of 10% (table 5).



Table 5. The probability for detecting the differences of LVEF(%) in the study group using 3DS at 15-mm slice distance.

% Difference	1%	2.5%	5%	6%	7.5%	10%
Absolute difference	$\pm 0.4$	$\pm 1$	$\pm 2$	$\pm 2.3$	$\pm 2.9$	$\pm 3.9$
Power	1%	10%	58%	80%	96%	99%

All abbreviations as in table 1

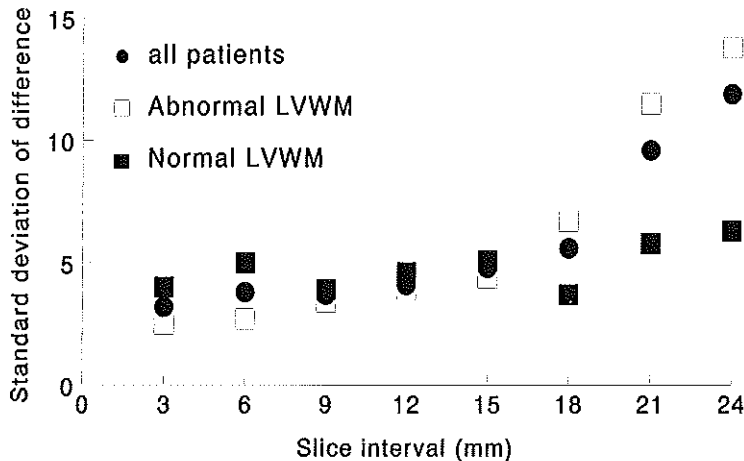


Figure 6. The standard deviation of the mean difference of left ventricular ejection fraction calculated by radionuclide angiography and that by three-dimensional echocardiography at different slice thickness (from 3 to 24 mm) plotted against the slice thickness, in the whole group of patients and in subdivision of patients with normal and abnormal left ventricular wall motion.

## DISCUSSION.

Calculation of left ventricular ejection fraction is frequently needed for the evaluation of patients with heart disease. Radionuclide angiography is an established method for the non-invasive measurements of left ventricular ejection fraction.<sup>3-4</sup> This technique is rather expensive and becomes impractical if repeated evaluation of left ventricular performance is needed.<sup>3-4-16</sup>

Two-dimensional echocardiography gained widespread use in clinical evaluation of left ventricular ejection fraction, as it allows comprehensive evaluation of anatomy and function in a short period of time, it is noninvasive, mobile, and relatively inexpensive when compared to radionuclide or other emerging imaging techniques like magnetic resonance imaging. However, assessments of left ventricular performance by two-dimensional echocardiographic techniques have suffered from a reputation of limited accuracy and reproducibility.<sup>17-18</sup> While fairly accurate estimates of volumes and ejection fraction can be made using quantitative methods, it continues to be based on geometric assumption.<sup>5-6</sup> Moreover, quantitative evaluation of left ventricular volume and function requires reconstruction of the true geometry of the heart, particularly in patients with a distorted left ventricular cavity.<sup>7-8</sup> Three-dimensional echocardiography provides accurate measurement of

left ventricular volume and function by the reconstruction of the true left ventricular geometry.<sup>19</sup>

This study is the first comparison in patients of left ventricular ejection fraction calculated by three-dimensional echocardiography, using precordial rotational technique with ECG and respiratory gating, with that calculated by an accepted clinical method, radionuclide angiography. Our results demonstrated an excellent correlation of left ventricular ejection fraction calculated by three-dimensional echocardiographic Simpson's method with that of radionuclide angiography. There were close limits of agreement and 95% CI between radionuclide angiography and three-dimensional echocardiographic Simpson's method.<sup>20</sup>

#### *Comparison with other studies.*

Our findings are in agreement with the study conducted by Gopal et al.,<sup>21</sup> who compared left ventricular ejection fraction calculated by radionuclide angiography and three-dimensional echocardiography in 51 patients with suspected heart disease. They calculated left ventricular volumes from a series of real-time parasternal short-axis images (7 to 10) acquired with a line-of-intersection display as a guide. This line is computed and displayed in each image to indicate the position and orientation of that image with respect to the other image. All images for ventricular reconstruction are acquired during suspended respiration. A polyhedral surface reconstruction algorithm has been adapted for left ventricular volume computation using the traced endocardial borders of the short axis image. In their patients left ventricular ejection fraction measured by radionuclide angiography ranged from 9 - 75% with a mean of 47%. They reported a very good correlation between three-dimensional echocardiography and radionuclide angiography,  $r = 0.94$  and  $r = 0.98$  for both three-dimensional echocardiographic observers, respectively.

Sapin et al.,<sup>22</sup> achieved higher correlation between left ventricular end-diastolic and end-systolic volume measured by three-dimensional echocardiography using the same method described by Gopal et al.,<sup>21</sup> and cineventriculography ( $r$  value for both observer = 0.97 and 0.98 respectively), than between two-dimensional echocardiography and cineventriculography ( $r$  value for both observer = 0.85 and 0.91 respectively). The same authors did not achieve a corresponding improvement in calculating left ventricular ejection fraction by three-dimensional echocardiography over two-dimensional echocardiography ( $r$  value for both observer = 0.82 and 0.80 respectively). In the same study the agreement (mean difference  $\pm 2$  SD) of three-dimensional echocardiographic end-diastolic and end-systolic volume measurements with that of cineventriculography ( $12.9 \pm 25.4$  and  $-0.7 \pm 24.8$  respectively) was better than that of two-dimensional echocardiography ( $21.1 \pm 54$  and  $2.4 \pm 44.8$  respectively), while for the ejection fraction a corresponding improvement in the agreement between both three-dimensional and two-dimensional echocardiography with that of cineventriculography ( $6.6 \pm 19.6$  and  $7.5 \pm 21.4$  respectively) was not obtained. They explained this discrepancy by the possible balance in volume error measurements of end-diastolic and end-systolic volumes by two-dimensional echocardiography and cineventriculography. These errors were nullified when calculating ejection fraction. On the other hand, end-diastolic and end-systolic volume errors by three-dimensional echocardiography were not correlated because they were derived from multiple cardiac cycles from which errors of ejection fractions were obtained.

Sapin et al.<sup>22</sup> found a lower correlation and wider limit of agreement for left ventricular ejection fraction calculation in comparison with the study by Gopal et al.<sup>21</sup> and the results of this study. This may be related to the different reference method used by Sapin et al (cineventriculography). Differences in methodology may also explain in part the discrepancy between our results and those of Sapin et al.<sup>22</sup> We performed left ventricular imaging for three-dimensional reconstruction from the apical window which allows the simultaneous identification of a basal and apical landmark for the long axis determination. They used the parasternal window from which it is often impossible to define these landmarks in a single cross section and two different long axis views are necessary. Three-dimensional image acquisition is then guided by a constructed line of intersection which is derived from two temporally dispersed short axis views selected from the two parasternal long axis views. Each acquired short axis is then readjusted by displaying this line of intersection several times. We used the standard apical four chamber view in which the longest left ventricular axis for rotational acquisition is identified to encompass the whole left ventricular cavity. In our technique image acquisition is ECG and respiratory gated, so that the cardiac images fall at the same moment in each accepted cardiac cycle. This allows more accurate three-dimensional left ventricular reconstruction and volume calculation. Sapin et al.<sup>22</sup> acquired their basic images at suspended end-expiration which were likely produces motion artefacts. The data set has then to be discarded and the procedure repeated. We reconstruct the heart from 90 cross sections planes which allows faithful reconstruction of the true geometry particularly in the presence of asynergy. Sapin et al. used 8 or 9 slices with wider gaps and hence the possibility to miss asynergic segments.

In our study, the intraobserver and interobserver variability for three-dimensional echocardiographic Simpson's method were at least similar to that of radionuclide angiography. This can be attributed to controlling the image acquisition by ECG and respiratory gating techniques and improvement of image selection by identifying the rotational long-axis.

In the study by Gopal et al.,<sup>21</sup> intraobserver and interobserver standard errors of the estimate of left ventricular ejection fraction measurements obtained by three-dimensional echocardiography were one-third to one half as compared with that of two-dimensional echocardiography (3.4 - 5.5 % versus, 7.5 - 9.0%) respectively. The limits of agreements also showed no systematic over or underestimation of left ventricular ejection fraction by three-dimensional echocardiography.

The present data showed that there were no significant differences between left ventricular end-diastolic and end-systolic volumes and ejection fraction calculated by three-dimensional echocardiography at 3 mm and those calculated from 6 to 24 mm slice thickness with stepwise increments of 3 mm. Nevertheless, with the increase of the slice distances there is a correlated corresponding increase in the standard deviation of the mean differences of left ventricular end-diastolic and end-systolic volumes and ejection fraction particularly above 15 mm slice distances (table 3). There was no significant difference between left ventricular ejection fraction calculated by radionuclide angiography and that calculated by three-dimensional echocardiography at different slice thickness from 3 to 24 mm with stepwise increments of 3 mm. With the increase of the slice thickness there is a correlated corresponding increase in the standard deviation of the mean differences of left ventricular ejection fraction particularly above 15 mm slice distances (table 4, figure 5). Accordingly,

applying 15-mm slice thickness instead of 3-mm will overcome the major limitation for the routine use of three-dimensional echocardiography for left ventricular volumes and ejection fraction calculations, as it reduces the number of short axis slices from (20 to 30) for 3-mm thickness to (5 to 8) when using 15mm slice thickness and consequently dramatically reducing the analysis time from 40 to 10 min on average.

In our group of patients, we calculated the probability of three-dimensional echocardiography Simpson's method at 15-mm slice distance to detect several differences of left ventricular ejection fraction (table 5). There was an acceptable probability of 80% to detect clinically relevant differences ( $>5\%$ ). Obviously, for detecting small differences (up to 5%) a larger study population would be required. By using 15 mm slice thickness, we reduce the analysis time by having a lower number of short axis slices. The analysis time at 15 mm slice thickness was 10 minutes in comparison to the 40 minutes needed in using 3 mm slice thickness. This eliminates the limitation imposed on three-dimensional echocardiography and provides a rapid and accurate method for calculating left ventricular ejection fraction.

### ADVANTAGES AND LIMITATIONS OF THE STUDY

Three-dimensional echocardiography allows calculation of left ventricular volumes and ejection fraction without any geometric assumption. Image processing of ultrasonic data is complicated by the presence of artefacts and a substantial amount of noise in the image. In our technique image conditioning is done using ROSA filter (Reduction of Spatial Artifacts). Image acquisition in a given plane is controlled by an algorithm considering both ECG and respiratory phase gated technology, so that the computer accepts cycles which fall in the preset range. Based on this information, cycles that do not meet the preset range are rejected, thus avoiding rotational and movement artefacts and allowing optimal temporal and spatial registration of the cardiac images. From the volumetric dataset, it is possible to adjust the reference image with the longest apical long axes which guide the short axis series and allows more accurate left ventricular volumes calculation. The time factor is the most important limiting factor that currently restricts the routine use of three-dimensional echocardiography. Developing faster computers and applying automated border recognition software for area and volume analysis technique will shorten the time needed for image acquisition, post-processing and data analysis. In addition, using slice thickness up to 15 mm will reduce the analysis time. Prolonged acquisition time increases the chances of patient motion or rotation artefacts which can be prevented by thoroughly explaining the procedure to the patient.

With radionuclide angiography left ventricular volumes were not calculated in this study. As left ventricular ejection fraction is more tolerant of volume errors than are absolute volumes, there is still a need to validate this technique for volumes with other well established techniques. In this study, patients with good image quality were selected. Thus, the value of three-dimensional echocardiography independent of image quality has to be proven. A larger population is required for the probability study of three-dimensional echocardiographic Simpson's method with use of 15-mm slice thickness to detect smaller differences ( $<5\%$ ) in left ventricular ejection fraction.

## CONCLUSIONS

Three-dimensional echocardiography has excellent correlation and close limits of agreement with radionuclide angiography for the calculation of left ventricular ejection fraction. Three-dimensional echocardiographic Simpson's method has at least equivalent intraobserver and interobserver variability as that of radionuclide angiography. Therefore, three-dimensional echocardiography may be a preferable test when serial assessment of left ventricular ejection fraction is requested. Based on the data at different slice distances we suggest to use slice thickness less than 15-mm for accurate and rapid left ventricular volume and ejection fraction measurements.

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## CHAPTER 4

# LEFT VENTRICULAR EJECTION FRACTION IN PATIENTS WITH NORMAL AND DISTORTED LEFT VENTRICULAR SHAPE BY TWO THREE-DIMENSIONAL ECHOCARDIOGRAPHIC METHODS A COMPARISON WITH RADIONUCLIDE ANGIOGRAPHY

*Nosir et al / LVEF by 3DE vs. RNA*

**Youssef FM Nosir MD\*, Alessandro Salustri MD, Jaroslaw D Kasprzak  
MD, Christian S Breburda MD Folkert J Ten Cate MD, Jos RTC  
Roelandt MD.**

With Technical Assistance of Wim B Vletter BSc, Ron T vanDomburg Msc, René Frowijn,  
Joyce Tjoa Postma Bsc, Ambroos EM Reijs MSc

From Thoraxcenter, AZR-Dijkzigt and Erasmus University, Rotterdam, The Netherlands,\*  
Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo,  
Egypt.

*J Am Soc Echocardiogr. 1998;11(6):620-630*

## STRUCTURED ABSTRACT.

**Objectives.** Serial evaluation of left ventricular (LV) ejection fraction (EF) is important for the management and follow up of cardiac patients. Our aim was to compare LVEF calculated from two three-dimensional echocardiographic (3DE) methods with multigated radionuclide angiography (RNA), in patients with normal and abnormal shaped ventricles.

**Methods:** 41 consecutive patients referred for RNA underwent precordial rotational 3DE acquisition of 90 cut-planes. From the volumetric dataset LVEF was calculated by, (a) Simpson's rule (3DS) through manual endocardial tracing of LV short axis series at 3-mm slice distance and (b) apical biplane modified Simpson's method (BMS), in 29 patients, by manual endocardial tracing of apical four chamber and its computer derived orthogonal view. Patients included three groups, (A) 17 patients with LV segmental wall motion abnormalities (SWMA), (B) 13 patients with LV global hypokinesis (GH) and (C) 11 patients with normal LV wall motion (N).

**Results.** For all the 41 patients, there was excellent correlation, close limits of agreement and non significant difference between 3DS and RNA for LVEF calculation [ $r=0.99$ ,  $(-6.7, +6.9)$  and  $p=0.9$ ] respectively.

For the 29 patients, excellent correlation and non significant differences between LVEF calculated by both 3DS and BMS and values obtained by RNA were found ( $r=0.99$  and  $0.97$ ) ( $p=0.7$  and  $p=0.5$ ) respectively. In addition, no significant difference existed between values of LVEF obtained from RNA, 3DS and BMS by the analysis of variance ( $p=0.6$ ). The limits of agreement tended to be closer between 3DS and RNA  $(-6.8, +7.2)$  than between BMS and RNA  $(-8.3, +9.7)$ . The intraobserver and interobserver variability of RNA, 3DS and BMS for calculating LVEF(%) were  $(0.8, 1.5)$ ,  $(1.3, 1.8)$  and  $(1.6, 2.6)$  respectively. There were closer limits of agreements between 3DS and RNA for LVEF calculation in A, B and C patients subgroup  $[(-3.5, +5)$ ,  $(-8.4, +5.6)$  and  $(-7.8, +8.6)]$ , than that between BMS and RNA  $[(-8.1, +10.7)$ ,  $(-11.9, +9.3)$  and  $(-9.1, +11.3)]$  respectively.

**Conclusions:** No significant difference existed between RNA, 3DS and BMS for LVEF calculation. 3DS has better correlation and closer limits of agreement than BMS with RNA for LVEF calculation particularly in patients with segmental WMA and GH. 3DS has a comparable observer variability with RNA. Therefore the use of 3DS for serial accurate LVEF calculation in cardiac patients is recommended.

*Key words:* ejection fraction, three-dimensional echocardiography, radionuclide angiography.

## INTRODUCTION

Serial evaluation of left ventricular (LV) ejection fraction (EF) is often needed for the management of cardiac patients. Therefore, the availability of a reproducible, accurate, and noninvasive method is desirable.<sup>1,2</sup>

Radionuclide angiography (RNA) is widely used for measurement of LVEF because it is noninvasive and does not rely on assumption of LV geometry. However, it is not optimal for serial assessment as it involves radiation energy.<sup>3-5</sup>

Echocardiography allows rapid comprehensive evaluation of anatomy and function and gained widespread use in evaluation of cardiac patients.<sup>6,7</sup>



M-mode echocardiography is limited by its inability to account for regional wall motion abnormalities.<sup>8</sup> While two-dimensional echocardiography is less restricted by segmental wall motion abnormalities (SWMA)<sup>9,10</sup> and fairly accurate estimates of LV volumes (V) can be made, it is still based on geometric assumption of LV shape.<sup>11-17</sup>

Three-dimensional echocardiography (3DE) allows quantification of LVV and function without geometric assumptions<sup>11,18</sup>, but few data are available on the comparison of LVV and EF calculation with other techniques.<sup>19-21</sup>

The aim of this study was to compare LVEF calculated from 3DE data sets using both Simpson's rule (3DS) and apical biplane modified Simpson's method (BMS) with values obtained by RNA in patients with normal and abnormal LV and to measure reproducibility of all techniques.

## SUBJECTS AND METHODS

Forty four consecutive patients in sinus rhythm and stable clinical condition underwent a multigated RNA study and 3DE. First a multigated RNA for evaluation of LVEF was performed in each patient. This was followed by a 3DE study on the same day in 36 patients and in 8 patients at a mean of 3.5 days later. Informed consent was taken from every patient after full explanation of the procedure.

From the 44 patients recruited in this study, 3 were excluded (2 for poor apical echocardiographic window and 1 for an error in the calibration procedure of rotational axis for 3DE). Of the 41 patients included, 29 were men with a mean age of  $51 \pm 17$  years (age range from 21 to 82 years). Patients were categorized into three groups, (A) patients with old myocardial infarction and SWMA, (B) patients with dilated cardiomyopathy and global hypokinesis (GH) and (C) patients with normal LV geometry who were evaluated during chemotherapy for a malignancy.

## MULTIGATED RADIONUCLIDE ANGIOGRAPHY

Multigated radionuclide angiography was performed in the 45° left anterior oblique view after in vivo labelling of the red blood cells with 15 mCi (540 MBq) of technetium-99m. Acquisition was performed during a six minute period with a Siemens (Orbiter) gamma camera equipped with a low energy all purpose collimator. Data were processed with standard software and background correction and the left ventricular ejection fraction was computed from the end diastolic and end systolic images.

## ECHOCARDIOGRAPHIC EXAMINATION

Echocardiographic studies were performed with a transducer in the apical position and the patient was comfortably lying in 45-degree left recumbent position. To acquire the cross-sectional images for reconstruction, the operator has to find the center axis around which the imaging plane is rotated to encompass the LV cavity in the conical volume. Since the spatial coordinate system changes with transducer movement, motion of the transducer must be avoided. Inadvertent patient movement during the image acquisition can be prevented by explaining the procedure prior to the study and ensure the cooperation of the patient.

### *The precordial transducer assembly and ultrasound system*

We used a custom-build hand-held transducer assembly on which a 3.75 MHz phased array transducer (Toshiba Sonolayer SSH-140A system) is mounted. The transducer assembly for precordial image acquisition consist of a cylindrical housing in which any standard precordial imaging transducer can be adapted. This cylindrical housing with the contained transducer fits into a cylindrical holder and is rotated via a wheel-work interface with a step-motor.<sup>22,23</sup> The step-motor is commanded by a software-based steering-logic (Echo-scan, Tom Tec GmbH, Munich, Germany) and the acquisition can be performed in steps of preselected intervals (in this study 2 degrees).

### THREE-DIMENSIONAL ECHOCARDIOGRAPHY

3D reconstruction of the LV from sequentially recorded echocardiographic images requires two basic steps: image acquisition and processing.

#### *Image acquisition:*

A software-based steering logic which considers a preset R-R intervals with a variability of  $\pm 150$  msec and phase of respiration (expiration) by thoracic impedance measurement activates the step-motor in the transducer assembly and controls the image acquisition. Only cross-sections which fall within the preset RR range and phase of respiration are used for 3DE reconstruction to insure optimal temporal and spatial registration in order to avoid artifacts. After a cardiac cycle is accepted the steering logic activates the step motor which rotates the imaging plane 2 degrees to the next position. The images within a cardiac cycle are sampled at 40 msec intervals (25 frames/sec), digitized, and stored in the computer memory. To fill the conical data volumes, 90 cross-sections from 0 to 178 degrees, recorded during a complete cardiac cycle must be obtained. (figure 1)

#### *Image processing:*

The recorded images are formatted in their correct rotational sequence according to their ECG phase in volumetric data sets ( $256 \times 256 \times 256$  pixel/each 8 bit). The post-processing of the data sets is performed off-line using the software program of the system. To fill the gaps in the far fields, a "trilinear cylindric interpolation" algorithm is used.<sup>21</sup>

#### *Image analysis:*

From the 3DE volumetric data sets, LVEF was calculated by both;

##### **(A) Simpson's rule.**

After selecting the long-axis view of the LV, end-diastolic (the first frame before closure of the mitral valve) and then end-systolic (the first frame before the opening of the mitral valve) volumetric data sets are selected. By this method LVV is calculated by manual endocardial tracing of sequential short-axis views of the LV from the apex to the mitral annulus at 3-mm intervals. The computer displays the corresponding short axis view in (1) a dynamic display which facilitates identification of the endocardium, and (2) a static display for manual endocardial tracing. When endocardial tracing of the short-axis views is completed, the slice volume is calculated by summing the voxels included in the traced area in 3-mm slice thickness. Slice by slice, the system sums the corresponding subvolumes in order to yield the end-diastolic and end-systolic LVV and EF<sup>21</sup> (figure 2).

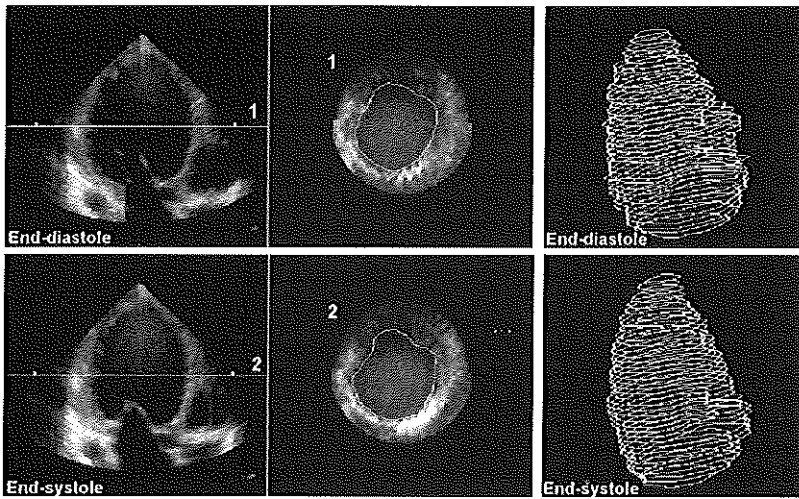


Figure 1. The principle of left ventricular volume measurement using a three-dimensional data set by Simpson's rule. An end-diastolic and end-systolic long-axis view is used as a reference view. The left ventricle is sliced at equidistant intervals to generate a series of short axis views. The surface area of each cross-section is measured by planimetry and the volume of each slice is calculated. Adding up the volumes of all slices provides the volume measurement of the whole left ventricle (Simpson's method). The figure shows an end-diastolic and end-systolic long axis views (panel A, upper and lower image respectively) on which the transverse sector 1 and 2 cut the left ventricular cavity at this level to give rise to the corresponding short-axis views at end-diastole and end-systole ( 1 and 2 ) respectively, shown in the middle panel B.

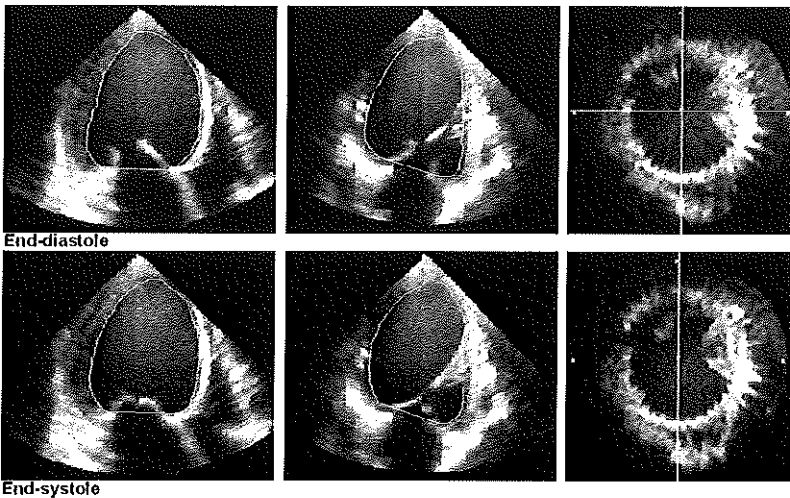


Figure 2. The principle of left ventricular volume measurement using a three-dimensional data set by computer derived apical biplane modified Simpson's method. Left ventricular end-diastolic (upper part) and end-systolic (lower part) volumes are calculated by manual endocardial tracing of apical four chamber view (panel A) and its computer derived orthogonal view (panel B) from the three-dimensional data set. Panel C shows the short axis with the orthogonal sectors for the two apical long axis views.

**(B) Apical biplane modified Simpson's method.**

The investigator selects the apical four chamber view in the volumetric data sets and the system gives its orthogonal view. LVV and EF were calculated by manual endocardial tracing of the two orthogonal long axis views at end-diastole and end-systole (figure 3). This was done in 29 out of the 41 patients, because this method was discarded from the new version of the software. For the manual tracing we trace on the bright endocardial side and the papillary muscles are included in left ventricular volume.

**STATISTICAL ANALYSIS**

LVEF calculation was performed for each technique [RNA and 3DE methods (3DS and BMS)] independently and blindly from the results of the other two techniques.

For the entire group of patients (n=41) LVEF was computed by RNA and 3DS. The Pearson correlation coefficient, paired Student t-test and limits of agreement as described by Altman and Bland<sup>24</sup>, for the whole group of patients as well as for A, B and C subgroups, were used for their comparison.

In 29 patients LVEF was calculated by RNA and 3DE methods (3DS and BMS) by two experienced observers blinded to each other's results. In addition, the first observer repeated the measurement after 7 days. Observer variabilities were analyzed by paired Student's t-test and expressed as the standard deviation of the difference of the two readings divided by the average value.

For the 29 patients as well as for its A, B and C subgroups, and to compare the three methods (RNA, 3DS and BMS) the analysis of variance was used. In addition, a paired t-test was performed to compare 3DE methods (3DS and BMS) with the values of RNA. Significance was stated at the 0.05 probability level. The p-value, the mean difference and the limits of agreement are reported. Pearson's correlation coefficients are presented.

Group A patients were studied with respect to the site of LV SWMA. Patients were grouped according to LV wall that included one or more segments with abnormal motion into 6 subgroups. The mean difference  $\pm$  SD, p. value and the limits of agreement between LVEF calculated by 3DE methods (3DS and BMS) with values of RNA were calculated. In addition, to compare the three methods (RNA, 3DS and BMS) the analysis of variance was performed.

**RESULTS*****Feasibility.***

3DE acquisition and reconstruction could be performed in 41 out of the 44 patients recruited in this study. Accordingly, in this study 3DE success rate was 93%. In 4 patients a second acquisition sequence was necessary because of inadvertent motion or loss of central rotational axis by the operator. All patients were in sinus rhythm, the difference between the patients heart rate (mean $\pm$ SD) during the RNA and 3DE study was not significant (80 $\pm$ 12 bpm versus 79 $\pm$ 11 bpm respectively, p=0.6). Echocardiographic examination revealed that 17 patients had SWMA (group A), 13 patients had GH (group B) and 11 patients had normal wall motion at rest (group C).

The examination including calibration, selection of the optimal gain settings and definition of a complete conical volume, few test runs and the actual image acquisition, requires approximately 8 -10 minutes in patients with sinus rhythm. Calibration and storage of the data in the computer memory required approximately 3 minutes. Off-line image processing required 15 minutes. Data analysis using 3 mm slice intervals required 30 to 40 minutes.

#### *Comparison between 3DS with RNA for LVEF calculation.*

The mean value  $\pm$  SD of LVEF calculated by 3DS and RNA for all the 41 patients and for A, B and C subgroups are presented in table 1. An excellent correlation, close limits of agreement and non significant difference between LVEF calculation by 3DS and RNA was found in all patients as well as in the subgroups (table 1) (figure 4).

### Comparison between 3DE and RNA

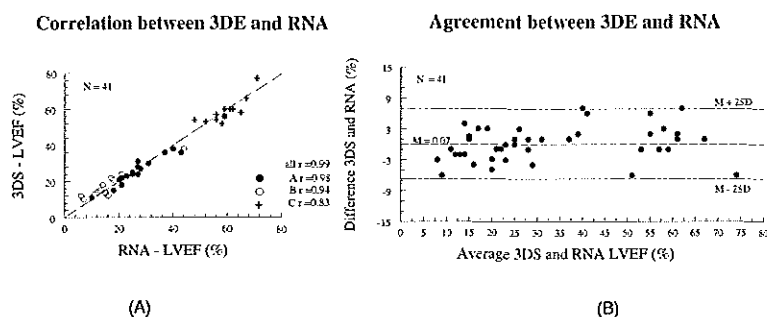


Figure 3. (A) Linear regression of left ventricular ejection fraction (LVEF) in all the 41 patients, measured by three-dimensional echocardiographic Simpson's rule (3DS) versus radionuclide angiography (RNA).  $n$  = number of patients,  $r$  = correlation coefficients, (A, B and C) are patients subgroups. The dashed line represents the identity line. (B) Difference of each pair of (radionuclide angiography - three-dimensional echocardiographic Simpson's rule) for left ventricular ejection fraction measurements plotted against the average value, in all the 41 patients.

4

Table 1. Mean $\pm$ SD of LVEF calculated by RNA and 3DS (Simpson's rule) methods, with the comparison between LVEF calculated by both methods in the whole group of patients (41 patients) and when these patients were divided into A, B and C subgroups.

	RNA (mean $\pm$ SD)	3DS (mean $\pm$ SD)	r	MD $\pm$ SD	p	Agreement
All Patients n=41	32.8 $\pm$ 19.6	32.8 $\pm$ 18.8	0.99	0.07 $\pm$ 3.4	0.9	-6.7, +6.9
Group A n=17	28.4 $\pm$ 11.32	27.4 $\pm$ 10.4	0.98	1 $\pm$ 2.4	0.1	-3.8, +5.8
Group B n=13	16.1 $\pm$ 9.4	17.5 $\pm$ 7.5	0.94	-1.4 $\pm$ 3.5	0.2	-8.4, +5.6
Group C n=11	59.5 $\pm$ 6.7	59.2 $\pm$ 7.2	0.83	0.4 $\pm$ 4.1	0.8	-7.8, +8.6

LVEF= left ventricular ejection fraction, RNA= radionuclide angiography, 3DS= three-dimensional echocardiography,  $r$  = correlation coefficient, MD $\pm$ SD= mean difference $\pm$ standard deviation, agreem.= limits of agreement.

### Observer variability of RNA and 3DE methods.

In 29 patients as well as for their A, B and C subgroups intraobserver and interobserver variabilities of RNA and 3DE methods (3DS and BMS) were comparable. There was no significant difference in LVEF obtained by the same observer in two different settings as well as between the two independent observers for all three methods (table 2, figure 5).

Observer variability (SEE) for LVEF calculation  
by RNA, 3DS and BMS

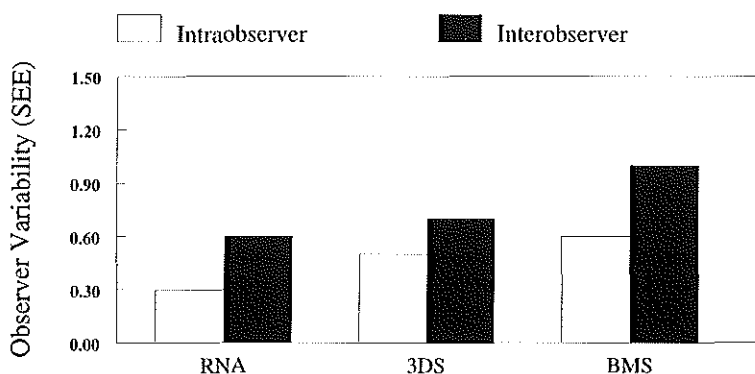


Figure 4. The intraobserver and interobserver variability of left ventricular ejection fraction calculation by radionuclide angiography and three-dimensional echocardiographic both Simpson's rule and apical biplane modified Simpson's, presented by the standard error of the estimate (SEE%), in all the 29 patients as well as in A, B and C subgroup of patients.

Table 2. Mean  $\pm$  SD of LVEF calculated by RNA, 3DS and apical biplane modified Simpson's (BMS) methods, with the observer variability of all methods for calculating LVEF in the 29 patients and when these patients divided into (A, B and C) subgroups.

		All patients, n=29	Group A, n=12	Group B, n=6	Group C, N=11
RNA	M $\pm$ SD	39 $\pm$ 20.1	30 $\pm$ 12	18 $\pm$ 14	60 $\pm$ 7
	Intraobs. SEE	0.3	0.7	0.7	0.4
	Interobs. SEE	0.6	0.8	0.8	1.0
3DS	M $\pm$ SD	38 $\pm$ 19	29 $\pm$ 11	20 $\pm$ 10	59 $\pm$ 7
	Intraobs. SEE	0.5	0.3	0.7	1.0
	Interobs. SEE	0.7	0.7	0.8	1.1
BMS	M $\pm$ SD	38 $\pm$ 19	28 $\pm$ 11	19 $\pm$ 9	58 $\pm$ 8
	Intraobs. SEE	0.6	0.8	0.5	1.2
	Interobs. SEE	1.0	1.1	0.7	2.1

SEE = standard error of estimate, C-SEE = corrected SEE for the mean value, other abbreviations as in table-1.

### 3DE (3DS and BMS) methods with comparison to RNA.

LVEF (mean  $\pm$  SD) obtained by RNA and 3DE (3DS and BMS) methods for the 29 patients and the 3 subgroups are presented in table 2. No significant difference existed between the three methods by the analysis of variance for the whole group ( $p=0.6$ ) and for A,

B and C subgroups (table 2). There was excellent correlation of values of LVEF by 3DE (3DS and BMS) methods with those obtained by RNA (table 3) (figure 6). There were closer limits of agreement and a non significant difference between LVEF obtained by 3DS and RNA than that between apical BMS method and RNA (table 3, figure 7).

### Comparison between 3DS and BMS with RNA for LVEF calculation

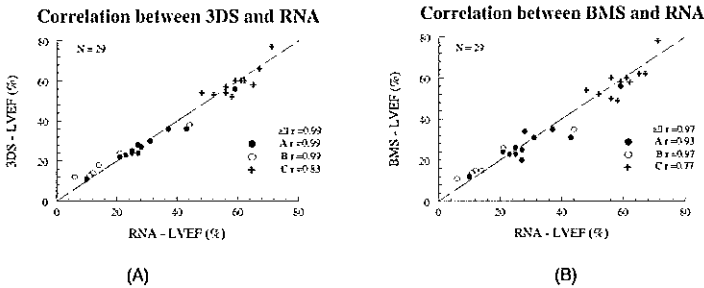


Figure 5.(A) Linear regression of left ventricular ejection fraction (LVEF) in the 29 patients as well as in A, B and C patients subgroups, measured by Simpson's rule (3DS) versus radionuclide angiography (RNA). n = number of patients, r = correlation coefficients. The dashed line represents the identity line. (B) Linear regression of left ventricular ejection fraction (LVEF) in the 29 patients as well as in A, B and C patients subgroups, measured by apical biplane modified Simpson's method (BMS) versus radionuclide angiography (RNA). n = number of patients, r = correlation coefficients. The dashed line represents the identity line.

### Comparison between 3DS and BMS with RNA for LVEF calculation

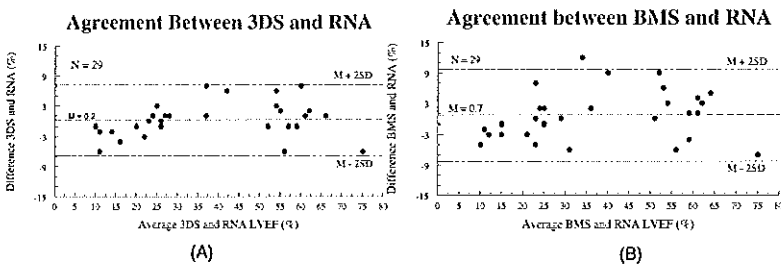


Figure 6. (A) Difference of each pair of (radionuclide angiography - Simpson's rule) left ventricular ejection fraction measurements plotted against the average value, in all the 29 patients. (B) Difference of each pair of (radionuclide angiography - apical biplane modified Simpson's method) left ventricular ejection fraction measurements plotted against the average value, in all the 29 patients.

### 3DE Accuracy with respect to the site of wall motion abnormalities.

For group A patients, the specification of type and site of resting LV SWMA are presented in table 4. No significant difference existed between the three methods by the analysis of variance (table 4). In addition, no significant difference existed in the mean difference between LVEF calculated by 3DE (3DS and BMS) methods with values obtained by RNA for each individual LV wall in group A (table 4). For each individual site of LV SWMA there was closer limits of agreement for LVEF calculation between 3DS and RNA than that between BMS method with RNA. (table 4, figure 8).

Table 3. Comparison between LVEF calculated by both 3DS and BMS and values obtained by RNA.

Subject	Differences	r.	MD±SD	p.	Agreement
All Patients	RNA-3DS	0.99	0.2±3.5	0.7	-6.8 +7.2
	RNA-BMS	0.97	0.7±4.5	0.5	-8.3, +9.7
Group A	RNA-3DS	0.99	1.0±2	0.1	-3, +5
	RNA-BMS	0.93	1.3±4.7	0.3	-8.1, +10.7
Group B	RNA-3DS	0.99	-1.4±3.5	0.2	-8.4, +5.6
	RNA-BMS	0.97	-1.3±5.3	0.6	-11.9, +9.3
Group C	RNA-3DS	0.83	0.4±4.1	0.8	-7.8, +8.6
	RNA-BMS	0.77	1.1±5.1	0.5	-9.1, +11.3

All abbreviation as in tables 1 and 2.

Table 4. Specification of segmental wall motion abnormalities (WMA) in group A patients, with comparison between both 3DS and BMS for calculating LVEF with values obtained by RNA in group A patients according to the site of LV-WMA.

		Apex	Anterior	Septum	Lateral	Posterior	Inferior
LV-WMA	Diskinetic	5	-	1	-	1	-
	Akinetic	3	-	6	-	5	6
	Hypokinetic	5	7	7	9	5	5
	Total	13	7	14	9	11	11
	MD±SD	0.7±2.1	-0.1±2.2	0.6±2.0	0.1±2.0	0.3±2.0	1.1±2.3
3DS-RNA	p	0.2	0.9	0.3	0.9	0.7	0.1
	Agreement	±4.1	±4.4	±4.0	±4.0	±4.0	±4.6
	MD±SD	0.4±3.6	0.0±4.3	0.4±3.6	-0.4±3.8	-0.1±3.7	1.2±4.5
BMS-RNA	p	0.7	1.0	0.7	0.8	0.9	0.4
	Agreement	±7.2	±8.6	±7.2	±7.6	±7.4	±9.0

All abbreviations as in tables 1 and 2.

## DISCUSSION.

3DE allows reconstruction of LV without geometric assumption. The method provides accurate measurements of LVV and function.<sup>21-23</sup>

In the total group, we found excellent correlation and close limits of agreement between 3DS with RNA for calculating LVEF ( $r=0.99$ ) and (-6.7, +6.9) respectively. These were also found in patients subgroups with SWMA (table 1).



Intraobserver and interobserver variability for 3DE (3DS and BMS) methods were similar to that of RNA (table 2). Excellent correlation between 3DE (3DS and BMS) methods with RNA was found for the calculation of LVEF ( $r=0.99$  and  $r=0.97$  respectively). There were closer limits of agreement between 3DS and RNA (-6.8, +7.2) than between BMS and RNA (-8.3, +9.7) (table 3). The limits of agreement between 3DS and RNA for LVEF calculation were less than half of that between BMS method and RNA when patients were classified according to site of LV SWMA (table 4).

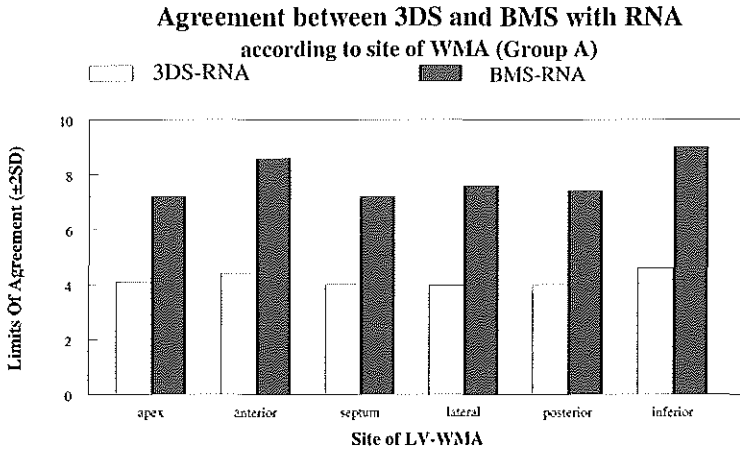


Figure 7. This diagram represents the limit of agreement ( $\pm 2SD$ ) for left ventricular ejection fraction calculated by 3DS and BMS with comparison to values obtained by RNA in group A patients with regards to the site of left ventricular wall motion abnormalities.

#### **Comparison with other 3DE studies.**

Our findings are in agreement with the study conducted by Gopal et al.,<sup>25</sup>, who compared LVEF calculated by RNA and 3DE in 51 patients with suspected heart disease. They calculated LVEF from a series of real-time parasternal short-axis images (7 to 10) acquired with a line of intersection display as a guide during suspended respiration. The traced endocardial borders of the short axis image were reconstructed by polyhedral surface reconstruction algorithm. They reported a very good correlation between 3DE and RNA,  $r = 0.94$  and  $r = 0.98$  for two 3DE observers, respectively. In addition, Gopal et al compared LVEF calculated by 3DE and two dimensional echocardiography using apical biplane summation of discs method with values obtained by RNA in 44 patients. They found that the limits of agreement between 3DE and RNA was 1.5 to 2 times lower than the corresponding values of two-dimensional echocardiography using subjective (visual estimation) and quantitative methods respectively. There was no significant systematic under-or overestimation of LVEF by 3DE, however underestimation was detected for the quantitative technique (+6.84) and by visual estimation (+8.3). Intraobserver and interobserver standard errors of the estimate of LVEF measurements obtained by 3DE were one-third to one half as

compared with that of two-dimensional echocardiography (3.4 - 5.5 % versus. 7.5 - 9.0%) respectively.

Sapin et al.,<sup>26</sup> using the same 3DE technique of Gopal et al.,<sup>27</sup> found a lower correlation and wider limit of agreement for LVEF calculation in comparison with the study by Gopal et al.<sup>25</sup> and our study. This may be related to the different reference method used by Sapin et al. (cineventriculography). In addition, differences in methodology<sup>21</sup> may in part also explain the discrepancy between our results and those of Sapin et al.

#### *Comparison with previous echocardiographic studies in patients with LV SWMA.*

SWMA and LV aneurysm are common complications of acute myocardial infarction which are detected by two-dimensional echocardiography with a high level of sensitivity (93%) and specificity (94%). However, both quantification of LVEF and aneurysmal volume by two-dimensional echocardiography are limited by its heterogeneous geometry, which restricts application of simple geometric models which assume symmetrical shape.<sup>27-28</sup> Albin et al.<sup>29</sup> measured LVEF using 6 different two-dimensional echocardiographic algorithms and compared the results with RNA in 49 patients with regional and diffuse WMA. They concluded that two-dimensional echocardiography can accurately assess LVEF in these patients. The apical biplane Simpson's formula was found the most accurate ( $r=84$ ,  $SEE=9.7$ ,  $p=0.17$  and agreement= $2\pm9.8$ ). Formulas including the LV short axis view consistently overestimate EF. In patients with anterior myocardial infarction and dilated cardiomyopathy, motion at the base of the heart is frequently preserved. Therefore, wall motion in the LV short axis views does not represent motion at all levels of the LV in patients with regional or diffuse WMA. The apical biplane formula, by measuring LV wall motion over the entire length in two orthogonal planes effectively integrates regional wall motion abnormalities and therefore yield a more accurate assessment of global LVEF.

Jiang et al.<sup>30</sup> studied the feasibility and accuracy of 3DE measurement of LVV and aneurysm volumes in 10 phantoms and 12 gel filled autopsied human hearts with aneurysms, comparing cavity volumes to those measured by fluid displacement; and in 4 dogs with surgically created LV aneurysms comparing total volumes with the actual instantaneous values measured by intracavitary balloon connected to external column for validation. They found that, in vitro calculated volumes agreed well with actual values ( $r=0.99$ ) and SEE of ( $3.2$  to  $6.1$   $\text{cm}^3$ ) for phantoms and ( $3.4$  to  $4.2$   $\text{cm}^3$ ) for autopsied hearts. In vivo LV end-diastolic, end-systolic, stroke volumes and EF calculated by 3DE correlated well with actual values ( $r=0.99$ ,  $0.99$ ,  $0.95$  and  $0.99$  respectively) and agreed closely with them ( $SEE=4.3$   $\text{cm}^3$ ,  $3.5$   $\text{cm}^3$ ,  $1.7$   $\text{cm}^3$  and  $2\%$  respectively). Recently, Buck et al.<sup>31</sup> demonstrated that in 23 patients with chronic stable LV aneurysms 3DE correlated and agreed favourably with magnetic resonance imaging for the calculation of end-diastolic LVV ( $r=0.97$ ,  $SEE=14.7$  ml), end-systolic LVV ( $r=0.97$ ,  $SEE=12.4$  ml) and LVEF ( $r=0.74$ ,  $SEE=5.6\%$ ).

#### *3DE: a technique to replace RNA for serial LVEF assessments.*

3DE allows faithful reconstruction of the cardiac geometry and hence avoid most of the limitations of two-dimensional echocardiography.

Biplane modified Simpson's method has been considered the best algorithm for LVEF and EF. The results of this study showed that, even under optimal conditions (ECG and respiratory gating data set, longest LV long axis and true computer derived orthogonal apical biplane views) for BMS method, 3DS is superior for calculating LVEF in terms of accuracy and reproducibility, particularly for patients with SWMA (all sites). Using 3DS with 15-mm slice thickness<sup>21</sup> reduces the number of slices to be traced from 30 to 7 slices for each phase and will significantly reduce 3DE analysis time from 40 to 10 minutes in average, and therefore make its routine use more practical. 3DS can be frequently repeated for patient follow up studies which is a limitation of RNA. The results of this study suggest that 3DS is accurate, reproducible and may replace RNA for serial evaluation of LVEF in patients with SWMA and GH.

#### *Advantages and limitations of the study.*

Image processing of ultrasonic data is complicated by the presence of artefacts and a substantial amount of noise in the image. Image conditioning in 3DE is done with ROSA filter (Reduction of Spatial Artifacts). Image acquisition is controlled by an algorithm considering both ECG and respiratory phase gated technology, this avoids rotational and movement artifacts and allows optimal temporal and spatial registration of the cardiac images for LV reconstruction. From the volumetric dataset, it is possible to adjust the reference image with the longest apical long axes which guide the short axis series and allows more accurate LVEF calculation. Analysis time is the most important limiting factor that currently restricts the routine use of 3DE. Using less cross sections in the dataset (rotational intervals at 20°), short axis series at 15-mm slice thickness and applying automated border recognition software for area and volume analysis technique will shorten the time needed for image acquisition, post-processing and data analysis. This study was designed as an extension of our previous paper,<sup>22</sup> to compare LVEF calculation by two 3DE methods (3DS and BMS) with values obtained by RNA in patients with SWMA and GH. Therefore, we continue to use 3DS at 3-mm slice thickness slices.

In this study, apical BMS method has better correlation and closer limits of agreement with RNA for LVEF calculation, than previous studies using conventional standard apical views. This can be attributed to the fact that, the two apical orthogonal planes were obtained from the 3DE dataset with ECG and respiratory gating to reduce spatial and temporal artifacts. In addition, 3DE data set allows faithful selection of the apical four chamber orthogonal view within the same LV long axis to avoid foreshortening of the LV apex.

#### **CONCLUSIONS**

No significant difference existed between RNA, 3DS and BMS for LVEF calculation. LVEF calculation by 3DE methods (3DS and BMS) correlate favourably and have close limits of agreement with RNA. 3DS measurements have a similar observer variability of RNA. In patients with distorted LV geometry, 3DS has better correlation and closer limits of agreement than BMS with RNA for LVEF calculation. Therefore, the use of 3DS is recommended for serial evaluation of LVEF in patients with left ventricular asynergy.

### Acknowledgements.

YFM Nosir is supported by The NUFFIC, The Hague, The Netherlands.

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## CHAPTER 5

### **THE APICAL LONG AXIS RATHER THAN THE TWO CHAMBER VIEW SHOULD BE USED IN COMBINATION WITH FOUR CHAMBER VIEW FOR ACCURATE ASSESSMENT OF LEFT VENTRICULAR VOLUMES AND FUNCTION**

**Youssef FM Nosir, Wim B Vletter, Eric Boersma, René Frowijn, Folkert  
J Ten Cate, Paolo M Fioretti, Jos RTC Roelandt.**

From the Thoraxcenter, Division of Cardiology and Department of Nuclear Medicine,  
University Hospital Rotterdam-Dijkzigt and Erasmus University, Rotterdam, The  
Netherlands.

YFM Nosir is supported by The NUFFIC, The Hague, The Netherlands and Cardiology  
Department, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt.

*Eur Heart J. 1997;18:1175-85*

## ABSTRACT

**Background.** Most biplane methods for the echocardiographic calculation of left ventricular volumes (LVV) assume orthogonality between paired views from the apical window. Our aim was to study the accuracy of biplane LVV calculation when either the apical two chamber or apical long axis views are combined with the apical four chamber view. LVV calculated from three-dimensional echocardiographic (3DE) data sets were used as a reference. Therefore, 27 patients underwent precordial 3DE using rotational acquisition of planes at 2-degrees intervals with ECG and respiratory gating. Calculation of end-diastolic (ED) and end-systolic (ES) LVV and ejection fraction (EF) from the 3DE data sets were done by (1) Simpson's method (3DS) at 3-mm short axis slice thickness (reference method) and (2) biplane ellipse from paired views using either apical four and two chamber views (BE-A) or apical four and long axis views (BE-B). Observer variabilities were studied by the standard error of the estimate % (SEE) in 19 patients for all methods.

**Results.** The spatial angles (mean $\pm$ SD) between the apical two chamber and apical long axis views and the apical four chamber view were  $63.3^{\circ}\pm 19.7$  and  $99.1^{\circ}\pm 25.6$  respectively. The mean $\pm$ SD of ED and ES LVV (ml) and EF (%) by 3DS were  $142.2\pm 60.9$ ,  $91.8\pm 59.6$  and  $39.6\pm 17.5$ , while that by BE-A were  $126.7\pm 60.4$ ,  $84.0\pm 57.9$  and  $39\pm 17$  and by BE-B were  $134.3\pm 62.4$ ,  $88.6\pm 59.7$  and  $39.1\pm 16.7$  respectively. BE-B intraobserver (8.4, 6.7 and 3.5) and interobserver (9.8, 11.5 and 5.4) SEE for ED and ES LVV and EF respectively, were smaller than that for BE-A (10.8, 8.8 and 4.1) and (11.4, 14.7 and 6.1) respectively. There was excellent correlation between 3DS and BE-A ( $r=0.99$ , 0.98 and 0.98) and BE-B (0.98, 0.98 and 0.98) for calculating ED-, ES-LVV and EF respectively. There were no significant difference between BE-A and BE-B with 3DS for ED and ES LVV and EF calculation ( $p=0.2$ , 0.3 and 0.4) and ( $p=0.5$ , 0.5 and 0.4) respectively. There were closer limits of agreement (MD $\pm$ 2SD) between 3DS and BE-B  $7.9\pm 18.8$ ,  $3.2\pm 14.2$  and  $0.8\pm 5.8$ , than that between 3DS and BE-A  $15.5\pm 19.6$ ,  $7.8\pm 16.2$  and  $1.1\pm 7.4$ , for calculating ED, and ES LVV and EF respectively.

**Conclusion.** Both apical two chamber and apical long axis views are not orthogonal to the apical four chamber view. Observer variabilities of BE-B were smaller than that for BE-A. BE-A and BE-B have excellent correlation and non significant differences with 3DS for LVV and EF calculation. There were closer limits of agreement between BE-B with 3DS for LVV and EF calculation than that between BE-A and 3DS. Therefore, we recommend to use the apical long axis rather than the two chamber view in combination with the four chamber view for accurate LVV and EF calculation.

## INTRODUCTION

Cross-sectional echocardiography allows comprehensive evaluation of cardiac anatomy and function. This widely available imaging method is relatively inexpensive when compared to radionuclide or other emerging non invasive imaging techniques like magnetic resonance imaging.<sup>1,2</sup>

A qualitative assessment of both global and regional left ventricular function is readily performed but their quantitation remains a challenge.<sup>3</sup> Quantitative assessment of left ventricular volume and function is based on the assumption of models for left ventricular



geometry. Unfortunately there is lack of consensus about the appropriate models and algorithms to apply.<sup>4</sup> Left ventricular volume and ejection fraction have been calculated from tomographic planes imaged from the apical window.<sup>5-8</sup> Although an estimation of volume can be obtained from single apical views, biplane calculations have a better reproducibility.<sup>9</sup> Most of the biplane methods assume orthogonality between paired apical views. The apical four chamber is a standard view in all algorithms, as it is the easiest and most reproducible to perform.<sup>9,10</sup> but there is still a controversy about its orthogonal view. The apical long axis view has been considered as the best orthogonal view to apical four chamber, as it is more easier to standardize because the aortic and mitral valves serve as anatomical landmarks.<sup>9-11</sup> However, the American Society of Echocardiography has recently recommended to use the apical two chamber view in conjunction with the four chamber view for biplane volume measurements.<sup>12,13</sup>

The aim of this study was to verify the spatial angle between both the apical two chamber and the apical long axis views relative to the apical four chamber view. In addition, left ventricular volumes were calculated by the biplane ellipse method using apical four chamber with either the apical two chamber or the apical long axis views. Measurements of left ventricular volumes and ejection fraction obtained by the previous paired orthogonal views were then compared with the measurements obtained by three-dimensional echocardiography (reference method). Observer variabilities were studied for all methods.

## PATIENTS AND METHODS

### *Study population.*

Data acquisition for three-dimensional echocardiography was performed in 27 patients for evaluation of left ventricular volume and function. Eleven patients had previous myocardial infarction, 5 had dilated cardiomyopathy 9 were evaluated during chemotherapy and 2 normal volunteers. Of the 27 patients 16 were men, patients ranged in age from 21 to 82 years with a mean age of  $51.3 \pm 17.4$  years (table 1). Informed consent was given by every patient after full explanation of the procedure. Patients with technically adequate apical windows were included in this study.

## ECHOCARDIOGRAPHIC EXAMINATION

Echocardiographic studies were performed with a transducer system in the apical position, while the patient was comfortable lied in the 45-degree left recumbent position. To acquire cross-sectional images for reconstruction, the operator has to find the centre axis around which the imaging plane is rotated to encompass the whole left ventricular cavity. Since the spatial coordinate system changes with transducer movement, motion of the transducer must be avoided. Inadvertent patient movement during the image acquisition can be prevented by thoroughly explaining the procedure before the study.

### *The precordial transducer assembly and image acquisition*

We used a newly developed custom-build hand-held transducer assembly that can be rotated with a step motor via a wheel-work interface.<sup>14,15</sup> A commercially available 3.75 MHz transducer (Toshiba Sonolayer SSH-140A system) is mounted in the probe assembly.

The step-motor is commanded by a steering-logic for controlled image acquisition (Echo-scan, TomTec GmbH, Munich, Germany).

A software-based steering logic activates the step-motor in the transducer assembly, which controls the image acquisition in a given plane by an algorithm that considers both heart rate variations (ECG-gating) and respiratory phase by thoracic impedance measurement. Prior to the actual image acquisition R-R intervals were predetermined with an acceptable variability of 150 msec or less and respiration was gated at the end-expiratory phase. Based on this information, the step-motor was commanded by the steering algorithm to acquire cross-sections of cardiac cycles that fell within the preset ranges. This allowed optimal temporal and spatial registration of the cardiac images. Prior to the actual image acquisition we performed test acquisition runs to make sure that the left ventricular outflow tract was included in the conical volume in every patient. After a cardiac cycle was selected by the steering logic, the cardiac images were sampled at 40 msec intervals (25 frames/sec), digitized, and stored in the computer memory. Then, the step motor was activated and used to rotate the transducer 2 degrees to the next scanning plane, where the same steering logic was followed. Cycles that did not meet the preset ranges were rejected. To fill the conical data volume, 90 sequential cross-sections from 0 to 178° had to be obtained, each during a complete cardiac cycle.

### *Image processing*

The recorded images were formatted in their correct rotational sequence according to their ECG phase in volumetric data sets (256\*x256\*x256\* pixel for each 8 bit). The post-processing of the data sets was performed off-line using the analysis program of the system.

### *Image analysis:*

#### **[a] Three-dimensional echocardiographic Simpson's method**

Left ventricular volumes and ejection fraction were calculated from the three-dimensional data sets by using Simpson's method. This method used left ventricular manual tracing of sequential short-axis views of the left ventricle from the apex to the mitral annulus to calculate left ventricular volume. After the long-axis view of the left ventricle was selected, the end-diastolic (the first frame before closure of the mitral valve) and then the end-systolic (the first frame before the opening of the mitral valve) data sets were selected. We then adjusted the parallel slicing through the data sets at 3-mm intervals. This resulted in generation of equidistant cross-sections of the left ventricle. The computer displayed the corresponding short axis view in (1) a dynamic display for better identification of the endocardium in a digitized complete cardiac cycle, and (2) a static display for manual endocardial tracing. When manual tracing of the displayed short-axis was completed, the system calculated the volume by summing up the voxels included in the traced area in 3-mm-thick slice. Slice by slice, the system summed the corresponding subvolumes and finally calculated the end-diastolic and end-systolic left ventricular volumes. The system then calculated and displayed the values of stroke volume and ejection fraction (figure 1).

### [b] Left ventricular volumes analysis using paired orthogonal views

The end-diastolic and the end-systolic data sets were selected as described in Simpson's method. Left ventricular volumes and ejection fraction were calculated by :

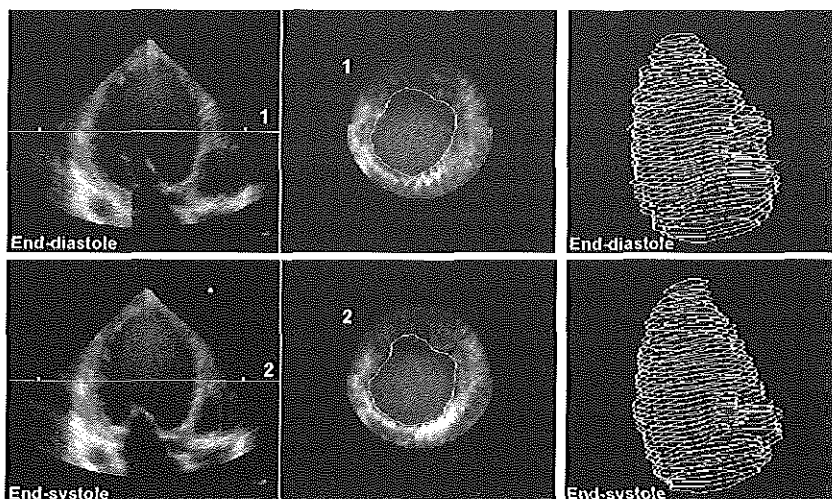


Figure 1. The principle of left ventricular volume measurement using a three-dimensional data set. An end-diastolic and end-systolic long-axis view is used as a reference view. The left ventricle is sliced at equidistant intervals to generate a series of short axis views. The surface area of each cross-section is measured by planimetry and the volume of each slice is calculated. Adding up the volumes of all slices provides the volume measurement of the whole left ventricle ( Simpson's method). This is performed for both end-diastolic and end-systolic data sets. The figure shows an end-diastolic and end-systolic long axis views (panel A, upper and lower image respectively) on which the transverse sector 1 and 2 cut the left ventricular cavity at this level to give rise the corresponding short-axis views at end-diastole and end-systole ( 1 and 2 ) respectively, shown in the middle panel B. Panel C shows reconstruction of the left ventricle using the planimetric contours of short axis views obtained at 3-mm intervals at end-diastole (upper part) and end-systole (lower part).

**Biplane ellipse method:** In this method, the apical four chamber view (with both mitral and tricuspid valves transected in their mid portion), the apical two chamber view (the mitral annular diameter is maximised and the aorta and right ventricle are not imaged) and the apical long axis view (the left atrium, left ventricular outflow tract, aortic valve and proximal part of the ascending aorta are imaged) were then identified, both in the end-diastolic and end-systolic data sets (figure 2) blindly and independently from the angle of rotation. The spatial angle between four chamber view and both apical two chamber and apical long axis views were then determined for each data set in end-diastole.

Left ventricular volumes were calculated by the biplane ellipse algorithm. Left ventricle was assumed to be an ellipsoid. It was defined by the two orthogonal ellipses whose long axis was the same and whose short axes were obtained by applying the area-length technique to the two orthogonal left ventricular images.<sup>16</sup> The long axis was measured from the apex to the mid mitral valve plane in the apical four chamber view. The papillary muscles are included in left ventricular volume.

The left ventricular volume ( $v$ ) was obtained as:

$$V = \frac{8 * A1 * A2}{3 * \pi * L1} \quad \text{Where;}$$

L1 = left ventricular long axis common for both apical orthogonal views.

A1 = left ventricular endocardial surface area at apical four chamber view. A2 = left ventricular endocardial surface area in the second apical view (two chamber or long axis).

Left ventricular end-diastolic and end-systolic volume and ejection fraction were calculated using apical four chamber and apical two chamber views (method A) and apical four chamber and apical long axis views (Method B).

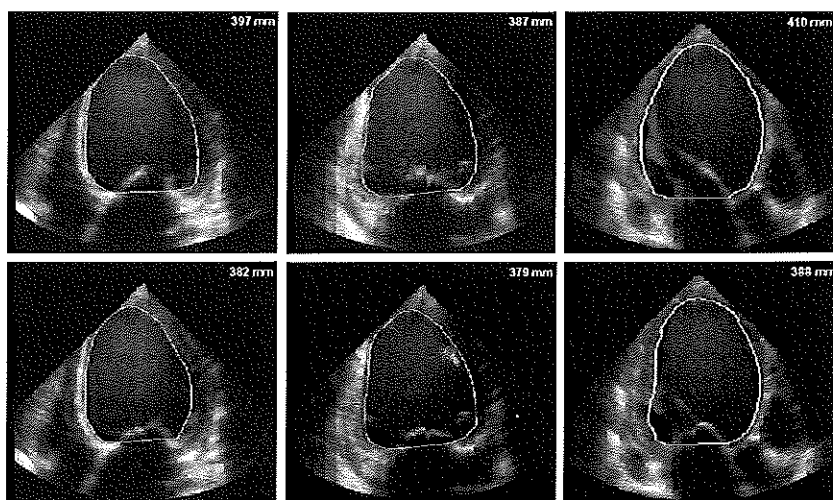


Figure 2. The principle of left ventricular volume measurement using biplane ellipse method. From the three-dimensional data set an end-diastolic and end-systolic long-axis view is used as a reference view. The best appearing apical four chamber (panel A), two chamber (panel B) and apical long axis (panel C) views are selected and endocardial borders are traced manually (endocardial surface area are displayed). Left ventricular volume are calculated by biplane ellipse using apical four chamber with apical two chamber views (method A), and apical four chamber with apical long axis views (method B).

## STATISTICAL ANALYSIS

The interval between measurements of left ventricular volume and ejection fraction for every method was two weeks and done independently. In 19 patients, for each method measurements of left ventricular volume and ejection fraction were calculated by two experienced observers blinded to each other's results. In addition, the first observer repeated the measurement after 7 days. Intraobserver and interobserver variabilities were calculated, and expressed as the standard error of the estimate.

Paired student t-tests were performed to compare left ventricular volumes and ejection fraction calculated by A and B biplane ellipse methods with measurements obtained by three-dimensional echocardiographic Simpson's method (reference method). Significance was stated at the 0.05 probability level. The p-value, the mean difference and the limits of agreement (mean difference $\pm$ 2SD)<sup>17</sup> are reported. Pearson's correlation coefficients are presented.

## RESULTS

### *Feasibility.*

Three-dimensional echocardiographic acquisition and reconstruction could be performed in all patients recruited in this study without difficulties. Three-dimensional echocardiographic acquisition was repeated in one patient on a separate day due to an error in the calibration procedure of the rotational axis. All patients included in this study were in sinus rhythm.

### **Spatial angle of apical two chamber and apical long axis views relative to apical four chamber view**

The angle between the apical two chamber and the apical four chamber views ranged between  $18^\circ$  and  $96^\circ$  (mean  $\pm$  SD =  $63.3^\circ \pm 19.7$ ) in end diastole. The angle of the apical long axis from the apical four chamber views ranged between  $34^\circ$  and  $138^\circ$  (mean  $\pm$  SD =  $99.1^\circ \pm 25.6$ ) (figure 3, table 1).

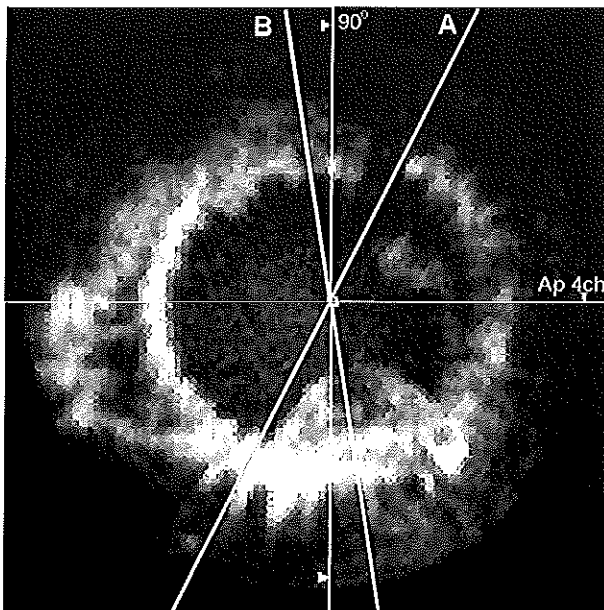


Figure 3. This figure represents the mean rotational angle of apical two chamber (A) and apical long axis (B) views from the apical four chamber view (transverse line) in relation to its true orthogonal view (vertical line) illustrated on the left ventricular short axis view.

### **Left ventricular volumes and ejection fraction**

The mean  $\pm$  SD of left ventricular end-diastolic and end-systolic volume and ejection fraction obtained by three-dimensional echocardiographic Simpson's rule were ( $142.2 \pm 60.9$ ,  $91.8 \pm 59.6$  and  $39.9 \pm 17.5$ ) and for biplane ellipse method A ( $126.7 \pm 60.4$ ,  $84 \pm 57.9$  and  $39.0 \pm 17.0$ ) and method B ( $134.3 \pm 62.4$ ,  $88.6 \pm 59.7$  and  $39.1 \pm 16.7$ ) respectively (tables 2 and 3).

### Observer variabilities of all methods

No significant differences existed between left ventricular volumes and ejection fraction calculated by the same observer as well as between the two independent observers for all methods. Three-dimensional echocardiography achieved the smallest observer variabilities, while intraobserver and interobserver variabilities of biplane ellipse B method were smaller than that for A method (table 4).

Table 1. Patients clinical data, site of left ventricular wall motion abnormalities (WMA) and the rotational angle of apical two chamber (Ap.2ch) and apical long axis (Ap.Lx) views .

Patient	Ag	Sex	Diagnosis	Type	WMA	Rotational Angel	
					Site	Ap. 2ch.°	Ap. Lx.°
1	29 <sup>e</sup>	F	NC			86	130
2	48	F	NC			56	110
3	48	F	NC			18	72
4	35	F	NC			30	78
5	35	M	NC			54	98
6	25	F	NC			70	118
7	32	F	NC			48	80
8	82	M	NC			70	96
9	31	M	NC			88	108
10	34	M	NC			68	92
11	21	M	NC			80	99
12	53	M	HF	GH		76	124
13	63	F	HF	GH		62	120
14	49	M	HF	GH		58	34
15	61	M	HF	GH		50	70
16	54	F	HF	GH		72	98
17	60	F	CAD	S	D(ap),A(inf.,post.,sep.)	72	116
18	68	F	CAD	S	A(ap.,sep.,inf.)	90	126
19	56	M	CAD	S	A(inf.),H(ant.,sep.,lat.,ap.,post.)	76	110
20	71	M	CAD	S	A(ap.),H(ant.,lat.,inf.,post.,sep.)	96	128
21	70	M	CAD	S	A(post.), H(lat.,inf.)	42	136
22	33	F	CAD	S	H(ap.,sep.)	72	52
23	58	M	CAD	S	A(inf.,post), H(ap.,sep.,ant.,lat.)	28	72
24	49	M	CAD	S	H(inf)	64	138
25	77	M	CAD	S	D(ap.), H(inf.,post.,ant.,sep.)	80	106
26	72	M	CAD	S	A(inf',post.), H(ap.,lat.,sep.)	45	83
27	70	M	CAD	S	D(ap.), H(inf.,post.,sep.)	78	100

F= female, M= male, NC= noncardiac, HF= heart failure, CAD= coronary artery disease, GH= global hypokinesis, S= segmental WMA, D= dyskinesis, A= akinesis H= hypokinesis, ap=apex, ant.=anterior, sep.=septum, lat.=lateral, inf.=inferior and post.=posterior.

Table 2. Left ventricular end-diastolic (EDV), end-systolic (ESV) volume and ejection fraction (EF) by three-dimensional echocardiographic Simpson's rule (3DS), and biplane ellipse using both apical four and two chamber views (BE-A) and apical four and apical long axis views (BE-B).

Patient	3DS			BE-A			BE-B		
	EDV	ESV	EF	EDV	ESV	EF	EDV	ESV	EF
1	126.9	51.0	59.6	102.2	45.5	55.5	108.7	50.6	53.5
2	128.2	53.6	58.1	113.3	50.2	55.3	128.4	53.6	58.3
3	152.4	64.3	57.7	133.6	64.7	51.8	137.7	65.2	52.7
4	116.9	50.4	56.9	99.5	47.3	52.5	107.2	50.1	53.2
5	168.5	80.2	52.4	142.1	76.6	46.1	152.1	80.0	47.4
6	102.7	48.2	53.1	98.5	51.9	47.3	108.9	54.1	50.3
7	75.2	30.0	60.0	66.1	26.8	59.4	71.5	28.2	60.5
8	72.0	21.3	70.4	58.1	16.5	71.6	65.0	19.8	69.5
9	65.4	29.7	54.5	56.3	39.2	45.9	58.3	30.4	47.8
10	112.4	49.9	55.0	91.2	37.1	59.3	96.1	44.6	53.5
11	149.6	61.2	59.1	127.3	52.3	58.9	136.7	55.6	59.3
12	226.9	194.8	14.2	218.0	186.6	14.4	227.9	192.6	15.5
13	215.4	188.7	12.4	194.3	174.4	10.2	206.5	184.2	10.8
14	197.2	150.7	23.3	205.9	161.4	21.6	213.1	166.1	22.1
15	189.4	162.6	14.1	159.9	138.3	13.5	165.8	142.1	13.7
16	42.7	26.9	37.9	32.5	20.5	36.8	38.7	24.9	35.7
17	144.0	112.7	22.0	134.5	98.9	26.4	136.1	102.5	24.7
18	175.6	135.4	22.9	163.5	123.2	24.7	170.5	129.4	24.1
19	234.9	179.7	23.5	230.7	169.8	26.4	237.5	178.4	24.8
20	174.0	114.1	34.3	141.0	88.3	37.9	147.6	95.6	35.2
21	108.8	76.0	30.1	100.1	65.5	34.4	104.2	68.9	33.9
22	59.9	26.5	55.7	42.9	16.5	61.7	42.8	18.2	60.2
23	305.0	232.0	23.9	285.1	226.2	20.6	299.5	236.0	21.7
24	80.7	52.1	35.3	78.3	51.8	33.8	80.2	53.8	32.9
25	146.1	104.7	28.2	120.5	90.7	24.7	136.4	99.8	26.8
26	126.7	78.3	35.0	95.4	58.1	36.8	106.3	64.8	39.0
27	103.4	143.1	27.7	131.0	97.9	25.4	141.9	101.9	28.4

Table 3. The mean  $\pm$  SD of left ventricular EDV (ml), ESV (ml) and EF %.

Mean $\pm$ SD	EDV(ml)	ESV(ml)	EF(%)
3DS	142.2 $\pm$ 60.9	91.8 $\pm$ 60.9	39.9 $\pm$ 17.5
BE-A	126.7 $\pm$ 60.4	84.0 $\pm$ 57.9	39.0 $\pm$ 17.0
BE-B	134.3 $\pm$ 62.4	88.6 $\pm$ 59.7	39.1 $\pm$ 16.7

All appreviation as table 2

### Comparison between biplane volumes calculation from orthogonal views with three-dimensional echocardiographic Simpson's rule

Biplane ellipse using both A and B methods has excellent correlation and non significant differences with three-dimensional echocardiographic Simpson's rule, for left ventricular volume and ejection fraction calculation (tables 5) (figure 4). The limits of agreement between BE-B and 3DS were closer than that between BE-A and 3DS (tables 5) (figure 5). Biplane ellipse using method B has lesser underestimation % values than biplane ellipse method A for left ventricular volumes and ejection fraction calculation compared to the reference method (table 5) (figure 6).

Table 4. Observer variability of 3DS, BE-A and BE-B presented by intraobserver (Intra.) and interobserver (Inter.) % standard error of the estimate (SEE).

	EDV		ESV		EF	
	Intra. SEE	Inter. SEE	Intra. SEE	Inter. SEE	Intra. SEE	Inter. SEE
3DS	3.1	4.9	3.6	6.6	2.4	5.1
BE-A	10.8	11.4	8.8	14.7	4.1	6.1
BE-B	8.4	9.8	6.7	11.5	3.5	5.4

All other appreciation as in table 2.

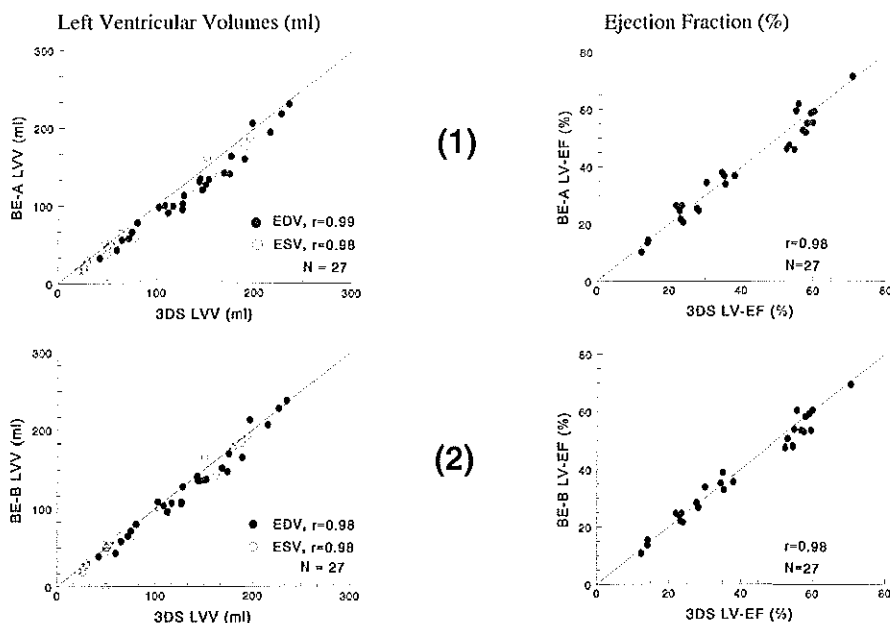


Figure 4. Linear regression of left ventricular end-diastolic and end-systolic volumes and ejection fraction, measured by three-dimensional echocardiographic Simpson's method (3DS) versus biplane ellipsis using either apical four and two chamber views (BE-A) upper part (1), or apical four chamber and apical long axis views lower part (2).  $n$  = number of patients,  $r$  = correlation coefficients. The dashed line represents the identity line.



Table 5. The mean difference (MD $\pm$ SD), % underestimation (underest.), p value, limit of agreement and correlation coefficient (r) between 3DS and both BE-A and BE-B for calculating EDV, ESV and LVEF

	3DS-BE-A			3DS-BE-B		
	EDV	ESV	EF	EDV	ESV	EF
MD $\pm$ SD	15.5 $\pm$ 9.8	7.8 $\pm$ 8.1	0.9 $\pm$ 3.7	7.9 $\pm$ 9.4	3.2 $\pm$ 7.1	0.8 $\pm$ 2.9
%Underest	11 $\pm$ 10	8.5 $\pm$ 11.5	2.3 $\pm$ 10.1	5.6 $\pm$ 8.5	3.5 $\pm$ 9.4	2.0 $\pm$ 7.6
p	0.2	0.3	0.4	0.5	0.5	0.4
r	0.99	0.98	0.98	0.98	0.98	0.98
Agreement	15.5 $\pm$ 19.6	7.8 $\pm$ 16.2	0.9 $\pm$ 7.4	7.9 $\pm$ 18.8	3.2 $\pm$ 14.2	0.8 $\pm$ 5.8

All appreciation as table 2

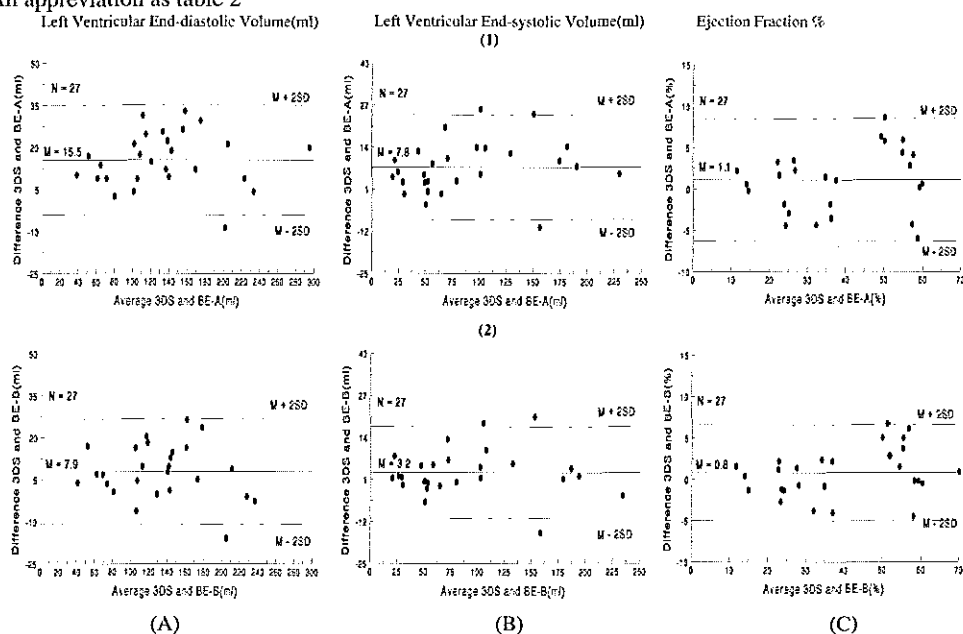


Figure 5. Limits of agreement of left ventricular end-diastolic (panel A), end-systolic (panel B) volume and ejection fraction (panel C) calculated by three-dimensional echocardiographic Simpson's method (3DS) versus biplane ellipsis using either apical four and two chamber views (BE-A) upper part (1), or apical four chamber and apical long axis views lower part (2). Difference of each pair of 3DS and either BE-A or BE-B for left ventricular end-diastolic, end-systolic volume and ejection fraction measurements plotted against the average value of both measurements.

## DISCUSSION

Three-dimensional echocardiography allows accurate calculation of left ventricular volume and ejection fraction without geometric assumptions, and has been validated against radionuclide angiography and magnetic resonance imaging.<sup>18-20</sup> Therefore, offers a faithful echocardiographic reference for left ventricular volume and ejection fraction calculation.

In practice apical views are used for biplane left ventricular volume and ejection fraction calculation. However, there is still lack of consensus whether to use the apical two chamber

view or the apical long axis view in combination with the apical four chamber view for biplane left ventricular volume calculation.

Our results demonstrated that, apical two chamber and apical long axis views are not consistently orthogonal to apical four chamber view. There was a wide range of rotational angle from apical four chamber view for both apical two chamber and apical long axis views. The mean value of apical long axis rotational angle was more closer to orthogonality than that of apical two chamber view which demonstrated a closer standard deviation of its mean.

Biplane ellipse using both A and B methods have excellent correlation with three-dimensional echocardiographic Simpson's rule for left ventricular volume and ejection fraction calculation. Among the limits of agreement between Simpson's rule and methods of paired orthogonal views, biplane ellipse B method has closer limits of agreement than biplane ellipse A method for left ventricular volumes and ejection fraction calculation. The underestimation of biplane ellipse A method compared to three-dimensional echocardiographic Simpson's method was ( $11\pm10\%$ ,  $8.5\pm11.5\%$  and  $2.3\pm10.1\%$ ) for end-diastolic and end-systolic left ventricular volume and ejection fraction respectively, while that of biplane ellipse B method compared to the reference method was ( $5.6\pm8.5\%$ ,  $3.5\pm9.4\%$  and  $2\pm7.6\%$ ) respectively. Thus, biplane volume calculation using the apical long axis and the apical four chamber views partially reduce the underestimation imposed on cross-sectional echocardiography by (5.4%, 5% and 0.3%) for end-diastolic and end-systolic left ventricular volume and ejection fraction calculation respectively.

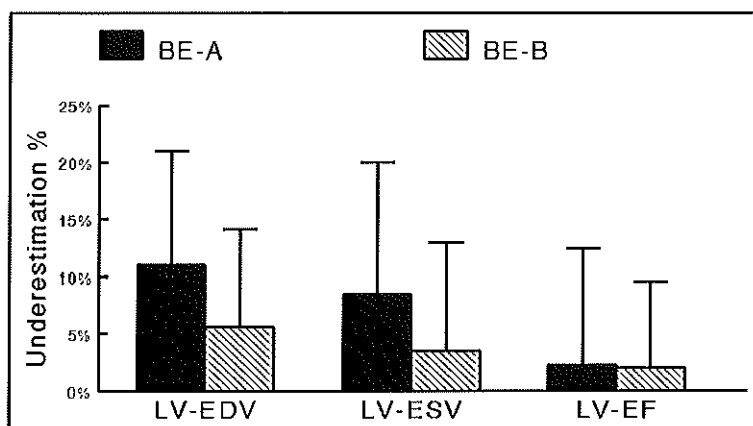


Figure 6. The (%) underestimation (mean  $\pm$  SD) of left ventricular end-diastolic and end-systolic volume and ejection fraction calculated by BE-A and BE-B compared to values obtained from 3DS.

### Comparison with previous studies using the apical four chamber and the apical long axis views for biplane volume measurements

The apical long axis represents a better orthogonal view to apical four chamber for biplane volume measurements than the apical two chamber view. Also, the apical long axis view is more reproducible due to the presence of anatomical landmarks of the aortic and mitral valve which allows better standardisation. The apical two-chamber view is frequently foreshortened resulting in a shorter long axis length (apex to midbase). If the difference in the axis lengths of the two orthogonal views is greater than 15%, biplane calculations are not valid.<sup>9</sup> Our results are in agreement with the study conducted by Jenni et al.<sup>11</sup> who compared left ventricular volume and ejection fraction calculation by two-dimensional echocardiography and biplane cineventriculography in 42 consecutive patients. Two orthogonal apical long axis views were recorded, the four chambers view and the 'RAO equivalent' view or apical long axis view which including the left ventricular outflow tract. They achieved excellent correlation between cine-ventriculography and two-dimensional echocardiography for calculating end-diastolic volume ( $r = 0.98$  and  $SEE = 21$  ml), end-systolic volume ( $r = 0.97$  and  $SEE = 17$  ml) and ejection fraction ( $r = 0.87$  and  $SEE = 5.4\%$ ).

### Comparison with previous studies using the apical four and two chamber views for biplane volume measurements

The American Society of Echocardiography recommends to calculate left ventricular volume from the dimensions and area measurements obtained from paired apical views (both two- and four-chamber) that may be considered nearly orthogonal.<sup>4</sup>

Katz et al.,<sup>13</sup> studied the assumption that apical four and two chamber views are perpendicular along the left ventricular long axis. The validity of this assumption was tested using custom-designed 3.5-Mhz transducers with an electric motor that rotated the transducer by 2.9° increments through 180° about a central axis. Images were acquired beginning at the best appearing apical four chamber views and rotating to the best appearing apical two chamber views. The mean degree of rotation between the apical four and two chamber views were  $95^\circ \pm 21^\circ$  (minimum =  $30^\circ$  and maximum =  $136^\circ$ ). They conclude that apical four and two chamber views represent pairs of orthogonal imaging planes within  $10^\circ$  of orthogonality in about half of the subjects, but this assumptions was inaccurate in many patients. Moreover, in their study they did not demonstrate the accuracy of volume measurements on applying this formula, and they did not adress the alternative approach of using apical long axis instead of two chamber as an orthogonal to the apical four chamber view.

Spain et al.,<sup>21</sup> studied biplane volume measurements using the apical four and two chamber views in 31 patients. Their aim was to determine whether use of the line of intersection display will improve positioning of the apical four chamber and apical two chamber views and thereby, improve the agreement between estimates of left ventricular volume by apical biplane echocardiography and cineventriculography. They found that, guided image positioning was not able to correct displacement of the ultrasound beam anterior to ventricular apex without deterioration of image quality in most patients. In addition, the underestimation and the agreement between echocardiographic and cineventriculographic volumes was not changed, for unguided images the correlation and the

limits of agreement are ( $r = 0.84$ ,  $\pm 62.4$  cc and  $r = 0.94$ ,  $\pm 49$  cc) for end-diastolic and end-systolic volumes respectively. While, that for the line of intersection guided views ( $r = 0.85$ ,  $\pm 60.8$  cc and  $r = 0.91$ ,  $\pm 52.2$  cc) respectively. Starling et al.,<sup>22</sup> demonstrated that cross sectional biplane echocardiography using the apical four chamber and the apical two chamber views underestimated left ventricular volume calculation by 28% compared with radionuclide angiographic volumes in 30 patients (26 with coronary artery disease and wall motion abnormalities). This underestimation of volume measurements was reported in many other studies using the apical four and the two chamber views for biplane left ventricular volumes calculation.<sup>6</sup>

### Advantages and limitations of the study

In this study we addressed most of the factors which may affect the accuracy of biplane volume measurements by standard cross-sectional echocardiography. We studied the spatial orientation of the apical long axis and two chamber views relative to the apical four chamber view. With the biplane ellipse model, these views are assumed to be orthogonal to the four chamber view. We used the three-dimensional data sets obtained from the apical window which encompassed the whole left ventricular cavity. The acquisition software allows to avoid artefacts resulting from respiratory variation and motion artefacts. Standard apical views were derived from the data set and the spatial position of the long axis and two chamber was measured relative to the apical four chamber view and should be correct.

We compared the results of volumes calculated with the two standard approaches based on a model assuming orthogonality between the two planes with those obtained from three-dimensional echocardiography using Simpson's rule as an echocardiographic gold standard technique. Three-dimensional echocardiographic Simpson's method was proved to be an accurate and reproducible method for calculating left ventricular volumes and ejection fraction with comparison to both radionuclide angiography and magnetic resonance imaging techniques.<sup>18-20</sup>

In this study the basic apical views for biplane volume measurement were obtained from the three-dimensional echocardiographic data set, therefore there is still a need to compare biplane volume calculation from the standard cross-sectional echocardiographic apical views.

### CONCLUSIONS

Apical two chamber and apical long axis views are not consistently orthogonal to apical four chamber view. Observer variabilities of Biplane ellipse-B method were smaller than that for Biplane ellipse-A. Biplane ellipse using both A and B methods has excellent correlation and non significant differences with three-dimensional echocardiographic Simpson's rule for left ventricular volume and ejection fraction calculation. Among the limits of agreement between Simpson's rule and methods of paired orthogonal views, biplane ellipse B method has closer limits of agreement than biplane ellipse A method for left ventricular volume and ejection fraction calculation. Therefore, we recommend the use of apical long axis rather than the two chamber with four chamber views for accurate biplane left ventricular volumes and ejection fraction calculation.

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## CHAPTER 6

### **PARAPLANE ANALYSIS FROM PRECORDIAL THREE-DIMENSIONAL ECHOCARDIOGRAPHIC DATA SETS FOR RAPID AND ACCURATE QUANTIFICATION OF LEFT VENTRICULAR VOLUME AND FUNCTION. A COMPARISON WITH MAGNETIC RESONANCE IMAGING**

**Youssef FM Nosir MD\*, Jaap Stoker MD PhD, Jaroslaw D Kasprzak MD, Maarten H Lequin MD, Anita Dall'Agata MD, Folkert J Ten Cate FACC, Jos RTC Roelandt FACC.**

**With Technical Assistance of Wim B Vletter BSc, Eric Boersma MSc, Ron T van Domburg MSc, René Frowijn.**

From Thoraxcenter, AZR-Dijkzigt and Erasmus University, Rotterdam, The Netherlands,

\*Department of Cardiology, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt.

*Am Heart J. (In Press)*

**ABSTRACT**

**Objectives:** Three-dimensional echocardiography (3DE) calculates left ventricular volumes (LVV) and ejection fraction (EF) without geometric assumptions, but prolonged analysis time limits its routine use. This study was designed to validate a modified 3DE method for rapid and accurate LVV and EF calculation with comparison to magnetic resonance imaging (MRI).

**Methods.** 40 subjects, included (a) 15 normal volunteers and (b) 25 patients with segmental wall motion abnormalities and global hypokinesis secondary to ischaemic heart disease, underwent 3DE using precordial rotational acquisition technique (2-degrees interval with ECG and respiratory gating) and MRI at 0.5 T, ECG-triggered multislice multiphase T1 weighted fast field echo. End-diastolic and end-systolic LVV and EF were calculated from both techniques using Simpson's rule by manual endocardial tracing of equidistant parallel left ventricular short axis slices. Slicing from the 3DE data sets were done by both 2.9-mm slice thickness (3DE-A) and by 8 equidistant short axis slices (3DE-B). While for MRI analysis, 9-mm slice thickness was used.

**Results.** Analysis time required for manual endocardial tracing of end-diastolic and end-systolic short axis slices was 10-minutes for 3DE-B method, compared to 40-minutes by 3DE-A method. For all 40 subjects the mean $\pm$ SD of end-diastolic LVV (ml) were 181 $\pm$ 76, 179 $\pm$ 73 and 182 $\pm$ 76, for end-systolic LVV (ml) 120 $\pm$ 76, 120 $\pm$ 75 and 122 $\pm$ 77 and for EF (%) 39 $\pm$ 18, 38 $\pm$ 18 and 38 $\pm$ 18 for MRI, 3DE-A and 3DE-B methods respectively. The differences between 3DE-A and 3DE-B with MRI for calculating end-diastolic and end-systolic LVV and EF were not significant for the whole group of subjects as well as for (a) and (b) subgroups. 3DE-B method had excellent correlation and close limits of agreement with MRI for calculating end-diastolic and end-systolic LVV and EF {(r= 0.98, 0.99 and 0.99), (-1.3 $\pm$ 26.6, -1.6 $\pm$ 21.2 and 0.2 $\pm$ 5.2)} respectively. The correlation between 3DE-A and MRI were (r=0.97, 0.98 and 0.98) and the limits of agreement were (-1.4 $\pm$ 36, -0.6 $\pm$ 26 and 0.6 $\pm$ 8) for calculating end-diastolic and end-systolic LVV and EF respectively. In addition, excellent correlation and close limits of agreement between 3DE-A and -B with MRI for LVV and EF calculation was also found for (a) and (b) subgroups. Intraobserver and interobserver variability (SEE) of MRI for calculating end-diastolic and end-systolic LVV and EF were (6.3, 4.7 and 2.1) and (13.6, 11.5 and 4.7) respectively, while that for 3DE-B were (3.1, 4.4 and 2.2) and (6.2, 3.8 and 3.6) respectively. Comparable observer variability was also found for (a) and (b) subgroups.

**Conclusions.** 3DE-A and -B methods have excellent correlation and close limits of agreement with MRI for calculating LVV and EF in both normal subjects and cardiac patients. 3DE-B method using paraplane analysis with 8 equidistant short axis slices has similar observer variability as MRI, reduces the 3DE analysis time to 10 minutes and therefore offers a rapid, reproducible and accurate method for LVV and EF calculation.

Calculation of left ventricular volume and ejection fraction has important diagnostic, prognostic and therapeutic implications. Therefore a rapid and accurate non-invasive method for their computation is desirable.<sup>1,2</sup>



Radionuclide angiography is an accepted method for ejection fraction calculation.<sup>3,4</sup> However, it is not accurate for left ventricular volume measurements, cannot be easily performed at bedside, may carry biological hazards for the patient and is relatively expensive when used for serial studies. Cineventriculography using biplane left ventricular angiography has been considered the reference method for left ventricular volume and ejection fraction calculation.<sup>5,6</sup> However, cineventriculography is invasive and angiographic measurements are highly dependent on the assumption of geometric models.

Magnetic resonance imaging is a non-invasive technique that has proven to be very accurate in determining left ventricular volume and ejection fraction both in normal subjects and patients.<sup>7-9</sup> However, the technique is not widespread available, expensive, time consuming and cannot be performed at bedside.

Two-dimensional echocardiography is widely available and commonly used for estimations of left ventricular volume and ejection fraction, but is also based on geometric assumptions.<sup>10,11</sup> Accurate calculation of left ventricular volume and ejection fraction requires the reconstruction of the true geometry of the heart, particularly in patients with distorted left ventricular shape.<sup>12-14</sup> Three-dimensional echocardiography has this potential. It has been demonstrated in vitro using phantoms and excised ventricles that the technique yield accurate volume determination.<sup>15-17</sup> Few data have been published so far on the comparison between three-dimensional echocardiographic calculation of left ventricular volume and ejection fraction with other imaging techniques in humans,<sup>18-20</sup> but prolonged analysis time still limits its routine use.

The aim of this study was to validate a modified precordial rotational three-dimensional echocardiographic method for rapid and accurate left ventricular volume and ejection fraction calculation. Magnetic resonance imaging was used as the reference method.

## SUBJECTS and METHODS

### Study population.

Three-dimensional echocardiography was performed in 40 subjects with no contraindication for magnetic resonance imaging and with adequate echocardiographic quality (assessed by checking the three standard apical views). Subjects included (a) 15 normal volunteers and (b) 25 patients with ischaemic heart disease (10 with global hypokinesia and 15 with segmental wall motion abnormalities including 4 with apical aneurysm). Subjects included 31 men; ranged in age from 26 to 72 years with a mean age of  $52 \pm 16.5$  years.

Informed verbal consent was obtained from each subject after they were given a full explanation of the procedure. In each subject magnetic resonance imaging for left ventricular volume and ejection fraction calculation was performed followed by a three-dimensional echocardiographic study on the same day.

## MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging was performed at 0.5 T (Gyrosan T5-11 Philips Medical Systems, The Netherlands). First, axial coronal and sagittal spin-echo localizing views were acquired. Multislice multiphase ECG-triggered T1 weighted fast field echo {repetition time =

800-1200 ms, echo time = 22ms, flip angle =  $70^\circ$ , field of view 240 x 300 mm, slice thickness 9 mm, inter slice gap 0.9 mm, imaging matrix (90 x 128)) was performed. Heart phase interval was 32-39 ms and the number of heart phases 14-32 (median 21).

The window level and width of all magnetic resonance imaging in every subject were selected for the optimal contrast between the relatively hypointense ventricular wall and the relatively hyperintense blood in the ventricular cavity. A short axis view was performed with a coronal and a sagittal survey. On the best images the short axis slices were positioned perpendicular to the septum.

Left ventricular volume measurements were done off line on a work station (Gyroviev HR). End-diastole was defined as the time frame with maximal left ventricular volume. End-systole was defined as the time frame with minimal left ventricular volume. End-diastolic and end-systolic left ventricular volume, stroke volume and ejection fraction were calculated by manual endocardial tracing of the short axis series spanning the left ventricle from the apex to the base.

### THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Echocardiographic studies were performed with a transducer system in the apical position, while the subject lay comfortably in the 45-degree left recumbent position. To acquire the cross-sectional images for reconstruction, the operator has to find the centre axis around which the imaging plane is rotated to encompass the whole left ventricular cavity. Reconstruction of the left ventricle by three-dimensional echocardiography requires three basic steps: image acquisition, image processing, and data analysis.

**Image acquisition:** We used a custom-build hand-held transducer assembly that can be rotated with a step motor via a wheel-work interface<sup>21-22</sup>. A commercially available 3.75 MHz sector scanning transducer (Toshiba Sonolayer SSH-140A system) is mounted in the probe assembly. The step-motor is commanded by a steering-logic for controlled image acquisition (Echo-scan, TomTec GmbH, Munich, Germany). A software-based steering logic activates the step-motor in the transducer assembly which controls the image acquisition in a given plane by an algorithm that considers both heart rate variations (ECG-gating) and respiratory phase by thoracic impedance measurement. Prior to the actual image acquisition the R-R intervals were predetermined with an acceptable variability of 150 msec or less and respiration was gated at the end-expiratory phase. Based on this information, the step-motor is commanded by the steering logic to acquire cross-sections of cardiac cycles that fall within the preset ranges. This allows optimal temporal and spatial registration of the cardiac images. The heart phases were adjusted at 12 phases/cardiac cycle. After a cardiac cycle is selected by the steering logic, the cardiac images are sampled at 80 msec intervals (12 frames/sec), digitized, and stored in the computer memory. Then, the step motor is activated and rotates the transducer 2 degrees to the next scanning plane, where the same steering logic is followed. Cycles that do not meet the preset ranges are rejected. To fill the conical data volume, 90 sequential cross-sections from  $0^\circ$  to  $178^\circ$  must be obtained each during a complete cardiac cycle.

**Image processing:** The recorded images are formatted in their correct rotational sequence according to their ECG phase in volumetric data sets (256\*x256\*x256\* pixel/each 8 bit).

The post-processing of the data sets is performed off-line using the analysis program of the system. To fill the gaps in the far fields, a "trilinear cylindric interpolation" algorithm is used.<sup>20</sup> To reduce motion artefacts that can be created by patient movement or probe movement, a dedicated image processing filter is used (ROSA filter: Reduction of Spatial Artefacts). In order to reduce the time needed for image processing, end-diastolic (the first frame before mitral valve closure) and then end-systolic (the first frame before mitral valve opening) phases are selected before starting the processing procedure. Through this technique we reduce the image processing time to be 5 minutes, which represents approximately 20% of the usual time needed for processing the whole data set.

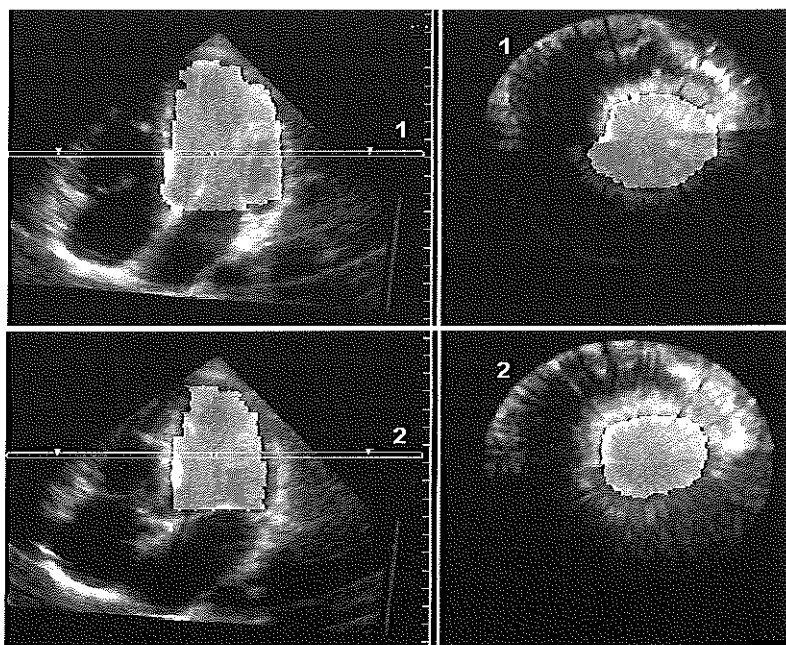


Figure 1. The principle of LVV measurement using a 3DE-A method, from the 3DE data set an end-diastolic and end-systolic long-axis views are used as a reference view. The left ventricle is sliced at equidistant intervals (2.9mm) to generate a series of short axis views. The surface area of each cross-section is measured by planimetry and the volume of each slice is calculated. Adding up the volumes of all slices provides the measurement of LVV (Simpson's method). This is performed for both end-diastolic and end-systolic data sets. The figure shows an end-diastolic and end-systolic long axis views (panel A, upper and lower image respectively) on which the transverse sector 1 and 2 respectively cut the left ventricular cavity at this level to give rise the corresponding short-axis views at end-diastole and end-systole shown in panels B upper and lower images respectively.

**Image analysis.** Left ventricular volume and ejection fraction are calculated from the three-dimensional echocardiographic data set by using Simpson's rule. By this method end-diastolic and end-systolic left ventricular volume are calculated by manual endocardial tracing of sequential short-axis views spanning the left ventricular cavity from the apex to the mitral annulus. After the long-axis view of the left ventricle was selected from the volumetric data set, end-diastolic and then end-systolic phases were loaded and reflected

around the selected long axis. Slicing of the left ventricular cavity was performed by using the “fixed slice thickness” (method 3DE-A) using the paraplane technique to generate a series of equidistant cross-sections at 2.9-mm intervals and a “fixed number of slices “ (method 3DE-B) a rapid paraplane method using 8 parallel equidistant slices at both end-diastole and end-systole. For both methods, when manual tracing of the displayed short-axis was completed, the system calculated the volume by summing the voxels included in the traced area in the pre-set slice thickness. Slice by slice, the system summed the corresponding subvolumes and finally calculated the end-diastolic and end-systolic left ventricular volume and ejection fraction (figures 1-2).

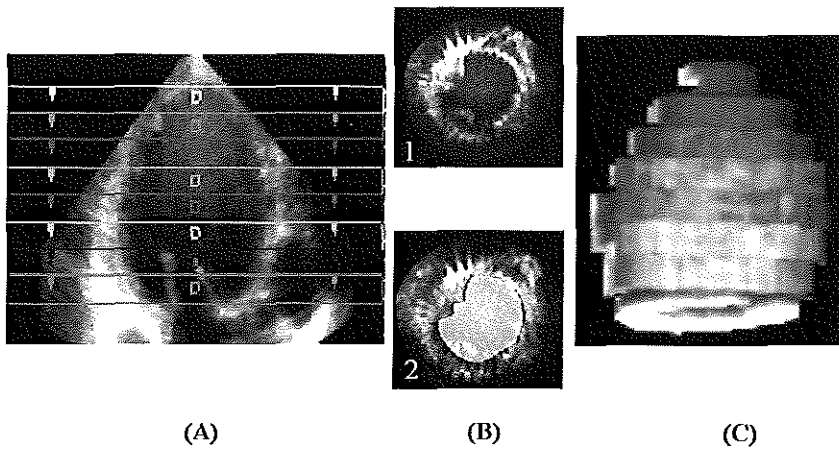


Figure 2. The principle of LVV measurement using a 3DE-B method, from the 3DE data set an end-diastolic and end-systolic long-axis view is used as a reference view. The left ventricle is sliced by the paraplane analysis into 8 equidistant parallel short axis slices that spanning the left ventricular cavity from the apex to mitral annulus (panel A). The surface area of each cross-section is measured by planimetry and the volume of each slice is calculated (panel B). Adding up the volumes of all slices provides the volume measurement of LVV at end-diastole and end-systole (Simpson's method) (panel C shows the reconstructed left ventricular cavity).

## STATISTICAL ANALYSIS

For each technique measurement of left ventricular volume and ejection fraction were performed by two experienced observers blinded to each other's results and the first observer repeated the measurement after at least 7 days. Observer variability was calculated, and expressed as the standard error of the estimate (SEE).

To compare the calculation of end-diastolic and end-systolic left ventricular volume and ejection fraction by 3DE-A and -B methods with magnetic resonance imaging the limits of agreement were computed using the method described by Altman and Bland.<sup>23</sup> A paired t-test was performed and significance was stated at the 0.05 probability level. The p-value, the mean difference and the limits of agreement are reported. Pearson's correlation coefficients are presented.

## RESULTS

### Feasibility

40 subjects out of 53 recruited in this study completed both three-dimensional echocardiography and magnetic resonance imaging. For three-dimensional echocardiography, 4 patients were excluded from the study (1 for an error in calibrating the central rotational axis for image acquisition, and 3 for poor uninterpretable echocardiographic image). While for magnetic resonance imaging, 9 patients were excluded from the study (4 due to claustrophobia and 5 due to incomplete magnetic resonance imaging acquisition). All subjects included in this study were in sinus rhythm, the mean  $\pm$  SD of their heart rate was  $79 \pm 9.5$ . In each case the time required for three-dimensional echocardiographic acquisition, processing and image analysis for both 3DE-A and 3DE-B are in table 1. With method 3DE-B the average slice thickness (mm)  $\pm$  SD were  $9.9 \pm 0.6$  and  $8.1 \pm 0.9$  for end-diastole and end-systole respectively.

Table 1. Comparison of the time required for all procedures of 3DE-A (using 2.9-mm slice thickness) and 3DE-B (using 8 parallel equidistant slices) methods.

Procedure	Time Required for 3DE-A (min)	Time Required for 3DE-B (min)	Time Required for MRI (min)
Image Acquisition	8 - 10	8 - 10	40 - 50
Calibration and	3	3	5
Image Processing	20 - 25	4 - 6	20
LVV analysis	30 - 40	10	30 - 40
Total	61 - 78	25 - 29	95 - 115

3DE = three-dimensional echocardiography, MRI = magnetic resonance imaging, LVV = end-diastolic and end-systolic left ventricular volumes.

Table 2. Observer variabilities of MRI and 3DE-B for calculating LV end-diastolic volume (EDV) and end-systolic volume (ESV) and ejection fraction (EF) for the whole group as well as for 1 and 2 subgroups.

Observer Variability			All Patient. n=40		Normals 1. n=15		Patients 2. n=25	
			SEE	C-SEE(%)	SEE	C-SEE(%)	SEE	C-SEE(%)
MRI	EDV	Intra.	6.3	3.5	6.5	5.8	3.9	1.8
		Inter.	13.6	7.5	10.6	9.4	15.2	6.8
	ESV	Intra.	4.7	3.9	6.4	13.6	3.2	2.0
		Inter.	11.5	9.6	7.5	16.0	14.7	9.1
	EF	Intra.	2.1	5.4	3.3	5.7	1.2	4.4
		Inter.	4.7	12.2	9.8	16.9	2.0	7.4
3DE-B	EDV	Intra.	3.1	1.7	3.0	2.7	3.3	1.5
		Inter.	6.2	3.4	6.6	5.9	3.9	1.7
	ESV	Intra.	4.4	3.6	5.1	10.9	3.1	1.9
		Inter.	3.8	3.1	6.8	14.5	2.5	1.5
	EF	Intra.	2.2	5.8	3.4	6.0	0.6	2.2
		Inter.	3.6	9.5	5.8	10.2	0.9	3.3

SEE = standard error of the estimate, C-SEE = corrected SEE to the mean value, Intra. = intraobserver, Inter = interobserver, other abbreviation as table 1.

### Observer variability of magnetic resonance imaging.

There were no significant differences in measurement of end-diastolic and end-systolic left ventricular volume and ejection fraction obtained by the same observer in two different settings {mean difference (SD) = 0.9(7.3)  $p=0.6$ , 0.1(3.0)  $p=0.9$  and 0.3(1.9)  $p=0.5$ }, with an intraobserver variability (SEE) of 6.3, 4.7 and 2.1 respectively. There were no significant differences in measurement of end-diastolic and end-systolic left ventricular volume and ejection fraction obtained by the two independent observers {mean difference (SD) = {-2.5(12.0)  $p=0.4$ , -0.2(3.5)  $p=0.8$  and -1.4(5.7)  $p=0.4$ }, with an interobserver variability of 13.6, 11.5 and 4.7 respectively.(table 2)

### Observer variability of three-dimensional echocardiography (3DE-B).

There were no significant differences in measurement of end-diastolic and end-systolic left ventricular volume and ejection fraction obtained by the same observer in two different settings {mean difference (SD) = -0.6(3.3)  $p=0.5$ , -1.0(2.4)  $p=0.1$  and 0.6(2.1)  $p=0.3$ }, with an intraobserver variability (SEE) of 3.1, 4.4 and 2.2 respectively. There were no significant differences in measurement of end-diastolic and end-systolic left ventricular volume and ejection fraction obtained by the two independent observers {mean difference (SD) = {2.5(7.2)  $p=0.4$ , 0.8(3.2)  $p=0.3$  and 0.9(3.3)  $p=0.3$ }, with an interobserver variability of 6.2, 3.8 and 3.6 respectively. (table 2)

Table 3. Mean  $\pm$  SD of end-diastolic (ED) and end-systolic (ES) LVV and EF calculated by magnetic resonance image (MRI) and 3DE-A and -B methods for the whole group as well as for 1 and 2 subgroups.

Mean $\pm$ SD	All subjects. n=40	Normals (1). n=15	Patients (2). n=25
MRI-EDV	181 $\pm$ 76	113 $\pm$ 16	222 $\pm$ 69
MRI-ESV	120 $\pm$ 76	47 $\pm$ 6	164 $\pm$ 63
MRI-EF	39 $\pm$ 18	58 $\pm$ 5	27 $\pm$ 12
3DEA-EDV	179 $\pm$ 73	111 $\pm$ 16	220 $\pm$ 62
3DEA-ESV	120 $\pm$ 75	47 $\pm$ 6	165 $\pm$ 61
3DEA-EF	38 $\pm$ 18	57 $\pm$ 5	27 $\pm$ 12
3DEB-EDV	182 $\pm$ 76	112 $\pm$ 16	224 $\pm$ 66
3DEB-ESV	122 $\pm$ 77	47 $\pm$ 6	167 $\pm$ 64
3DEB-EF	38 $\pm$ 18	58 $\pm$ 5	27 $\pm$ 12

SD = standard deviation, other abbreviation as table 1 and 2.

### Three-dimensional echocardiography versus magnetic resonance imaging.

The mean  $\pm$  SD values of left ventricular volume and ejection fraction obtained by magnetic resonance imaging and 3DE-A and -B methods for all subjects as well as 1 and 2 subgroups are presented in table 3. There was an excellent correlation between the measurements of end-diastolic and end-systolic left ventricular volume and ejection fraction obtained by 3DE-B and MRI (r value = 0.98, 0.99 and 0.99 respectively) (figure 3). Excellent correlation was also obtained between 3DE-A and magnetic resonance imaging (r value = 0.97, 0.98 and 0.98 respectively). No significant difference existed in the mean difference between left ventricular volume and ejection fraction obtained by both 3DE-A and

-B methods magnetic resonance imaging. In addition, there were close limits of agreement between the measurements of left ventricular volume and ejection fraction obtained by 3DE-A and -B methods with magnetic resonance imaging (figure 4) (table 4).

### Correlation Between 3DE-B and MRI For LVV and EF Calculation

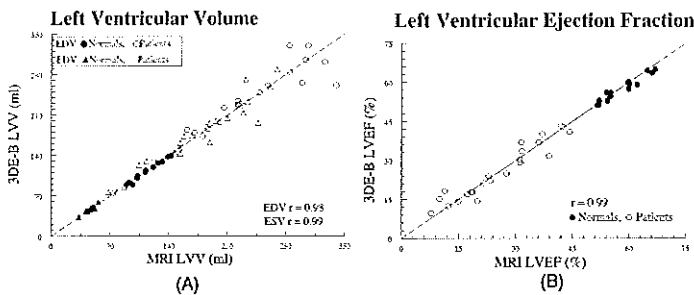


Figure 3. Linear regression of end-diastolic and end-systolic LVV (panel A) and EF (panel B) calculated by 3DE-B method using 8 short axis slices versus MRI. n = number of subjects, r = correlation coefficient. The dashed line represents the identity line.

Table 4. Comparison between both 3DE-A and 3DE-B with MRI for calculating ED and ES LVV and EF.

		MRI - 3DEA				MRI - 3DEB			
		r	MD±SD	p	Agreem.	r	MD±SD	p	Agreem.
All	EDV	97	1.4±18.3	0.5	1.4±36.6	98	-1.3±13.3	0.6	-1.3±26.6
	ESV	98	-0.6±13.4	0.4	-0.6±26.8	99	-1.6±10.6	0.8	-1.6±21.2
	EF	98	0.6±4.0	0.6	0.6±8.0	99	0.2±2.6	0.4	0.2±5.2
Normal	EDV	96	1.7±4.8	0.1	1.7±9.6	99	0.9±2.3	0.2	0.9±4.6
	ESV	94	-0.6±1.9	0.2	-0.6±3.8	93	-0.7±2.1	0.2	-0.7±4.2
	EF	95	0.7±1.7	0.1	0.7±3.4	97	0.6±1.4	0.1	0.6±2.8
Patient	EDV	94	1.2±23.1	0.4	1.2±26.2	97	-2.6±16.7	0.8	-2.6±33.4
	ESV	96	-0.6±17.0	0.4	-0.6±34.0	98	-2.1±13.4	0.9	-2.1±26.8
	EF	92	0.5±4.9	0.9	0.5±9.6	96	-0.03±3.1	0.6	-0.03±6.2

r = correlation coefficient, MD = mean difference, SD = standard deviation of the mean differences, p. = p value, agreem. = limits of agreement, other abbreviation as table 1 and 2.

## Limits of Agreement Between 3DE-B and MRI For LVV and EF Calculation

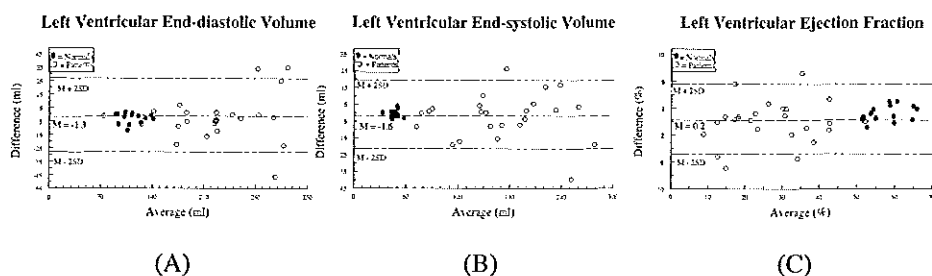


Figure 4. Limits of agreement of end-diastolic (panel A), end-systolic (panel B) LVV and EF (panel C) calculated by MRI - 3DE-B method using 8 short axis slices. Difference of each pair of MRI - 3DE-B end-diastolic, end-systolic LVV and EF measurements plotted against the average value of both measurements.

### DISCUSSION

Calculation of left ventricular volume and ejection fraction is important for the evaluation of patients with heart disease. Segmental wall motion abnormality and left ventricular aneurysm are common complications of acute myocardial infarction.

Quantification of left ventricular volume by two-dimensional echocardiography are limited by its heterogeneous geometry, which restricts application of simple geometric models which assume symmetrical shape.<sup>24-26</sup>

Three-dimensional echocardiography provides an accurate measurement of left ventricular volume and function by the reconstruction of the true left ventricular geometry, but remains time consuming. This study was performed to validate the 3DE-B as a rapid method for left ventricular volume and ejection fraction calculation against magnetic resonance imaging. Our results demonstrate an excellent correlation and close limits of agreement between left ventricular volume and ejection fraction measured by three-dimensional echocardiography using two different methods (A and B) and magnetic resonance imaging for the whole subjects recruited in this study as well as for (a) and (b) subgroups (table 4). Thus, with the rapid 8 parallel equidistant slice method we have achieved at least the same accuracy as with the time consuming 2.9-mm fixed slice thickness method.



In average for 3DE-B the analysis time was reduced from 40 to 10 minutes, in addition the required time for the whole 3DE-B procedures were reduces to 25% of that required for 3DE-A method (table 1).

### Comparison with other studies

Our findings are in agreement with the study conducted by Gopal et al.,<sup>18</sup> who compared end-diastolic and end-systolic left ventricular volume and ejection fraction in 15 normal volunteers measured by magnetic resonance imaging and three-dimensional echocardiography. These authors calculated their echocardiographic left ventricular volume from a series of (8 to 9) nonparallel, unequally spaced real-time parasternal short-axis images which were acquired with a line-of-intersection display as a guide. This line is computed and displayed in each image to indicate the position and orientation of that image with respect to the other image. All images for ventricular reconstruction are acquired during suspended respiration. A polyhedral surface reconstruction algorithm has been adapted for left ventricular volume computation using the traced endocardial borders of the short axis images. The interobserver variability for three-dimensional echocardiography was 5% and 8%, while that magnetic resonance imaging was 6.6% and 9%. Both methods were in close agreement for end-diastolic volume ( $r = 0.92$ , SEE = 6.99 ml) and for end-systolic volume ( $r = 0.81$ , SEE = 4.01 ml).

Sapin et al.,<sup>19</sup> studied two- and three-dimensional echocardiography in 35 patients 1 to 3 hours before left ventricular cineventriculography and used the same method described by Gopal et al.,<sup>18</sup> for three-dimensional echocardiography. The correlation and limits of agreement between end-diastolic and end-systolic left ventricular volume measured by three-dimensional echocardiography and cineventriculography is better than between two-dimensional echocardiography and cineventriculography. However, they did not find an improvement in calculating ejection fraction by three-dimensional echocardiography over two-dimensional echocardiography. They explained this by the possible balance in volume error calculations of end-diastolic and end-systolic volume by two-dimensional echocardiography and cineventriculography. These errors were nullified when calculating ejection fraction. On the other hand end-diastolic and end-systolic volume errors by three-dimensional echocardiography were not correlated because they were derived from multiple cardiac cycles from which errors of ejection fraction were obtained.

Our results demonstrated excellent correlation and close limits of agreement between three-dimensional echocardiography and magnetic resonance imaging for calculating both left ventricular volume and ejection fraction. Differences in methodology<sup>22</sup> may in part explain the discrepancy between our results and those of Sapin et al.<sup>19</sup> In addition, this can be attributed to the different reference method used by Sapin et al., the cineventriculography.

Three-dimensional echocardiography has been shown to yield accurate left ventricular volume with comparison to actual volumes in the in vivo study conducted by Jiang et al.,<sup>27</sup> using 4 dogs with surgically created left ventricular aneurysms. They found that, left ventricular end-diastolic, end-systolic, stroke volumes and ejection fraction calculated by three-dimensional echocardiography correlated well with actual values ( $r=0.99$ , 0.99, 0.95 and 0.99 respectively) and agreed closely with them (SEE=4.3 cm<sup>3</sup>, 3.5 cm<sup>3</sup>, 1.7 cm<sup>3</sup> and 2% respectively).

### **Three-dimensional echocardiography with 8 short axis slices is optimal for accurate left ventricular volume and ejection fraction calculation**

The mean  $\pm$  SD of slice thickness with 3DE-B, using 8 equidistant parallel slices, were within the recommended limits for slice thickness previously reported. Accurate left ventricular volume and ejection fraction requires a slice thickness of less than 15-mm.<sup>20</sup>

This was also in agreement with the previous recommendation of Weiss et al.,<sup>28</sup> for accurate and reproducible two-dimensional echocardiography calculation of left ventricular volume by Simpson's rule. They used different progressively decreasing number of short axis slices (from 19 to 1) and concluded that high accurate volumes with low variability in measurement can be obtained, but this accuracy begins to deteriorate significantly when fewer than four cross sections ( $>15$ -mm thickness) were used.

Siu et al.,<sup>29</sup> studied the influence of number of component images on accuracy of left ventricular volume quantification by three-dimensional echocardiography using the nonparallel intersecting images. They concluded that, accurate calculation of left ventricular volume and ejection fraction can be obtained by three-dimensional echocardiography with as few as 8 to 12 nonparallel intersecting images.

In our study, there were closer limits of agreement and comparable intraobserver and interobserver variability between 3DE-B method and magnetic resonance imaging for left ventricular volume and ejection fraction calculation. This can be explained by the fact that both methods calculate left ventricular volume using Simpson's rule with almost the same slice thickness. We therefore recommend the use of paraplane analysis from three-dimensional echocardiography with 8 equidistant parallel slices for rapid, reproducible and accurate left ventricular volume and ejection fraction calculation.

### **Advantages and limitations of 3DE in this study**

Three-dimensional echocardiography allows the calculation of left ventricular volume without geometric assumption. The prolonged analysis time which was the most important limiting factor that currently restricts the routine use of three-dimensional echocardiography, is now partially solved by using the rapid analysis method with 8 parallel equidistant short axis slices. In future, developing faster computers and applying automated border recognition software for area and volume analysis technique will shorten more the time needed for three-dimensional echocardiographic procedures.

Since the spatial co-ordinate system changes with transducer movement, motion of the transducer must be avoided. Inadvertent patient movement during the image acquisition can be prevented for the most part by thoroughly explaining the procedure before the study, in addition a dedicated image processing filter is used (ROSA filter: Reduction of Spatial Artefacts).

Precordial rotational three-dimensional echocardiographic acquisition from the apical window necessitate the identification of the longest left ventricular long axis around which data will be acquired. However, sometimes its identification was not possible and the left ventricle was foreshortened because of rib interference and narrow intercostal space. With 3DE-B method we have achieved accurate left ventricular volume and ejection fraction calculation within acceptable time consumption.

Using 1.5 T magnetic resonance imaging with breath-hold and semiautomated border detection algorithm provides better image resolution, shortens the procedure and reduce motion and respiratory artefacts.

## CONCLUSIONS

3DE-A and -B methods have excellent correlation and close limits of agreement with magnetic resonance imaging for calculating left ventricular volume and ejection fraction in both normal subjects and cardiac patients with segmental wall motion abnormalities and global hypokinesis. 3DE-B method using paraplane analysis with 8 equidistant short axis slices has similar observer variability as magnetic resonance imaging, reduces the three-dimensional echocardiographic analysis time to 10 minutes and therefore offers a rapid, reproducible and accurate method for left ventricular volume and ejection fraction calculation.

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**CHAPTER 7****MEASUREMENTS AND DAY TO DAY VARIABILITIES  
OF LEFT VENTRICULAR VOLUMES AND EJECTION  
FRACTION BY THREE-DIMENSIONAL  
ECHOCARDIOGRAPHY AND COMPARISON WITH  
MAGNETIC RESONANCE IMAGING**

**Youssef FM Nosir MD\*, Maarten H Lequin MD, Jaroslaw D Kasprzak  
MD, Ron T. van Domburg MSc, Wim B Vletter BSc, Jiefen Yao MD,  
Jaap Stoker MD, Jos RTC Roelandt MD FACC.**

From the Heart Center and Thoraxcenter, Division of Cardiology, University Hospital  
Rotterdam-Dijkzigt, Erasmus University, Rotterdam, The Netherlands \*Cardiology  
Department, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt.

*Am J Cardiol. 1998;82:209-214*

## ABSTRACT

The aim of this study was to assess day-to-day variability of left ventricular (LV) volume and ejection fraction (EF) calculated from 3-dimensional echocardiography (DE) and to compare the reproducibility of the measurement with magnetic resonance imaging. 46 subjects were examined including 15 normal volunteers (group A) and 31 patients with LV dysfunction (group B). Precordial 3DE acquisition was performed at 2-degree rotational intervals and repeated one week later. Magnetic resonance imaging was performed at 0.5 T. End-diastolic and end-systolic LV volume were derived using Simpson's rule by manual endocardial tracing of 8 equidistant parallel LV short axis slices with 3DE, while 9-mm slices was used with magnetic resonance imaging. The mean $\pm$ SD of end-diastolic and end-systolic LV volume (ml) and EF (%) from magnetic resonance imaging were (182 $\pm$ 75, 121 $\pm$ 76 and 39 $\pm$ 18), while those from 3DE were (182 $\pm$ 76, 121 $\pm$ 77 and 39 $\pm$ 18) respectively. Day-to-day measurements of end-diastolic and end-systolic LV volume, and EF from 3DE were not significantly different with standard error of the estimate of (2.7, 1.1 and 2.4) respectively. Intra- and inter-observer standard error of the estimate for calculating end-diastolic and end-systolic LV volume and EF for magnetic resonance imaging were (6.3, 4.7 and 2.1) and (13.6, 11.5 and 4.7) respectively, while those for 3DE were (3.1, 4.4 and 2.2) and (6.2, 3.8 and 3.6) respectively.

**Conclusions.** Day-to-day variability of LV volume and EF calculation from 3DE were small and not significantly different for normal and dysfunctional left ventricles. Observer variabilities of 3DE were smaller than that of magnetic resonance imaging. Therefore, 3DE is recommended for serial assessment of LV volume and EF in normal and abnormally shaped ventricles.

Left ventricular (LV) volume and function is affected in many clinical situations. Serial monitoring of LV volume and function changes is important for clinical decision making, prediction of the outcome in many cardiac disorders and following various medical or surgical interventions.<sup>1-2</sup> The currently used two-dimensional methods including angiography,<sup>3-7</sup> radionuclide angiography<sup>8-10</sup> and echocardiography<sup>11-16</sup> have to employ geometric assumptions for LV. Magnetic resonance imaging produces accurate measurement of LV volumes,<sup>17-19</sup> but is not widely available. Three-dimensional echocardiography (3DE) allows accurate LV volume and EF calculation by obviating geometric assumptions.<sup>20-27</sup> Few data are available concerning the reproducibility of LV volume and function assessment by volume rendered 3DE using sequential data acquisition and day-to-day variability of these measurements has not been investigated. Therefore, this study was designed to evaluate day-to-day variability of LV volume and EF from 3DE and the accuracy and reproducibility of the measurements using magnetic resonance imaging as a reference.

## SUBJECTS AND METHODS

3DE and magnetic resonance imaging were performed in 46 subjects including 36 men and 10 women (aged 51  $\pm$  17 years, ranging from 26 to 72 years). Group A included 15 healthy volunteers (aged 32  $\pm$  7 years, men only). Group B included 31 patients (21 men and 10 women, aged 54  $\pm$  18 years) with the diagnosis of ischaemic heart disease demonstrating

either regional (n=19) or global (n=12) wall motion abnormalities. All subjects studied were in sinus rhythm. The mean  $\pm$  SD of their heart rate was  $78 \pm 10$  beats / minutes. Informed verbal consent was obtained from each subject after a full explanation of the procedure had been given. In each subject, magnetic resonance imaging of the left ventricle was performed, on the same day, as 3DE study. A second 3DE acquisition was performed one week later in 15 patients, provided that the clinical conditions of the patient remained stable and no therapeutic changes were made between the 2 studies.

### MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging was performed at 0.5 T (Gyrosan T5-11 Philips Medical Systems, The Netherlands). Axial, coronal and sagittal spin-echo was used to localize views of the left ventricle. The multislice multiphase electrocardiogram-triggered T1 weighted fast field echo was performed with a repetition time of 800-1200 ms, echo time 22ms, flip angle  $70^\circ$  and the field of view 240 x 300 mm. The level and width of magnetic resonance imaging window in every subject were selected to obtain an optimal contrast between the relatively hypointense ventricular wall and the relatively hyperintense blood pool in the ventricular cavity. The best images were chosen for data collection of short axis slices perpendicular to the septum following a coronal and a sagittal survey. Sequential images of the heart were collected using 9 mm slice thickness with 0.9 mm inter-slice gap and imaging matrix (90 x 128). Heart phase interval was 32-39 ms with the number of heart phases 14-32 (the median at 21). Left ventricular volume measurement was carried out off line on a work station (Gyroview HR) by two independent observers (MHL and JS) separately, both unaware of the 3DE measurements. The end-diastole was defined as the frame with the largest LV cavity size and the end-systole the smallest LV cavity size. The endocardial border of the left ventricle was traced manually on all short axis views to derive end-diastolic and end-systolic LV volume and EF. The image acquisition required from 45 to 60 minutes. Image analysis required 30 minutes on average.

### THREE-DIMENSIONAL ECHOCARDIOGRAPHIC EXAMINATION

A commercially available ultrasound unit (Toshiba Sonolayer SSH-140A) with the transducer frequency of 3.75 MHz was coupled with a 3DE processing computer (Echo-scan, TomTec GmbH, Munich, Germany) for data acquisition.<sup>28,29</sup> The echocardiographic images of the left ventricle were collected from an apical window in rotational format at  $2^\circ$  intervals, gated to proper R-R intervals of electrocardiogram and thoracic impedance of expiration, while the patient was resting comfortably in a  $45^\circ$  left recumbent position. Images were readjusted in their correct spatial and temporal sequence and were reformatted digitally. Gaps between the images of end-diastolic and end-systolic phases were interpolated using a "trilinear cylindric interpolation" algorithm.<sup>26</sup> A voxel based volumetric data set was thus resulted.

From the 3DE data set, the end-diastolic and end-systolic LV volumes were calculated off line by two independent observers (YFMN and JDK) on a 3DE work station (TomTec system Echo View 3.1) using Simpson's rule. After a reference LV long axis view was defined, 8 parallel equidistant short-axis slices spanning the LV cavity from the apex to the

mitral annulus were derived automatically by the computer. The endocardial border of the left ventricle on each slice was traced in frames with biggest and smallest cavity areas. The volume was calculated automatically by the computer using a summation of the voxels included in the traced area. An accumulation of the subvolumes on all slices yielded the LV volumes at end-diastole and end-systole, from which the EF was calculated. (figure 1) One of the observers (YFMN) repeated the same measurements after 7 days or longer. Data from the second 3DE acquisition was analyzed in the same manner by the same observer to examine day-to-day variability of LV volume and EF. In each case the examination, including the calibration procedures, selection of optimal gain setting and conical volume, and image acquisition, required approximately 8-10 minutes. Calibration and storage of the data in the computer memory required approximately 3 minutes. Off-line image processing and analysis required on average 15 minutes..

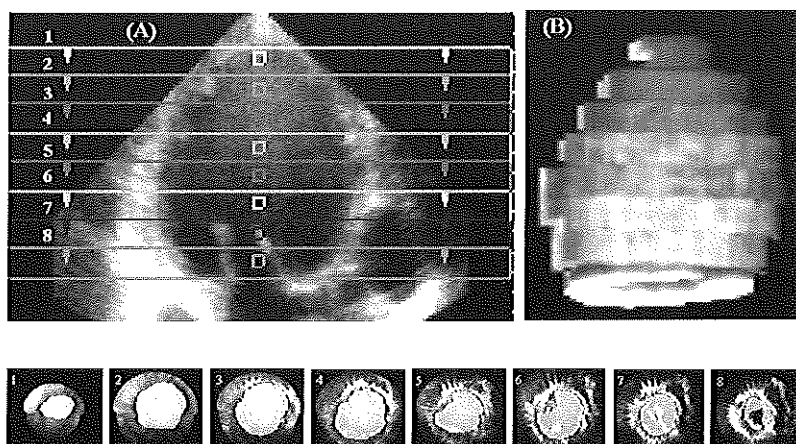


Figure 1. The principle of left ventricular volume measurement using Simpson's rule with volume rendered three-dimensional echocardiography. A long-axis view is selected as a reference image from the three-dimensional echocardiographic data set. The left ventricle is sliced by paraplane analysis method into 8 equidistant parallel short axis slices spanning the left ventricular cavity from the apex to mitral annulus (panel A). The endocardial border of the left ventricle on each cross-section is traced manually [as the white label (lower panel from 1 to 8 short axis slices )]. The volume of the traced region on each slice is calculated. Adding up the volumes of all slices provides the left ventricular volume at a chosen phase (end-diastole or end-systole). The reconstructed left ventricular cavity is shown in (panel B).

## STATISTICAL ANALYSIS

All values of the measurements were expressed as mean  $\pm$  SD. To compare the calculation of end-diastolic and end-systolic LV volume and EF by 3DE with magnetic resonance imaging, the limits of agreement were computed using the method described by Altman and Bland<sup>30</sup>. A paired t-test was performed and significance was stated at the 0.05 probability level. The p-value, the mean difference and the limits of agreement (mean differences  $\pm$  2SD) are reported. Pearson's correlation coefficients are presented.



Intraobserver and interobserver variabilities were calculated as the standard error of the estimate (SEE). Intraobserver and interobserver measurements and day-to-day variability of end-diastolic and end-systolic LV volume and EF were studied by the limits of agreement using the method described by Altman and Bland.<sup>30</sup> Statistical significance was defined at the 0.05 probability level. Pearson's correlation coefficients were derived.

## RESULTS

The mean  $\pm$  SD of end-diastolic and end-systolic LV volumes and EF calculated by 3DE and magnetic resonance imaging from all the subjects as well as from groups A and B are presented in table 1. The results from both techniques showed excellent correlation ( $r = 0.98$ ,  $0.98$  and  $0.98$ ) with close limits of agreement (Mean difference  $\pm 2SD$ 's)<sup>30</sup> ( $-1.4 \pm 27$ ,  $-1.5 \pm 21$  and  $0.2 \pm 5.1$ ) and non-significant differences ( $p = 0.6$ ,  $0.7$  and  $0.5$ ) for calculating LV end-diastolic and end-systolic volume and EF, respectively (figure 2)

## REPRODUCIBILITY OF MAGNETIC RESONANCE IMAGING

There were no significant differences between intraobserver measurements of end-diastolic and end-systolic LV volumes and EF ( $p=0.2$ ,  $0.1$  and  $0.3$ ) with the intraobserver standard error of the estimate of  $6.3$ ,  $4.7$  and  $2.1$ , respectively. Also, no significant differences were found between interobserver measurements of end-diastolic and end-systolic LV volumes and EF ( $p=0.2$ ,  $0.1$  and  $0.4$ ) with the interobserver variability of  $13.6$ ,  $11.5$  and  $4.7$ , respectively. Excellent correlation's and small limits of agreement were observed between intraobserver and interobserver measurements of LV volumes and EF by magnetic resonance imaging from all subjects as well as from groups A and B. (table 2 and figures 3,4)

## REPRODUCIBILITY OF 3DE

There was no significant difference between intraobserver measurements of end-diastolic and end-systolic LV volumes and EF ( $p=0.4$ ,  $0.6$  and  $0.3$ ) with the intraobserver variability (SEE) of  $3.1$ ,  $4.4$  and  $2.2$ , respectively. Similarly no significant difference was found between interobserver measurements of end-diastolic and end-systolic LV volumes and EF ( $p=0.4$ ,  $0.5$  and  $0.6$ ) with the interobserver variability of  $6.2$ ,  $3.8$  and  $3.6$ , respectively, in all subjects. Groups A and B revealed similar results. There were excellent correlation and close limits of agreement between intraobserver and interobserver measurements of LV volumes and EF by 3DE from all the subjects as well as from groups A and B. (table 2 and figures 3,4)

## DAY-TO-DAY VARIABILITY OF 3DE MEASUREMENTS

No significant difference was found in day-to-day measurements of end-diastolic and end-systolic LV volumes and EF with the mean difference (SD) of  $-1.2(11.3)$  ( $p=0.2$ ),  $-0.9(9.3)$  ( $p=0.4$ ) and  $-0.5(4.2)$  ( $p=0.2$ ) and the day-to-day variability (SEE) of  $2.7$ ,  $1.1$  and  $2.4$ , respectively. There were excellent correlation and close limits of agreement between day-to-day measurements of LV volumes and EF by 3DE from all the subjects as well as from groups A and B. (table 2 and figure 3)

Table I. Mean  $\pm$  SD of end-diastolic (ED) and end-systolic (ES) left ventricular volumes (LVV) and ejection fraction (EF) calculated by MRI and 3DE for the whole group as well as for A and B subgroups.

		MRI			3DE		
		EDV (ml)	ESV (ml)	EF (%)	EDV (ml)	ESV (ml)	EF (%)
All Subjects, n=46		182 $\pm$ 75	121 $\pm$ 76	39 $\pm$ 18	182 $\pm$ 76	121 $\pm$ 77	39 $\pm$ 18
Group A, n=15		114 $\pm$ 16	47 $\pm$ 7	58 $\pm$ 5	113 $\pm$ 16	47 $\pm$ 6	58 $\pm$ 5
Group B, n=31		223 $\pm$ 68	165 $\pm$ 62	28 $\pm$ 11	224 $\pm$ 67	166 $\pm$ 65	27 $\pm$ 11

MRI= magnetic resonance imaging, 3DE= three-dimensional echocardiography, SD= standard deviation.

Table II. Observer variabilities of magnetic resonance imaging (MRI) and 3DE for calculating LV end-diastolic volume (EDV) and end-systolic volume (ESV) and ejection fraction (EF) for the whole group as well as for A and B subgroups.

		All Patient, n=46				Group A, n=15				Group B, n=31			
		r	p	Agreem.	SEE	r	p	Agreem.	SEE	r	p	Agreem.	SEE
MR	EDV Intra.	97	0.2	-0.3 $\pm$ 28.2	6.3	97	0.6	0.9 $\pm$ 14.6	6.5	98	0.1	-0.2 $\pm$ 42	3.9
	Inter	98	0.2	6.1 $\pm$ 42.4	13.6	96	0.4	2.5 $\pm$ 24	10.6	96	0.1	13.2 $\pm$ 60	15.2
	ESV Intra.	98	0.1	-0.2 $\pm$ 23.4	4.7	98	0.9	0.1 $\pm$ 6.0	6.4	97	0.2	-0.4 $\pm$ 36	3.2
	Inter	98	0.1	4.9 $\pm$ 34.6	11.5	97	0.8	-0.2 $\pm$ 7.0	7.5	97	0.1	12.8 $\pm$ 54	14.7
	EF Intra.	98	0.3	0.1 $\pm$ 12.2	2.1	98	0.5	0.3 $\pm$ 3.8	3.3	98	0.3	0.1 $\pm$ 13.8	1.2
	Inter	98	0.4	-1.1 $\pm$ 12.2	4.7	96	0.4	-1.4 $\pm$ 11.4	9.8	96	0.5	-1.1 $\pm$ 13.6	2.0
3DE	EDV Intra.	95	0.4	-0.3 $\pm$ 20.2	3.1	97	0.5	-0.6 $\pm$ 6.6	3.0	98	0.5	-0.2 $\pm$ 29	3.3
	Inter	96	0.4	-1.1 $\pm$ 23.2	6.2	97	0.4	2.5 $\pm$ 14.2	6.6	97	0.7	-1.5 $\pm$ 32.2	3.9
	ESV Intra.	96	0.6	-0.6 $\pm$ 17.8	4.4	98	0.1	-0.1 $\pm$ 4.8	5.1	98	0.8	-0.9 $\pm$ 27.2	3.1
	Inter	96	0.5	-0.8 $\pm$ 18.8	3.8	98	0.3	0.8 $\pm$ 6.4	6.8	99	0.8	-0.7 $\pm$ 20.8	2.5
	EF Intra.	96	0.3	-0.4 $\pm$ 7.4	2.2	98	0.3	0.6 $\pm$ 4.2	3.4	96	0.6	-0.3 $\pm$ 5.6	0.6
	Inter	97	0.6	-0.4 $\pm$ 8.2	3.6	98	0.3	0.9 $\pm$ 6.6	5.8	92	0.9	-0.04 $\pm$ 7.6	0.9
3DE	EDV	97	0.2	-1.2 $\pm$ 22.6	2.7	98	0.3	2.1 $\pm$ 11.4	3.4	99	0.4	-1.3 $\pm$ 11	1.5
-DD	ESV	98	0.4	-0.9 $\pm$ 18.6	1.1	99	0.2	0.6 $\pm$ 6.2	1.4	99	0.7	-0.4 $\pm$ 7.2	1.0
	EF	98	0.2	-0.6 $\pm$ 10.2	2.4	99	0.3	0.7 $\pm$ 5.8	2.3	99	0.2	-0.3 $\pm$ 1.8	2.5

SEE = standard error of the estimate, Intra. = intraobserver, Inter = interobserver, DD = day-to-day variability of 3DE, other abbreviation as table I.

## DISCUSSION

Accurate and reproducible assessment of LV volume and function has important clinical significance in most cardiac disorders. 3DE has been shown to be accurate for evaluating LV volume and function in comparison with many accepted techniques.<sup>20-27</sup> The results of this study demonstrate that 3DE is a highly reproducible technique and is more favorable than magnetic resonance imaging in evaluating LV volume with low observer variability. This is consistent with our previous study<sup>26</sup> using the same method as well as studies by other authors using random images acquired.<sup>24,25,27</sup> Importantly, small day-to-day variability of the measurements in subjects with a stable cardiac condition indicates that 3DE can become the preferred technique for serial evaluation of LV volume and EF.

### Intraobserver Variability of MRI and 3DE

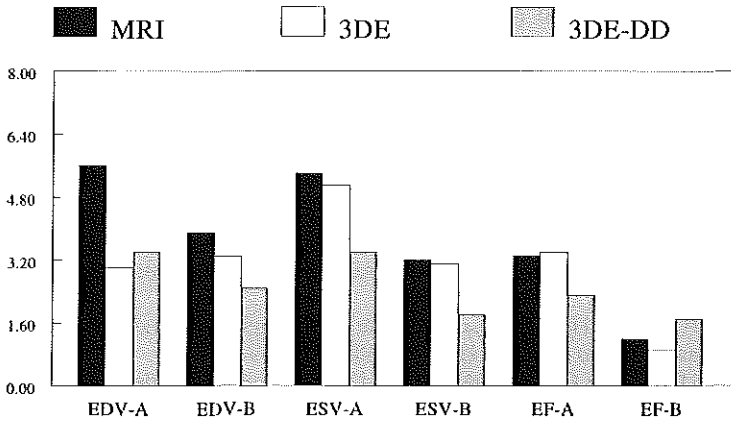


Figure 2. Comparison between the intraobserver variability of magnetic resonance imaging and three-dimensional echocardiography and day to day variability of three-dimensional echocardiography for calculating end-diastolic- and end-systolic-left ventricular volume and ejection fraction in A and B groups.

### Interobserver Variability of MRI and 3DE

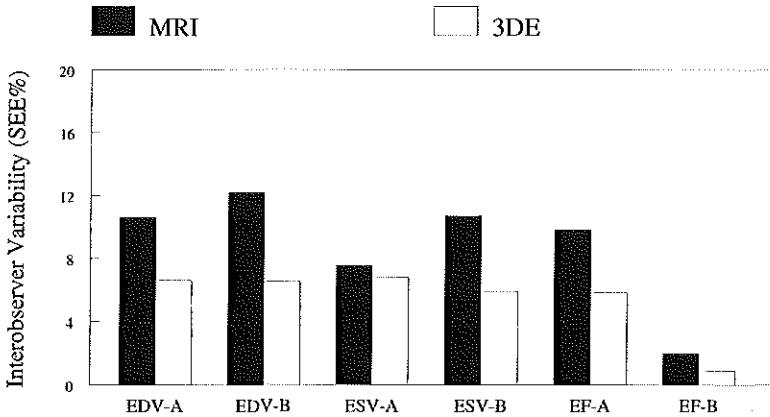


Figure 3. Comparison between the interobserver variability of magnetic resonance imaging and three-dimensional echocardiography for calculating end-diastolic- and end-systolic-left ventricular volume and ejection fraction in A and B groups.

#### LIMITATION OF THE STUDY.

As in all previous studies with 3DE, manual tracing of the LV endocardial border is laborious and very time consuming. In the future, faster computers will shorten the data acquisition

time and application of automated border detection algorithms will facilitate its application in routine studies. For practical reasons, we did not repeat magnetic resonance imaging for comparison with the second 3DE acquisition and for studying day-to-day variability of this method. However, the present measurements have proven the reliability of 3DE for serial assessment of LV volumes and EF.

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## CHAPTER 8

### OPTIMAL ROTATIONAL INTERVAL FOR THREE-DIMENSIONAL ECHOCARDIOGRAPHIC DATA ACQUISITION FOR RAPID AND ACCURATE MEASUREMENT OF LEFT VENTRICULAR FUNCTION

*Nosir et al, Optimal 3DE rotational intervals*

**Youssef FM Nosir MD\*, Wim B Vletter BS, Jaroslaw D Kasprzak MD, Eric Boersma MSc, Maarten H Lequin MD, Jaap Stoker MD, Jiefen Yao MD, Abdou Elhendy MD, Christian S Breburda MD, Folkert J Ten Cate MD, Jos RTC Roelandt FACC.**

From The Thoraxcenter, The Heart Center and Erasmus University, Rotterdam, The Netherlands, \*The Cardiology Department, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt.

YFM Nosir is supported by the Nuffic, Den Haag, The Netherlands.

*Submitted*

**ABSTRACT**

**Background.** Prolonged three-dimensional echocardiographic acquisition time may lead to motion artifacts, caused by inadvertent patient or operator movements and currently limits its routine use for calculating left ventricular ejection fraction.

**Objectives.** Our aim was to reduce the acquisition time by defining the largest rotational acquisition interval, which still allows three-dimensional echocardiographic reconstruction for accurate and reproducible left ventricular volume and ejection fraction calculation.

**Methods.** 21 subjects (5 normals and 16 patients with abnormal shaped left ventricle) underwent magnetic resonance imaging and precordial three-dimensional echocardiography with 2° acquisition intervals. The images were processed to result in data sets containing images at 2°, 4°, 8°, 16°, 32° and 64° intervals by excluding the interjacent images. Using the paraplane feature, 8 equidistant short axis slices were generated from each data set. The suitability of these short axis slices for manual endocardial tracing was scored visually by 4 independent experienced observers. Left ventricular volume and ejection fraction were calculated using Simpson's rule from three-dimensional echocardiographic data sets with 2°, 8° and 16° intervals and the results were compared with values obtained from magnetic resonance imaging. The probability of three-dimensional echocardiography to detect left ventricular volume and ejection fraction differences was calculated.

**Results.** All patients were in sinus rhythm with a mean±SD heart rate of 72±12 bpm. Visual estimation of endocardial border adequacy for tracing the left ventricular short axis views generated from data sets reconstructed with images at different interpolation intervals, by the four observers, showed that images obtained from data sets with rotational scanning intervals of 16° allowed left ventricular endocardial tracing in all subjects. While data sets obtained at 32° and 64° were inadequate for endocardial tracing. There was good correlation, close limits of agreement and non-significant differences between values of left ventricular volume and ejection fraction calculated with three-dimensional echocardiography at 2°, 8° and 16° rotational intervals and those obtained with magnetic resonance imaging. At steps of 16°, three-dimensional echocardiography had excellent correlation ( $r = 98, 99$  and  $99$ ), close limits of agreement ( $\pm 38, \pm 28.6$  and  $\pm 4.8$ ) and non-significant differences ( $p = 0.5, 0.8$  and  $0.2$ ) with values obtained from MRI for calculating end-diastolic and end-systolic left ventricular volume and ejection fraction, respectively.

With the small number of subjects (21), three-dimensional echocardiography using 16° rotational intervals could detect 15 ml differences in end-diastolic volume with a probability of 95%, 11 ml differences in end-systolic volume with a probability of 92 % and 2 % differences in ejection fraction with a probability of 95%.

**Conclusions.** Three-dimensional echocardiographic data sets reconstructed with images selected at 16° intervals from data sets obtained at 2° precordial rotational acquisition interval, allowed the generation of left ventricular short axis images with adequate quality for endocardial border tracing. This study therefore proves that precordial acquisition at 16° intervals would be sufficient for the reconstruction of three-dimensional echocardiographic data sets for left ventricular function measurement. This approach would result in a significant reduction in acquisition time with enough accuracy for clinical decision making and therefore make three-dimensional echocardiography more practical as a routine method.



**Key Words:** Three-dimensional echocardiography, left ventricular volume, ejection fraction, magnetic resonance image.

Left ventricular volumes and ejection fraction may vary in many clinical situations and following various medical or surgical interventions and thus often require serial monitoring for accurate detection of early changes.

Three-dimensional echocardiography allows accurate left ventricular volume and ejection fraction calculation without geometric assumptions<sup>1-8</sup> and is therefore an ideal tool for serving this purpose. However, prolonged data acquisition time is one of the limitations that hinder the clinical application of three-dimensional echocardiography for routine left ventricular volume and ejection fraction calculation.

Therefore, this study was designed to define a faster method for precordial three-dimensional echocardiographic acquisition and to evaluate its accuracy for left ventricular volume and ejection fraction calculation by comparison with magnetic resonance imaging.

## SUBJECTS AND METHODS

Three-dimensional echocardiography and magnetic resonance imaging were performed on the same day in 21 subjects including 15 males and 6 females (age  $49 \pm 16$  years, ranging from 26 to 66 years). These subjects included 5 healthy volunteers and 16 patients with left ventricular abnormalities (12 with ischaemic segmental wall motion abnormalities and 4 with global hypokinesis due to dilated cardiomyopathy). Informed verbal consent was obtained from each subject after a detailed explanation of the procedure.

## MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging was performed at 0.5 T (Gyroscan T5-11 Philips Medical Systems, The Netherlands). The multislice multiphase ECG-triggered T1 weighted fast field echo was performed with a repetition time of 800-1200 ms, echo time 22ms, flip angle 70° and the field of view 240 x 300 mm. The level and width of magnetic resonance imaging window in every subject were selected to obtain an optimal contrast between the relatively hypointense ventricular wall and the relatively hyperintense blood pool in the ventricular cavity. Axial, coronal and sagittal spin-echo was used to select optimal short axis views of the left ventricle for image acquisition. Sequential images of the heart were collected using 9 mm slice thickness with 0.9 mm inter slice gap and imaging matrix (90 x 128). Heart phase interval was 32-39 ms with the number of heart phases 14-32 and a median at 21.

Left ventricular volume measurement was carried out off line on a work station (Gyrovew HR) using Simpson's rule by two independent experienced observers (MHL and JS). The end-diastole was defined as the frame with the largest left ventricular cavity size and end-systole as the frame with the smallest left ventricular cavity size. The endocardial border of left ventricle was traced manually on all short axis views to derive end-diastolic and end-systolic left ventricular volume and ejection fraction.

## THREE-DIMENSIONAL ECHOCARDIOGRAPHIC EXAMINATION

A commercially available ultrasound unit (Toshiba Sonolayer SSH-140A) with the transducer frequency of 3.75 MHz was coupled with a 3DE processing computer (Echo-scan,

TomTec GmbH, Munich, Germany) for data acquisition.<sup>9,10</sup> The echocardiographic images of the left ventricle were collected from the apical window in a rotational format at 2° intervals, gated to proper R-R intervals of ECG and thoracic impedance of expiration, while the patient was resting comfortably in a 45° left recumbent position.

The acquired data were processed and analyzed off line on a three-dimensional echocardiographic work station (TomTec Inc. system). Images selected at intervals of 2°, 4°, 8°, 16°, 32° and 64° from the original data set were readjusted in their correct spatial and temporal sequence, digitally reformatted and processed to obtain 6 different data sets. Gaps between the images were interpolated using a "trilinear cylindric interpolation" algorithm<sup>7</sup> to produce voxel based volumetric data sets (figure 1).

With the paraplane option 8 parallel and equidistant short axis slices of the left ventricle were derived from each data set at end-diastole and end-systole, respectively. The adequacy for endocardial border tracing of the left ventricular short axis images, generated from the reconstructed data sets with different interpolation intervals, was scored visually by 4 independent experienced observers.

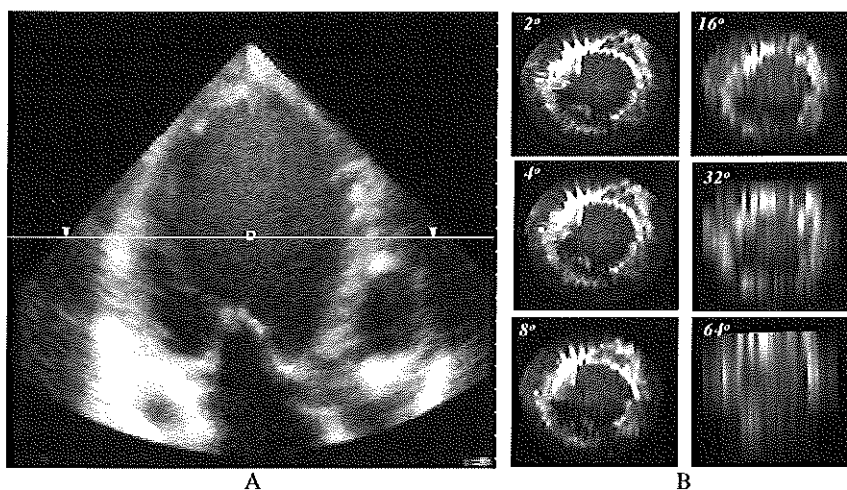


Figure 1. Reconstructed left ventricular short axis views from three-dimensional echocardiographic data sets at different degrees of rotational acquisition. Panel A shows the left ventricular long axis (the reference image), with the transverse section indicator sector at the level of the papillary muscle. Panel B shows the corresponding short axis views reconstructed at different rotational degrees of acquisition (at 2°, 4°, 8°, 16°, 32° and 64°).

The end-diastolic and end-systolic left ventricular volume were calculated by two independent experienced observers (YFMN and JDK) using Simpson's rule for the three-dimensional echocardiographic data sets obtained with images selection at 2°, 8° and 16° intervals. Measurement of left ventricular volume at 2°, 8° and 16° was performed independently with at least 2 days apart. After a reference image of the left ventricular long axis view was defined, 8 parallel equidistant short-axis slices spanning the left ventricular cavity from the apex to the mitral annulus were derived. The end-diastolic and end-systolic endocardial border of the left ventricle was traced in each slice.

The volume of the left ventricle on each slice was calculated automatically by the computer using a summation of the voxels included in the traced area. An accumulation of the subvolumes on all slices yielded the left ventricular volume at end-diastole and end-systole, from which the ejection fraction was calculated. (figure 2)

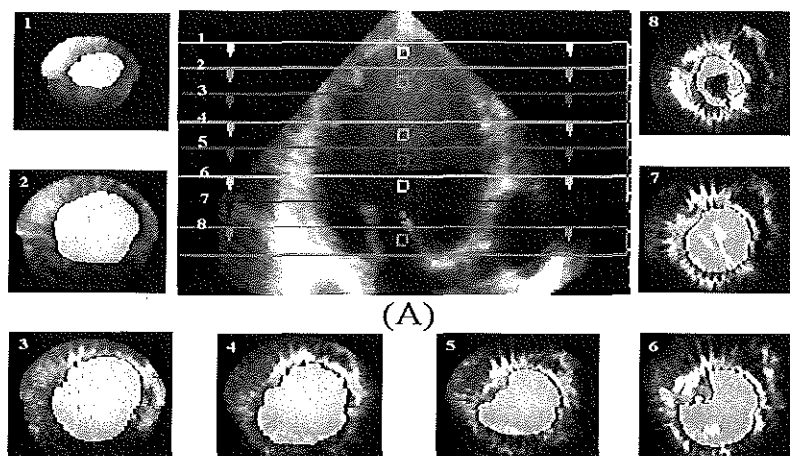


Figure 2. The principle of left ventricular volume measurement using Simpson's rule with volume rendered three-dimensional echocardiography. A long-axis view is selected as a reference image from the three-dimensional echocardiographic data set. The left ventricle is sliced by paraplane analysis method into 8 equidistant parallel short axis slices spanning the left ventricular cavity from the apex to mitral annulus (panel A). The endocardial border of the left ventricle on each cross-section is traced manually delineating the white label (short axis slices from 1 to 8). The volume of the traced region on each slice is calculated. Adding up the volumes of all slices provides the left ventricular volume at a chosen phase (end-diastole or end-systole).

## STATISTICAL ANALYSIS

All images were scored by four independent observers. We define the feasibility of endocardial tracing on left ventricular short axis views from the three-dimensional echocardiographic data sets as very good (endocardial borders are clearly identified and completely present in all left ventricular short axis slices), good (endocardial borders can be identified and completely traced in all short axis slices), possible (endocardial borders can be identified and traced in at least 75% of left ventricular short axis slices) and impossible (endocardial borders are not clearly identified or incomplete in most left ventricular short axis slices).

Left ventricular volume and ejection fraction were calculated by two independent observers (YFMN and JDK for 3DE) and (MHL and JS for MRI). All values of the left ventricular volume and ejection fraction measurements were expressed as mean  $\pm$  SD. Interobserver variability were calculated as the standard error of the estimate (SEE). To compare the calculation of end-diastolic and end-systolic left ventricular volume and ejection fraction from three-dimensional echocardiographic data sets at 2°, 8° and 16° rotational intervals with values obtained by magnetic resonance imaging, the limits of agreement were

computed using the method described by Altman and Bland.<sup>11</sup> A paired t-test was performed and significance was stated at the 0.05 probability level. Pearson's correlation coefficients were used.

Power analysis was performed to determine the possibilities of a beta error in the comparison with the 2°, 8°, and 16° of rotation to detect differences in left ventricular volume and ejection fraction with comparison to magnetic resonance imaging.

RESULTS

Three-dimensional echocardiographic data acquisition and analysis were possible in all subjects recruited in this study. All subjects studied were in sinus rhythm with a mean ± SD heart rate of 72 ± 12 bpm. A data set at 2° rotational scanning intervals was acquired in each subject. By interpolating images at 2°, 4°, 8°, 16°, 32° and 64° intervals during data processing, a total of 6 data sets of the left ventricle were obtained. The average slice thickness (mm) ± SD were 9.9 ± 0.8 and 8.2 ± 0.9 for end-diastole and end-systole respectively.

Visual estimation of manual endocardial tracing feasibility at different rotational intervals for three-dimensional echocardiography.

The endocardial border definition of the left ventricular short axis images was scored by four observers and the average values are shown in table 1 (figure 3).

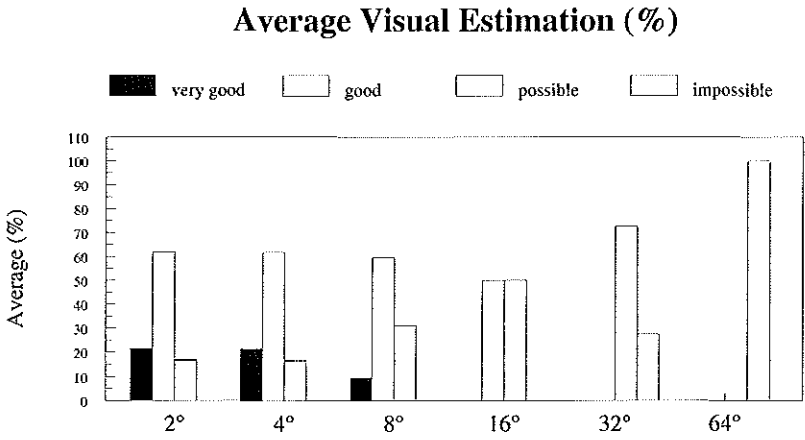


Figure 3. The average % value of the four independent observers that visually scored the suitability of 3DE data sets obtained at variable degrees of rotation (at 2°, 4°, 8°, 16°, 32° and 64°), for manual endocardial tracing.

Observer variability of magnetic resonance imaging and three-dimensional echocardiography at 2°, 8 °and 16° of rotational intervals.

Interobserver variabilities for calculating end-diastolic and end-systolic left ventricular volume and ejection fraction with magnetic resonance imaging and with three-dimensional

echocardiography at 2°, 8 °and 16° intervals were calculated and presented as the standard error of the estimate between the two observers (table 2).

Table 1. Visual scoring of suitability of left ventricular (LV) short axis, obtained from different three-dimensional echocardiographic (3DE) acquisition degree, for manual endocardial tracing.

	Observer 1				Observer 2				Observer 3				Observer 4				Average (%)			
	a	b	C	d	a	b	c	d	a	b	c	d	a	b	c	d	a	b	C	d
2°	5	13	3	-	6	14	1	-	3	11	7	-	4	14	3	-	21.4	61.9	16.7	-
4°	5	13	3	-	6	14	1	-	3	11	7	-	4	14	3	-	21.4	61.9	16.7	-
8°	2	14	5	-	4	14	3	-	-	9	12	-	2	13	6	-	9.5	59.5	31	-
16°	-	12	9	-	-	12	9	-	-	6	15	-	-	12	9	-	-	50	50	-
32°	-	-	18	3	-	-	21	-	-	-	5	16	-	-	17	4	-	-	72.6	27.4
64°	-	-	-	21	-	-	-	21	-	-	-	21	-	-	21	-	-	-	-	100

a =very good, b = good, c = possible and d = impossible.

Table 2. Mean  $\pm$  of left ventricular volume (LVV) and ejection fraction (EF), together with interobserver standard error of the estimate (SEE), calculated by MRI and 3DE at 2, 8 and 16 of rotational acquisition.).

		EDV	ESV	EF
MRI	Mean $\pm$ SD	218 $\pm$ 98	154 $\pm$ 98	34.7 $\pm$ 17.9
	Interobserver SEE	11.7 (ml)	10.5 (ml)	4.7 (%)
3DE-2°	Mean $\pm$ SD	217 $\pm$ 95	155 $\pm$ 99	34 $\pm$ 17.9
	Interobserver SEE	4.2 (ml)	3.8 (ml)	1.1 (%)
3DE-8°	Mean $\pm$ SD	216 $\pm$ 95	153 $\pm$ 98	34 $\pm$ 17.7
	Interobserver SEE	3.9 (ml)	4.1 (ml)	1.2 (%)
3DE-16°	Mean $\pm$ SD	215 $\pm$ 94	153 $\pm$ 99	34 $\pm$ 18
	Interobserver SEE	4.6 (ml)	3.9 (ml)	1.4 (%)

MRI = magnetic resonance imaging.

### Comparison between measurements of left ventricular volume and ejection fraction by three-dimensional echocardiography at 2°, 8 °and 16° intervals and values obtained by magnetic resonance imaging.

Mean  $\pm$  SD of end-diastolic and end-systolic left ventricular volume and ejection fraction for magnetic resonance imaging and three-dimensional echocardiography at 2°, 8°and 16° image interpolation intervals are presented in table 2. There was excellent correlation, close limits of agreements and non significant differences between measurements of end-diastolic and end-systolic left ventricular volume and ejection fraction from three-dimensional echocardiography at 2°, 8°and 16° intervals and that obtained from magnetic resonance imaging (table 3, figure 4).

At 16° intervals, three-dimensional echocardiography had excellent correlation ( $r = 98, 99$  and  $99$ ), close limits of agreement ( $\pm 38, \pm 28.6$  and  $\pm 4.8$ ) and non significant differences ( $p = 0.5, 0.8$  and  $0.2$ ) with values obtained from magnetic resonance imaging for the calculation of end-diastolic and end-systolic left ventricular volume and ejection fraction, respectively.

Table 3. Comparison between measurements of LV end-diastolic volume (EDV) and end-systolic volume (ESV) and EF obtained from 3DE at 2°, 8° and 16° with values obtained by MRI.

	MRI	3DE-2°				3DE-8°				3DE-16°			
	Mean±SD	r	MD±SD	P	Agree.	r	MD±SD	p	Agree.	r	MD±SD	p	Agree.
EDV	218±98	0.99	0.9±14.9	0.8	±29.8	0.98	2.5±18.7	0.5	±37.4	0.98	3.1±19	0.5	±38
ESV	154±98	0.99	-0.7±10.4	0.8	±20.8	0.99	0.7±13.6	0.8	±27.2	0.99	0.8±14.3	0.8	±28.6
EF	34.7±17.9	0.99	0.9±2.3	0.1	± 4.6	0.99	0.7±2.4	0.2	± 4.8	0.99	0.7±2.4	0.2	± 4.8

r= correlation coefficient, MD±SD= mean differences±standard deviation, p= p value and Agree.= limits of agreements, other bbreviations as table 1-2.

Agreements between 3DE and MRI for LVV and EF calculation

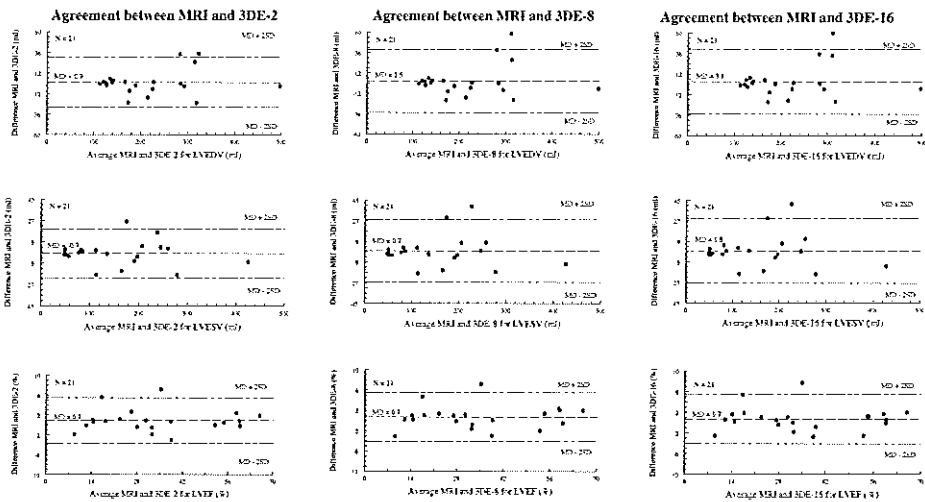


Figure 4. Limits of agreement of end-diastolic (panel A), end-systolic (panel B) LVV and EF (panel C) calculated by MRI - 3DE at different degree of rotational acquisition at 2° (upper part), 8° (middle part) and 16° (lower part). Difference of each pair of MRI - 3DE end-diastolic, end-systolic LVV and EF measurements plotted against the average value of both measurements.

Power of three-dimensional echocardiography at 2°, 8°and 16° intervals to detect left ventricular volume and ejection fraction differences.

There was an acceptable probability of three-dimensional echocardiography at 2°, 8° and 16° intervals to detect variable differences in left ventricular volume and ejection fraction with comparison to magnetic resonance imaging (table 4 and figure 5). At 16° intervals, three-dimensional echocardiography has a probability of 95% for detecting 15 ml differences in end-diastolic left ventricular volume, 92% to detect 11 ml differences in end-systolic left ventricular volume and 95 % to detect 2 % differences in ejection fraction.

Table 4. Probability of 3DE at 2°, 8° and 16° of rotational acquisition to detect variable differences in LVV and EF with comparison to MRI.

	EDV (ml)				ESV (ml)				EF (%)		
Differences	2	5	10	15	1.5	4	7.5	11	1	1.5	2
2 degrees	5	40	85	99	10	40	90	99	50	85	98
8 degrees	1	25	70	95	5	30	70	95	50	81	97
16 Degrees	0	20	65	95	5	25	65	92	45	80	95

All abbreviation as table 1-2

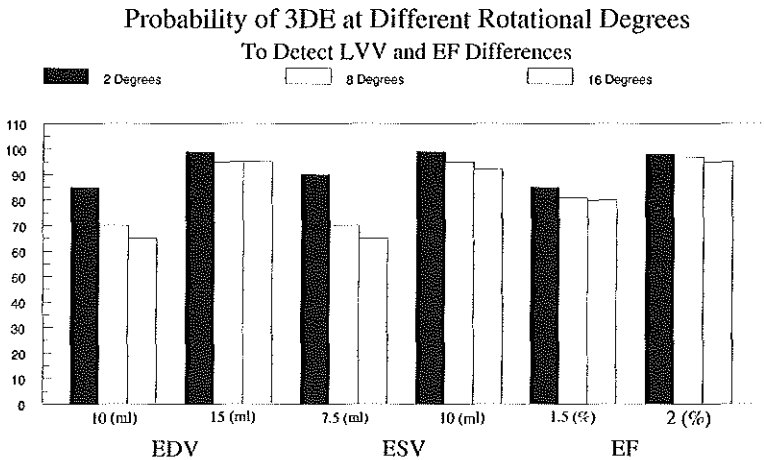


Figure 5. The probability of three-dimensional echocardiography at 2°, 8° 16° of rotational acquisition to detect variable differences in end-diastolic and end-systolic left ventricular volume (ml) and ejection fraction (%).

## DISCUSSION.

Accurate and reproducible assessment of left ventricular volume and function is important for predicting the outcome of various medical or interventional procedures.<sup>12-13</sup>

The results of this study demonstrated that left ventricular short axis images from precordial three-dimensional echocardiographic data sets with images acquired at 16° rotational intervals, may still be adequate for endocardial border tracing and accurate quantification of left ventricular volume. This implies that the data acquisition time may be reduced from 5 minutes to 30 seconds in average, as only 12 instead of 90 cutting planes are required. In addition, despite the small number of subjects recruited in this study, a 16° interpolation interval provides an acceptable probability level for the detection of differences ( $\pm 8\%$  of the mean value) in left ventricular volume and ejection fraction.

The results of this study are in agreement with the study conducted by Siu et al.,<sup>27</sup> in which the influence of number of component images on accuracy of left ventricular volume quantification by three-dimensional echocardiography using the nonparallel intersecting images was examined. They concluded that, accurate calculation of left ventricular volume and ejection fraction can be obtained by three-dimensional echocardiography with as few as 8

to 12 nonparallel intersecting images. They demonstrated that in both symmetric and asymmetric ventricles, the error in calculating volume was relatively constant when the number of images was at least 8 (3 long axis and 5 short axis) but increased progressively when the number of images was lower.

### CLINICAL IMPLICATIONS

Most of the currently available imaging techniques such as contrast angiography,<sup>14-18</sup> radionuclide angiography<sup>19-21</sup> and echocardiography<sup>22-25</sup> are either invasive or employ geometric assumptions of the left ventricle. Although magnetic resonance imaging is able to produce accurate measurement of left ventricular volume,<sup>26-28</sup> it has limitations for repeated studies, is not portable and is not widely available.

Volume rendered three-dimensional echocardiography, using sequentially collected images, produces reproducible data sets of the left ventricle and therefore, is an ideal technique for repeated measurements of left ventricular volume<sup>29</sup>. Rotational 3DE data acquisition at 2° requires 90 cutting planes of the heart with each containing images of a whole cardiac cycle. With ECG and respiratory gating, the acquisition usually requires approximately 5 minutes. This is a limitation for the routine use of this technique. In addition, a prolonged acquisition time increases the possibility of patient or operator induced artifact that may lead to inaccurate or unreadable data and the need to repeat the procedure.

Since the introduction of three-dimensional echocardiography, efforts have been directed to find a simple, rapid and accurate protocol that would facilitate its routine use in clinical practice. The results of this study enable us to reach this goal. Precordial rotational acquisition at 16° will shorten the acquisition time to 30 seconds. Selecting end-diastolic and end-systolic data sets before image processing will take approximately 2 minutes with the software used in this study. Processing time, however, will be negligible with the new software generation. The contour tracing time using the parplane option with 8 parallel equidistant short axis slices which is sufficiently accurate will take approximately 10 minutes. In addition, the application of automated border recognition software for area and volume analysis technique will be integrated soon.

Because the numbers of subjects recruited in each group were small we did not analyse the accuracy of left ventricular volume and ejection fraction measurements in normal and deformed left ventricle but we could show an acceptable probability level for detecting left ventricular volume and ejection fraction differences.

### CONCLUSIONS

Three-dimensional echocardiographic data sets reconstructed with images selected at 16° rotational intervals, from data set obtained at 2° acquisition rotational interval, allowed the generation of a three-dimensional echocardiographic data set from which left ventricular short axis slices could be obtained with adequate quality for endocardial border tracing. This study therefore proves that precordial acquisition at 16° intervals would be sufficient for obtaining three-dimensional echocardiographic data sets for left ventricular function measurement. This approach would result in a significant reduction in acquisition time with



enough accuracy for clinical decision making and therefore make it more practical as a routine method.

#### *Acknowledgment.*

We would like to thank Rene Frowijn for his technical assistance throughout this work. YFM Nosir is supported by The NUFFIC, The Hague, Netherlands.

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## **CHAPTER 9**

# **ACCURATE QUANTIFICATION OF LEFT VENTRICULAR VOLUME AND FUNCTION BY THREE-DIMENSIONAL ECHOCARDIOGRAPHY**

**Jiefen Yao, MD, Youssef F.M. Nosir, MD, Jos R.T.C. Roelandt, MD.**

From Thoraxcenter, AZR, Erasmus University, Rotterdam, The Netherlands

***SUBMITTED***

Accurate quantification of left ventricular volumes and function is important in clinical practice of cardiology. The previously employed methods for measuring left ventricular volumes and function have various limitations. Two-dimensional echocardiographic approaches often have to apply geometric assumptions to the left ventricle by using a few standard views. Three-dimensional echocardiography is able to overcome those limitations by obtaining a volumetric data set of the left ventricle and thus obviates the need for any geometric assumptions. Various methods for three-dimensional data acquisition, data processing, data analysis and three-dimensional image reconstruction have been developed along with different algorithms for volumetric calculation. In this article, we reviewed the currently employed three-dimensional echocardiographic methods for measuring left ventricular volumes and the results obtained from previous studies in comparison with other established methods. Three-dimensional echocardiography has proven to be accurate in quantitative measurements of left ventricular volumes and function both experimentally and clinically and is ready to serve as a new standard for volumetric measurements.

Left ventricular volume is an important index of global cardiac performance and an indicator of the adaptation of left ventricle to various pathological conditions and response to interventional procedures. Accurate determination of left ventricular volume and function is important in clinical management for stratification of high risk patients after myocardial infarction or with dilated cardiomyopathy and for time selection of surgical therapies in patients with valvular diseases.<sup>1-7</sup> Although various other techniques including invasive angiography,<sup>8-11</sup> radionuclide angiography<sup>12-14</sup> and magnetic resonance imaging<sup>15-16</sup> have been used, echocardiography is the most commonly applied modality for quantifying left ventricular volume and function in cardiological practice due to its easy manipulation, proved accuracy and non-invasive nature.<sup>17-21</sup> However, all the previously used two-dimensional methods have to extrapolate left ventricular volume from only one or a few selected cutting planes by employment of certain geometric assumptions for the left ventricle. Three-dimensional echocardiography, on the other hand, encloses the whole left ventricle with more image information and thus allows more accurate measurement of left ventricular volumes without the need of any geometric assumptions and thus is able to predict the left ventricular function more reliably.<sup>22-26</sup>

### **Currently Available Techniques for Measuring Left Ventricular Volumes and Function**

There are various techniques currently available for calculating left ventricular volumes and function. The earliest being used technique is invasive angiography.<sup>8-11</sup> The left ventricular volume is assessed using either a single plane or two orthogonal planes of the left ventriculogram based on the assumption that the left ventricle is ellipsoid in shape. Although biplane angiography has frequently served as a reference standard, the geometric assumption hinders its accuracy for measuring left ventricles of various shapes and the requirement of invasive cardiac catheterization prevents it from daily employment and repeated studies.

Radionuclide angiography has also been used for determination of left ventricular volume.<sup>12-14</sup> Though non-invasive, injection of radioactive agents is well known for the side effects caused by ionizing energy. In addition, it employs the same geometric assumptions as in invasive angiography.

Magnetic resonance imaging has proven to be accurate in determining left ventricular volume and ejection fraction both in normal subjects and in patients.<sup>15-16</sup> By adding up the volumes of left ventricular cavity on all slices, no geometric assumption is needed for left ventricular volume measurement. Though noninvasive, this technique is not being widely used since it is very expensive, time consuming and cannot be performed at bedside.

M-mode echocardiography, a one dimensional ultrasound scanning of the cardiac structures, was developed in the early 1970's. It was immediately used for volume and function assessment of the left ventricle for its simple algorithm and non-invasiveness.<sup>17</sup> Ejection fraction was calculated simply by a percentage derived from the mid left ventricular diameters in end-systole and end-diastole. Though satisfactory results were achieved, problems were raised in asynergic ventricles with myocardial infarction.<sup>27-28</sup>

Two-dimensional echocardiography, with the ability of imaging the heart in cross-sectional views and easier access to various cutting planes, improved the accuracy of left ventricular volume measurement.<sup>18-21</sup> Among different mathematical models, modified biplane Simpson's rule has provided accurate data in both animal and human studies and in symmetric as well as asymmetric left ventricles.<sup>29</sup> Algorithms for automatic border detection and on-line calculation left ventricular volume and ejection fraction have been developed, but its clinical application is limited by the quality of ultrasound images. Because of the noninvasiveness and portability, two-dimensional echocardiography has become a routine examination clinically for left ventricular volume and function assessment. However, geometric assumptions are still needed for left ventricular volumetric measurements.

Expectation of a technique that could overcome limitations of the above mentioned techniques was realized by the advent of three-dimensional echocardiography which led to immediate utilization in volumetric assessment of left ventricle in both experimental and clinical studies and accurate results were obtained in comparison with established methods.<sup>22-26, 30-32</sup>

### **Three-dimensional Echocardiography for Left Ventricular Volume Quantification**

With the ability of reconstructing cross-sectional views of the left ventricle and other cardiac structures into three-dimensional images, the advantage of three-dimensional echocardiography in left ventricular volume measurement is the obviation of any geometric assumptions of the left ventricle. Over the last twenty years or more, various techniques has been developed for three-dimensional reconstruction and volume measurement of the left ventricle. The currently available techniques for three-dimensional data acquisition, processing, reconstruction and volume quantification are discussed below.

### **Polygonal imaging**

A simple way of three-dimensional reconstruction of the left ventricle is to acquire 3 to 4 orthogonal long-axis views of the left ventricle from the apical window. With or without interpolation of short-axis views, a polygonal image of the left ventricle can be reconstructed and its volume measured automatically by the computer.<sup>31-32</sup> The endocardial borders of the left ventricle need to be traced manually. Diastolic and systolic volumes of the left ventricle can be measured by endocardial tracing of the respective images. Stroke volume and ejection fraction can then be derived from these values. This method is easy to apply and has proved accurate for gross volume and mass measurement of the left ventricle. But in severely asymmetric ventricles, the reconstructed three-dimensional image cannot depict the regional shape of the cavity or movement of the myocardium in detail.

### **Random imaging**

For accurate measurement of left ventricular volumes, accurate spatial registration of randomly acquired cross-sectional images is necessary. Different devices (such as mechanical arm, acoustic or magnetic sensors) have been developed for locating the ultrasound transducer or the cutting plane of the images.<sup>33-35</sup> This allows imaging of the left ventricle from any optimal acoustic windows by moving the transducer freely at one acoustic window or at different acoustic windows. An intersectional line or an image plane (usually longitudinal view of the left ventricle) is usually used to guide the position and orientation of other imaging planes and to document the local curvature of the left ventricular wall. The endocardial border of the left ventricle on each cross-sectional view is manually traced. All the traced lines are connected according to their spatial order form a three-dimensional wire-frame image. This fashion of reconstruction is also named line-of-intersection display. Volume of the left ventricle can then be computed by the computer. Accurate results from this mode of reconstruction have been achieved in both symmetrical or aneurysmal left ventricles as well as in right ventricle or other objects.<sup>22-25, 36-38</sup> The limitation of this method is that the spaces between the sampled cross-sectional images are uneven and mistakes may result from interpolation of big gaps between imaged planes. Furthermore, the reconstructed three-dimensional images are usually static and lack of tissue depiction. Therefore, performance of the myocardium, especially regional myocardial thickening, can not be judged with this technique.

### **Sequential imaging**

To image the heart in averagely spaced cutting planes and to retain the ultrasound characteristics of the cardiac tissue, different algorithms have been developed for computer-controlled sequential imaging of the heart.<sup>39</sup> The probe or transducer is moved in pre-defined manners with equal incremental steps while cross-sectional images of the heart are collected using ECG and respiratory gatings (the former being used for temporal registration and the

later for minimizing respiration-related artifacts). At present, parallel, fan-like and rotational modes of data acquisition are available (Fig 1), with the latter being used most frequently for both left ventricular volumetric evaluation and assessment of other cardiac problems.<sup>26, 40-42</sup> These modes of data acquisition can collect closely and evenly distributed images that cover the whole left ventricle. By automatic interpolation, spaces between the imaging planes are filled by the computer and the collected images are transferred into a voxel-based three-dimensional data set. Three-dimensional reconstruction from voxel-based data set can be realized without manual tracing of the endocardial border and, with volume-rendering and various shading techniques, the reconstructed image accurately portrays the tissue characteristics and depth of the cardiac anatomy. In addition, the volumetric three-dimensional data set can be electronically dissected in different manners resulting in numerous possible cross-sectional views of the left ventricle and other cardiac structures. Anyplane and paraplane methods provide arbitrarily arranged or equally spaced parallel cutting planes allowing systematic cross-sectional review of the three-dimensional data set and the latter also provides accurate measurement of the left ventricular volume by endocardial tracing using disc summation method without the necessity of any geometric assumptions.<sup>43</sup> Using various cutting planes, volume-rendered three-dimensional echocardiography is able to display dynamically the interior of the heart such as the cardiac chambers and valves in different display projections.<sup>39</sup> Not only the sizes and shapes of the left ventricle, but also the regional thickening and wall motion of the myocardium can be observed and measured with this technique.<sup>44</sup>

#### Parallel Scanning      Fan-like Scanning      Rotational Scanning

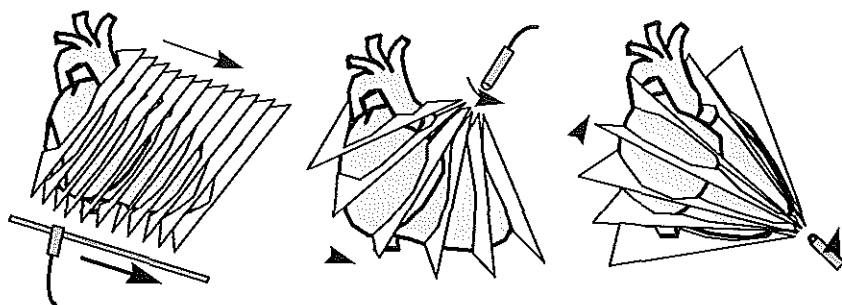


Figure 1. Schematics showing 3 different modes of sequential data acquisition for three-dimensional left ventricular reconstruction. The motion of the probe or the transducer inside the probe is predefined and automatically controlled.

#### *Real-time imaging*

The most idealistic way of three-dimensional echocardiography is on-line data acquisition and display of three-dimensional images of the heart.

A volumetric pyramidal ultrasound imaging probe has been developed and preliminary experience has proved its promising prospects both in on-line display of three-dimensional cardiac anatomy and in quantification of ventricular volume and function.<sup>45-47</sup> The advantage of this technique is that it acquires directly three-dimensional images of the heart, saving computer interpolation of the cross-sectional images, and thus could avoid spatial motion artifacts and result in anatomically accurate three-dimensional data set.

### Review of Literature on Left Ventricular Volume Measurement by Three-Dimensional Echocardiography

Many studies have been directed in quantification of left ventricular volumes and function by three-dimensional echocardiography in comparison with previously established conventional methods.<sup>22-26, 30-31, 33, 48-49</sup> An overview of the results of these studies is summed up and shown in the table below. Here in this article, we will discuss two most sophisticated and presently most commonly used methods for left ventricular volume and function measurements.

Table. Three-dimensional echocardiographic left ventricular volume and function measurements in comparison with other established methods

Authors	3D Measurements	Validation Methods	Linear Regression	N	r	SEE	p	MD $\pm$ SD
Nixon et al <sup>30</sup>	LVVed	angiography	$y=0.39x+101$	9	.95	9ml	<.001	
	LVVes		$y=0.75x+21$	9	.94	7ml	<.001	
Fazzalari et al <sup>31</sup>	LVVed&es	angiography	$y=0.73x-1.73$	24	.86	8.51ml	<.05	
	LVS SV		$y=0.51x+1.01$	12	.88	4.40ml	<.001	
	LVVed&es	2D Echo (area-length)	$y=1.09x-0.09$	52	.99	2.60ml		
	LVS SV		$y=1.06x+0.09$	26	.99	1.67ml		
	LVVed&es	2D Echo (biplane)	$y=1.1x-0.6$	52	.97	5.47ml		
	LVS SV		$y=1.25x-0.73$	26	.97	2.43ml		
Zoghbi et al <sup>33</sup>	LVVed	angiography	$y=0.8x+3.7$	24	.92	23ml		
	LVVes		$y=0.97x-1$	24	.96	16ml		
	LVEF		$y=1.17x-4$	24	.82	10%		
Gopal et al <sup>23</sup>	LVVed	MRI	$y=0.84x+22$	15	.92	6.99ml	<.001	
	LVVes		$y=0.51x+18.2$	15	.81	4.01ml	<.001	
Handschoemacher et al <sup>33</sup>	LVS SV	actual value 2DE (Doppler)	$y=0.99x+0.11$	11	.99	5.9ml		4.6ml
	LVS SV		$y=0.97x+0.94$	28	.95	3.2ml		2.1ml
Siu et al <sup>24</sup>	LVS SV	actual value	$y=1.0x-0.79$	84	.98	3.58ml		0.8 $\pm$ 3.6ml
	LVS SV		$y=0.98x-0.15$	38	.96	2.99ml		-0.6 $\pm$ 3.0ml
	LVEF		$y=0.99x+0.29$	38	.96	5.64ml		-0.3 $\pm$ 5.6ml
King et al <sup>49</sup>	LVVed	MRI	$y=0.84x+22$	15	.92	6.99ml	<.001	
	LVVes		$y=0.81x+18.2$	15	.81	4.01ml	<.001	
	LVVed		$y=0.72x+29.7$	10	.90	7.0ml	<.001	
	LVVes		$y=0.45x+20.2$	10	.88	3.1ml	<.001	
Sapin et al <sup>25</sup>	LVVed	angiography	$y=0.88x+1.9$	35	.97	11ml	<.0001	12.9 $\pm$ 12.7ml
	LVVes		$y=0.86x+8.8$	35	.98	10.2ml	<.0001	-0.7 $\pm$ 12.4ml
	LVEF		$y=0.79x+0.57$	35	.82	.103%	<.0001	6.6 $\pm$ 9.8%
Gopal et al <sup>22</sup>	LVEF (observer 1)	RNA	$y=0.79x+9.39$	51	.94	5.35%		0.57 $\pm$ 6.65%
	LVEF (observer 1)		$y=0.80x+7.72$	51	.97	3.64%		1.37 $\pm$ 5.54%
Nosir et al <sup>26</sup>	LVEF	RNA	$y=0.9x+3.7$	25	.99			

3D = three-dimensional echocardiography; N = number of subjects; SEE = standard error of estimate, MD = mean difference; LVS = left ventricular volume, ed = end-diastolic; es = end-systolic; SV = stroke volume; LVEF = LV ejection fraction; MRI = magnetic resonance imaging; RNA = radionuclide angiography.



Wedge summation method

This method for left ventricular volume measurement is employed in three-dimensional data set acquired using free-hand imaging with a line or image plane for spatial alignment reference.<sup>22-25, 33, 49</sup> For measurement of end-diastolic or end-systolic left ventricular volume, the respected frame from each acquired cine loop is selected and the endocardium traced.

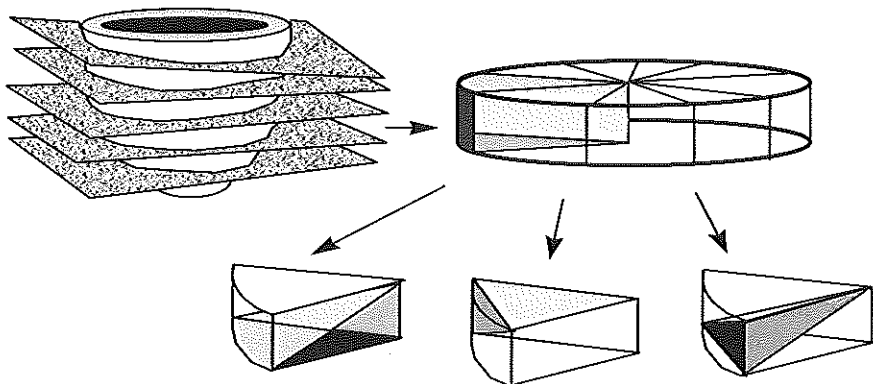


Figure 2. Schematic drawings showing the principle of left ventricular volume measurement by summation of wedges method. The three-dimensional data set of left ventricle is obtained randomly. The slices of left ventricular cavity between traced endocardial borders are divided into multiple (180) sectors or wedges. Each wedge will then be subdivided into three tetrahedrons. The volume of each tetrahedron will be calculated automatically by the computer as well as the volume of each wedge. The summation of the volume of all the wedges of all slices yield the total volume of the left ventricle at a given frame(cardiac phase).

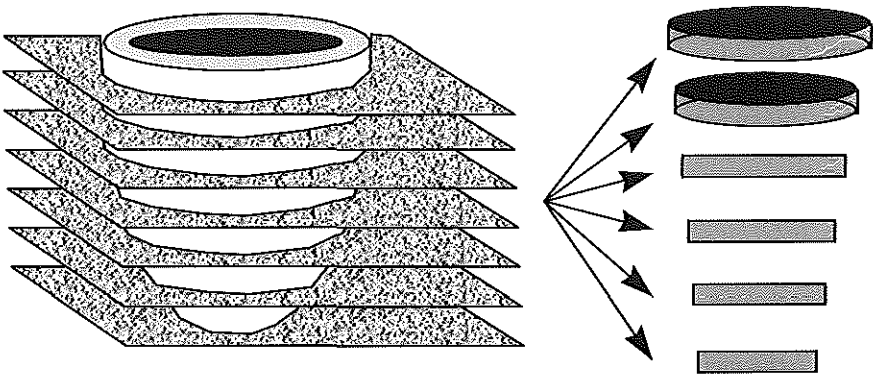


Figure 3. Schematics showing the principle of left ventricular volume measurement by summation of discs method. The sequentially acquired volumetric three-dimensional data set of the left ventricle can be sectioned into multiple equidistant parallel slices or discs. The left ventricular endocardial border on each slice is traced and the area as well as the volume of each disc derived by the computer. Summation of the volumes of the traced cavity on all slices yield the total volume of the left ventricle at a given time (such as end-diastole or end-systole).

The traced borders are divided into 180 equidistant segments by interpolation and a centroid is defined automatically for each traced endocardial border. Consecutive pairs of corresponding points on adjacent borders are connected forming a pair of triangles that is also connected to the centroid of each tracing so as to define a sector or wedge resulting in 180 wedges enclosing the volume between the two traced boundaries. Then each wedge is decomposed into three tetrahedrons and the volume of each tetrahedron and the total volume of the 540 tetrahedrons between the two boundaries are yielded. Volume between all tracings are in turn calculated and summed up to yield the total volume of the left ventricle at end-diastole or end-systole (Fig. 2).

### **Disc summation method**

With voxel-based or volumetric three-dimensional data set acquired with sequential or on-line image collection, the left ventricle can be electronically sectioned into multiple parallel equidistant short-axis slices (discs). The left ventricular cavity is traced along the endocardium on each short-axis image. Area of the traced region on each slice is derived and the volume is calculated by the computer provided with the known slice thickness. A summation of the segmental left ventricular volumes on all slices yields the total volume of the left ventricular cavity at that time point (end-diastole or end-systole) (Fig. 3).<sup>26</sup> Subtraction of end-systolic volume from end-diastolic volume results in stroke volume of the left ventricle. The percentage of stroke volume over end-diastolic volume represents left ventricular ejection fraction.

### **Voxel-Based Three-Dimensional Echocardiography: The Standard for Left Ventricular Volume and Function Assessment**

Voxel-based three-dimensional echocardiography, for its ability of accurately measure left ventricle volumes and function as well as tissue-depicting demonstration of global and regional left ventricular myocardial performance in various clinical settings, has a great potential of becoming a new gold standard for left ventricular volumetric measurements instead of invasive angiography, radionuclide angiography and magnetic resonance imaging. With their many limitations that have been discussed above, these methods should no longer be used for routine clinical left ventricular volume measurement unless other purposes that need their specific diagnostic abilities such as coronary angiography are to be carried out at the same time. Three-dimensional echocardiography, on the other hand, is noninvasive without any clinically recorded side effects and can be performed in many clinical scenarios and thus is ideal for daily performance and for serial follow-up examinations of left ventricular volume and function. Volume-rendered three-dimensional echocardiography has been used for re-evaluation and refinement of the standard two-dimensional echocardiographic methods for left ventricular volume quantification.<sup>50-51</sup>

### Present Limitations and Future Directions

Regardless of the many improved techniques in three-dimensional echocardiography, time consumption has been the major limitation that hampers its routine employment for daily diagnostic echocardiography and for left ventricular volume and function assessment. Sequential data acquisition with ECG and respiration gatings takes several to 10 minutes, movement of the patient or probe during this period may lead to motion artifacts in the acquired data set and error in volume measurements. Faster data acquisition that is being investigated using high speed transducer or a volumetric real-time three-dimensional echocardiographic transducer rotation will minimize this drawback. Data processing and three-dimensional image reconstruction has been accelerated and on-line processing and reconstruction is under investigation. Manual endocardial tracing needed for volume measurement is both laborious and prone for subjective errors. Development of various automatic border detection algorithms along with the improvement of ultrasound spatial resolution and advances in other novel modalities such as digital imaging, power-mode Doppler tissue imaging and development of stable intravenous ultrasound contrast agents that enhance the delineation of endocardium should be able to avoid the need of manual border tracing and provide automatic, even on-line, volume measurement.

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## CHAPTER 10

### ACCURATE MITRAL VALVE AREA ASSESSMENT IN PATIENTS WITH MITRAL STENOSIS BY THREE- DIMENSIONAL ECHOCARDIOGRAPHY

Qingwei Chen MD, Youssef F.M. Nosir MD, Wim B. Vletter BSc, Peter P. Kint RN,  
Alessandro Salustri MD and Jos R.T.C. Roelandt MD

From the Thoraxcenter, Division of Cardiology, University Hospital Rotterdam - Dijkzigt and  
Erasmus University, Rotterdam, The Netherlands

*J Am Soc Echocardiogr. 1997;10:133-40*

## ABSTRACT

**Objectives:** The accuracy of mitral valve orifice area (MVA) measurement from three-dimensional echocardiographic (3DE) image data-sets obtained by a transthoracic or transesophageal rotational imaging probe was studied in 15 patients with native mitral stenosis. The smallest MVA was identified from a set of 8 parallel short-axis cutplanes of the mitral valve between the annulus and the tips of leaflets (paraplane echocardiography) and measured by planimetry. In addition, MVA was measured from the two-dimensional short axis view (2DE). Values of MVA measured by 3DE and 2DE were compared with those calculated from Doppler pressure half-time (PHT) as a gold standard. Observer variabilities were studied for 3DE.

**Results:** MVA measured from PHT ranged between 0.55 to 3.19cm<sup>2</sup> (mean±SD: 1.57±0.73), from 3DE ranged between 0.83 and 3.23cm<sup>2</sup> (mean±SD: 1.55±0.67) and from 2DE ranged between 1.27 and 4.08cm<sup>2</sup> (mean±SD: 1.9±0.7). The variability of intra- and interobserver measurements for 3DE measurements were not significantly different (p=0.79 and p=0.68, respectively), and interobserver variability was (SEE=0.25). There was excellent correlation, close limits of agreement (mean difference±2SD) and nonsignificant differences between 3DE and PHT for MVA measurements {r=0.98, (0.02±0.3) and p=0.6} respectively. While, there was moderate correlation, wider limits of agreement and significant difference between 2DE and PHT for MVA measurements {r=0.89, (-0.32±0.66) and p=0.002} respectively. This may be related to the difficulties in visualization the smallest orifice in precordial short-axis views.

**Conclusions:** The present study suggests that three-dimensional image data-sets by providing the possibility of "computer slicing" to generate equidistant parallel cross-sections of the mitral valve independent from physically dictated ultrasonic windows allow accurate and reproducible measurement of the mitral valve orifice area.

## INTRODUCTION

Accurate measurement of the mitral valve orifice area is essential in the evaluation of patients with mitral stenosis. Calculation of mitral valve area from hemodynamic data obtained at cardiac catheterization<sup>1,2</sup> is still considered the reference method. However, the method is invasive and influenced by mitral valve geometry,<sup>3</sup> cardiac output,<sup>4</sup> pressure gradients<sup>5</sup> and severity of concomitant mitral regurgitation.<sup>6</sup> Accordingly, both the evaluation and follow-up of patients with mitral stenosis requires a more direct and noninvasive method to assess mitral valve area.

Two-dimensional echocardiography allows imaging of the stenotic orifice and its direct measurement by planimetry. Consequently, the method rapidly became accepted as an alternative method to assess the severity of mitral stenosis.<sup>7</sup> However, two-dimensional echocardiography is highly dependent on the examination technique particularly in locating the stenotic mitral orifice in its short-axis.<sup>8,9</sup>

Pressure half-time (PHT) derived mitral valve area from Doppler echocardiography has also gained widespread acceptance.<sup>10,11</sup> Limitations of this method include concomitant moderate or severe aortic regurgitation and poor left ventricular compliance.<sup>12,13</sup>



Recently, three-dimensional echocardiography has been introduced, and theoretically offers advantages for quantitation, by allowing to generate a series of equidistant parallel cross-sections through the mitral valve apparatus.<sup>14,15</sup> Thus, the smallest orifice area can be identified and planimetry performed.

The purpose of this study was to determine the feasibility and reproducibility of three-dimensional echocardiography for calculating mitral valve area in patients with mitral stenosis. In addition, the accuracy of mitral valve area measurement from three-dimensional echocardiography and two-dimensional echocardiography were compared with values obtained by Doppler PHT.

## METHODS

### Study patients

We studied 15 consecutive patients (11 women, aged from 20 to 74 years, mean 50.9 years) referred to the outpatient clinic with native mitral stenosis between January 1994 and July 1996. All patients were in sinus rhythm and 4 patients had atrial fibrillation (AF). Ten patients were in functional class I and five patients in class II New York Heart Association. None of patients had undergone surgery or valvuloplasty before. Four patients had mild mitral regurgitation but non as a predominant lesion, and 6 patients had grade 1<sup>+</sup> aortic regurgitation. Six patients had mild degree mitral valve calcification (2 at the anterior leaflet and 4 at the posterior leaflet) (see table 1). They all underwent Doppler, two-dimensional echocardiography and three-dimensional echocardiographic examinations. Informed consent for three-dimensional echocardiographic examination was obtained.

## ECHOCARDIOGRAPHIC STUDIES

Two-dimensional echocardiography and continuous-wave Doppler studies were performed with a Vingmed CFM 800 using a 2.5 MHz phased-array transducer. Two-dimensional echocardiographic images were recorded on VHS videotape. Doppler velocity traces were recorded with a strip chart recorder at a paper speed of 100 mm/s.

Two-dimensional echocardiographic analysis of the mitral valve area were made from the precordial parasternal short-axis views.<sup>16</sup> The smallest orifice of the mitral valve was identified by scanning from the left atrium in the direction of the left ventricular apex. The gain settings were adjusted until the lowest level was determined at which the circumference of the mitral orifice was still visible. After identification of the videoframe with the orifice at its maximal opening in early diastole, mitral valve area was measured by planimetry of its contours using a digitizing tablet. The mean value of five consecutive mitral valve area measurements of cardiac cycles was used. Two-dimensional echocardiographic measurement of mitral valve area was repeated in one patient (patient 4) due to error in the calibration procedure.

For Doppler analysis, continuous-wave Doppler recordings of transmitral blood flow velocity were made in the apical four-chamber view. Doppler velocity recordings were traced on a digitizing graphics tablet and analyzed with an off-line computer analysis system. Mitral valve area was determined by the PHT method.<sup>10,11</sup> A mean value was calculated from

analysing 10 consecutive beats from a series of 16 beats in each patient with sinus rhythm, while 15 beats were used in patients with AF.

### THREE-DIMENSIONAL ECHOCARDIOGRAPHY

#### *Image acquisition procedure:*

Transesophageal acquisition (TEE) of the cardiac cross-sections for reconstruction was performed in 6 patients (patients 1-6, table 1) using a 5 MHz, 64-element rotational-array transducer (Delft Medical Imaging B.V, Delft, The Netherlands) mounted at the distal end of a standard gastroscope.<sup>17,18</sup> The control knob on the multiplane probe is mechanically rotated via a custom-build wheel-work interface by a step motor which is commanded by a computer algorithm which controls the acquisition of cross-sections which fall within preset ranges of heart cycle length by ECG-gating and respiratory phase by thoracic impedance measurement, for optimal temporal and spatial registration. Standard transesophageal examination procedures were followed.<sup>19</sup> The imaging transducer was positioned at the mid-esophageal level to acquire the cross-sectional images of the mitral valve for the three-dimensional reconstruction.

Transthoracic acquisition (TTE) was performed in 9 patients (patients 7-15, table 1) with a custom-build transducer assembly.<sup>20</sup> A commercially available 2.5 MHz transducer is fixed in a cog-wheel which fits into a cylindrical holder. The transducer is rotated by a step-motor which is commanded by the same computer algorithm as used for the transesophageal acquisition. The patient was lying in a 45-degree left recumbent position and the transducer placed over the apical window which allowed best visualization of the mitral valve.

Both the transesophageal and precordial transducer systems were interfaced with a Toshiba SSH-140A system and the video output connected to the three-dimensional reconstruction system (Echo-scan, Tom-Tec GmbH, Munich, Germany). The operator has to locate the center axis around which the imaging plane is rotated to encompass the mitral valve. The cross-sections are sampled at 40 ms intervals (25 frames/s), digitized and stored in the computer memory. After for a given cross-section the preset cardiac cycle and respiration phase criteria are fulfilled, this cardiac cycle is accepted and the step-motor is activated to rotate the transducer 2 degrees to the next scanning plane. Then, the same steering-logic is followed. To fill the conical data volume, 90 sequential cross sections must be obtained each during a complete cardiac cycle. Inadvertent patient and probe movement during the image acquisition must be avoided. In some instances two acquisition sequences are necessary.

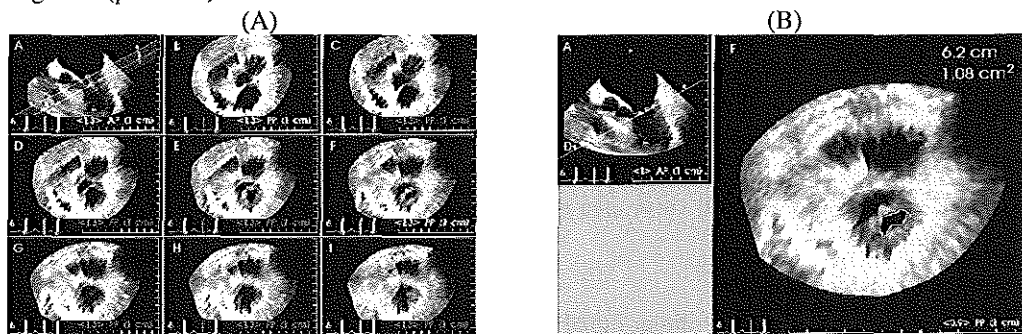
#### *Image processing:*

The acquired cardiac images are formatted in their correct sequence according to their ECG phase in volumetric data sets (256\*256\*256\* pixel/each 8 bit). The post-processing of the data set is performed off-line using the reconstruction software. To fill the gaps between images conversion from polar to Cartesian coordinates is necessary. A ROSA (Reduction Of Spatial Artefacts) filter is used to reduce motion artefacts created by patients, probe movement or respiration.

#### *Image display:*

The mitral valve can be visualized in computer generated long-axis and short-axis views from the three-dimensional data-set. The mitral valve is transected in short axis planes from the

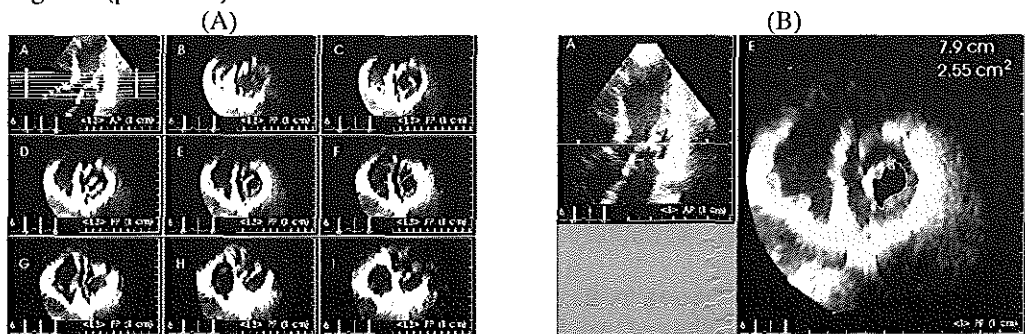
Figure 1 (patient 2).



A. From the original three-dimensional data set obtained with the multiplane transesophageal approach, 8 parallel cutplanes in the optimal orientation through the mitral valve are generated (panel A). The corresponding two-dimensional images are represented in panels B to I. This allows parallel slicing of the stenotic mitral valve in a way similar to computed tomography or magnetic resonance. The smallest orifice area is represented in panel F.

B. The function of "zooming" is used to enlarge the image of the mitral orifice area for more accurate tracing

Figure 2 (patient 10)



A. Panel A shows an apical long axis view of the left ventricle reconstructed from the transthoracic three-dimensional data set in patient with mitral stenosis. The cutplanes B to I indicate the short-axis views from the mitral annulus to the tips of the mitral leaflets. This allows accurate identification of the smallest orifice area of mitral valve by three-dimensional echocardiography.

B. After identification the slice with the smallest orifice area, the zoom facility is used to enlarge the image for accurate planimetry

annulus to the tips of the leaflets in early diastole when the valve is maximally opened by equidistant 8 parallel cutplanes at 3-mm intervals. The smallest mitral valve area is visually identified from these images. The mitral valve area measurement procedure is illustrated in figures 1 and 2.

#### *Image analysis:*

After identifying the cross-section with the smallest orifice area, a "zoom" function is used to enlarge the mitral orifice area for more accurate planimetric measurement of the mitral valve area. The mitral valve area is determined as the mean value of 10 circumference measurements

#### *Feasibility*

Acquisition of the three-dimensional echocardiographic data-set and reconstruction was possible in all patients. Calibrating the system, optimizing the position of the probe and gain settings and acquisition required approximately 10 minutes. Off-line image post-processing and analysis required approximately 60 minutes. Both transthoracic and transesophageal approaches provided adequate visualization of the mitral valve area for quantitative analysis.

#### **STATISTICAL ANALYSIS**

All values are expressed as mean  $\pm$  SD. Mitral valve area obtained with the different methods was compared by analysis of variance for measurement. Significant differences between groups were assessed using the paired two-tailed student's test. Differences were considered statistically significant at a p value of  $<0.05$ . The correlation between mitral valve area obtained from the three-dimensional echocardiographic data set and two-dimensional echocardiographic planimetric methods with values obtained by Doppler PHT was determined by using linear regression analysis. The limits of agreement between mitral valve area obtained from the three-dimensional echocardiography data set and Two-dimensional echocardiography planimetric methods with values obtained by Doppler PHT were assessed as described by Altman and Bland.<sup>21</sup>

#### **RESULTS**

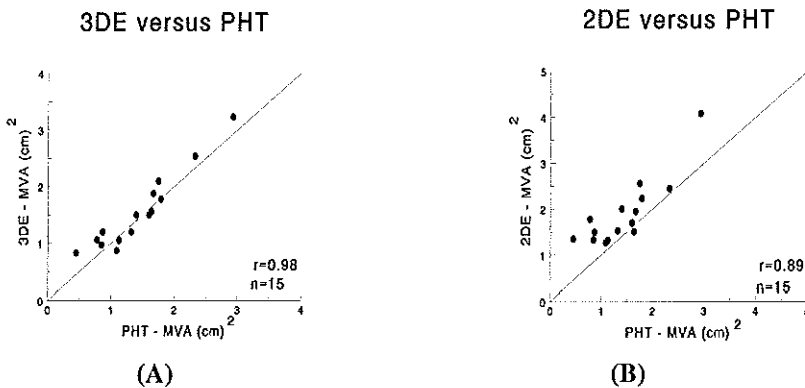
##### **Intra- and interobserver variability of the three-dimensional echocardiographic measurements**

The mitral valve area measurements of 15 patients determined from Doppler PHT, three-dimensional echocardiography and two-dimensional echocardiography are presented in Table 1. To assess the variability of the measurement of the mitral valve area by the three-dimensional echocardiography method, the measurements were repeated in 10 patients by the same observer 3 weeks after the initial evaluation. Another observer independently performed the determination in all patients to obtain interobserver variability. Observers were blinded to each other's results. The correlation coefficient obtained between the two observers was 0.99 ( $y=0.01+0.99x$ ,  $SEE=0.25$ ). Intra- and interobserver measurements were not significantly different ( $p=0.79$  and  $p=0.68$ , respectively).

**TABLE 1:** Clinical data and mitral valve area (MVA) in 15 patients with mitral stenosis

	Age	Gender	AF	Calcif.	MVA (cm <sup>2</sup> )			AR grade
					PHT Mean(Range)	3DE Mean(Range)	2DE Mean(Range)	
1	67	F	-	+, post.	1.96(1.79-2.00)	1.78(1.71-1.80)	2.23(2.18-2.39)	-
2	41	F	-	-	1.14(1.13-1.16)	1.05(0.92-1.17)	1.32(1.27-1.37)	+
3	66	F	-	-	1.40(1.32-1.49)	1.20(1.13-1.34)	1.53(1.44-1.58)	+
4	52	F	-	+, ant.	0.55(0.45-0.65)	0.83(0.72-0.91)	1.35(1.25-1.45)	-
5	51	F	-	-	0.93(0.85-1.04)	0.97(0.86-1.02)	1.33(1.29-1.36)	-
6	74	M	-	+, post.	1.71(1.64-1.79)	1.56(1.42-1.61)	1.51(1.43-1.59)	-
7	43	M	-	-	0.89(0.78-1.02)	1.06(0.94-1.15)	1.78(1.64-1.84)	-
8	51	F	-	-	1.74(1.67-1.84)	1.88(1.82-1.89)	1.95(1.91-2.02)	+
9	20	F	-	-	3.19(2.93-3.34)	3.23(3.13-3.34)	4.08(3.98-4.15)	-
10	28	F	-	+, ant.	2.55(2.33-2.62)	2.54(2.40-2.61)	2.45(2.25-2.52)	-
11	72	M	+	-	2.3 (1.75-3.1 )	2.1 (1.88-2.39)	2.56(2.52-2.80)	+
12	62	F	+	-	1.1 (0.87-1.36)	1.2 (1.09-1.32)	1.5 (1.46-1.66)	+
13	37	M	+	+, post.	1.4 (1.03-1.77)	1.47(1.24-1.68)	1.76(1.63-1.91)	+
14	61	F	+	+, post.	1.09(0.74-1.33)	0.87(0.51-0.92)	1.27(0.85-1.40)	-
15	38	F	-	-	1.60(1.39-1.89)	1.5 (1.19-1.61)	1.7 (1.66-1.83)	-

AF=atrial fibrillation, 3DE=three-dimensional echocardiography; Calcif.= calcification, PHT=pressure half-time; 2DE=two-dimensional echocardiography; AR=aortic valve regurgitation: + present, - absent, ant.=anterior mitral valve leaflet, post.=posterior mitral valve leaflet, values between brackets represents the range of MVA measurements for each patient.

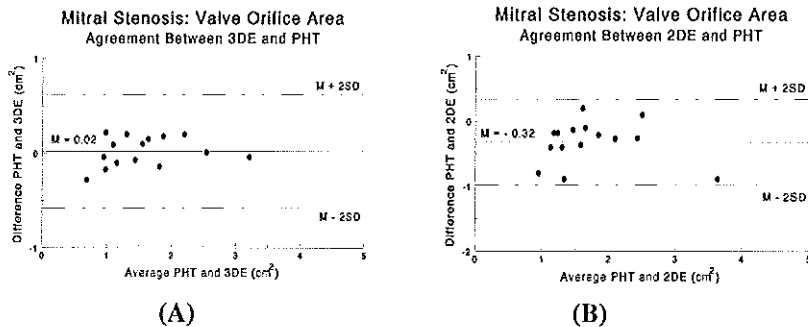


**Figure 3.** (A) Linear-regression analysis compares the 3DE with the Doppler PHT method for the calculation of MVA.  $r=0.98$ . (B) Linear-regression analysis compares the 2DE with the Doppler PHT method for the calculation of MVA.  $r=0.89$ .

### Three-dimensional echocardiography versus Doppler PHT method.

Mitral valve area determined by three-dimensional echocardiography ranged from 0.83 to 3.23 cm<sup>2</sup> (mean±SD: 1.55 ± 0.67). These values correlated well with the calculated PHT mitral valve area (range 0.55 - 3.19 cm<sup>2</sup>; mean±SD: 1.57±0.70), the correlation coefficient being 0.98 (Fig 3A). There was no statistically significant difference and close limits of

agreement between the mitral valve area obtained by three-dimensional echocardiography and that measured from the Doppler PHT ( $p=0.62$ ) (agreement =  $0.02 \pm 0.3$ ) (Fig 4A).



**Figure 4.** (A) Agreement between the 3DE and the Doppler PHT estimates of MVA. Difference in MVA (y axis) is plotted against the mean valve of the two areas (x axis; average MVA). There were close limits of agreement between the values obtained by the two methods ( $-0.28, +0.32$ ). (B) Agreement between the 2DE and the Doppler PHT estimates of MVA. Difference in MVA (y axis) is plotted against the mean valve of the two areas (x axis; average MVA). There were wide limits of agreement between the values obtained by the two methods ( $-0.98, +0.34$ ) and 2DE overestimate PHT MVA by ( $0.32 \text{ cm}^2$ ).

### Two-dimensional echocardiography versus Doppler PHT method.

Mitral valve area measured from two-dimensional echocardiography ranged between  $1.27$  and  $4.08 \text{ cm}^2$  ( $1.9 \pm 0.73$ ). There was moderate correlation between the two-dimensional echocardiography and PHT mitral valve area determinations ( $r=0.89$ ) (Fig 3B). There was a statistically significant difference between the two methods ( $p=0.002$ ) and a wider limits of agreement ( $-0.32 \pm 0.66 \text{ cm}^2$ ) (Fig 4B). Two-dimensional echocardiography overestimated the PHT determined mitral valve area by an average of ( $0.32 \text{ cm}^2$ ).

## DISCUSSION

Despite many limitations, the Gorlin formula, described 40 years ago, is still considered the reference method to calculate the stenotic mitral valve area in native and prosthetic valves. However, mitral valve area is not directly measured, and the method requires accurate measurement of stroke volume or cardiac output, the diastolic filling period and the mean pressure difference across the stenotic valve.<sup>4</sup> At present, pre-operative cardiac catheterization for assessment of the severity of mitral stenosis is reserved for selected patients with either complex valvular disease or those in whom uncertainty exists after clinical and noninvasive assessment.<sup>22</sup>

Assessment of the stenotic mitral valve area is now more and more being performed noninvasively by tracing mitral valve area in two-dimensional echocardiographic images or by the PHT method derived from Doppler velocity recordings of transmitral blood flow. Most decision-making on surgical and valvuloplasty procedures is currently based on both of these methods. However, faithful visualization of the smallest mitral valve area by two-dimensional echocardiography does not only depend on optimal machine gain settings but also on visualizing the plane transecting the smallest mitral valve area from a parasternal window.

The stenotic mitral valve is a deformed funnel-shaped three-dimensional structure and the smallest orifice may be difficult to visualize. Even though one tries to circumvent this limitation by sweeping up and down the interrogating imaging plane through the valve, it is not always possible to find this optimal cross-section.<sup>9,23</sup> Our study, although a limited number of patients was included, suggests that the mitral valve area determined by the anyplane and parplane analytic facilities using a three-dimensional echocardiographic data set is feasible and correlates well with mitral valve area measured from Doppler PHT.

Mitral valve area derived from two-dimensional echocardiography overestimates PHT determined mitral valve area. This may be explained by limitations of visualizing the smallest orifice in parasternal short-axis views. Overestimation of 0.04 to 0.27 cm<sup>2</sup> with correlation coefficients ranging from 0.41 to 0.95 have been reported.<sup>16,22,24-28</sup> In our study, two-dimensional echocardiography overestimated the PHT determined mitral valve area by an average of (0.32 cm<sup>2</sup>). This discrepancy between hemodynamic and echocardiographic mitral valve area measurements may in part be explained by the inability to find the optimal cross-section through the smallest orifice area from a limiting precordial acoustic window.<sup>6,16,25</sup>

In our study, no significant differences were found between mitral valve area derived by three-dimensional echocardiography and values obtained by Doppler PHT methods, even though there were six patients associated with mild aortic regurgitation. Previous studies<sup>12,28,29</sup> indicated that Doppler PHT is not influenced by mild aortic regurgitation.

In our study, there were 6 patients with mild degree of mitral valve calcification but this did not interfere with echocardiographic quantification of mitral valve area. The value of two-dimensional echocardiography in judging the pliability and the degree of calcification is well documented.<sup>30</sup> However, in patients with massive calcification measurement of mitral valve area by two-dimensional echocardiography will be more difficult due to diffuse thickening of the leaflets with irregular mitral valve orifice and fused commissures. Parplane analysis from the three-dimensional echocardiographic data set is superior to two-dimensional echocardiography, as it allows faithful screening of the mitral valve leaflet for the extent of calcification and its effect on the valve motion together with the identification of the smallest valve orifice despite the degree of calcification.

### Validity and advantages of the present method

The greatest advantage of acquiring a three-dimensional echocardiographic image data set is that, cross-sectional images of a structure can be generated in any desired plane independent from orientations dictated by the acoustic windows. Electronic parallel slicing allows the selection of parallel cut-planes in a way similar to computed tomography or magnetic resonance imaging to select the cut-plane with the smallest orifice area. Three-dimensional echocardiography, thus allows more accurate measurement of the orifice area in patients with mitral stenosis.

### Limitation of the study

At present, the major limitation of three-dimensional echocardiography is the time-consuming process of image acquisition, post-processing and data analysis. Developing faster computer and automated border recognition software for area analysis will stimulate the routine use of this method.

In theory, three-dimensional echocardiographic reconstructions from precordial images are of less quality than those from transesophageal images, because they have a better resolution and the probe has a closer position to the mitral valve.

## CONCLUSIONS

Three-dimensional echocardiography offers advantages for the morphologic assessment of the stenotic mitral valve. The image data set also allows accurate and reproducible measurement of the stenotic mitral valve area. It appears that this new technique has the potential for a more comprehensive assessment of the severity of mitral stenosis.

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## CHAPTER 11

### QUANTIFICATION OF THE AORTIC VALVE AREA IN THREE-DIMENSIONAL ECHOCARDIOGRAPHIC DATASETS ANALYSIS OF ORIFICE OVERESTIMATION RESULTING FROM SUBOPTIMAL CUTPLANE SELECTION

*3D echo evaluation of aortic valve area*

**Jaroslaw D. Kasprzak\* MD,PhD, Youssef F.M. Nosir MD, Anita Dall'Agata MD, Abdou Elhendy MD, Meindert Taams MD,PhD, Folkert J. Ten Cate MD,PhD Jos R.T.C. Roelandt MD,PhD**

Thoraxcenter, Division of Cardiology, Erasmus University and University Hospital Rotterdam - Dijkzigt, Rotterdam, The Netherlands \*Cardiology Department, Medical University of Łódź, Poland

*Am Heart J 1998;135:995-1003*

## ABSTRACT

**Background.** Our study was designed to determine the feasibility of three-dimensional echocardiographic (3DE) aortic valve area planimetry and to evaluate potential errors resulting from suboptimal imaging plane position.

**Methods.** Transesophageal echocardiography with acquisition of images for 3DE was performed in 27 patients. Aortic valve orifice was planimtered in two-dimensional echocardiogram (2DE) and in two-dimensional views reconstructed from 3DE datasets optimized for the cusp tips level. To evaluate the errors caused by suboptimal cutplane selection, orifice was also measured in cutplanes angulated by 10°, 20° and 30° or shifted by 1.5 to 7.5 mm.

**Results.** Planimtered orifice areas was similar in 2DE and 3DE studies:  $2.09 \pm 0.97 \text{ cm}^2$  vs  $2.07 \pm 0.92 \text{ cm}^2$ . Significant overestimation was observed with cutplane angulation ( $0.09 \text{ cm}^2$ ,  $0.19 \text{ cm}^2$  and  $0.34 \text{ cm}^2$  at 10° increments) or parallel shift ( $0.11 \text{ cm}^2$ ,  $0.22 \text{ cm}^2$ ,  $0.33 \text{ cm}^2$ ,  $0.43 \text{ cm}^2$  and  $0.63 \text{ cm}^2$  at 1.5mm increments). 3DE measurement reproducibility was very low and superior to that of 2DE.

**Conclusions.** 3DE allows the accurate aortic valve area quantification with excellent reproducibility. Relatively small inaccuracy in cutplane adjustment is a major source of errors in aortic valve area planimetry.

## INTRODUCTION

Two-dimensional (2DE) and Doppler echocardiography are principal noninvasive tools used to obtain quantitative information concerning the aortic valve. In transthoracic echocardiography, the most common approach includes Doppler evaluation of aortic valve flow, enabling quantification of transvalvular gradient and valve resistance. Valve area calculation is usually indirect, based upon the continuity equation.<sup>1</sup> Transesophageal echocardiography provides a better acoustic window and superior image resolution, enabling direct aortic valve area planimetry in the majority of patients.<sup>2-6</sup> This approach has been well validated and the best results are achieved by multiplane transesophageal probes. However, in some patients an optimal two-dimensional imaging plane for true aortic orifice cannot be obtained, leading to area overestimation. Recently introduced, three-dimensional echocardiography (3DE) allows the objective visualization and quantification of cardiac structures.<sup>7-10</sup> The method can be used for the imaging of the aortic valve<sup>11,12</sup> but its value for area planimetry has not been assessed. Our study was conducted to analyze the feasibility, accuracy and reproducibility of the measurements of aortic valve area in two-dimensional views reconstructed from a three-dimensional echocardiographic dataset. In addition, the unique opportunity of unrestricted cutplane manipulation in registered dataset allowed us to quantify the errors resulting from planimetry in suboptimally selected cross-sectional images.

## METHODS

The study group consisted of 7 patients with a normal aortic valve and 20 consecutive patients with aortic valve abnormalities diagnosed by transesophageal echocardiography and subsequently undergoing transesophageal study. All patients were in sinus rhythm. The group included 13 women and 14 men of mean age  $53.2 \pm 17.7$  years (range 22-82). Aortic pathology included 3 patients with bicuspid valve and 15 patients with acquired valve lesions; 2 patients had undergone aortic valve replacement with Ross procedure. Calcification of the aortic valve was identified in 5 patients. There was no preselection of the patients for three-dimensional echocardiographic examination based on two-dimensional image quality.

**Two-dimensional echocardiography** was performed using a Toshiba SSH-140A system with a 5 MHz, 64-element multiplane transesophageal transducer and a transthoracic 3.75 MHz probe. In the transesophageal study, standard precautions, patients preparation and probe insertion procedure were followed as described elsewhere.<sup>13</sup> For the aortic valve area planimetry, a short-axis view of the aortic valve, optimized for the smallest orifice area was used. The gain was set at the lowest value providing complete delineation of cusps.

Transthoracic imaging was used to collect the data used in continuity equation. Left ventricular outflow tract (LVOT) diameter was measured immediately below the aortic anulus in a long axis parasternal view and its area was calculated assuming a circular geometry. The LVOT flow velocity was registered at the same level using pulsed wave Doppler in apical five-chamber view. The peak transaortic flow velocity was measured with continuous wave Doppler from the apical, right parasternal or suprasternal window.

### Three-dimensional echocardiographic data acquisition and processing

Informed consent for three-dimensional echocardiographic examination was obtained from all patients. After the diagnostic multiplane transesophageal study had been finished, the probe was located at mid-esophageal level. A test sequence with 180° rotation of the transducer array was performed to ensure whether the aortic valve is encompassed within the conical acquisition volume. The basic images were acquired at 2° intervals and sampled at 25 Hz using a three-dimensional echocardiographic system (Echo-Scan 3.0, TomTec GmbH, Munich, Germany). The system has been described in detail elsewhere.<sup>8</sup>

Data processing was performed off-line by the analysis program of three-dimensional echocardiographic system. Rewritable optical disks were used for the permanent storage of data.

### Aortic valve area measurements.

#### (1) Two-dimensional echocardiography

After the identification of the video frame with the maximal opening of the aortic valve in early systole, the area was measured by tracing of the inner cusps contours using a digitizing tablet. The mean value of five consecutive measurements was calculated.

Measurements were made independently by two experienced observers, blinded to each other's results. Additional measurements were performed after 7 days for the evaluation of the intraobserver variability.

### ***(2) Aortic valve area measurement by continuity equation***

Planimetry of a stenotic aortic valve may be less reliable due to orifice non-planarity and calcifications. Therefore, in the subgroup of patients with planimetered aortic valve area below 2 cm<sup>2</sup>, additional calculation of aortic valve orifice area was performed using the continuity equation (1). The mean value of five consecutive measurements was calculated.

### ***(3) Anyplane three-dimensional echocardiography***

The dataset was used to generate two-dimensional cross-sectional views of the aortic valve at its maximal opening during a heart cycle. A series of long-axis views was displayed as a reference for localization of the level at which the separation of aortic cusps tips was the smallest (Figure 1). A cut-line was placed at this level and a corresponding orthogonal (short-axis) view was reconstructed. Subsequently, a fine angulation of this cross-sectional image was performed to ensure a continuous orifice outline. This optimized view was used to trace the inner contour of aortic cusps using the 3DE system software. The mean value of five consecutive measurements was calculated. Measurements were made independently by two experienced observers, blinded to each other's results and to those from two-dimensional planimetry. These measurements were repeated after 7 days for the evaluation of intraobserver variability.

### ***4. Evaluation of suboptimal cutplanes***

In order to evaluate possible errors in aortic valve area calculation, a series of suboptimal valve cross-sections images was analyzed. Aortic valve area was measured in 5 parallel planes shifted toward the aortic anulus in 1.5 mm intervals and in three planes, angulated by 10°, 20° and 30° from the initially selected, optimal plane through the valve (Figure 1). The mean value of three consecutive measurements was used for each plane.

## **STATISTICAL ANALYSIS**

All data are expressed as mean  $\pm$  standard deviation. Linear regression was used to evaluate relations between measurements obtained with two methods and Bland-Altman<sup>14</sup> analysis was performed for agreement assessment. Limits of agreement were defined as mean  $\pm 1.96 \times$  standard deviation of differences. Repeated-measures analysis of variance was used to assess the influence of imaging plane shift and angulation upon measurement of the aortic valve area. Pairwise comparisons against the optimal plane were performed with Dunnett test. A value of  $p < 0.05$  was considered statistically significant. Equality of variances was tested with F test. Observer variability was expressed in coefficients of variation (calculated as standard deviation of differences between measurements divided by the mean area value).

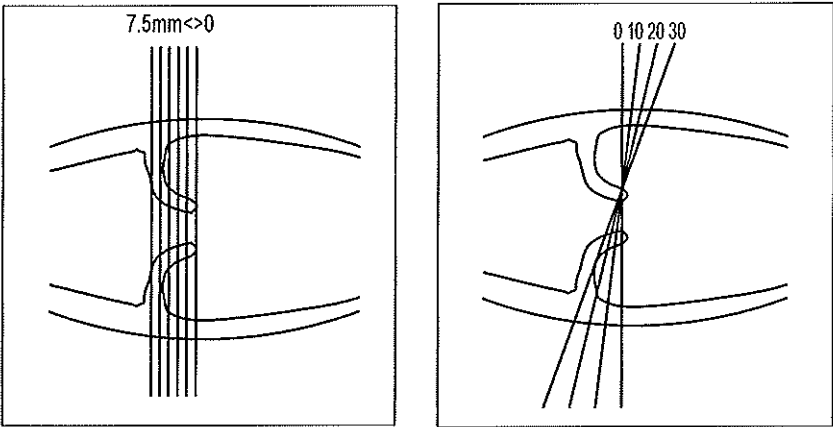


Figure 1. The principle of two-dimensional echocardiographic planimetry error evaluation. Left panel - cutplane adjustment with parallel shifts towards the anulus at 1.5mm interval from the optimal plane. Right panel - cutplane angulation at 10° interval from the optimal plane.

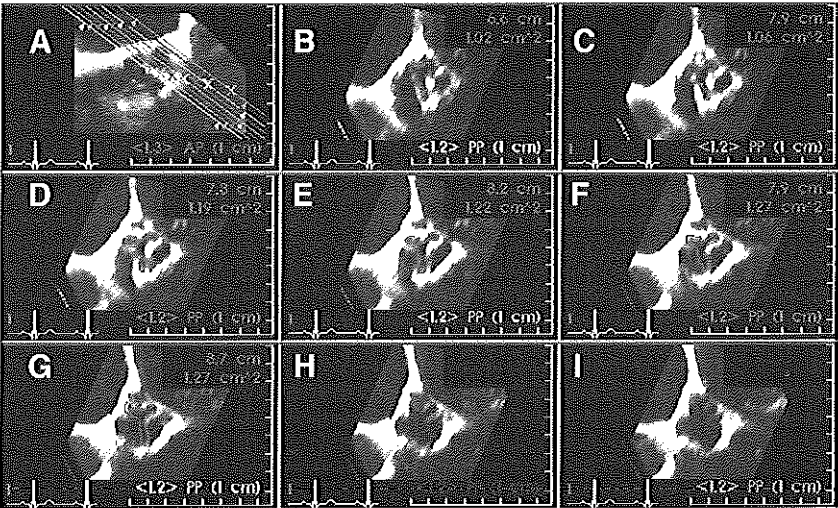
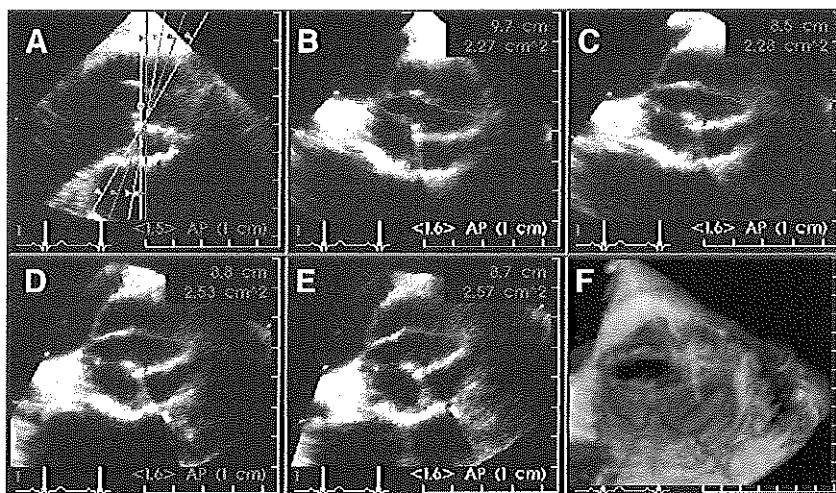


Figure 2. Parplane echocardiography using the three-dimensional dataset of a patient with a stenotic aortic valve. All the two-dimensional views are computer-reconstructed Panel A displays a reference long-axis image enabling the placement of the short-axis cutplanes at different levels through the valve (distance between cutplanes 1.5mm) - panels B-G. Optimized short-axis cross-section through the orifice at the level of cusp tips is shown at the panel B. Panels H and I (shift of 9mm and 10.5mm) did not contain the area information and were not used for analysis.



**Figure 3.** Anyplane echocardiography using the three-dimensional dataset of a patient with a bicuspid aortic valve. All the two-dimensional views are computer-reconstructed Optimized short-axis cross-section through the orifice at the level of cusp tips is shown at the panel B. Panel A displays a reference long-axis image enabling the placement of the angulated cutplanes (10° - C, 20° - D, 30° - E). Panel F is a corresponding volume-rendered view, not used for direct planimetry with current software.

## RESULTS

### Feasibility of two- and three-dimensional echocardiographic aortic valve area measurements

Transesophageal echocardiography with image acquisition for three-dimensional reconstruction was successfully performed in all patients. Additional examination time required for the calibration procedures and the 3DE data acquisition never exceeded 10 minutes. The time required for data postprocessing ranged from 5 to 15 minutes and for image analysis - between 5 and 15 minutes.

In 2DE, aortic valve planimetry was feasible in 26/27 studies (96%) - in one patient an adequate short-axis image of the aortic valve could be obtained. Planimetric measurements of aortic orifice in reconstructed anyplane views, optimally positioned at the level of cusp tips could be performed in 26/27 patients (Figure 2). In one three-dimensional dataset the measurements were precluded by a motion artifact; minor artifacts, not interfering with aortic valve planimetry were found in 6 other studies.

### Aortic valve area measurements

Head-to-head analysis was feasible in 25 patients (one exclusion because of low quality 2DE planimetry and one due to a large artifact in 3DE dataset). Aortic valve area measured in 2DE ranged from 0.6 to 4.31 cm<sup>2</sup>, mean 2.09 ± 0.97 cm<sup>2</sup>.



The values obtained in three-dimensional planimetry were similar, ranging 0.64 to 3.92 cm<sup>2</sup>, mean  $2.07 \pm 0.92$  cm<sup>2</sup>. Excellent correlation between the area estimates in both methods was found:  $r=0.982$ ,  $p<0.0001$ ,  $y = 1.033x - 0.04$ ,  $SEE=0.19$  cm<sup>2</sup>, Figure 3). Mean difference between methods was not statistically significant with close limits of agreement ( $0.02 \pm 0.19$  cm<sup>2</sup>) as shown in Figure 3.

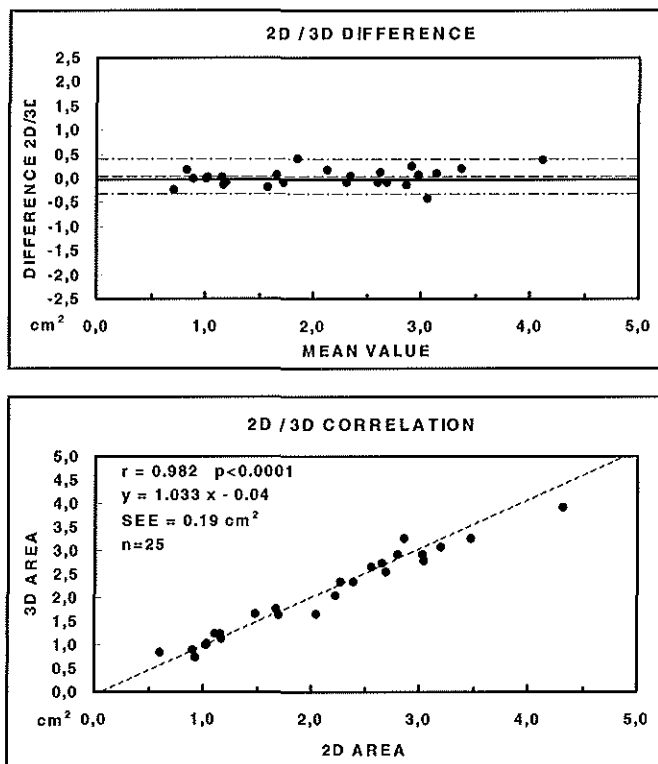


Figure 4. Upper panel - plot of agreement between the 3- and 2-dimensional echocardiographic estimates of the aortic valve area. Difference in area (y axis) is plotted against the mean value of the two measurements (x axis). There are close limits of agreement between the values obtained by the two methods (-0.34, +0.40). Lower panel - a linear regression plot of area values obtained in two-dimensional (x axis) and three-dimensional echocardiography (y axis).

### Importance of optimal cutplane position

A significant area overestimation (O) was observed at each cutplane angulation ( $O = 0.09$  cm<sup>2</sup> at 10°,  $0.19$  cm<sup>2</sup> at 20° and  $0.34$  cm<sup>2</sup> at 30°) and confirmed by repeated-measures analysis of variance ( $p<0.001$ ) with Dunnett test.

Overestimation was linearly correlated to the angle ( $r=0.992$ ,  $p<0.008$ ). Similarly, every parallel shift of viewing plane caused a significant overestimation of the area ( $O = 0.11\text{cm}^2 / 1.5\text{ mm}$ ,  $0.22\text{cm}^2 / 3\text{ mm}$ ,  $0.33\text{cm}^2 / 4.5\text{ mm}$ ,  $0.43\text{cm}^2 / 6\text{ mm}$  and  $0.63\text{cm}^2 / 7.5\text{ mm}$ ), ANOVA  $p<0.001$ . Linear correlation of overestimation and plane shift was found ( $r=0.993$ ,  $p<0.001$ ). The degree of error was not correlated with the optimal planimetered area of the valve. The influence of cutplane optimization on mean measured valve area is summarized in Figure 3.

### Variability

Intraobserver and interobserver variability of aortic valve area planimetry in 3DE was very low (mean difference  $0.03 \pm 0.08\text{cm}^2$ ,  $0.01 \pm 0.11\text{cm}^2$  resp.), coefficients of variation: intraobserver 3.9%, interobserver 5.3%. The variability of 3DE measurements compared favorably against 2DE: mean intraobserver difference  $0.04 \pm 0.10\text{ cm}^2$ , coefficient of variation 4.8%, F test against 3D:  $p=\text{NS}$  and mean interobserver difference  $0.10 \pm 0.21\text{ cm}^2$ , coefficient of variation 10.0%, F test against 3D:  $p=0.002$ .

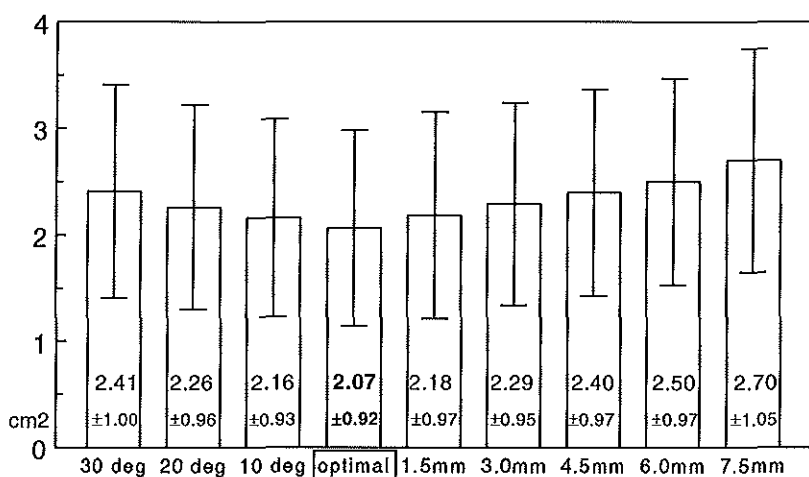


Figure 5. Bar plot demonstrating an increase in measured aortic valve area in angulated (30 deg, 20 deg, 10 deg) cutplanes and parallel shifted cutplanes (1.5mm, 3mm, 4.5mm, 6mm, 7.5mm) as compared to the optimal cutting plane. Abbreviations: deg - degree.

## DISCUSSION

### Invasive aortic valve area quantification

The formula of Gorlin and Gorlin,<sup>15</sup> introduced in 1951, is still used as a reference method for aortic valve area calculation but its significant limitations are known.<sup>16</sup> The area estimates are clearly flow-dependent and related to the functional rather than anatomical orifice. In practice, it is sometimes difficult to obtain accurate values for cardiac output and a mean transvalvular pressure difference. The method requires tedious standardization and due to the invasive

character is expensive and not suited for everyday routine use and repetitive studies. Recently described, accurate measurement of aortic valve area with intracardiac ultrasound probes shares the same limitation.<sup>17,18</sup> Nowadays, the use of pre-operative cardiac catheterization for the assessment of aortic stenosis severity is decreased and reserved for patients with inconsistency between clinical symptoms and non-invasive imaging data. Therefore, a need exists for a cheaper, noninvasive technique for the calculation of the aortic valve area.

### **Two-dimensional echocardiographic assessment of the aortic valve**

Transthoracic two-dimensional and Doppler echocardiography are the main techniques used for the noninvasive assessment of aortic valve stenosis. Aortic valve area can be calculated with the continuity equation but small inaccuracy in data collection may result in major error. Direct planimetry of the aortic valve area is limited by valve calcifications and not widely used in clinical practice. This may improve with better images of new generation echocardiographs.<sup>19</sup>

Most limitations encountered in precordial studies are overcome by transesophageal approach. Recently reported, the use of the continuity equation for aortic valve area calculation has been reported using this modality.<sup>20</sup> A more common and simple approach, however, is to measure aortic valve area using direct planimetry. Higher frequency ultrasound transducers providing better image resolution with no chest wall interference enable such evaluation and yield reliable values of aortic valve area. The method has been well validated and provides values close to those calculated with the Gorlin formula.<sup>2-5</sup> A recent study by Kim et al.,<sup>6</sup> demonstrates that the aortic valve area estimates from both methods are practically equivalent. Optimal feasibility and accuracy was found with multiplane transesophageal echocardiography, due to easier image plane manipulation than single plane or biplane probes.<sup>5,21</sup> The variability of transesophageal echocardiographic planimetry of the aortic valve area in our study is similar to the values reported previously.<sup>2-6,21</sup>

Although the results obtained with transesophageal 2DE are encouraging, the alignment of viewing plane with real short axis of the aortic valve is subjective and remains a major problem. During the data collection there are no obvious anatomical landmarks confirming that imaging plane is positioned at the smallest anatomical area, which is at the tips of aortic cusps exactly in the plane of the valve orifice. To the best of our knowledge, the quantitative aspects of improper cutplane location on aortic valve area quantification have not been investigated yet.

### **Three-dimensional echocardiography**

The reconstruction of cardiac morphology from 3DE datasets represents a major advance in noninvasive imaging techniques. The structures of the heart can be displayed in "anatomical" or "surgical" perspectives,<sup>22</sup> with direct perception of correct spatial relations. Recognition of complex anatomy and pathology is thus facilitated.<sup>23</sup> Three-dimensional reconstruction of the aortic valve with transesophageal approach is feasible and provides reliable information in various types of pathology.<sup>11,24,25</sup> Three-dimensional echocardiographic datasets allow unrestricted off-line manipulation, unlike the images stored on videotapes. Off-line reconstruction of any desired view, even not present in originally acquired images can now be

performed (anyplane mode). However, only preliminary data are available about the quantification of aortic valve area with this approach. Good feasibility and agreement versus Gorlin or continuity equation method<sup>26,27</sup> as well as direct intraoperative measurements were reported.<sup>28</sup>

An important part of our study was dedicated to the evaluation of potential errors, resulting from the measurements in inappropriate short-axis cutplanes. Significant overestimation of the area was caused by as little displacement as 1.5mm parallel shift or  $10^\circ$  angulation. Overestimation was linearly related to angle or distance in the analyzed range of values. Majority of images obtained at  $10^\circ$  and  $20^\circ$  angles or 1.5mm and 3mm was visually pleasing and could be mistaken for the optimal short axis view. This identifies a potential source of errors in two-dimensional studies taken by less experienced operators. Such overestimation may be of clinical importance in borderline cases, considering that the absolute magnitude of error was similar in valves with stenotic and with normal orifice. Noteworthy, this kind of error analysis could be performed exclusively with use of three-dimensional datasets, because no other technique allows the controlled modification of cutplane parameters in the same analyzed heart cycle.

In our study the feasibility of aortic valve planimetry in optimal cross-sections obtained from three-dimensional datasets was good and similar to that obtained in 2DE. The measurements of aortic valve area, obtained for a wide range of values, were in close agreement with those provided by two-dimensional planimetry and, in a subgroup of patients with the most diseased valves, by continuity equation. Excellent reproducibility of three-dimensional measurements compared favorably with two-dimensional data, the difference reaching statistical significance for interobserver variability. This can be explained by the unique possibility of unrestricted off-line cutplane selection from the 3DE dataset which allows to precisely align a viewing plane with the true orifice of the valve. In our study, a long axis view of the ascending aorta was used to optimize the selection of orthogonal short-axis view. Such visual feedback can explain better reproducibility due to easier selection of an optimal cutplane used for planimetry in three-dimensional dataset.

### **Clinical potential and limitation of the study**

The quantification of aortic valve area from three-dimensional datasets acquired using a rotational method can be performed in the vast majority of patients. The time necessary for both reconstruction and selection of optimized two-dimensional imaging planes with modern hardware is acceptable. The method is more time-consuming, however, than 2DE, and requires some experience for efficient data manipulation. The possibility to reconstruct a short-axis image of aortic orifice from original imaging planes, aligned parallel to the long axis of the valve, provides a potential to minimize the artifacts caused by calcifications as the artifacts are cast off the plane of aortic orifice. Three-dimensional planimetry of the aortic valve can be an additional tool in unequivocal cases and, due to its low variability, might be useful to monitor the progression of borderline aortic valve stenosis.

Invasive aortic valve area assessment with Gorlin formula, still considered as a reference method, was not available in our patients. However, recent studies suggest that the Gorlin formula and multiplane transesophageal planimetry provide very similar values of aortic valve area.<sup>6</sup> Transesophageal data collection can be considered semi-invasive but transthoracic images of a thin, rapidly moving object such as aortic valve do not provide sufficient quality of data for reliable three-dimensional reconstruction and area quantification in majority of adult patients. The flow-dependence of aortic valve area is another potential source of variability in studies comparing different quantitative techniques, particularly when measurements are taken at different points of time and under variable medication regimens. In our study, however, all measurements were taken within one hour (including transthoracic imaging) in hemodynamically stable patients so that significant changes in cardiac output were unlikely. As regards the error evaluation, the measurements were taken from the same dataset that was used for optimized 3DE planimetry and this source of variability was completely eliminated.

In spite of technological progress, three-dimensional technique is still subject to limitations. The acquisition of images may be complicated in patients with very irregular arrhythmia. Inadvertent patient or transducer movements during data acquisition often produce significant artifacts in three-dimensional datasets. In our experience, a rotational transesophageal approach provides a sufficient stability and appropriate instructions given to a patient before the procedure help to acquire acceptable quality data. Spatial and temporal resolution of computer-reconstructed two-dimensional views are worse than original two-dimensional data, possibly leading to area underestimation. However, the agreement of both methods was good in our study, suggesting sufficient three-dimensional data quality. Finally, current software does not allow area measurements in volume-rendered three-dimensional views, which provide most direct visual information about the valve orifice (Figure 3F). This implementation may simplify the planimetry procedure in future software updates.

## CONCLUSIONS

Our study demonstrates that three-dimensional echocardiography can be used for aortic valve area planimetry with excellent reproducibility. The results are in close agreement with transesophageal two-dimensional planimetry and continuity equation estimates. Our observations confirm the risk of significant, clinically relevant aortic valve area overestimation resulting from relatively small inaccuracy in two-dimensional imaging plane adjustment. Off-line cutplane optimization, feasible in three-dimensional datasets, improves measurement accuracy and reproducibility by elimination of errors related to inappropriate viewing plane selection.

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## CHAPTER 12

### ASSESSMENT OF LEFT VENTRICULAR OUTFLOW TRACT IN HYPERTROPHIC CARDIOMYOPATHY USING ANYPLANE AND PARAPLANE ANALYSIS OF THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Alessandro Salustri MD, PhD; Marcel JM Kofflard MD; Jos RTC  
Roelandt MD, PhD; Youssef Nosir MD; Giuseppe Trocino MD; David  
Keane, MB, MRCPI; Wim B Vletter BSc; Folkert J Ten Cate MD, PhD.

Thoraxcenter, Department of Cardiology, University Hospital Rotterdam-Dijkzigt and  
Erasmus University, Rotterdam, The Netherlands.

*Am J Cardiol* 1996;78:462-8

## ABSTRACT

This study analyzes the alterations in size and geometry of the left ventricular (LV) outflow tract which occur in hypertrophic cardiomyopathy (HC) using transthoracic 3-dimensional echocardiography. Transthoracic 3-dimensional echocardiography was performed in 17 patients with HC (4 after myectomy) and in 10 normal subjects. Images were acquired with the rotational approach, with electrocardiographic and respiratory gating. From the 3-dimensional datasets, short-axis parallel slicing of the LV outflow tract at 1-mm distance was performed at the onset of systole. For each slice, cross-sectional area and maximal and minimal diameter were calculated. Reconstruction of the LV outflow tract could be displayed in 3 dimensions in all patients, allowing orientation and clear definition of the irregular geometry. In patients with HC, the minimal LV outflow tract cross-sectional area was smaller than in normal subjects ( $2.3 \pm 1.0 \text{ cm}^2$  vs  $5.0 \pm 0.9 \text{ cm}^2$ ,  $p < 0.0001$ ). The ratio between maximal and minimal cross-sectional areas was higher in HC than in normals ( $2.6 \pm 0.9$  vs  $1.4 \pm 0.2$ ,  $p < 0.0001$ ). The ratio between maximal and minimal diameter of the smallest cross-section of the LVOT was also significantly higher in HC than in normals ( $1.6 \pm 0.3$  vs  $1.2 \pm 0.1$ ,  $p < 0.001$ ) and a value of 1.36 separated normals from HC-patients without previous myectomy. In conclusion, precordial 3-dimensional echocardiography allows detailed qualitative and quantitative information on the LV outflow tract. Patients with HC are characterized by a highly eccentric and asymmetric shape of the LV outflow tract, and by a smaller minimal cross-sectional area compared to normal subjects.

## INTRODUCTION

Postmortem studies and intraoperative findings indicate that 2-dimensional echocardiography may fail to give the full picture of the left ventricular (LV) outflow tract in patients with hypertrophic cardiomyopathy (HC).<sup>1-6</sup> Three-dimensional echocardiography is a new imaging modality which provides unique information on the spatial geometry of a given structure.<sup>7</sup> Based on our experience in an unselected population,<sup>8,9</sup> we felt that the alterations in size and geometry of the LV outflow tract in patients with HC could be more accurately analyzed with precordial 3-dimensional echocardiography. With these concepts in mind, we designed this study to gain further insight into the complex geometry of the LV outflow tract in patients with HC. With this aim, analysis of the LV outflow tract was performed using the 3-dimensional datasets obtained after acquisition of precordial echocardiographic images.

## METHODS

### STUDY PATIENTS

We prospectively selected 17 patients (13 men and 4 women; mean  $\pm$  SD age  $39 \pm 15$  years, range 19 to 65) with HC referred to the outpatient clinic of our institution for routine transthoracic echocardiographic follow-up. High-quality images was a pre-requisite for inclusion in this study. The diagnosis of HC was based on M-mode and 2-dimensional echocardiographic demonstration of a non-dilated hypertrophic left ventricle in the absence of other cardiac or systemic disease that could produce LV hypertrophy.<sup>10</sup> According to a previously established classification,<sup>11</sup> the patterns of distribution of left ventricular hypertrophy were type I-1 patient, type II-3 patients, type III-12 patients, and type IV-1 patient. Systolic anterior motion of the mitral valve was present in 12 patients and its severity was evaluated

semiquantitatively from 0=absence to 3+=contact with the interventricular septum during systole.<sup>5</sup> At the time of the echocardiographic study a pressure difference was calculated from Doppler LV outflow tract velocity recordings, and obstruction (gradient >30 mm Hg under basal conditions) was detected in 4 patients. A septal myectomy had been performed in 4 patients.

Ten asymptomatic subjects without evidence of LV hypertrophy were also studied for comparison. These controls were 20-49 years old (mean  $28 \pm 8$  years) and 8 were male.

### **Examination procedure**

Two-dimensional echocardiographic studies were performed with a commercially available system (Vingmed CFM 750 or Toshiba Sonolayer SSH-140A) equipped with a 3.5 MHz transducer, while the patient was lying in the 45-degree left recumbent position. After the follow-up 2-dimensional echocardiographic study, the probe was positioned either at the left parasternal or apical window for acquisition of the tomographic images of the LV outflow tract for 3-dimensional reconstruction. Patient movement during the image acquisition can be prevented by thoroughly explaining the procedure before the study. The operator has to find the central axis of rotation so that the conical datasets encompass the LV outflow tract. During the acquisition, movements of the transducer holder must be avoided diligently. Mirror images of the first and the final cut plane indicate a correct 180-degree rotation. Informed consent was obtained in all subjects.

## **THREE-DIMENSIONAL ECHOCARDIOGRAPHY**

### ***Image acquisition***

After the standard 2-dimensional examination, the video output of the echocardiographic system is interfaced to the acquisition system (Echo-scan, TomTec GmbH, Munich, Germany) and the transducer is fixed into a cylindrical holder. A step-motor mounted on this holder can rotate the probe around its longitudinal axis via a wheel-work interface. The step-motor is connected to the acquisition system which command the rotation of the probe at 2-degree intervals over a span of 180 degrees. Respiratory and electrocardiographic gating are performed after the operator has selected the end-expiratory phase by thoracic impedance measurement and an adequate R-R interval. Thus, only those beats falling in the predetermined R-R interval and at the end-expiratory phase are selected by the steering logic of the system and acquired. Cycles that do not meet the preset ranges are rejected. Ninety sequential cross-sections are acquired each during a complete heart cycle, encompassing a 3-dimensional conical volume. After distance calibration, images are stored in the computer memory for subsequent analysis.

### ***Image processing***

The raw data are resampled off-line according to their temporal and spatial location. The coordinates of each point are converted from a polar to a rectangular system, and the space between contiguous points is electronically filled with a trilinear cylindric interpolation. Several algorithms are used to reduce noise and artifacts which can be created by patient and probe movements.

### ***Image display and analysis***

Images were analyzed as follows:

- 1) After thorough examination of the 3-dimensional datasets with analysis of cardiac cross-

sections in any desired plane ("anyplane echocardiography"), a cut-plane is selected where the LV outflow tract is visualized along its longitudinal axis.

2) The onset of ventricular systole is selected, as the first frame during the cardiac cycle in which the mitral valve appears closed.

3) Electronic parallel slicing ("paraplane echocardiography") of the LV outflow tract perpendicular to the vertical axis is performed at 1-mm intervals, from the hinge point of the anterior mitral leaflet to the point of coaptation of the mitral leaflets, and the corresponding 2-dimensional images (both the stop frame at onset of systole and the dynamic sequence) are displayed.

4) On the stop frame image at the onset of systole, the endocardial contour of the cross-section is manually traced for automatic area measurement, and maximal and minimal diameters are also measured.

5) Finally, reconstruction of the LV outflow tract at the onset of ventricular systole is displayed in wire frame mode and the representative image can be rotated on the screen for versatile 3-dimensional evaluation (Figure 1).

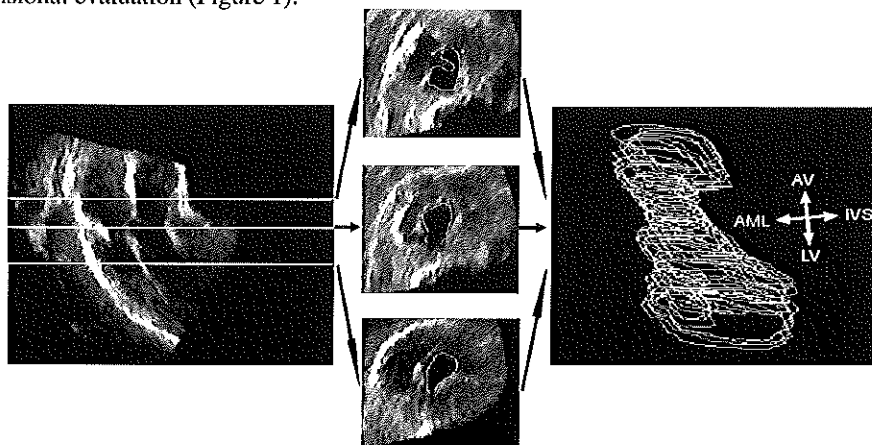


Figure 1. Analysis of the LV outflow tract in a patient with hypertrophic cardiomyopathy. From the three-dimensional dataset, parallel slicing of the LV outflow tract perpendicular to the long-axis (paraplane echocardiography) is performed at 1 mm intervals, at the onset of ventricular systole. In the left panel, three representative cut-planes are indicated. The corresponding cross-sectional two-dimensional images with the manually traced endocardial contours are shown in the middle panels. The final wire frame mode display represented in the right panel can be rotated on the screen along the three main axes for versatile qualitative three-dimensional evaluation. AML = anterior mitral leaflet; AV = aortic valve; IVS = interventricular septum, LV = left ventricle.

From the analysis of the 3-dimensional datasets, the following measurements of the LV outflow tract at the onset of systole were considered:

1) minimal cross-sectional area; 2) ratio between maximal and minimal cross-sectional area (max/min cross-sectional area), as an index of the "eccentricity" of the LV outflow tract (the higher the value the greater the variations of the cross-sectional area throughout the length of the LV outflow tract; 3) ratio between maximal (latero-medial) and minimal (antero-posterior) diameter (max/min diameter) at the level of the cross-section with the minimal area, as an index

of the "asymmetry" of the LV outflow tract (a ratio of 1 indicates a circular shape, with the highest values corresponding to the more elliptical shape of the cross-sections).

Inter- and intraobserver reproducibility for the measurements of LV outflow tract with 3-dimensional echocardiography was assessed in all 27 patients. To assess interobserver variability, two observers (A.S., Y.N.) independently measured the outflow tract area from the 3-dimensional datasets without prior knowledge of clinical data and without preselection of cut-planes. In addition, LV outflow tract cross-sectional area measurements were performed by one observer (A.S.) on two occasions (3 months apart, without preselection of cut-planes from the 3-dimensional datasets) to assess intraobserver variability.

### STATISTICAL ANALYSIS

Values are given as mean $\pm$ SD. Student's unpaired t test was used to compare the differences between HC and control subjects. Values of  $p<0.05$  were considered to be significant. Reproducibility of the LV outflow tract measurements was expressed in terms of mean differences and the 95% confidence intervals (C.I.).<sup>12</sup>

### RESULTS

Three-dimensional acquisition could be performed successfully in all patients. Echocardiographic acquisition of the image of the LV outflow tract for 3-dimensional reconstruction was performed either from the parasternal ( $n=20$ ) or apical ( $n=7$ ) windows, according to the image quality. The examination including the calibration procedure, selection of the optimal axis of rotation, a number of test runs, and the actual image acquisition required approximately 10 minutes in addition to the time required for the standard 2-dimensional echocardiogram. Three-dimensional reconstruction of the images was possible and of good quality in all patients. The time required for post-processing the raw data, reconstruction and analysis of the images was approximately 20 minutes. Demographics, echocardiographic characteristics, and measurements of the LV outflow tract in the individual patients with HC are reported in Table 1.

#### LV outflow tract in HC vs normals.

*a) Cross-sectional area.* The values of minimal cross-sectional area of the individual subjects are plotted in Figure 2. The minimal LV outflow tract cross-sectional area calculated with 3-dimensional echocardiography was significantly smaller in patients with HC than in the control group ( $2.3\pm1.0$  vs  $5.0\pm0.9$  cm<sup>2</sup>,  $p<0.0001$ ). Thirteen of the 17 patients with HC had a value smaller than the controls, and 2 of the 4 HC patients with higher values (nr. 6 and 17) were evaluated after myectomy. After correction for body surface area the values were  $1.3\pm0.5$  and  $2.7\pm0.6$  cm<sup>2</sup>, respectively ( $p<0.0001$ ).

*b) Shape.* From the 3-dimensional datasets, the reconstructed LV outflow tract could be displayed as observed from different viewpoints. This facilitates the appreciation of the geometry and shape as well as the localization of the narrowing of the LV outflow tract in patients with HC (Figure 3). A similar display in a normal patient is shown in Figure 4. Some examples of three-dimensional reconstruction of the LV outflow tract in normal subjects and in patients with HC are shown in Figure 5.

Table 1. Demographics, patient characteristics, and measurements of the left ventricular outflow tract in patients with hypertrophic cardiomyopathy.

Patient t	Age/ Sex	Type LVH	Therapy	Gradient	SAM	CSA (cm <sup>2</sup> )	Max/Min CSA	Max/Min Diameter
1	19M	III	V	58	3+	2.9	2.0	1.9
2	21M	III	-	<10	2+	2.4	2.5	1.7
3	22M	I	-	<10	1+	3.0	1.8	1.4
4	24M	IV	-	<10	2+	2.9	2.4	1.6
5	25M	III	V	<10	2+	2.7	2.4	1.6
6	31F	III	S, V	50	3+	1.3	4.2	2.0
7	38F	II	V	<10	0	2.4	2.7	1.7
8	39F	III	V	<10	0	3.2	2.1	1.6
9	41M	III	V	20	1+	1.9	1.7	1.8
10	46F	II	A, V	<10	2+	0.7	4.1	1.4
11	53M	III	-	<10	1+	1.5	3.8	1.9
12	63M	II	M	100	3+	1.5	3.0	2.6
13	65M	III	V	35	3+	2.0	3.0	1.6
M±S	37±15					2.2±0.7	2.7±0.8	1.75±0.3
14	31M*	III	-	<10	0	2.1	2.4	1.3
15	34M*	III	S	<10	1+	0.9	3.9	1.2
16	44M*	III	S, V	<10	0	4.7	1.5	1.3
17	59M*	III	V	<10	0	3.0	1.6	1.3
M±S	42±12					2.7±1.6	2.3±1.1	1.27±0.05
M±S	39±15					2.3±1.0	2.6±0.9	1.6±0.3
D(all)								

\* = patients evaluated after myectomy, A= amiodarone, CSA = cross sectional area; LVH = left ventricular hypertrophy, M, metoprolol, Max/Min= maximal/minimal, S=sotalol, SAM= systolic anterior movement, V=verapamil.

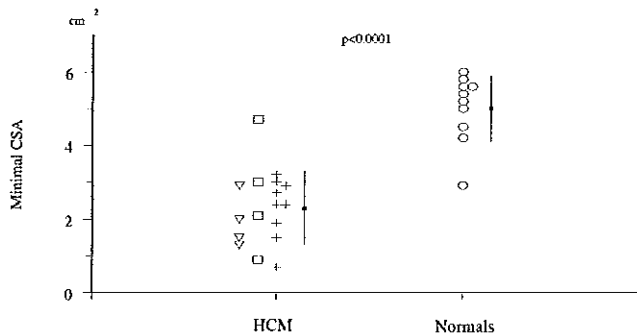


Figure 2. Minimal cross-sectional area (CSA) of the LV outflow tract in patients with hypertrophic cardiomyopathy (HC) and in normal subjects (n). + = patients without obstruction; □ = patients after myectomy; △ = patients with obstruction.

Max/min cross-sectional area ("Eccentricity index"). The max/min cross-sectional area of the LV outflow tract derived from the 3-dimensional datasets are displayed in Figure 6. From this figure, it is apparent that patients with HC had higher values (2.6±0.9) with a broad range of

values (from 1.5 to 4.2) indicative of many irregular different shapes of the LV outflow tracts in HC patients. In contrast, normal subjects had smaller ratios ( $1.4 \pm 0.2$ ) with a narrow range of values (from 1.1 to 1.6). In particular, each of the controls had a ratio of 1.6 or less, whereas 15 of 17 patients with HC had a ratio of greater than 1.6. The two patients with max/min cross-sectional area of 1.6 or less (nr. 16 and 17) were evaluated after myectomy. Thus, an outflow tract area ratio of 1.6 appeared to separate patients with from subjects without HC.

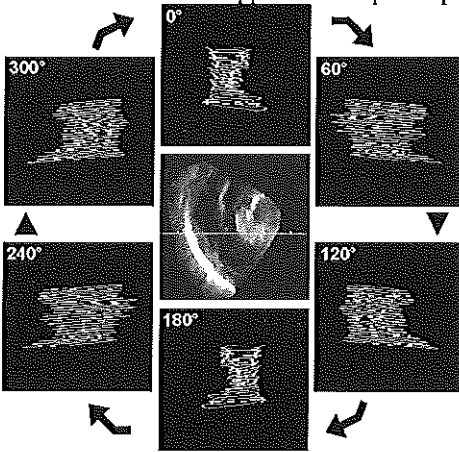


Figure 3. In this patients with hypertrophic cardiomyopathy, the wire frame display of the reconstructed LV outflow tract is represented as observed from different viewpoints. The view at 0° corresponds to the cut-plane represented in the central panel. The images obtained after incremental 60° clockwise rotation are displayed in the corresponding panels. There is an eccentric and asymmetric shape of the LV outflow tract. From these images it is also apparent that the narrowing is localized at the middle-caudal part of the LV outflow tract and is mainly related to a reduction in the antero-posterior diameter.

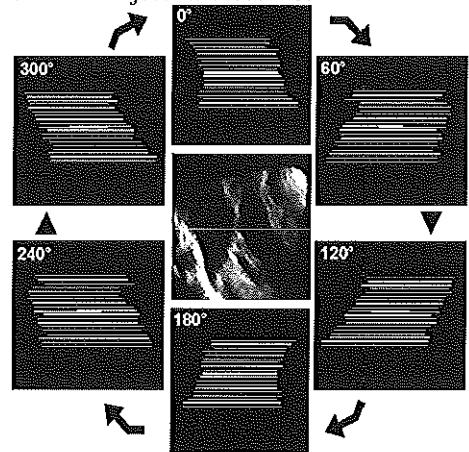


Figure 4. Three-dimensional reconstruction of the LV outflow tract in a normal subject, with the same display as in Figure 3. Note the uniformity (indicated by the minimal variations of the diameters throughout the length of the LV outflow tract) as well as the symmetry (indicated by the similar diameters of individual cross-sections from different viewpoints) of the LV outflow tract.

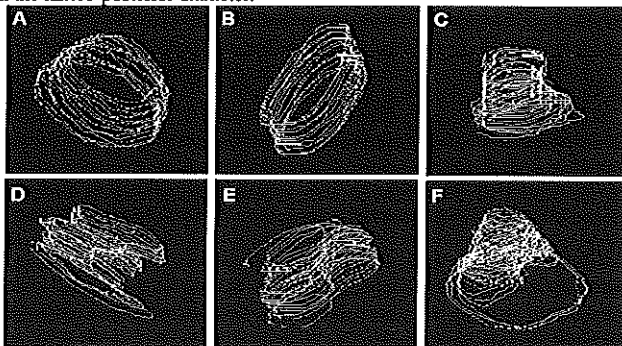


Figure 5. Three-dimensional reconstruction of the LV outflow tract with wire frame display in normal subjects (panels A-C) and in patients with hypertrophic cardiomyopathy (panels D-F). The different irregular configuration of the LV outflow tract in patients with hypertrophic cardiomyopathy can be evaluated.

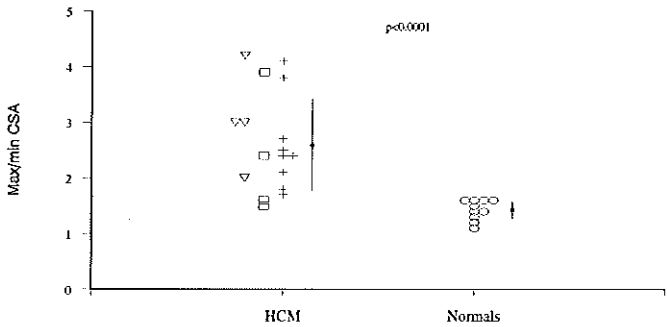


Figure 6. Ratio between maximal and minimal cross-sectional area (max/min CSA) of the LV outflow tract in patients with hypertrophic cardiomyopathy (HC) and in normal subjects. A high ratio indicates an eccentric shape of the LV outflow tract. Symbols as in Figure 2.

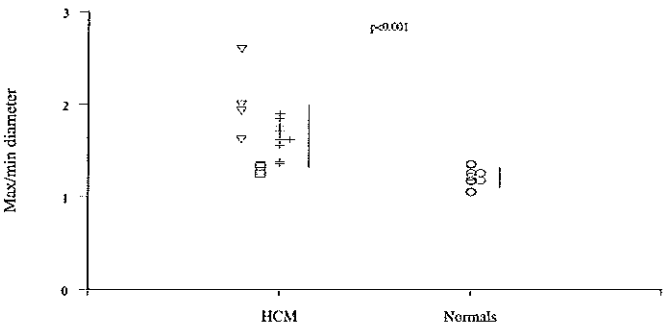


Figure 7. Ratio between maximal and minimal diameter (max/min diameter) measured at the cross-section of the LV outflow tract with the minimal area, in patients with hypertrophic cardiomyopathy (HC) and in normal subjects. A high ratio indicates an asymmetric shape of the LV outflow tract. Symbols as in Figure 2.

Max/min diameter ("Asymmetry index"). The individual values of max/min diameter of the LV outflow tract cross-section are displayed in Figure 7. This ratio was significantly higher in patients with HC than in normal subjects ( $1.6 \pm 0.3$  vs  $1.2 \pm 0.1$ ,  $p=0.001$ ). Of interest, patients evaluated after myectomy had the lowest values, while in contrast the highest values were found in patients with HC and LV outflow tract obstruction. An index of 1.36 appeared to separate normal subjects from non-operated HC patients.



**Reproducibility analysis of three-dimensional echocardiography.**

*Interobserver variability.* The difference between the two observers for measurements of the LV outflow tract was compared with the average of the two measurements for each patient. The mean difference between the measurements of the two observers was  $0.04 \text{ cm}^2$  (95% C.I.  $-0.08$  to  $0.12 \text{ cm}^2$ ) for cross-sectional area.

*Intraobserver variability.* The difference between the two measurements made by the same observer was compared with the average of the two measurements for each patient. The mean difference between the two measurements was  $0.13 \text{ cm}^2$  (95% C.I.  $-0.01$  to  $0.25 \text{ cm}^2$ ) for cross-sectional area.

**DISCUSSION**

Hypertrophic cardiomyopathy is a disease with a great individual variability and "no two hearts are alike".<sup>13</sup> The results of the present study indicate that 3-dimensional echocardiography allows visualization of the varied complex geometry of the LV outflow tract in patients with HC. With the quantitative analysis of the 3-dimensional datasets, we demonstrated that in patients with HC the minimal cross-sectional area is smaller than in normal subjects. In addition, the vast majority of patients with HC have an irregular shape of the LV outflow tract as demonstrated by an "eccentricity" index of 1.5 or greater. In normal subjects this index is always 1.6 or less, indicating a uniform shape of the LV outflow tract, without significant variation of the cross-sectional area throughout its length. We have also demonstrated that the cross-sectional shape of the LV outflow tract is more elliptical in patients with HC than in normal subjects, as indicated by a higher ratio of max/min diameter measured at the plane of the minimal cross-sectional area. This finding is in agreement with the concept that in HC the hypertrophic ventricular septum narrows the LV outflow tract mainly along its antero-posterior diameter. Of interest, this "asymmetry" index was highest in patients with HC and obstruction of the LV outflow tract at rest. In contrast, in HC neither the minimal cross-sectional area nor the "eccentricity" index of the LV outflow tract separated this subgroup. This finding indicates that for similar cross-sectional area the asymmetry of the LV outflow tract play an important role in determining the presence of significant obstruction at rest.

Patients who had undergone myectomy had a minimal cross-sectional area similar to other patients with HC, including those with obstruction (Figure 2). However, from Figure 7 it is clear that after myectomy the "asymmetry" index was lowest, indicating that the surgical remodelling of the LV outflow tract was adequate for the relief of the obstruction despite the finding that the cross-sectional area remained small compared to normal controls and in the same range of the other HC patients without previous myectomy. Thus, in patients with HC precordial 3-dimensional echocardiography has the potential to play a major role in tailoring the standard surgical resection of the interventricular septum to the individual patient's anatomy which is crucial for safe and efficacious performance of myectomy, and also in the evaluation of the results of surgery.

**Evaluation of LV outflow tract using 3-dimensional echocardiography**

Previous experience with 3-dimensional echocardiography for the evaluation of the LV outflow tract was based on morphologic analysis with volume rendered display.<sup>14</sup> In contrast, for

the quantitative analysis of the LV outflow tract performed in the present study we selected a multitude of cut-planes ("anyplane echocardiography") and performed a parallel scanning of the LV outflow tract at 1-mm intervals ("paraplane echocardiography"). This rate of sampling of the dataset is similar to the analysis done with magnetic resonance imaging or computed tomography, and allows detailed spatial information.<sup>15</sup> While some display modalities such as volume rendering are more indicated for representation of anatomical details,<sup>16-18</sup> the wire frame display format appears particularly suited to 3-dimensional reconstruction of the cardiac cavities, where areas, volumes, size and shape can be adequately evaluated.

### Limitations of three-dimensional echocardiography.

In this study, patients were selected on the basis of high-quality images at 2-dimensional echocardiography, which yielded a success rate of 3-dimensional reconstruction of 100%. The same results cannot be expected from an unselected population where poor quality precordial images may prevent adequate quality of the reconstruction.

Echocardiographic images were acquired by an experienced technician and reconstruction were performed by a cardiologist after a learning period of over 50 studies. This previous experience of 3-dimensional echocardiography prevented artifacts in the 3-dimensional datasets, limited the time required both for acquisition and reconstruction, and resulted in a minimal variability for the measurements.

### ACKNOWLEDGEMENTS

Dr Nosir is supported by the Nuffic, The Netherlands, and Al-Azhar University Hospital, Department of Cardiology, Cairo, Egypt. Dr Keane is the recipient of a travel grant from Peel Medical Research Trust, London, United Kingdom. The expert technical assistance of Renè Frowijn, BSc for the preparation of the illustrations is greatly acknowledged.

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## CHAPTER 13

### IMPROVED QUANTIFICATION OF MYOCARDIAL MASS BY THREE-DIMENSIONAL ECHOCARDIOGRAPHY USING DEPOSIT CONTRAST AGENT

Jaroslav D. Kasprzak\* MD, Wim B. Vletter Msc, Jan R. van Meegen  
BS, Youssef F.M. Nosir MD, Richard Johnson PhD\*\*, Folkert J. Ten  
Cate MD and Jos R.T.C. Roelandt MD.

Thoraxcentre, University Hospital Rotterdam - Dijkzigt and Erasmus University, Rotterdam,  
The Netherlands,

*Ultrasound Med&Biol 1998;24,5:647-53*

## ABSTRACT

**Aims.** Two-dimensional echocardiography is a common noninvasive approach to calculate myocardial mass. The method requires geometrical assumptions and suboptimal definition of endocardial and epicardial borders remains an important source of measurement variability. Our study was aimed to determine whether the myocardial enhancement with a novel contrast agent can improve the reproducibility of mass quantification assessed with three-dimensional echocardiography in a porcine model.

**Methods.** Three-dimensional reconstruction of the left ventricular myocardium was performed from echo images obtained with rotational epicardial acquisition in 8 open-chested pigs. Imaging was performed before and after left atrial injection of a deposit echocardiographic contrast agent - Quantison Depot<sup>TM</sup>.

**Results.** Myocardial enhancement was retained in three-dimensional datasets. Three-dimensional echocardiographic myocardial mass values had close agreement with weighed mass (differences  $-1.6 \pm 5.0$ g for end-diastolic frame,  $-2.8 \pm 4.5$ g for end-systolic frame,  $1.0 \pm 1.0$ g for end-diastolic frame with contrast and  $0.6 \pm 2.0$ g for end-systolic frame with contrast,  $p=NS$ ). Values obtained after the contrast injection were more accurate (correlation with a real mass at  $r=0.99$ ) and measurements reproducibility after contrast injection was improved.

**Conclusions.** Myocardial mass calculation using three-dimensional echocardiography is feasible and accurate. Injection of a deposit contrast agent allows to further improve measurement reproducibility.

## INTRODUCTION

Quantification of left ventricular hypertrophy is important and has both therapeutic and prognostic implications in a variety of cardiovascular diseases.<sup>1-4</sup> Measurement of myocardial mass in vivo is feasible by M-mode and two-dimensional echocardiography<sup>5-7</sup> but irregular shape of left ventricular myocardium is a challenge for methods based upon geometrical assumptions.<sup>8</sup> Recently introduced three-dimensional echocardiography (3DE) enables the analysis of complex anatomical structures in off-line reconstructed cutplanes.<sup>9-12</sup> The quantification of complicated shapes using a disc summation approach allows to improve the accuracy. Another problem in myocardial volume measurements, a suboptimal delineation of epicardial and endocardial contour could be overcome by echocardiographic contrast agents. Recently introduced, echocardiographic deposit contrast agent - Quantison Depot<sup>TM</sup> provides long-term myocardial enhancement, suitable for 3DE data acquisition with currently used equipment.

The purpose of our study was to test the additional advantage of myocardial contrast enhancement for improved quantification of myocardial mass using three-dimensional reconstruction with an internal reference echocardiographic system.

## MATERIALS AND METHODS

### *The animal study design.*

The experiments were performed according to the principles of care and use of animals approved by the Council of American Physiological Society (DHEW Publication No [NIH]

80-23,1980) under the regulations of the animal care committee of the Erasmus University Rotterdam, The Netherlands. The study was conducted on 8 Yorkshire pigs, weighing 21.5 - 31kg (mean  $25.8 \pm 3.1$ kg). Animals were sedated with i.m. 25 mg/kg ketamine HCl, followed by i.v. 20 mg/kg pentobarbital. During the experiments a continuous i.v. infusions of 10 mg/kg/hr pentobarbital and 0.25 ml/kg/min physiological saline were given. The pigs were intubated and ventilated with a mixture of oxygen and nitrogen (1:2) under gasometric control using a Bourns BV-502 (Medical Systems Inc., Riverside, CA, USA) ventilator. After the muscle relaxation with 4 mg pancuronium bromide, median sternotomy was performed and the heart was suspended in a pericardial cradle. A catheter was positioned in the left atrium for contrast injection. Heart rate, ECG, aortic pressures, left ventricular pressures and their derivatives were monitored throughout the experiments.

#### *Experimental protocol*

Before the contrast study, i.v. indomethacin 0.2mg/kg/body weight was given. As soon as the hemodynamic parameters stabilized after the animal preparation, 3DE data acquisition was performed. After one minute, the contrast agent was injected through the left atrial catheter in the dose of 20 ml. In three previous pilot experiments, not described in the present study, this dose was empirically found to be safe and providing optimal myocardial opacification. As soon as the contrast agent had been washed away from the heart cavities, the second 3DE image acquisition was performed. Animals were monitored until 30 minutes after the contrast injection. The left ventricular muscle mass (with papillary muscles excised) was weighed after animal sacrifice.

#### *Three-dimensional contrast echocardiography*

**Deposit contrast agent:** Quantison Depot<sup>TM</sup> (Andaris Ltd, Nottingham, UK) consists of air filled albumin microcapsules with an average diameter of 10  $\mu$ m and less than 2% exceeding 20  $\mu$ m. The walls of the microcapsules are composed of human serum albumin cross-linked to confer stability in the microcirculation. The agent is formulated as dry powder for suspension in an aqueous diluent providing a concentration of  $5 \times 10^7$  microcapsules/ml.

**Three-dimensional echocardiography.** Epicardial acquisition of two-dimensional images was performed for three-dimensional reconstruction.<sup>13</sup> Data were collected using a 5 MHz, 64-element transesophageal multiplane probe (Delft Instruments Medical Imaging BV, Delft, Holland) connected to a Sonos 500 (Hewlett-Packard, Andover, MA, USA) system. Video output of the echocardiograph was interfaced to a 3DE system (Echo-Scan 3.0, TomTec GmbH, Munich, Germany).

**Image acquisition.** The probe was placed epicardially over the middle of the right ventricular wall. The imaging window was optimized so that during a 180° rotation of the imaging plane the entire left ventricular muscle was encompassed. The standard settings of two-dimensional images (except for a linear postprocessing curve) providing optimal visualization of left ventricular endocardium were used during acquisition. The images for 3DE reconstruction were acquired during computer-controlled rotation of the transducer at 2° intervals (internal reference system) using ECG gating. Data processing was performed off-line by the 3DE system software. Digitized data were reformatted from the original polar orientation into Cartesian coordinates (256 x 256 x 256 voxels, i.e. "volume pixels").

The gaps between adjacent cross-sections were filled with interpolation procedures. Additional computer procedures were applied to reduce noise, enhance edges and reduce artifacts.

**Image display and evaluation.** The postprocessed dataset was used for reconstruction of eight parallel short-axis cutplanes perpendicular to the operator-selected left ventricular long axis (paraplane echocardiography), independent from the original ultrasonic window. Slice thickness was adjusted as 1/8 of the distance between apical epicardium and the plane of mitral anulus so that entire left ventricular muscle volume was encompassed in 8 adjacent slices. Epicardial and endocardial left ventricular muscle contours were manually traced by 2 observers in end-diastolic and end-systolic frames to calculate myocardial volume using Simpson's method with the software of 3DE system, according to the quantification method validated in the Thoraxcentre (Fig. 1).<sup>14</sup> Corresponding muscle mass was calculated as: volume x muscle density (1.05 g/ml). Measurements were repeated after 3 months by observer 1 (J.D.K.) to evaluate long-term intraobserver reproducibility of the results.

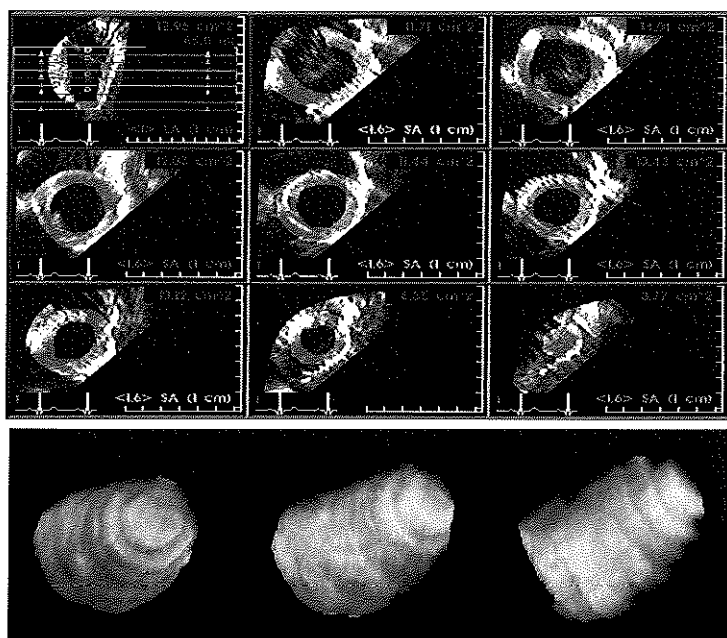


Figure 1. Panel A. Measurement of left ventricular myocardial volume using reconstructed paraplane cross-sections. Top left panel displays the reference long-axis view with line marks indicating the relationships of eight adjacent parallel cross-sections reconstructed at 8mm intervals. The traced epicardial and endocardial muscle contours are superimposed on the cross-sections. The calculated muscle volume is 65.6 ml, corresponding with real weight 68.8 g in the example shown.

Panel B. Three-dimensional representation of left ventricular myocardial shape viewed from different angles.

### Statistical analysis.

Numerical data are expressed as mean  $\pm$  standard deviation. Linear regression was used to determine the correlation between 3DE estimates of myocardial mass and gross specimen weight. Analysis of agreement for muscle mass calculations was performed according to the



method proposed by Bland and Altman.<sup>15</sup> Limits of agreement were defined as mean  $\pm$  1.96 x standard deviation of differences. Comparison of data obtained at different stages of experiment was made using repeated-measures analysis of variance with pairwise comparisons according to the Dunnett method. Additional comparisons of numerical variables were performed using paired t-test. Differences were considered significant at  $p < 0.05$ . Variability coefficients were calculated as the standard deviation of the differences between measurements expressed as a percent of the average value. Equality of variances was controlled with F test. Calculations were made with SYSTAT 5.0 for Windows (SYSTAT Inc. 1990-92) package.

## RESULTS

### *Contrast effectiveness and hemodynamic effects of the deposit agent.*

The data obtained by hemodynamic monitoring of pigs during the experiment disclosed no adverse hemodynamic effects of Quantison depot<sup>TM</sup> administration. After the left atrial injection, Quantison depot<sup>TM</sup> caused a visible increase in echointensity of myocardium in two-dimensional echocardiographic images. Enhancement started within few beats after the injection, improving endocardial and epicardial definition. Intense myocardial opacification was observed in all pigs until the end of experiment (30 minutes), whereas the agent disappeared from the heart cavities within 2 minutes.

### *Three-dimensional contrast echocardiography.*

A total of twelve 3DE acquisitions was successfully performed. The complete procedure, preceded by optimization of probe position, system calibration and a few test runs required 5-8 minutes. Off-line image postprocessing and analysis was completed within 70 minutes per animal. Contrast enhancement of the perfused muscle was visible in computer-reconstructed cross-sections. Reconstruction quality allowed the delineation of left ventricular myocardium in every study. Minor motion artifacts were present in 4 datasets, not precluding the myocardial mass evaluation.

### *Myocardial mass quantification.*

Slice thickness in Simpson's method calculation ranged 7.1 - 10.3mm in diastolic frames and 6.2 - 9.3mm in systolic frames. Weighed myocardial mass ranged from 64.1 - 102.3g (mean  $79.5 \pm 13.2$ g). 3DE myocardial mass estimates showed excellent agreement with real mass as shown in Table 2. Mean difference between 3DE and real mass was  $-1.6 \pm 5.0$ g in end-diastolic frame,  $-2.8 \pm 4.5$ g in end-systolic frame,  $1.0 \pm 1.1$ g in end-diastolic frame with contrast and  $0.6 \pm 2.0$ g in end-systolic frame with contrast. The differences were not significant according to ANOVA analysis and Dunnett method. Linear regression analysis confirmed high correlation of 3DE estimates with real mass as shown in Table 1. Measurements taken after the contrast injection yielded more accurate results, reflected by closer correlation with a real mass ( $r = 0.99$ ) and lower standard error of estimate (Table 1). Limits of agreement of 3DE mass values significantly decreased after contrast injection (F test  $p = 0.0004$  and  $0.05$  for end-diastolic and end-systolic measurement, respectively).

### *Measurement reproducibility.*

For the evaluation of short-term intraobserver variability, the values obtained in end-systolic and end-diastolic frames were compared.

There were no significant differences between mean values of myocardial mass estimates as shown in Table 2. There were no statistically significant differences in the reproducibility of myocardial mass measurement in different phases of heart cycle but the differences between end-systolic and end-diastolic frame measurement showed less variance after contrast injection (F test  $p=0.005$ ). Similarly, values obtained after 3 months did not differ from the initial results. Interobserver and long-term intraobserver measurement reproducibility after contrast injection was significantly improved (Table 2).

Table 1. Correlation of myocardial mass calculated with three-dimensional echocardiography (3DE) in comparison with weighed myocardial mass.

3DE mass calculation vs weighed myocardial mass	3DE mass values (Dunnett $p=NS$ )	Regression equation r	p	SEE
End-diastolic frame	$77.8 \pm 14.6g$ (range 58.0-107.0g)	$y=0.85x + 13.2$ 0.940	0.001	4.86
End-systolic frame	$76.6 \pm 11.1g$ (range 65.2-94.9g)	$y=1.12x - 6.8$ 0.947	0.0004	4.60
End-diastolic frame after contrast injection	$80.5 \pm 13.0g$ (range 65.0-102.9)	$y=1.02x - 2.2$ 0.997	<0.0001	1.05
End-systolic frame after contrast injection	$80.0 \pm 13.1g$ (range 65.7-100.7g)	$y=1.00x - 0.7$ 0.988	<0.0001	2.17

3DE= three-dimensional echocardiography, p : probability, NS= not significant, r= Pearson's correlation coefficient, and SEE= standard error of the estimate.

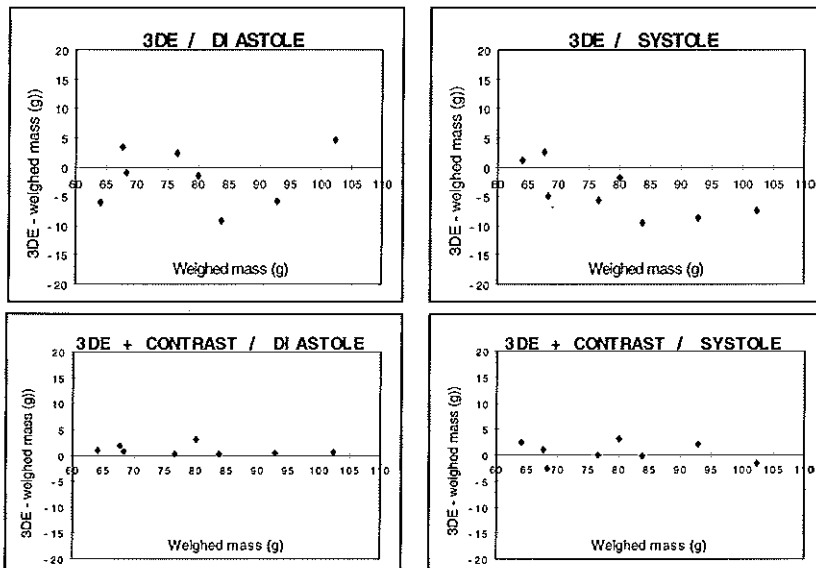


Figure 2. Agreement plots of the three-dimensional echocardiographic myocardial mass data with weighed mass - in end-diastole (A), in end-systole (B), in end-diastole after contrast injection (C) and in end-systole after contrast injection (D). Dashed lines mark the bias and limits of agreement (95% confidence intervals).

Table 2. Reproducibility of three-dimensional echocardiographic (3DE) measurements of myocardial mass.

Variability	Difference between measurements (p=NS)	F test p value	Variability coefficient
Intraobserver short-term (end-diastole vs. end-systole)	2.7 ± 5.7 g	0.005	7.5%
Idem, after contrast injection	0.5 ± 1.7 g		2.2 %
Intraobserver long-term (end-diastolic frame)	2.9 ± 4.9 g		6.1%
Idem, after contrast injection	1.7 ± 2.4 g	0.091	3.0%
Intraobserver long-term (end-systolic frame)	1.4 ± 7.3 g		9.4%
Idem, after contrast injection	1.9 ± 2.8 g	0.022	3.5%
Interobserver (end-diastolic frame)	0.4 ± 7.8g		10.1%
Idem, after contrast injection	1.2 ± 3.4g	0.043	4.2%
Interobserver (end-systolic frame)	1.7 ± 7.0g		9.2%
Idem, after contrast injection	1.6 ± 3.4g	0.076	4.3%

F test p value = significance of variance differences in baseline and contrasted images, other abbreviations as table 1.

## DISCUSSION

### *Myocardial mass quantification using three-dimensional echocardiography.*

The main finding of our study is that myocardial mass can be accurately measured in vivo using 3DE voxel imaging and that myocardial signal enhancement with a deposit contrast agent facilitates accurate delineation of epicardial and endocardial contours, improving accuracy and measurement error. Conventional M-mode using Penn convention [5,6] as well as more refined two-dimensional echocardiographic algorithms,<sup>7,16,17</sup> commonly used for left ventricular mass quantification, suffer from simplified geometrical assumptions. Complex spatial shape of myocardium, particularly in diseased hearts, cannot be precisely reflected in a single cross-section, which precludes in accurate calculation. Operator-dependent cutplane selection is another major source of error. Therefore, 3DE<sup>18</sup> is a possible solution for those issues. Most evidence for the improvement in quantification of left ventricular mass with 3DE was obtained using external reference systems - with acoustic or magnetic locator. With this approach, the endocardial and epicardial surface is reconstructed using several randomly acquired and manually traced cardiac cross-sections and a polyhedral surface reconstruction algorithm. This technique is efficient for left ventricular mass quantification as demonstrated in the experimental setting<sup>19-21</sup> and in human studies.<sup>9,22</sup> Low measurement error and good reproducibility was reported, with an error 2-3 times lower than with two-dimensional echocardiography and even more than with M-mode.<sup>23,24</sup>

In our study, we used 3DE voxel imaging. The systematic, computer controlled acquisition of basic echo data encompassing the region of interest is theoretically more complete and uniform. The disc summation method is possible by off-line reconstruction of operator-selected two-dimensional cross-sections allowing volume quantification of any anatomical structure. Preliminary reports exist regarding the application of voxel imaging for the myocardial mass quantification.<sup>25-27</sup> Results recently reported by Kühl et al.,<sup>28</sup> were superior to those obtained with the Penn convention. Although the optimal strategy for image acquisition and analysis is still unclear,<sup>25,27</sup> our data support the usefulness of a rotational data acquisition and modified Simpson's algorithm.<sup>14</sup> The calculation of myocardial mass was feasible in all three-dimensional datasets and the results achieved in beating porcine

hearts are comparable with those of Kühl et al.<sup>28</sup> Main problem in the mass quantification procedure is suboptimal delineation of myocardial borders. The injection of a deposit contrast agent offers a solution of this problem as demonstrated by improvement in measurement reproducibility and closer limits of agreement.

#### *Deposit contrast agent.*

Commonly used myocardial contrast agents are rapidly removed from the myocardial microcirculation. Quantison depot<sup>TM</sup>, with its relatively large and thick-walled bubble, is a deposit agent. Myocardial signal enhancement appears within few beats after injection and persists long after the contrast has disappeared from heart cavities. The benefits of such approach include lack of attenuation from cavity contrast and long temporal window for data acquisition, essential for high quality three-dimensional reconstruction with presently available equipment. These properties are related to prolonged stay of the agent in capillaries, similarly to radiolabelled microspheres. This implies microembolization of a number of microvessels, and concerns about safety arise. In our study, no hemodynamic effects of contrast injection were observed. It is known from studies using radiolabelled microspheres of 15µm diameter that a dosis of  $5 \times 10^5$ / gram tissue is needed to arrest the heart.<sup>29</sup> To our knowledge, no data are available for microspheres with sizes comparable to the microcapsules used in the present study. The dosage was chosen after a number of pilot experiments. Nevertheless, safety studies are needed before Quantison depot<sup>TM</sup> can be applied in humans.

The properties of the new agent encouraged us to investigate a novel application - to improve the definition of myocardium. Until now the application of myocardial contrast enhancement was aimed at the evaluation of perfusion. No data are available concerning the impact of contrast enhancement on the accuracy of myocardial mass quantification. In agreement with preliminary reports,<sup>30,31</sup> the contrast effect is reliably reproduced in three-dimensional datasets. The enhancement of myocardial signal markedly facilitates the delineation of endocardium, epicardium and atrioventricular groove, thus improving measurement reproducibility of contrast-enhanced images as compared to baseline.

#### *Limitations of this study.*

Our study included a relatively small number of animal experiments. The deposit contrast agent used in our study, Quantison depot<sup>TM</sup>, is still investigational and its safety and clinical usefulness has to be further studied.

We have used the epicardial acquisition technique which will be replaced in clinical practice by the use of transesophageal or transthoracic acquisition as an extension of a routine examination. Epicardial data acquisition poses some specific problems, which can affect the measurement accuracy. The transducer placed on a beating heart cannot be perfectly stabilized which may result in motion artifacts. Moreover, even with the epicardial right ventricular window, the left ventricle can be close to the transducer, sometimes precluding to encompass the entire muscle volume within the conical dataset. This is a possible source of volume underestimation, particularly in end-diastole.

Three-dimensional echocardiography, despite major progress in software and instrumentation still suffers from temporal and spatial resolution problems. Data processing requires time and real-time three-dimensional echocardiography may be relieved of this

problem.<sup>32</sup> Implementation of advanced border detection techniques can shorten the analysis time by elimination of tedious manual tracing.

## SUMMARY

This study demonstrates the feasibility and accuracy of three-dimensional echocardiographic determination of myocardial mass in vivo. The measurement accuracy and reproducibility is further improved by a deposit contrast agent, facilitating the detection of myocardial borders. Future developments in three-dimensional echocardiographic instrumentation and contrast agents may simplify the procedure and expand its clinical applicability.

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## CHAPTER 14

### CONCLUSIONS

Rapid developments have taken place in three-dimensional echocardiography (3DE) in the last few years and clinical applications are rapidly expanding. The technique potentially meets most of the requirements for the ideal diagnostic tool. The technique is noninvasive and can be performed frequently for follow up studies. Currently available experience suggests that 3DE visualization and quantification of cardiac structures has a role in patients with valvular disorders, congenital heart disease, mass lesions, aortic abnormalities and for the assessment of left ventricular function.

The studies presented in this thesis were designed to assess the feasibility and the accuracy of 3DE for quantification of valve disease and ventricular function.

#### *3DE for quantification of left ventricular volume (LVV) and function*

In this part we have studied the feasibility, reproducibility and accuracy of 3DE for calculating LVV and ejection fraction (EF) with comparison to values obtained from radionuclide angiography (RNA) and magnetic resonance imaging (MRI). Furthermore, we evaluated a faster 3DE method suitable for serial LVV and functional quantification. This is relevant for routine LV studies. We demonstrated that 3DE has an excellent correlation and close limits of agreement with RNA for EF calculation (*chapter 3*). In addition, 3DE has a closer limits of agreement than biplane modified Simpson's method (which used 2DE with two orthogonal cut planes) with RNA for EF calculation particularly in ischaemic patients with segmental and global left ventricular wall motion abnormalities (*chapter 4*). Segmental wall motion abnormalities and left ventricular shape abnormalities are common complications of coronary artery disease and affect both the accuracy and the reproducibility of LVV quantitation with conventional two-dimensional echocardiography (2DE). Our results show that 3DE allows assessment of the LV wall and provides more accurate calculation of EF using Simpson's rule than that by the biplane modified Simpson's method when compared with RNA. This was also validated for patients with segmental wall motion abnormalities and when classified according to the site of the wall motion abnormality (*chapter 4*). When MRI was used as a reference method, 3DE provided accurate calculations of LVV and EF with comparable observer variability (*chapter 6*). In addition, 3DE has a small day-to-day variability, which is important for serial evaluation of LVV and EF in cardiac patients (*chapter 7*).

In order to make the 3DE quantitation method more practical for routine LV function calculation, we found that LV short axis sections obtained at 15 mm slice intervals allow accurate calculation of LVV and EF with acceptable probability level for detecting variable differences in EF when compared with RNA method (*chapter 3*). Automated paraplane selection of 8 equidistant short axis slices from base to apex is now incorporated and is accurate enough for calculating LVV and EF with Simpson's rule as compared to MRI

method (*chapter 6*). This approach can reduce the analysis time to 10 minutes. Increasing the angular intervals reduces the acquisition time and avoids motion artefacts. We found that reducing the number of component sections by selecting 16° rotational intervals the acquisition time can be reduced to 30 seconds and still allowing accurate calculation of LVV and EF with acceptable probability for detecting variable differences of LVV and EF for clinical decision making (*chapter 8*).

3DE volumetric data sets allow us to study the spatial angle between the apical two chamber and the apical long axis views relative to the apical four chamber view and to study the accuracy of the biplane ellipse method for LVV calculation. Our data demonstrated that neither the apical two chamber view nor the apical long axis view was orthogonal to the apical four chamber view. It appears that the biplane ellipse method using the apical four chamber view with the apical long axis view rather than the apical two chamber view is more accurate for LVV and EF calculation (*chapter 5*).

### ***3DE in the assessment of valvular heart disease***

3DE allows optimal visualization of the smallest valve orifice area by paraplane analysis through the long axis of valve apparatus in patients with mitral or aortic valve disease. Mitral valve area derived from 3DE data sets showed excellent correlation, closer limits of agreement and non significant difference with areas calculated from Doppler pressure half time. 2DE derived valve areas showed moderate correlation, wider agreement and significant difference with comparison to the Doppler reference method (*chapter 10*). Aortic valve orifice area measurements were similar in both 2DE and 3DE studies. However, with cutplane angulation or parallel shift, significant overestimation of aortic valve area was observed (*chapter 11*).

### ***3DE in the assessment of patients with hypertrophic cardiomyopathy (HCM) and calculation of LV mass***

Our 3DE data demonstrated that patients with hypertrophic cardiomyopathy are characterized by a highly eccentric and asymmetric LV outflow tract and by smaller minimal cross sectional area compared to normal subjects (*chapter 12*). Calculation of myocardial mass by 3DE had close agreement with weighted mass. Intravenous contrast injection improved both the accuracy and the reproducibility of LV mass calculation by 3DE through enhancing epicardial and endocardial border delineation for planimetry (*chapter 13*).

### **3DE FUTURE DIRECTIONS AND NEW APPLICATIONS**

3DE using real time volumetric scanning provides on-line data acquisition and display of 3DE images of the heart. 3DE using the ultrafast acquisition by continuously rotating phased array transducer will reduce the acquisition time to seconds and therefore facilitate its routine use. This has advantages to use during stress echocardiography and myocardial perfusion agents. It will also facilitate peri-operative assessment of patients with valvular and congenital heart diseases.

3DE allows to obtain an unlimited number of cutting planes through the heart which is not possible with standard 2DE.

The ability to electronically dissect a specific structure and display it in any projection has advantages in planning surgical procedure of valve replacement or repair in patients with mitral valve disease. Volume rendered technique can assess in diagnosis of complex congenital anomalies and planning surgical procedures. As in patients with atrial septal defect (ASD) and ventricular septal defect (VSD), 3DE can assess the flow through the defect and also to detect the size, site and relations of the defect for device closure.

In future virtual reality from 3DE data can simulate surgical and interventional procedures in a computer model. This will allow the surgeon to better plan the procedure. 3DE computer model can also be used in teaching and training of various procedures.

Paraplane analysis from 3DE allows to span and to measure the volume of any cardiac or intracardiac structure and abnormal flow jet. With the application of myocardial contrast we can see the myocardial perfusion defect not only on 2DE but also in 3DE paraplane slices that can be labeled and extracted. This would allow quantification of the mass of the perfused, the ischaemic and the infarct areas and to correlate their magnitude.

Manual endocardial tracing is laborious and time consuming. 3DE with automated border detection algorithm needs to be validated for accurate and rapid volume and function quantification. In addition, endocardial border delineation can be enhanced by using the second harmonic mode and by intravenous ultrasound contrast agents in reconstruction methods using standard equipment.

Dynamic 3DE reconstruction can be used in the future to quantify abnormal flow jets in all its directions. Together with accurate LVV measurement, the assessment of severity of valve regurgitation well be improved.

Continuous advances in computer and ultrasound technology will strengthen the application of 3DE and will guarantee echocardiography to dominate other imaging techniques in clinical cardiology.

## SUMMARY

We demonstrated that,

3DE is an accurate and reproducible technique for LVV and EF calculation and compares favorably with both RNA and MRI.

We suggest the following protocol for 3DE reconstruction and quantification of LV:

- \* Precordial rotational acquisition at 16° intervals,
- \* Image processing of end-diastolic and end-systolic phases,
- \* Paraplane analysis using 8 parallel equidistant short axis slices

We found that the use of the apical four chamber view in combination with the apical long axis view provides accurate LVV and EF calculation using the biplane modified Simpson's method.

3DE allows reproducible measurement of the stenotic valve area which has similar accuracy as presently used Doppler methods.

Precordial 3DE provides detailed qualitative and quantitative information on the LV outflow tract. Patients with hypertrophic cardiomyopathy are characterized by a highly eccentric and asymmetric shape of the LV outflow tract, and by a smaller minimal cross-sectional area compared to normal subjects.

Myocardial mass calculation using 3DE is feasible and accurate. Injection of a deposit contrast agent enhanced epicardial and endocardial border delineation and allows further improvement of measurement reproducibility.

## SAMENVATTING

Quantificatie van cardiale functie parameters heeft belangrijke diagnostische, prognostische en therapeutische consequenties.

Daarom is het gewenst over een methode te beschikken die de cardiale functie snel, nauwkeurig, reproduceerbaar en op een niet bloedige wijze bepaalt.

Met driedimensionale echocardiografie kunnen sommige beperkingen van tweedimensionale echocardiografie worden voorkomen. Dit staat een betrouwbare quantificatie van de cardiale functie toe zonder gebruik te maken van geometrische aannames.

## CONCLUSIES

1. Driedimensionale echocardiografie heeft bewezen een nauwkeurige en reproduceerbare techniek te zijn voor de berekening van linker kamer volumina en ejectiefractie met een goede vergelijkbaarheid met radionucleide angiografie en magnetische resonantie.
2. We stellen het volgende protocol voor ter bestudering van een snelle en nauwkeurige 3D echocardiografische reconstructie en kwantificering van de linker kamer functie.
  - \* precordiaal roterende acquisitie met een interval van 16 graden.
  - \* beeldverwerking van einddiastolische en eindsystolische perioden.
  - \* parallelle analyse door gebruik te maken van 8 korte as doorsneden met een gelijke onderlinge afstand.
3. We stellen voor om de apikale lange as doorsnede (3 kamer doorsnede ) te samen met de apikale 4 kamer doorsnede te gebruiken i.p.v. de apikale 2 kamer doorsnede te samen met de apikale 4 kamer doorsnede voor een nauwkeurige bepaling van linker kamer volumina en ejectiefractie.
4. Driedimensionale echocardiografie heeft voordelen voor de morfologische bestudering van de mitraal - en aortakleppen. Uit de geregistreerde dataset kan een nauwkeurige reproduceerbare meting van de oppervlakte van de mitralis- en aortaklep worden bepaald.
5. Precordiale driedimensionale echocardiografie geeft gedetailleerde kwalitatieve en kwantitatieve informatie over de linker ventrikel uitstroombaan. Patiënten met hypertrofische cardiomyopathie worden gekenmerkt door een sterk excentrische en asymmetrische vorm van de linker ventrikel uitstroombaan en door een kleinere doorsnede indien vergeleken met normalen.
6. Bepaling van de myocardiale massa m.b.v. 3D echocardiografie is mogelijk en nauwkeurig. Indien een echografisch contrastmiddel wordt gebruikt, blijkt de reproduceerbaarheid van de meting toe te nemen.

## ACKNOWLEDGEMENT

My deepest appreciation goes to Prof. Jos RTC Roelandt, who provided the unique opportunity to work at the Thoraxcenter. He encouraged me to start the validation of 3DE for cardiac quantitation purposes. Indeed this was laborious and time consuming. He told me in clinical research you have to invest a lot of time to solve one simple problem, but this is the only way to solve bigger problems. His creativity and determination to achieve the intended goal enable us to continue and emphasize our efforts to find a clinically applicable protocol for cardiac quantification using 3DE. I am very grateful for the hours he has spent in reviewing the articles of this thesis. It is true to say that this project wouldn't have succeeded without his support.

I am particularly indebted to Prof. Mokhtar M Gomaa for his continuous encouragement and support. He was the impetus for my fellowship at the Thoraxcenter in Rotterdam. A most kind and generous individual. Prof. Gomaa was a constant source of stimulation and he supported me in every possible way to continue and complete this work. Words are not sufficient to express my gratitude to him.

I would like to convey my appreciation to my co-promotor Dr. Folkert J Ten Cate and also to Dr. Paolo M Fioretti for their support throughout my fellowship period at the Thoraxcenter Rotterdam. Their invaluable scientific criticism and ideas had a decisive influence which enabled this work to become reality.

I would like to thank Wim B Vletter as he provided me with great support and with many valuable suggestions to complete this thesis. I am very grateful to Eric Boersma and Ron T van Domburg for supporting my studies with the appropriate statistical analysis. I am also grateful to René Frowijn for his patience assistance with the compute technology.

I would like to thank Ad van Drunen, Willeke Korpershoek, Marianne Eichholtz, Yvonne Kalkman-Schotting, and Arita Orgers for their valuable help and advice.

I would like to thank every member of the big family of The Thoraxcenter particularly those working in The Echocardiography Laboratory and members of The Department of Nuclear Medicine and The Department of Radiology, Dijkzigt Hospital, for the help I received to complete these studies.

I would like to convey my deepest appreciation to all the staff members and my colleges at The Cardiology Department, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt, for their continuous encouragement and support to complete this work.

As the Thoraxcenter is really a multinational center, I have enjoyed the friendship and to work with many fellows. They include Kasprzak JD (Poland), Salustri A (Italy), El-Said EM (Egypt), Elhendy A (Egypt), Cornel J (Netherlands), Poldermans D (Netherlands), Geleijnse M (Netherlands), Dall'Agata A (Italy), Rambaldi R (Italy), Lajos V (Hungary), Chen Q (China), Yao J (China), Aiazian (Russia), Olaf F (Germany), Bernard Paelinck (Belgium), Rocchi G (Italy) and Chlebus K (Poland).

I would like also to convey my deepest appreciation to Wagdy and Mohamed (my brothers) and more particularly to the soul of my father-in-law Lotfy Nosir, for their indispensable support, encouragement and devotion.

Finally I would like to thank my wife Ghada and my sons Mahmoud and Ahmed, who provided the understanding and the emotional support which enabled me to continue and complete this work.

Support by a Fellowship of the NUFFIC (*Netherlands organization for international cooperation in higher education*) is gratefully acknowledged

Met dank aan:

*Andaris Limited, Schering Nederland BV, Tom Tec Imaging Systems, Hewlett Packard, Toshiba Medical System BV, Pfizer BV, Boeringer Ingelheim BV.*



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## Curriculum Vitae

Name: Youssef F.M. Nosir.  
Nationality: Egyptian.  
Birth Date: 25-01-1960.  
Place of Birth: Cairo, Egypt.  
Marital State: Married with Ghada L.M. Nosir.  
Having 2 sons (Mahmoud and Ahmed).

### Education.

1966-72: Ahmed Amin primary school, Cairo, Egypt.  
1972-75: Al-Mohamadia prep school, Cairo, Egypt.  
1975-78: Banba Kaden Secondary School, Cairo, Egypt.  
1978-85: Faculty of medicine, Al-Azhar University, Cairo, Egypt.  
1986-87: House Officer, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt  
1988-91: Resident of cardiology, Cardiology Department, Al-Hussein University Hospital, Al-Azhar University, Cairo, Egypt.  
1991-98: Assistant Lecturer of Cardiology, Cardiology Department, Al-Azhar University, Cairo, Egypt.  
1994-99: Research Fellow, Thoraxcenter, Academic Hospital Rotterdam, Erasmus University, Rotterdam, The Netherlands.

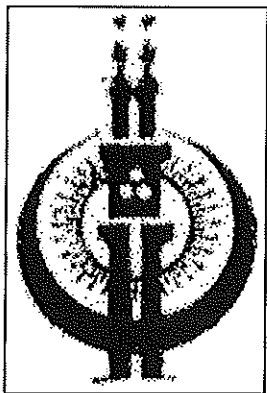
### Certificates.

M.B.B.Ch.: 1985 from Faculty of Medicine, Al-Azhar University, Cairo, Egypt.  
M.Sc.: 1991 Master degree of Cardiology, Al-Azhar University, Cairo, Egypt.  
M.D.: 1991 Registered for M.D. in Cardiology, Al-Azhar University, Cairo, Egypt

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Al-Azhar University,  
Cairo, Egypt



Erasmus University,  
Rotterdam, The Netherlands