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Real-time three-dimensional echocardiography: technological gadget or clinical tool?

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The complex anatomy of cardiac structures requires three-dimensional spatial orientation of images for a better understanding of structure and function, thereby improving image interpretation. Real-time three-dimensional echocardiography is a recently developed technique based on the design of an ultrasound transducer with a matrix array that rapidly acquires image data in a pyramidal volume. The simultaneous display of multiple tomographic images allows three-dimensional perspective and the anatomically correct examination of any structure within the volumetric image. As a consequence, it is less operator-dependent and hence more reproducible. Dedicated software systems and technologies are based on high-performance computers designed for graphic handling of three-dimensional images by providing possibilities beyond those obtainable with echocardiography. This methodology allows simultaneous display of multiple superimposed planes in an interactive manner as well as a quantitative assessment of cardiac volumes and ventricular mass in a three-dimensional format without a pre-established assumption of cardiac chamber geometry. In addition, myocardial contraction and/or perfusion abnormalities are clearly identified. Finally, real-time three-dimensional colour Doppler flow mapping enables complete visualisation of the regurgitant jet and new ways of assessing regurgitant lesion severity. Thus, this technique expands the abilities of non-invasive cardiology and may open new doors for the evaluation of cardiac diseases. In this article, current and future clinical applications of real-time three-dimensional echocardiography are reviewed. *J Cardiovasc Med* 8:144–162 © 2007 Italian Federation of Cardiology.

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The heart has a complex anatomy and is in constant motion. Conventional echocardiography can only provide partial information about the spatial and temporal relationship of cardiac structures during the cardiac cycle. Furthermore, conventional two-dimensional echocardiography (2DE) requires a difficult mental process by the operator to reconstruct a stereoscopic image of the heart based on the interpretation of multiple tomographic slices. Sometimes, the mental exercise of reconstruction may be inadequate to obtain a precise diagnosis even for an experienced observer, especially when dealing with complex congenital abnormalities of the heart. In addition, it may be difficult to convey or demonstrate a meaningful representation of cardiac pathology to those not fully conversant with 2DE views and appearances. The advent of three-dimensional echocardiography (3DE) may lead to a more readily appreciated, intuitive, objective and quantitative evaluation of cardiac anatomy and physiology that would reduce the subjectivity in image interpretation [1]. Data regarding clinical applications of 3DE are growing. This review details the current status of 3DE technology with its clinical applications and limitations.

Three-dimensional echocardiographic techniques

Until very recently, with the onset of 'real-time' or 'live' 3DE (RT-3DE) attempts at 3DE have been performed by reconstructing 3D images from multiple 2D images acquired using free-hand transthoracic or transoesophageal imaging [2]. This technique required spatial information about the ultrasound probe itself, and gating to the cardiac and respiratory cycle before starting an off-line, time-consuming reconstruction of the collection of 2D images into a 3D rendering. These techniques were hampered by long acquisition and reconstruction times in combination with limited image quality and frequent presence of artefacts.

Newly developed ultrasound systems have taken advantage of the dramatic improvements in microprocessor and transducer technology, allowing almost real-time

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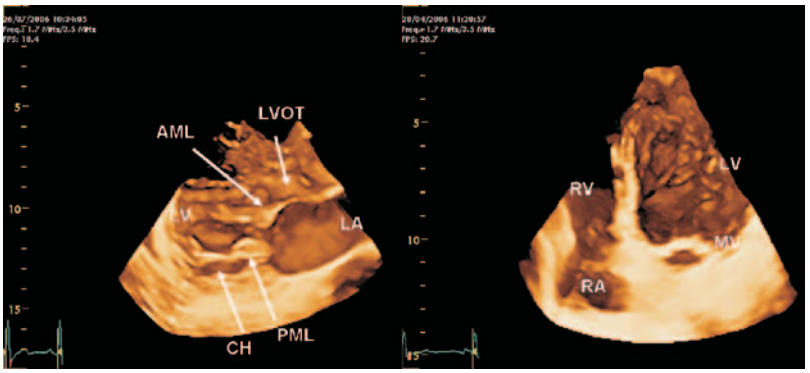
Fig. 1



Real-time three-dimensional echocardiographic study of the left ventricle. Left panel, sagittal (long-axis or longitudinal) section viewed from the left. Right panel, oblique coronal (frontal) section (the section has been tilted in a four-chamber equivalent view to facilitate understanding). AML, anterior mitral leaflet; CH, mitral chordal apparatus; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; MV, mitral valve; PML, posterior mitral leaflet; RA, right atrium; RV, right ventricle.

collection and handling of increasingly complete and accurate 3D data sets representing true volumetric images. Unlike off-line 3DE reconstruction techniques, RT-3DE allows on-line acquisition of a volumetric data set without the need for reference systems and electrocardiographic or respiratory cycle gating. Since the first prototype of real-time volumetric ultrasound imaging system developed at the Duke University in 1990 by the group of von Ramm [3,4], a number of remarkable technological advances have allowed major ultrasound system manufacturers to develop full matrix-array transducers capable of providing simultaneous visualisation of the beating heart and excellent image quality (Fig. 1).

Current generations of such transducers consist of 2D arrays with 3000–4000 simultaneously active ultrasound elements. Multidirectional beam steering and signal processing take place automatically with use of the scanning probe. While the transducer is maintained in fixed orientation, the ultrasonic beam can steer automatically in multiple directions. The multidirectional beam steering capability enables simultaneous visualisation of two or three views of the heart using split screen technology (Fig. 2). The ultrasonic beam goes along the predetermined x-axis and produces the first scanning line (i.e., 2D display). Then, the scanning line performs azimuth steering along the y-axis in the phased-array mode and produces a 2D sector image. Finally, the 2D sector image performs elevation steering along the z-axis and produces a pyramidal 3D data set that permits real-time visualisation of part of the heart chambers or valve structures in real time. In a real-time mode, a smaller pyramidal volume of data is obtained that is approximately $60 \times 30^{\circ}$; alternatively, a larger volume data set of up to 100×100 can be obtained by 'stitching' together up to seven sub-volumes obtained in real time over several consecutive cardiac cycles. In this latter 'full-volume' mode, it is possible to capture the entire heart within the data set. This creates an on-line rendered image of the scanning sector with a time resolution of around 40–50 ms equivalent to a frame rate of 20–25 volumes/s. Each cardiac cycle of RT-3DE has an amount of data that requires 15–60 cardiac cycles to obtain using 2DE. The innovative RT-3DE shows the heart dynamics in a realistic fashion with instantaneous on-line volume-rendered reconstruction [5,6]. It allows fast acquisition from a single acoustic view of dynamic pyramidal data structures that encompass the entire heart [7–9] without the need for reference system, and electrocardiographic and respiratory gating. It represents an important advance in 3DE techniques and is less time-consuming both for data acquisition and analysis: the mean time required to perform an RT-3DE examination after completing the learning curve is about 1.4 min [10].

Acquired images can be sliced in several planes and rotated in order to achieve a more accurate study of individual cardiac structures. This is particularly useful because it enables the heart to be visualised from multiple perspectives in the same way as the surgeon would see it during an operation. Furthermore, RT-3DE is the only 3D imaging technique based on real-time volumetric scanning, as compared with cardiac magnetic resonance (CMR) and computed tomography, which are based on post-acquisition reconstruction and not on volumetric scanning.

With the latest technical developments, RT-3DE transducer frequency is now higher than that of transducers used for reconstruction techniques. However, the main limitation of RT-3DE compared to 3DE reconstruction technique is that spatial and temporal resolution remains lower than that obtained with rotational 3DE.

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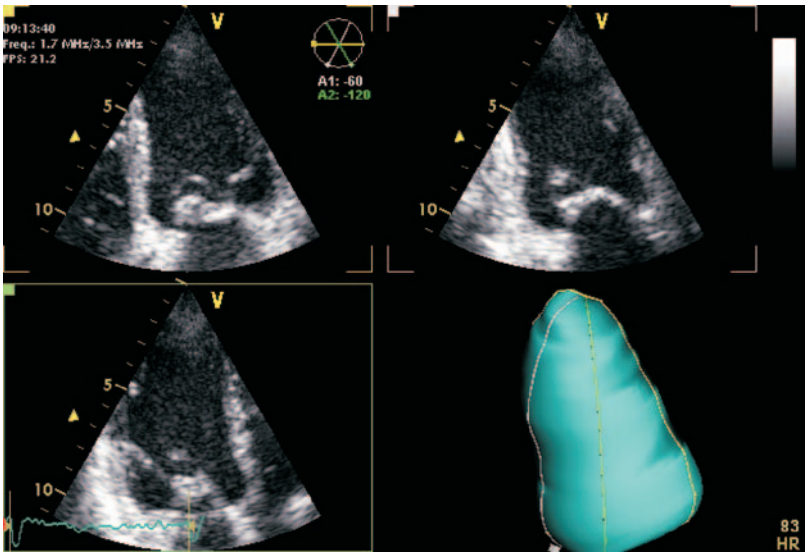
Fig. 2

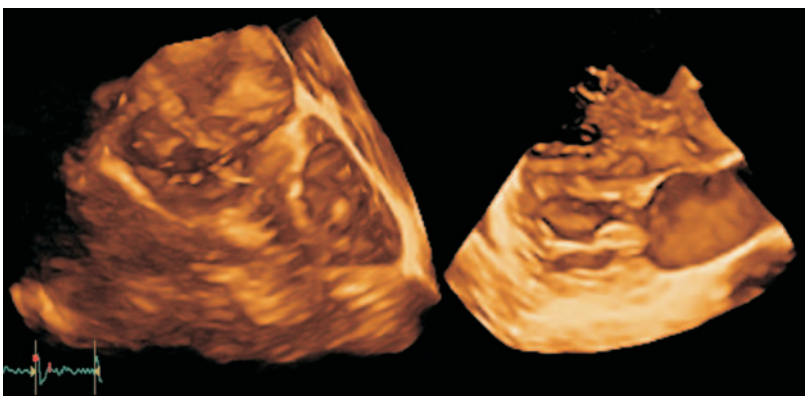


The multidirectional beam steering capability of the matrix-array transducer enables the multiplane (triplane) real-time study of the left ventricle from the apical approach showing four-chamber, two-chamber and long-axis views (predefined angles of 60° among the different views may be changed by the operator). From manual tracing of endocardial borders of these views, a mathematical model of the left ventricle is obtained. End-diastolic and end-systolic volumes and the resulting left ventricular ejection fraction are obtained from these data.

Image display and analysis

Acquisition of volumetric images in real time generates the problem of how to visualise the moving structures contained within the volume on a flat, 2D monitor. Volume rendering is a process whereby the intracardiac structures are reconstructed by the computer so that the volumetric data set can be sectioned electronically in any plane. Viewing a volume-rendered 3D data set of the heart is analogous to standing outside a house and being unable to see in without taking some or part of the walls away (Fig. 3, left panel). Once cropped away part of the data set, you can see inside the heart but, necessarily, the image that is presented to the observer for interpretation is only part of all the information contained within the 3D volume (Fig. 3, right panel). To understand this problem, imagine yourself standing in the middle of a room: at any given point in time, you can only see the part of the room that is in front of you. To add information from what is behind you need to rotate or change your position in space in relation to the rest of the room. In other words, despite the fact that the 3D structure of the room and its contents are available for examination, only part of it can

Fig. 3



Full-volume mode acquisition from the parasternal approach. (left panel) Pre-processed image containing complete three-dimensional data set. (right panel) Post-processed image (obtained by rotating the data set and cropping the anterior wall) that resembles a standard parasternal long-axis view with the three-dimensional perspective owing to the volume-rendering display.

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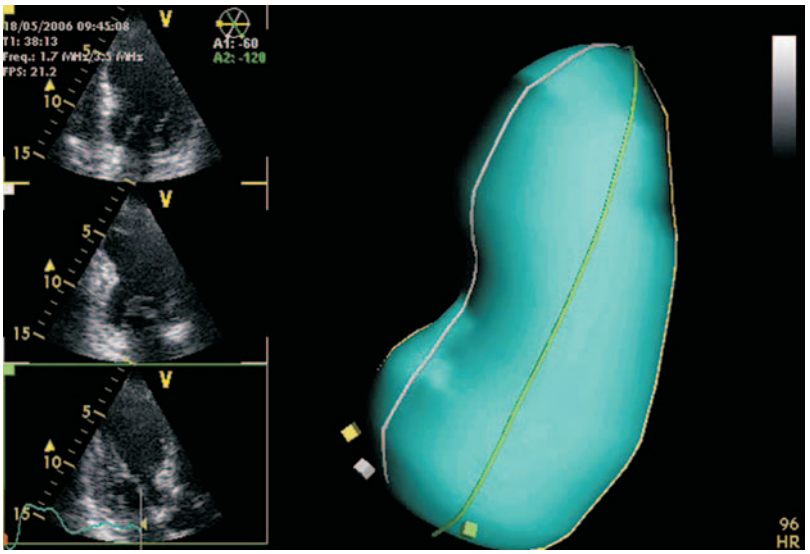
Fig. 4



Surface rendering technique that displays the left ventricular surface as a solid structure. This technique is mainly used for volume and systolic function analysis.

be visualised at any given point in time from any given fixed position.

In order to display intracardiac structures, the volume-rendered 3D data set of the heart can be opened by choosing a cutting plane and reconstructing the image beyond this plane as if the heart were cut by a surgeon. The display and analysis of size, shape, and motion of cardiac structures may be examined from any desired perspective by manipulation of the cutting plane and rotation of the 3D image until the desired view is obtained. Mitral and tricuspid valves can be viewed from above (electronically simulating atriotomy) or from below (as with ventriculotomy). Similarly, the aortic valve can be examined from above with electronic aortotomy and from the left ventricular (LV) outflow tract. Interatrial and interventricular septa can be visualised *en face* with better understanding of their spatial relationship with adjacent structures.

The display is usually 2D. However, thanks to advances in shading techniques, an impression of anatomic perspective and depth can be created (Fig. 1). For this purpose, a few rendering techniques are available. The simplest one, wire-frame rendering, is mainly used for volume analysis and enables viewing a cage-like image of the analysed cavity. The surface rendering technique results in displaying the surfaces of the analysed object facing the observer as a solid structure (Fig. 4). Wire-frame or surface-rendered reconstructions of selected structures are obtained from manually or electronically derived contours generated from the data set. This approach allows the assessment of shape providing improved visualisation of cardiac chamber volume and function.

Clinical applications

Data regarding clinical applications of RT-3DE are growing. This review will focus on several areas of clinical cardiology for which the use of RT-3DE has been proposed trying to identify the areas in which existing literature supports its clinical use.

Left ventricular shape, size and function (Tables 1 and 2)

Accurate and repeat non-invasive assessment of LV function and size is essential for the clinical cardiologist since LV ejection fraction and end-systolic volumes have been demonstrated to be powerful predictors of long-term survival in patients affected by a wide spectrum of heart diseases. To be suitable for serial comparisons, the optimal method for LV quantification must be fast, inexpensive, reproducible, and non-invasive. These characteristics do not apply to angiography and to semi-invasive techniques like 3D transoesophageal echocardiography. Costs and limited availability reduce the routine use of CMR imaging although it may serve as a 'gold standard'.

M-mode echocardiography and 2DE have been used to assess LV volumes in clinical practice. M-mode assessment of LV volume assumes that the left ventricle may be assimilated to a prolate ellipse and its volume may be calculated by measuring its minor axis dimension and cubing it. There are many flaws in this assumption

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Table 1 Assessment of left ventricular volume and function by real-time three-dimensional (RT-3D) echocardiography and conventional two-dimensional (2D) echocardiography in comparison with MRI

		RT-3D echocardiography			2D echocardiography		
Author	No. patients	*r*	SEE	Mean difference ± SD	*r*	SEE	Mean difference ± SD
Zeidan *et al.* [8]	15						
EDV				−6 ± 11			
ESV				−4 ± 9			
EF				2 ± 5%			
Corsi *et al.* [9]	16						
EDV		0.99	2.1	2.9 ± 12 ml			
ESV		0.99	4.3	2.8 ± 7 ml			
EF		0.98	−1.8	−1 ± 5%			
Jenkins *et al.* [12]	50						
EDV				−4 ± 29			−54 ± 33
ESV				−3 ± 18			−28 ± 28
EF				0 ± 7			−1 ± 13
Kuhl *et al.* [13]	24						
EDV		0.98		−13.6 ± 18.9			
ESV		0.98		−12.8 ± 20.5			
EF		0.98		0.9 ± 4.4			
Caiani *et al.* [14]	14						
EDV		0.97	17 ml	−4.1 ± 29 ml	0.80	39 ml	−23 ± 86 ml
ESV		0.97	16 ml	−3.5 ± 33 ml	0.90	26 ml	−19 ± 60 ml
EF		0.93	6%	−8 ± 14%	0.91	7.7%	+3.7 ± 16%
Shiota *et al.* [15]	28						
EDV		0.97	27 ml	−43 ± 65			
ESV		0.94	29 ml	−37 ± 67			
EF		0.98	4%	1 ± 4%			
Lee *et al.* [16]	25						
EDV		0.99	11 ml				
ESV		0.99	10 ml				
EF		0.92	6%				
Chan *et al.* [17]	30						
EDV		0.90	26.9	−10.4 ± 26.4			
ESV		0.94	16.9	−0.9 ± 18.8			
Sugeng *et al.* [18]	31						
EDV		0.94					
ESV		0.93					
EF		0.93					
Nikitin *et al.* [19]	64						
EDV		0.97		7 ± 28			
ESV		0.98		3 ± 22			
EF		0.94		−1 ± 10			
Jacobs *et al.* [20]	50						
EDV		0.96		−14 ± 17	0.89		−23 ± 29
ESV		0.97		−6.5 ± 16	0.92		−15 ± 24
EF		0.93		−1 ± 6	0.86		1 ± 9

EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; SEE, standard error of the estimate.

and, since it is cubed, any mistake in the minor axis measurement results in a large error in final volume calculation. This method for LV volume calculation is not recommended any more [11]. Measurement of LV volumes with 2DE relies on geometrical assumptions that do not necessarily apply to all patients and test–retest reliability has been found to be limited. In addition, such assumptions make LV volume measurements inaccurate in those patients for whom they are most needed (i.e. patients with previous myocardial infarction or cardiomyopathies with an asymmetric or distorted left ventricle).

Table 2 Current clinical applications of real-time three-dimensional echocardiography (RT-3DE) in assessing ventricular geometry and function

Ventricular parameter	Performance of RT-3DE compared to conventional 2DE
Left ventricular volume	More accurate, reproducible and faster assessment (see also Table 1)
Left ventricular mass	More accurate, reproducible and faster assessment (see also Table 2)
Left ventricular function, wall motion abnormalities (stress studies included)	More sensitive. Allows the exact localisation of infarct and ischaemic areas in patients with CAD
Left ventricular dyssynchrony	Assessment of regional timing and haemodynamics to assist in selecting and monitoring heart failure patients undergoing CRT
Left ventricular perfusion	Needs further validation
Right ventricular volume and function	Needs further validation

2DE, two-dimensional echocardiography; CAD, coronary artery disease; CRT, cardiac resynchronisation therapy.

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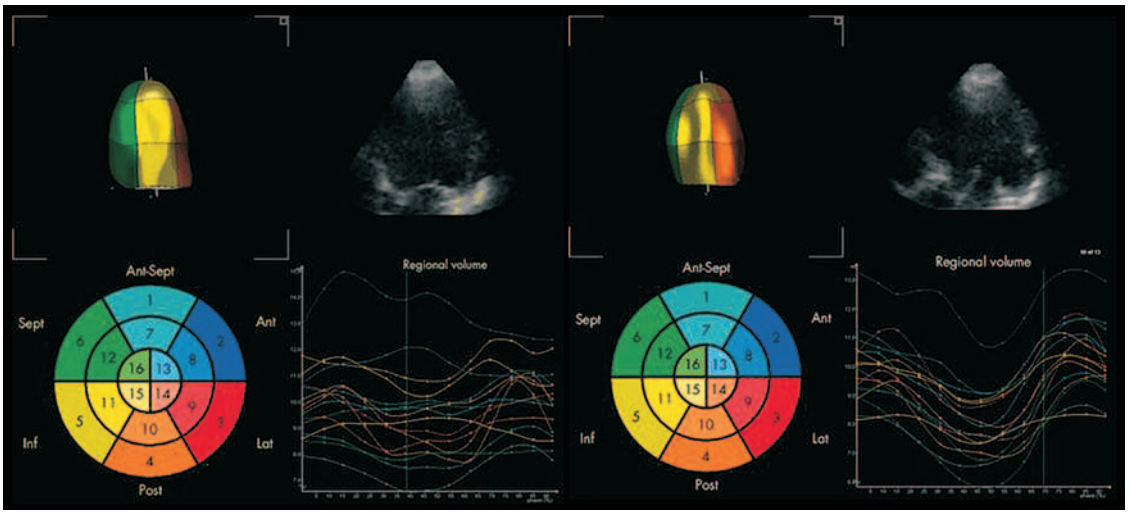
Fig. 5



Example of intraventricular mechanical dyssynchrony assessment using real-time three-dimensional echocardiography before (left panel) and after (right panel) cardiac resynchronisation therapy. A surface-rendered left ventricular cast is obtained using dynamic reconstruction of the ventricle after semi-automated endocardial border analysis. Using internal anatomical landmarks, the left ventricular cast is automatically divided into 17 segments. Segmental time-volume curves are calculated and plotted frame by frame throughout the cardiac cycle to derive the time-to-minimum systolic volume.

RT-3DE overcomes the geometric limitations of 2DE. The major advantage of RT-3DE resides in the possibility of quantifying LV volume without any pre-established assumption of LV geometry. Results of LV volume and ejection fraction calculated with RT-3DE have been validated against CMR (Table 1) [8,9,12–20]. Overall, the various studies showed a close correlation between RT-3DE and CMR-derived LV volumes and increased accuracy and reproducibility over 2DE (Table 1). A more accurate assessment of LV volume results in a more precise calculation of the sphericity index, which has been demonstrated to reflect left ventricular shape: in fact, as the left ventricle becomes more circular, the sphericity index approaches unity. A RT-3DE-derived sphericity index has been shown to be an earlier and more accurate predictor of LV remodelling after acute myocardial infarction than other clinical, electrocardiographic, and echocardiographic variables [21].

Using available software, a LV cast or mathematical model of the left ventricle can be obtained utilising semi-automated endocardial border tracking from the 3D data set. Following identification of a few anatomical landmarks, the cast is automatically segmented into the standard 16 or 17 segments. The volume of each segment (relative to the centre of gravity) and the volume of the ventricular cavity can be calculated frame by frame and plotted against time (Fig. 5).

Left ventricular dyssynchrony and cardiac resynchronisation therapy (Table 2)

Cardiac resynchronisation therapy (CRT) consisting of biventricular pacing has been demonstrated to improve symptoms and quality of life, and to reduce complications and the risk of death [22]. CRT is currently indicated in patients with symptomatic heart failure, poor LV function, refractory to medical treatment, and QRS duration of >120 ms [23]. However, there is growing evidence that the timing and extent of mechanical dyssynchrony are poorly related to QRS duration, and that 27–56% of patients with heart failure and a QRS complex duration of <120 ms may have significant LV mechanical dyssynchrony [24], whereas 30–40% of patients with left bundle branch block do not show intraventricular mechanical dyssynchrony [25]. As a consequence, QRS-based methods have been shown to select 30–40% of patients who subsequently fail to respond to CRT. These observations have resulted in a number of echocardiographic studies evaluating many different parameters to detect mechanical LV dyssynchrony and predict response to CRT more accurately [26].

RT-3DE is emerging as a promising tool to provide new specific indicators of mechanical dyssynchrony beyond QRS duration in selecting and monitoring patients with heart failure undergoing biventricular pacing [27]. At present, two different approaches are available on the market. One is based on a LV cast reconstruction obtained from an apical full-volume acquisition. Using internal anatomic landmarks, the cast is automatically divided into the standard 16 segments described by the American Society of Echocardiography [28]. The centre of gravity of the left ventricle/cast is calculated and the volume of the pyramid represented by each LV segment relative to the centre of gravity is calculated and plotted frame by frame throughout the cardiac cycle (Fig. 5).

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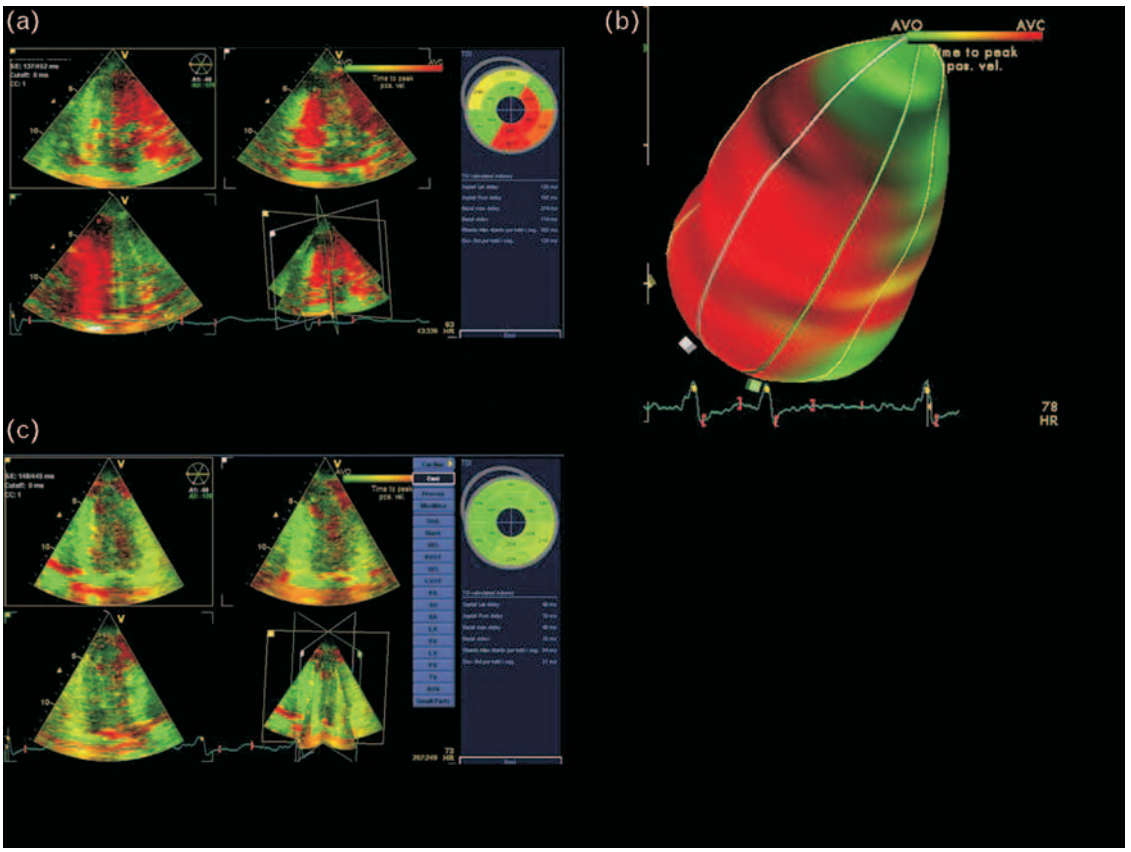
These curves may be analysed off-line to derive the time-to-minimum systolic volume. A systolic dyssynchrony index (SDI) is calculated as the standard deviation of these timings [29]. A higher SDI denotes increasing intraventricular dyssynchrony. Kapetanakis *et al.* [29] assessed a SDI in 89 volunteers and 174 patients using RT-3DE. They demonstrated a significant reduction in the SDI (from 16.9 ± 1.1 to $6.9 \pm 1\%$, $P < 0.0001$) associated with increased LV ejection fraction (from 17 ± 2.2 to $31.6 \pm 2.9\%$, $P < 0.0001$) in patients submitted to cardiac resynchronisation based on SDI criteria. The advantages of SDI to quantify dyssynchrony are the following: it takes all the segments into account, standard deviation of times to peak are reproducible with a variability of $<10\%$ and it is effective in patients with either normal LV systolic function or varying degrees of systolic dysfunction, whilst sensitive to changes associated with differences in LV systolic function. The drawbacks of this approach based on full-volume acquisition are related to a low frame rate (20–25 fps), to the fact that the procedure is time-consuming (it can take 5 min for an experienced operator to perform a dyssynchrony analysis [1]), it is critically dependent on endocardial visualisation and absence of significant cardiac translation and, since full-volume acquisition requires four consecutive and stable cardiac cycles, it cannot be performed in patients with atrial fibrillation or other major arrhythmias. Improvements in 3D technology and use of contrast agents to enhance endocardial border detection will achieve better results.

A completely different approach is marketed by GE Healthcare (Waukesha, Wisconsin, USA) that, despite not being a true RT-3DE, it uses the same probe to apply the well established tissue synchronisation imaging analysis to a triplane data set acquired from the apex in a single cardiac cycle (Fig. 6). This approach has the advantages of assessing 12 LV segments (six basal and six mid-ventricular segments) simultaneously, maintaining an elevated frame rate (95–100 fps), being less dependent on image quality, and being easy and quick to perform [30]. The main drawbacks are related to the

Fig. 6



Multiplane tissue synchronisation imaging. (a) Colourimetric display of left intraventricular delay using the three apical views (four-chamber, two-chamber, and long-axis) obtained simultaneously from a single cardiac beat. On the left, a bull-eye display of the delays of the different left ventricular segments. (b) Surface-rendering technique used to display three-dimensionally the extent and localisation of the intraventricular delay. The most delayed segments are displayed in red. (c) The same patient after cardiac resynchronisation therapy.

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fact that it suffers from the same limitations as 2D tissue synchronisation imaging, and only basal and mid-ventricular segments can be assessed. However, preliminary data show that the method is accurate in identifying responders to CRT, and its predictive power is significantly greater than that of 2D tissue synchronisation imaging and other echocardiographic methods used to assess LV mechanical dyssynchrony [31].

Studies are ongoing to compare the accuracy of new 3D-based measures of dyssynchrony with more conventional methods based upon tissue Doppler.

Left ventricular mass (Tables 2 and 3)

Several studies have shown that increased LV mass is an independent predictor of cardiovascular morbidity and mortality in the general population, particularly in hypertensive patients [32,33]. In addition, echocardiography has extensively been used in studies performing serial LV mass measurements, such as epidemiological and clinical trials testing the effects of antihypertensive drugs. Quantification of LV mass by echocardiography has traditionally been based on M-mode measurement of LV wall thickness, coupled with geometric LV modelling, or geometric model-based calculations from manually traced endocardial and epicardial contours obtained from 2D images. However, M-mode echocardiography has been shown to overestimate LV mass measurements as a result of inadvertent use of oblique cuts [34–36], and the 95% confidence interval width of replicate measurements of LV mass was found to be 59 g, a value that exceeds usual decreases in mass during antihypertensive treatment [37]. Conversely, 2D methods led to underestimation of LV mass measurements as a result of foreshortening of apical views [34,38]. Because of inaccuracies and poor reproducibility of conventional echocardiographic methods for LV mass calculation, it has been proposed that CMR should be used in LV hypertrophy regression studies. Increased procedural costs using CMR will be balanced by significantly less patients required to enrol to obtain significant results.

At present, RT-3DE allows quantitative measurements of LV mass without the need to rely on geometric assumptions. Using the same full-volume 3D data set of LV volume calculation, it is possible to identify epicardial boundaries of the LV wall. The latter is used to calculate an epicardial cast of the left ventricle at end-diastole. The volume of this cast is then subtracted from the epicardial cast and the volume of the LV myocardium is obtained. By multiplying myocardial volume by the specific weight of the myocardium, LV mass is derived. This method has been shown to be accurate and reproducible when compared to CMR (Table 3) [12,39–43].

Right ventricular morphology and function (Table 2)

Right ventricular (RV) volume and function are significant determinants of clinical outcome in various forms of congenital and acquired heart diseases. However, the crescent-like geometry of the right ventricle, the limited number of well defined landmarks and its position in the chest in relation to the usual acoustic windows limit accurate assessment of RV volume and function by conventional 2DE.

RT-3DE may allow complete assessment of RV geometry and ejection fraction in a true 3D volume data set providing new insights into its physiology [44]. Experimental data show that RV volume calculation in animals with chronic volume overload either studied with open chests or with echo boundaries enhanced by saline contrast agents is accurate [45–47], but further investigations are warranted to validate RT-3DE in the evaluation of RV volumes in humans [44]. Newly available software utilising mathematical models adapted for RV shape appears to show great promise for the calculation of RV volumes and ejection fraction.

Heart valve morphology and function(Table 4)

The assessment of morphological and functional changes that occur in stenotic or regurgitant heart valves is of key importance for the comprehensive diagnosis and treatment of valvular heart disease. RT-3DE findings may be crucial to evaluate suitability for valve repair or to provide surgical guidance, since it can provide stereoscopic views of the heart valve apparatus.

Mitral valve disease: qualitative and quantitative assessment

Motion and shape of the mitral valve leaflets and annulus, together with underlying valve apparatus, undergo

Table 3 Left ventricular mass calculation by real-time three-dimensional (RT-3D) echocardiography and conventional two-dimensional (2D) echocardiography in comparison with MRI

		RT-3D echocardiography			2D echocardiography		
Author	No. patients	*r*	SEE	Mean difference ± SD	*r*	SEE	Mean difference ± SD
Jenkins *et al.* [12]	50			0 ± 38			16 ± 57
Mor-Avi *et al.* [39]	19	0.90		−4 ± 17	0.79		−39 ± 29
Caiani *et al.* [40]	19	0.96	10.5 g	−2.1 ± 11.5	0.79	20 g	−34.9 ± 24.8
Qin *et al.* [41]	27	0.92	29 g	−9 ± 33	0.84	45 g	−15 ± 47
Oe *et al.* [42]	20	0.95	20 g	−14.1 ± 29.1	0.70	58 g	−10.7 ± 83.7
Van den Bosch *et al.* [43]	20	0.98	9.8 g	2 ± 20			

SEE, standard error of the estimate.

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Table 4 Current clinical applications of real-time three-dimensional echocardiography (RT-3DE) in assessing valve morphology and function

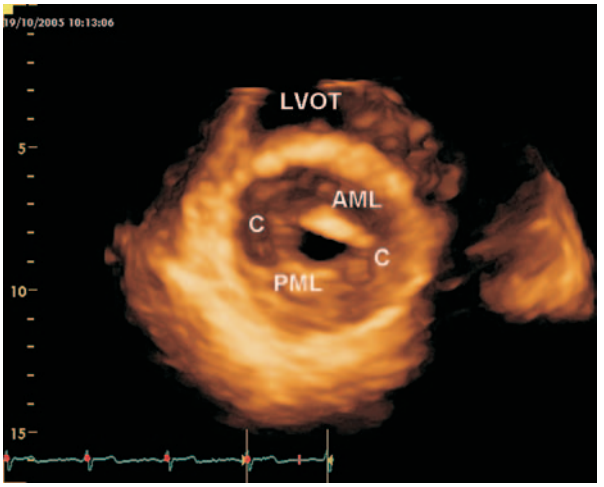
Valve disease	Performance of RT-3DE compared to conventional 2DE
Mitral valve	
Stenosis	Improved morphological assessment
	More accurate orifice area measurement
	Accurate visualisation during invasive procedures
	Follow-up after valvuloplasty
Prolapse	More accurate diagnosis: new diagnostic signs
	Prolapsing scallop definition
	Dynamic visualisation
	Delineation of annulus dilatation
	May replace preoperative transoesophageal echocardiography
Regurgitation	Limited to morphological assessment
	Future validation of RT-3DE colour Doppler
Aortic valve	
Stenosis	Limited to morphological assessment
	Future validation of vena contracta method
Regurgitation	Limited to morphological assessment
	Severity grading by vena contracta method
Tricuspid valve	Limited to morphological assessment

2DE, two-dimensional echocardiography.

deformation and strain during the whole cardiac cycle depending upon valve competence. The unique ability of RT-3DE to depict the atrioventricular valves both from the atrium and ventricle with access to en-face view allows a better anatomical definition of the valve apparatus and of its function in relation to adjacent cardiac structures [48].

In order to identify the best therapeutic strategy in patients with rheumatic mitral valve stenosis, clinical data and accurate measurements of mitral valve area are needed. Doppler-derived methods are heavily influenced by cardiac rhythm, haemodynamic status and angle of incidence; accordingly, methods based on direct planimetry of the anatomic valve orifice should be more accurate. However, direct planimetry of mitral valve area from 2DE images has several limitations: the major one is overestimation of the valve orifice area owing to imaging and measurement in an oblique plane. RT-3DE has overcome this limitation as we may easily identify the correct plane on the 3D acquired data set that represents the plane of valve opening. By cropping the image in that particular plane, we will get the smallest opening area of the leaflets and the actual mitral valve orifice area (Fig. 7). RT-3DE visualisation of the actual mitral stenotic orifice could be accomplished from either the left ventricle or the left atrium. Severity of stenosis, position and degree of leaflet fusion and thickening, as well as fused and thickened chordae tendineae, can be visualised by RT-3DE (Fig. 8). Compared to all other echocardiographic Doppler methods for assessing residual mitral valve orifice area, RT-3DE has the best agreement with invasive methods [49–51]. Zamorano *et al.* [49] compared RT-3DE with 2DE to assess mitral valve area in mitral stenosis using cardiac catheterisation as the reference standard (all 29 patients underwent balloon

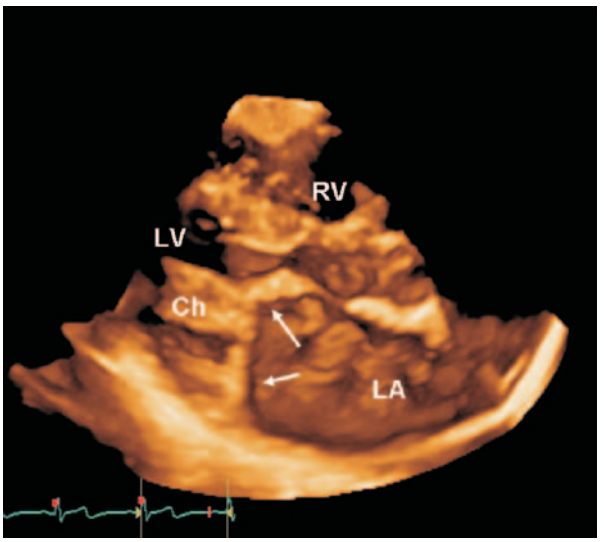
Fig. 7



Mitral valve stenosis. Transverse (short-axis) section viewed from the apex. The residual mitral valve orifice is clearly delineated. The anterior mitral leaflet (AML) is thickened but it slightly opens. The posterior mitral leaflet (PML) is immobile. The two fused commissures (C) are clearly identified. LVOT, left ventricular outflow tract.

mitral valvuloplasty 1 h after echocardiographic assessment). They found that planimetric valve area measured from the left ventricle using RT-3DE showed the least bias ($0.06 \pm 0.19\ cm^2$) and the tightest limits of agreement (-0.44 to 0.32) of all 3D views. The proximal isovelocity

Fig. 8



Mitral valve stenosis. Sagittal (long-axis or longitudinal) section viewed from the left. The thickened mitral leaflets (arrows) and the fused mitral chordae (Ch) are clearly identified. In diastole the anterior mitral leaflet is doming, whereas the posterior mitral leaflet is immobile. Details about the papillary muscle, the left atrium (LA) and left ventricular outflow tract are displayed. LV, left ventricle; RV, right ventricle.

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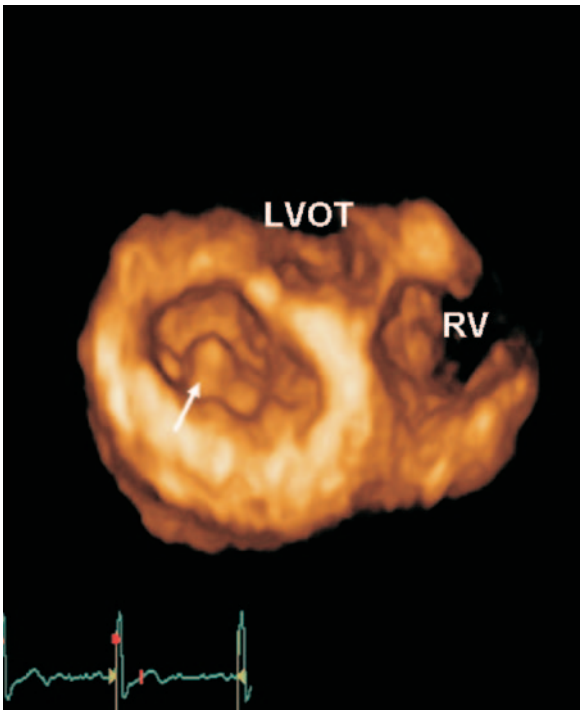
surface area method was the most accurate 2DE technique (bias $0.09 \pm 0.34\,cm^2$), followed by Doppler pressure half-time and planimetry. In another study, Zamorano *et al.* [50] assessed mitral valve area by RT-3DE planimetry and Wilkins score in 80 patients with rheumatic mitral valve stenosis and compared the results with 2DE parameters (220/pressure half-time included) and invasive assessment (Gorlin's equation). Compared with 2DE parameters, RT-3DE mitral valve area assessment had the best correlation with invasive results (intraclass correlation coefficient of 0.90). Similar good results were obtained by Xie *et al.* [51], who demonstrated a correlation between mitral valve area determined by RT-3DE and 2DE pressure half-time ($r = 0.90$).

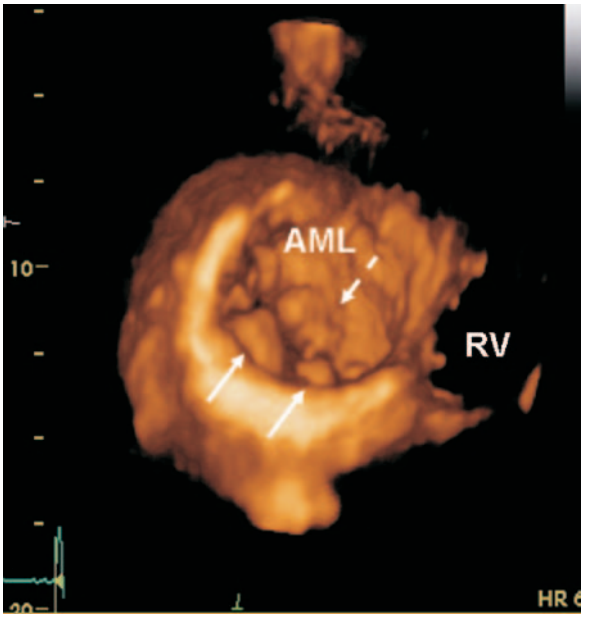
Mitral valve prolapse can be a controversial diagnosis performed by 2DE. Due to the non-linear relationship between the annulus and the leaflets, prolapse of the scallops may be seen in one view but not in another at 2DE. 3DE is able to provide detailed images of the scallops involved and their relationship with cardiac structures. When mitral leaflets are viewed from the atrial side ('surgical view'), a bulging of the prolapsing leaflets into the left atrium occurs during ventricular systole (Figs 9 and 10), whereas viewing from the LV side will disclose a hollow in that leaflet. Thus, RT-3DE

Fig. 9



Mitral valve prolapse. Transverse (short-axis) section viewed from the atrium. The precise anatomy (P2 and partially P3) of the prolapse of the posterior mitral leaflet is displayed in a surgical view. LVOT, left ventricular outflow tract; RV, right ventricle.

Fig. 10



Complex mitral valve prolapse. Transverse (short-axis) section viewed from the atrium showing prolapse of P2 and P3 (arrows) scallops of the posterior mitral leaflet, as well as of the A2 scallop (broken arrow). AML, anterior mitral leaflet; RV, right ventricle.

transthoracic images allow exact identification and sizing of the prolapsing scallops with an accuracy approaching that of transoesophageal echocardiography. In a consecutive series of 112 patients undergoing mitral valve repair, the accuracy of transthoracic and transoesophageal 2DE and 3DE in the localisation of mitral valve prolapse (compared with surgical inspection) has recently been evaluated [52]. Ttransthoracic 3DE (90%) and transoesophageal 2DE (85%) showed similar accuracy, slightly lower than 3D transoesophageal echocardiography (96%) but significantly higher than transthoracic 2DE. 3D techniques were particularly useful in cases with complex mitral valve prolapse (commissular lesions, bileaflet lesions, P1 and P3 prolapse). This information is mandatory to plan appropriate surgery. In addition, with use of this new imaging modality, the surgeon can visualise dynamically *in vivo* what is happening at the level of the mitral valve.

Using RT-3DE, Goktekin *et al.* [53] diagnosed mitral valve prolapse in 77% of patients and demonstrated the applicability of this technique in daily clinical practice to diagnose mitral valve prolapse. Annulus enlargement is often coexisting in case of mitral valve prolapse and can be accurately assessed with RT-3DE [54]. In addition, RT-3DE may contribute to better clarify the mitral valve prolapse pathology by allowing a clear visualisation of chordal anatomy. Finally, the widespread use of RT-3DE is leading to increased clinical applications and

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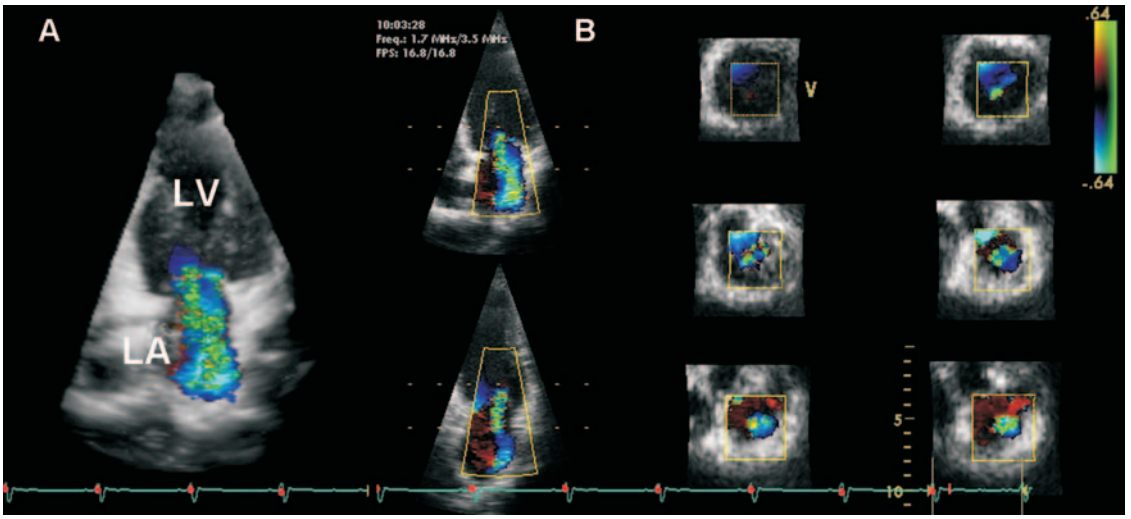
Fig. 11



Three-dimensional colour Doppler flow imaging of mitral regurgitation. (a) Location, phase, direction, length, width, area, course and severity of mitral regurgitation. (b) Six-slice technique used to identify the oblique plane on three-dimensional acquired data set that represents the plane of the true vena contracta of the mitral regurgitant flow. In this patient, the shape of the vena contracta region is quite different from the commonly assumed circular or elliptical shape. LA, left atrium; LV, left ventricle.

experience providing new echocardiographic signs such as 'mitral eversion' or 'pseudo-cleft' [55]. Mitral eversion is defined as an image of negative relief of the mitral leaflets in systole with respect to the annulus observed from the LV side in the apical three-chamber view. A normal mitral valve produces a positive relief with tent shape. The pseudo-cleft is defined as a line along the leaflet from the free border to the annulus appearing as valvular discontinuity or as a clear relief in its surface.

Quantification of mitral valve regurgitation is mandatory to plan treatment options. The advantage of RT-3DE is the visualisation of regurgitant jets in relation to cardiac structures. 3D colour Doppler flow mapping is another diagnostic tool that adds supplementary information about the morphology of regurgitant jets. Colour reconstruction of regurgitant jets allows exact definition of jet origin, its relation to adjacent structures, its geometry and size [56] (Fig. 11). Sitges *et al.* [57] successfully validated colour Doppler RT-3DE in animals to evaluate the flow convergence zone for quantification of mitral valve regurgitation. The initial clinical experience in 22 patients demonstrated a very good correlation ($r = 0.93$) with the reference method. Recently, this method has been validated in humans in comparison to the proximal isovelocity surface area method [58].

Tricuspid valve disease

The assessment of tricuspid valve morphology has been demonstrated to be feasible and very useful [59]. RT-3DE supplements 2DE and transoesophageal echocardiography with detailed images of valve morphology including leaflet size and thickness, annulus, myocardial walls and their anatomic relationships. RT-3DE with its unique capability of obtaining a short-axis plane of the tricuspid valve provides simultaneous visualisation of the three leaflets moving during the cardiac cycle. As a consequence, leaflet coaptation and commissural separation can be displayed (Figs 12 and 13).

Aortic valve disease

RT-3DE is complementary to 2DE or aortography for imaging the aortic valve (Fig. 14). Kasprzak *et al.* [60] demonstrated feasibility and clinical utility of 3DE thanks to an optimal quality of anatomic characteristics. At present, the applicability of RT-3DE to grade severity of aortic valve stenosis has not been specifically described. Shandas *et al.* [61] used an in-vitro model to investigate the validity of 3DE in the measurement of effective flow area (vena contracta area) to grade aortic stenosis severity. They used RT-3DE imaging in an in-vitro stenotic valve model (areas 0.785–1.767 cm^2) under pulsatile flow conditions (60 bpm; 40–80 ml/beat). The agreement to actual vena contracta areas measured with a previously validated laser method was 0.98 (standard error of the estimate 0.158 cm^2). It remains to be established whether these techniques are feasible *in vivo* and provide additional useful information over that already available from conventional spectral Doppler studies.

Assessment of regurgitant flow

3D colour Doppler flow mapping is able to qualitatively visualise the size and shape of valvular and paravalvular

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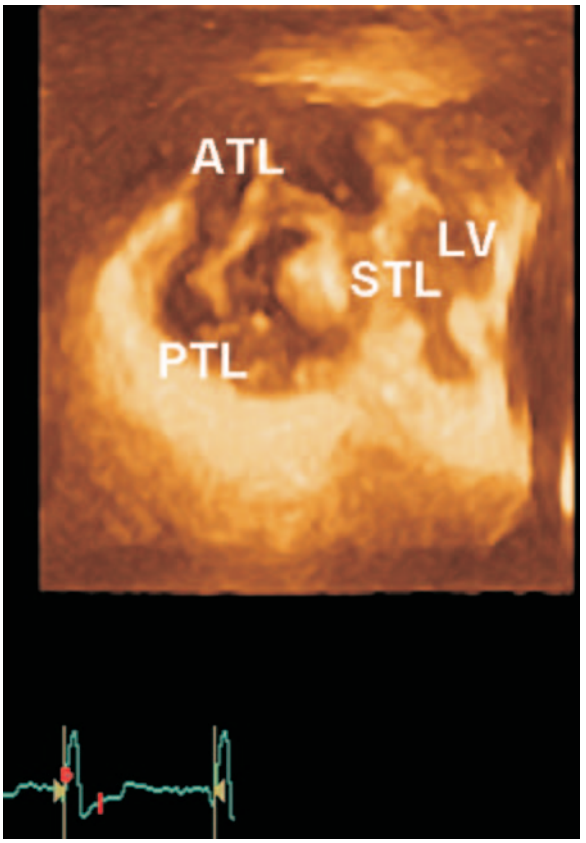
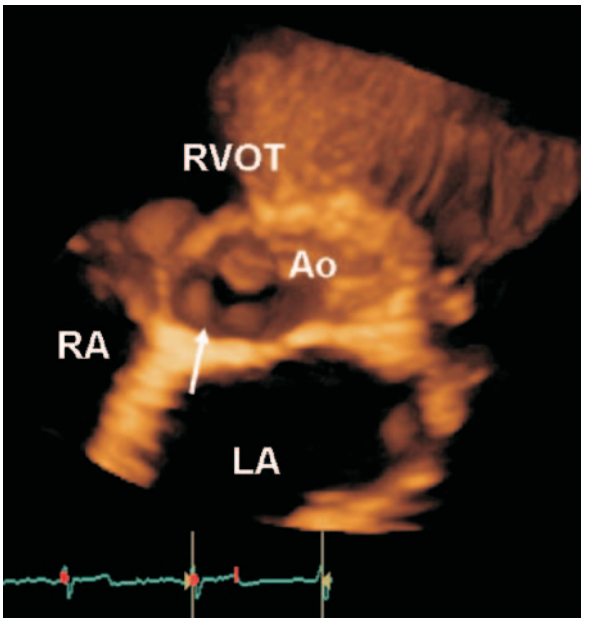
Fig. 12



Tricuspid regurgitation (same patient as in Fig. 10). Transverse (short-axis) section viewed from the ventricle that allows simultaneous visualisation of the three tricuspid valve leaflets, and their loss of coaptation and incomplete systolic closure. The tricuspid annulus is visualised as well. ATL, anterior tricuspid leaflet; LV, left ventricle; PTL, posterior tricuspid leaflet; STL, septal tricuspid leaflet.

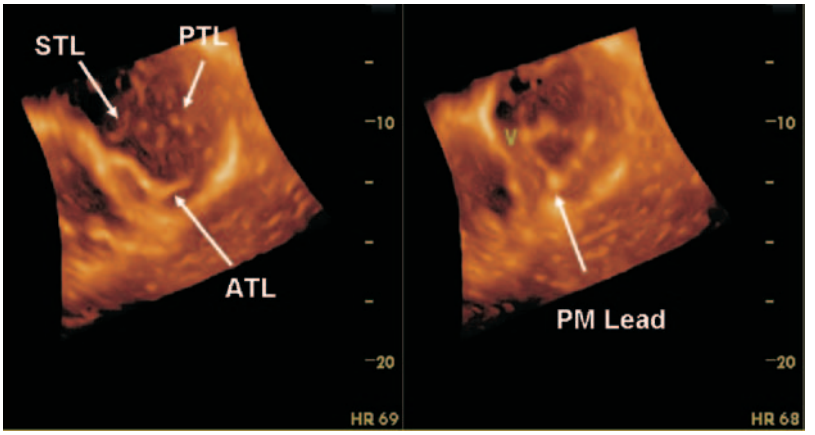
Fig. 14



Rheumatic aortic stenosis. Transverse (short-axis) section viewed from the ventricle allowing simultaneous visualisation of the three aortic valve leaflets, which are thickened. The commissure between the right and the non-coronary cusps is fused and the two leaflets are immobilised. Ao, aorta; LA, left atrium; RA, right atrium; RVOT, right ventricular outflow tract.

regurgitations as well as the underlying pathology, enabling exact definition of jet origin and its relationship with adjacent structures (Fig. 11). Moreover, the colour reconstruction of the regurgitant jets can also be analysed after removing superimposed tissue data, which allows viewing the jets in their entirety, providing information

Fig. 13



Tricuspid regurgitation caused by a pacemaker (PM) lead. Real-time three-dimensional echocardiography (en-face view of the tricuspid valve from the right atrium) showing immobilisation of the anterior valve leaflet by a ventricular PM lead. Left panel, diastolic frame; right panel, systolic frame. ATL, anterior tricuspid leaflet; PTL, posterior tricuspid leaflet; STL, septal tricuspid leaflet.

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Table 5 Current clinical applications of real-time three-dimensional echocardiography (RT-3DE) in assessing congenital heart diseases

Congenital heart disease	Performance of RT-3DE compared to conventional 2DE
Interatrial septal defect	Anatomic definition of location, size, configuration, type, motion and spatial relations. Quantification of defect size Detection of the extent of the rim around the defect useful for referring patients to percutaneous closure Accurate visualisation during percutaneous closure
Interventricular septal defect	Anatomic definition of location, size, configuration, type, motion and spatial relations. Quantification of defect size
Bicuspid aortic valve	Quantification and shape of the aortic orifice

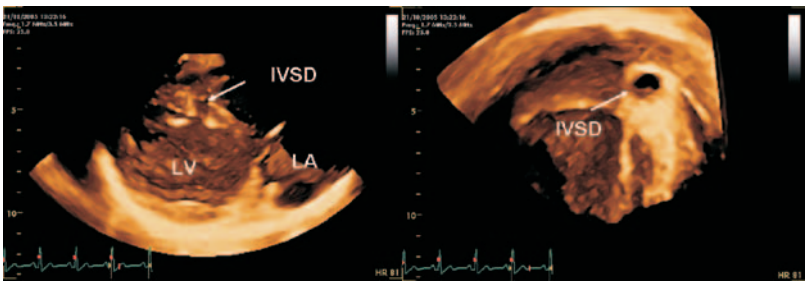
2DE, two-dimensional echocardiography.

about spatial geometry, propagation and size of the jet (Fig. 11a). Furthermore, using the slicing method (Fig. 11b), we can easily identify the oblique plane on the acquired 3D data set that represents the plane of the true vena contracta, and the shape of vena contracta region – which is often significantly different from the commonly assumed circular or elliptical shape.

Congenital heart disease (Table 5)

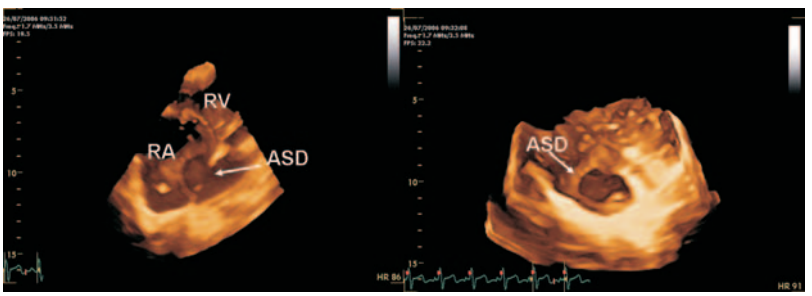
In children and young adults with excellent acoustic window, transthoracic RT-3DE represents the optimal technique to visualise and understand the complex anatomy of congenital heart disease. This technique allows a better appreciation of the position of cardiac structures in relation to each other and it is applicable in various congenital heart diseases including valvulopathy, shunts and aortic pathology [62–64]. In patients with atrial or ventricular septal defects, the location, size, configuration, type and motion of the defect with the neighbouring structures can be displayed from both the left and right side of the septum [65–67] (Figs 15 and 16). RT-3DE produces novel views of congenital septal defects and improves quantification of defect size as demonstrated by a better correlation with surgical findings ($r = 0.92$ versus $r = 0.69$ of 2DE) [68]. Kasliwal *et al.* [56] compared conventional echocardiographic methods with RT-3DE to assess the adequacy of rims for device closure and its relation to surrounding structures. RT-3DE-derived maximal atrial septal defect diameter and area showed the best correlations with invasively determined balloon occlusive diameter ($r = 0.93$; $P = 0.0001$).

Fig. 15



Ventricular septal defect. The arrow points to the interventricular septal defect (IVSD). Left panel, oblique sagittal (long-axis) section from the left. Right panel, an en-face view of the left surface of the interventricular septum enables better understanding of the shape and size of the lesion, and its dynamic changes during the cardiac cycle. LA, left atrium; LV, left ventricle.

Fig. 16



Atrial septal defect (ASD). The arrow points to the ASD. Left panel, oblique coronal (frontal) section viewed from the right atrium. Right panel, an en-face view of the right surface of the interatrial septum enables better understanding of the shape and size of the defect, and its dynamic changes during the cardiac cycle. RA, right atrium; RV, right ventricle.

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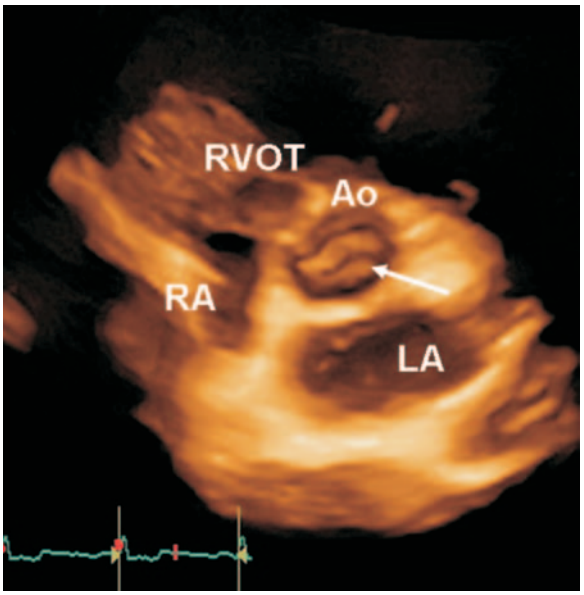
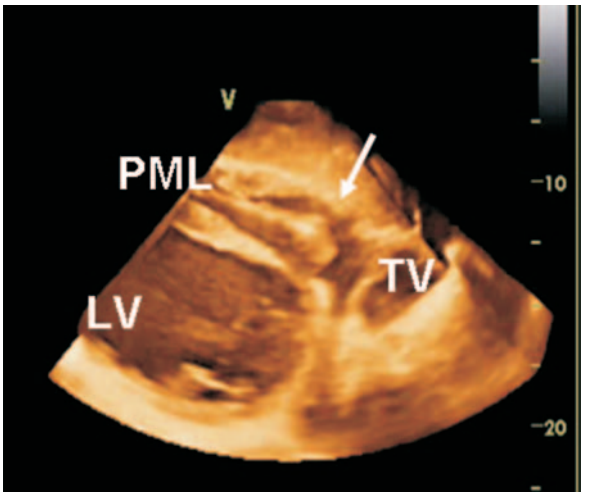
Fig. 17



Bicuspid aortic valve. Transverse (short-axis) section viewed from the left ventricle clearly showing a two-cusp aortic valve (Ao) with a diastolic prolapse of the posterior cusp. LA, left atrium; RA, right atrium, RVOT, right ventricular outflow tract.

Fig. 18



Infective endocarditis on a permanent pacemaker lead (PML). The arrow points to the vegetation attached to the ventricular PML. LV, left ventricle; TV, tricuspid valve.

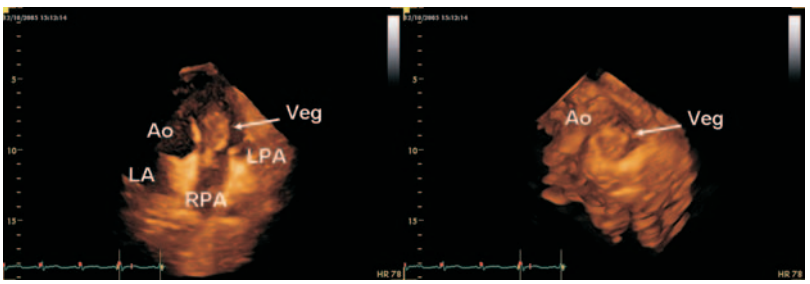
In patients who have undergone surgical (suture or patch) or percutaneous (occluder device) closure of ventricular or atrial septal defects, the entire shapes, dimensions, and sites of the patches or occluders, and their spatial relations, could be clearly viewed with RT-3DE. Sinha *et al.* [69] reported four cases of atrial septal defect or patent foramen ovale using RT-3DE and 3D colour Doppler to assess the efficacy of the Amplatzer transcatheter occluder device and postoperative complications, such as presence and magnitude of residual shunt and device malposition. Kasliwal *et al.* [56] also demonstrated the feasibility of RT-3DE in patients with different congenital heart diseases like ventricular septal defects, patent ductus arteriosus, sinus of Valsalva aneurysm, Ebstein's anomaly, and supramitral rings. RT-3DE gave additional information over standard 2DE by providing spatial orientation of the anatomical structures.

RT-3DE has also been shown to reliably define anatomic details of bicuspid aortic valves (Fig. 17).

Infective endocarditis

RT-3DE can show the 3D configuration and attachment of vegetations, mobility of vegetations with blood flow, and potential complications such as valve prolapse and perforation (Figs 18 and 19). In addition, the capacity of acquiring detailed en-face images of the valve results in the precise localisation of vegetations, including size, morphology, attachment points and their relationship with anatomical structures [70,71]. Therefore, the

Fig. 19



Infective endocarditis on a pulmonary valve. Left panel, transverse (short-axis) section allowing visualisation of the pulmonary valve, pulmonary artery trunk, bifurcation and proximal right (RPA) and left (LPA) pulmonary arteries. Right panel, oblique section showing a short-axis view of the pulmonary valve. Vegetation (Veg) is visible as a large mass attached to the medial pulmonary valve cusp, which prolapsed into the main and right pulmonary arteries, and caused almost complete obliteration of the RPA lumen during systole. Ao, aorta; LA, left atrium.

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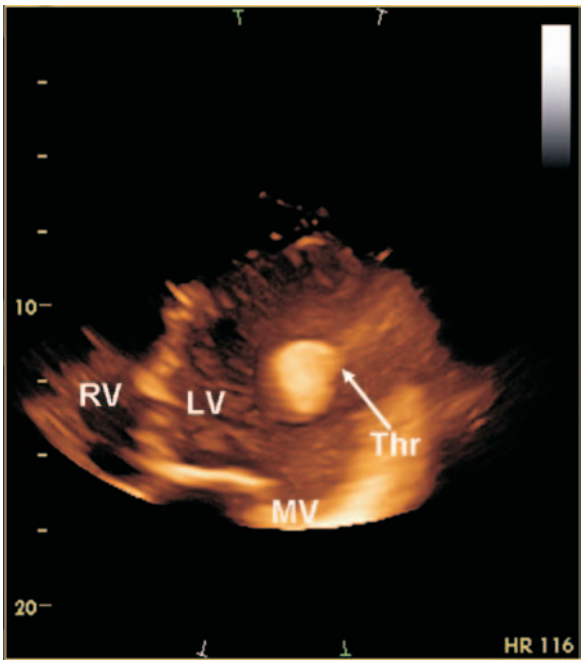
Fig. 20



Intraventricular thrombus (Thr). Oblique section showing a large intraventricular Thr attached to the lateral wall of the left ventricle (LV). The point of attachment of the mass (arrow) can be localised. RV, right ventricle; MV, mitral valve.

information provided by RT-3DE is both accurate and direct since it is similar to what the surgeon may find in the operating room [70].

Cardiac masses

In daily clinical practice, 2DE and transoesophageal echocardiography are mandatory for preoperative evaluation of cardiac masses. RT-3DE is emerging as a reliable diagnostic tool thanks to its excellent delineation of cardiac masses and structures, and its capacity of visualising intracardiac masses in the same way as the surgeon would see them [72,73] (Fig. 20). Besides assessment of morphology, size and location, RT-3DE allows 'electronic tumourectomy' and sequential sectioning of the mass to be performed so as to better define the internal structure [56].

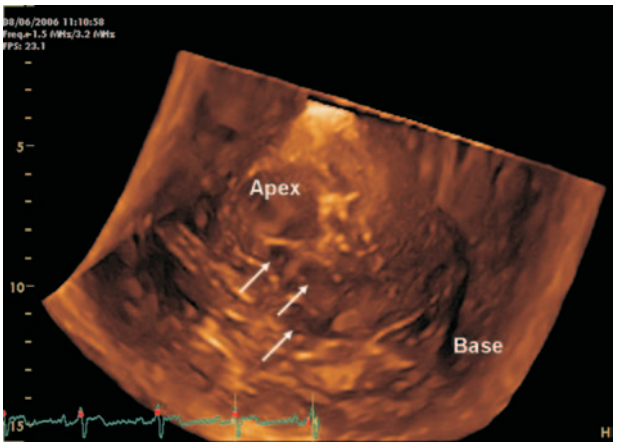
Cardiomyopathy: ventricular non-compaction

The clinical value of RT-3DE in diagnosing LV non-compaction has previously been described [74,75]. The ability of this technique to quantify the depth of penetration of intertrabecular recesses and to assess the segmental extent of involvement helps make a more definitive and precise diagnosis of ventricular non-compaction (Fig. 21).

Current limitations

Second-generation RT-3DE represents a technological solution to many drawbacks of 3D off-line reconstruction

Fig. 21



Non-compaction of the ventricular myocardium. Oblique section viewed from the left ventricular apex (that has been cropped) showing the posterolateral myocardial wall from inside the left ventricular wall. The location and extent of some large trabeculations are shown (arrows).

technique [76]. Despite its documented clinical value, however, it is not devoid of limitations.

RT-3DE is currently available only for transthoracic examination and 3D image quality is highly dependent on the quality of acoustic window. Furthermore, apart from the latest paediatric 3D transducers, transducers for adults are so large that, in presence of narrow intercostal spaces, the acoustic window restricts the penetration of the ultrasound beam.

Since full-volume and 3D colour mode images are not true real-time images, but are the result of fusion of several (from 4 to 7) small real-time data sets acquired during suspended respiration and fused, using electrocardiographic gating, respiration and movement of the patient may affect the formation of images and artefacts may occur. In addition, these acquisitions are not feasible in patients with atrial fibrillation or other major cardiac arrhythmias. However, the last generation of 3D systems allows a temporally determined acquisition of the data set without relying on the electrocardiogram, thus overcoming the limitation deriving from the presence of significant arrhythmias.

RT-3DE is still limited by a relatively low temporal resolution (20–25 fps), which in certain clinical situations might be a practical limitation (i.e. stress echocardiography using dobutamine or exercise, assessment of intraventricular synchrony). Similarly, spatial resolution is usually inferior to that provided by high-end 2D systems. Again, the most recently released 3D systems can provide frame rates up to 35 fps, higher spatial resolution and a full-volume data set of 100×100. In addition, for the 3D colour Doppler flow imaging currently used, the velocity

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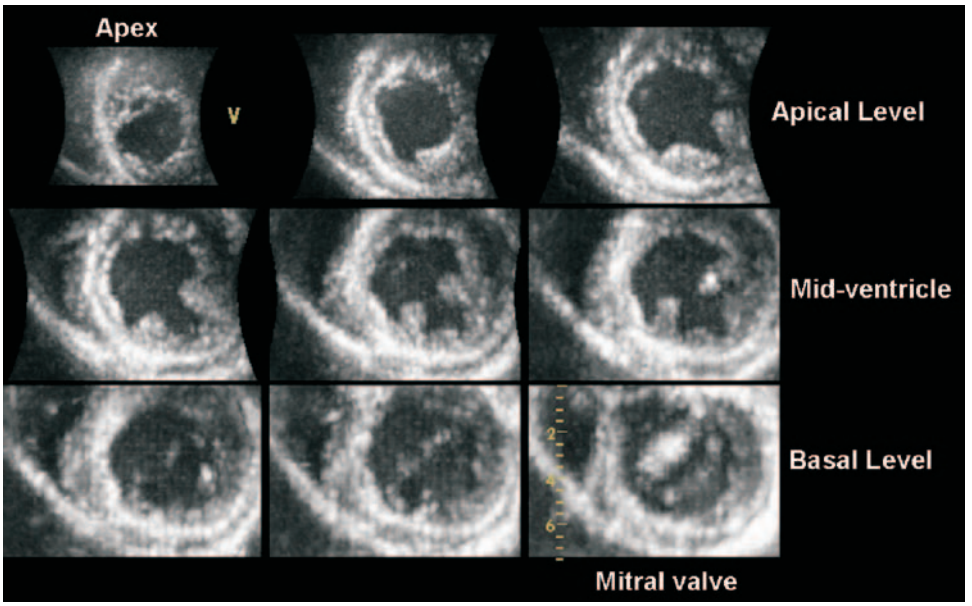
Fig. 22



Nine transversal equidistant slices of the left ventricle (from base to apex) obtained slicing the full-volume data set of the heart.

represents project velocity, which is different from velocity in conventional 2D colour Doppler.

On-line measurement of 3D distances and volumes has not yet been implemented. Current measurements have to be made off-line using dedicated software.

Finally, the high costs of transducers and dedicated software as well as the lack of standardisation of visualisation and recording of 3D images may be all limiting factors for a number of laboratories. The publication of a proposal for an examining protocol for RT-3DE will hopefully standardise routine clinical examinations [77]. Nevertheless, it is unlikely that these limitations will outweigh the diagnostic potential of this novel imaging technique.

Future perspectives and applications

RT-3DE as an integrated part of high-end echocardiographic equipment will become a routine modality in the echocardiographic laboratories. Advances in both micro-industrial design and computer technology will further reduce the size of matrix-array transducers, improve spatial and temporal resolution, reduce the time needed for quantitative analysis and change the display of 3D data of the heart.

Progress in miniaturisation technology of matrix-array transducers will enable development of RT-3D trans-oesophageal transducers. This will allow high-quality images to be obtained from patients with obesity, emphysema, and narrow intercostal spaces that hinder the transthoracic approach.

Stress echocardiography is employed to detect inducible myocardial ischaemia by identifying new regional wall motion abnormalities when comparing wall motion in pre-stress and post-stress ultrasound images. Complete LV acquisition by RT-3DE has the unique possibility of visualising all LV segments during one breath hold [78–81] (Fig. 22). Sensitivity and specificity of this technique will improve by increasing spatial and temporal resolution and with use of contrast agents.

Virtual dynamic systems, known as virtual reality (i.e. dynamic holographic imaging), can assist with the interpretation of 3D data of the heart in space and makes it possible to 'dive' into the actual 3D anatomy of the heart. Virtual reality models will assist in the interpretation of 3D data of the heart and will be useful as a reference environment for diagnosis and assist in planning the surgical or catheter-interventional procedures [82–84]. Furthermore, use of a communication network may allow different specialists (not necessarily cardiologists) to take part in training and even decision-making in the future.

Conclusions

RT-3DE is a novel technique based on the semi-instantaneous acquisition of volumetric images. This permits a comprehensive evaluation of cardiac anatomy and function in a single acquisition and expands the

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possibility of non-invasive cardiology. It allows an echocardiographic assessment of the heart that is less operator-dependent and, therefore, more reproducible. In addition, it provides the possibility of quantifying global and regional LV function and mass without pre-established assumptions regarding cardiac chamber geometry.

As any novel technique, however, it has several limitations. Further developments and improvements for widespread routine applications include faster acquisition, processing and reconstruction, improved image quality, and easier approaches to quantitative analysis. The perspective is that RT-3DE might become the standard echocardiographic examination procedure.

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