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Measurement of cardiac output and studies of velocity profiles in aortic and mitral flow using two- and three-dimensional colour flow imaging.

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List of papers:

I. A new method describing cross-sectional blood flow velocity profiles in the left ventricular outflow tract of patients with atrial fibrillation with the use of high- frame rate 2-dimensional color flow imaging. Haugen BO, Bjærum S, Samstad SO, Skjærpe T, Torp H. J Am Soc Echocardiogr.2001;14:50-56.

II. Volumetric Blood Flow Measurement Using dynamic Three-dimensional Ultrasound Color Flow Imaging. Berg S, Torp H, Haugen BO, Samstad S. J Am Soc Echocardiogr 2000; 13: 393-402.

III. Measurement of volumetric mitral and aortic blood flow based on a new freehand three-dimensional colour flow imaging method. An in vivo validation. Haugen BO, Berg S, Brecke KM, Samstad SO, Skjærpe T, Slørdahl SA, Torp H. Eur J Echocardiogr. 2000. 1; 204-212.

IV. Velocity profiles in mitral blood flow based on three-dimensional freehand colour flow imaging acquired at high frame rate. Haugen BO, Berg S, Brecke KM, Samstad SO, Skjærpe T, Slørdahl SA, Torp H. Eur J Echocardiogr. 20001;252-256.

V. Blood flow velocity profiles in the aortic annulus: A three-dimensional freehand color flow imaging study. Haugen BO, Berg S, Brecke KM, Samstad SO, Torp H, Slørdahl SA, Skjærpe T. 2000. Submitted for publication.

Introduction:

Ultrasound has been widely used as a clinical non-invasive tool in calculations of stroke volumes and thus cardiac output (CO) [1], regurgitant fractions [2], shunts [3] and for estimations of the flow area in aortic stenosis using the equation of continuity [4].

Doppler echocardiography has been applied to volumetric flow measurements at the tricuspid valve orifice [5], pulmonary artery [6], mitral annulus [7], mitral valve orifice [8], left ventricular outflow tract (LVOT) [1], aortic valve orifice and ascending aorta [9-11].

In all methods in which a single Doppler sample volume has been used to measure the velocity time integral (VTI), one basic assumption was made: The blood flow velocity profile was flat [1]. This meant that any random sample in the flow area was representative of the entire cross sectional flow area. A number of studies have shown that this was not the case. A skewed velocity profile has been described in the aortic annulus and distal LVOT [12-17], the aortic root and ascendens [18-21], the mitral annulus and at the tip of the mitral leaflets [22-27,28] and in the pulmonary artery [29].

In aortic flow, a commonly used volumetric method has been to combine measurements of the area of the aortic annulus with pulsed wave (PW) Doppler recordings of the velocity time integral in the distal LVOT [1](2D PW Doppler method). In echocardiographic examinations of patients suffering from atrial fibrillation, VTI from 5-10 heart cycles were averaged to compensate for variations in stroke volumes [1]. If the profile is skewed, and the skew changes from stroke to stroke in an unpredictable manner, another uncertainty and

limitation is introduced in the pulsed wave Doppler technique. A skew in the velocity profile in these patients as well as beat-to-beat changes in the velocity profile has not been described previously.

Variation in flow area was another difficulty. The 2D PW Doppler method assumed a specific geometry shape that did not vary during the heart cycle [1, 9]. The shape and motion of the mitral valves during the biphasic flow in diastole represented a particular challenge.

The angle dependence of the Doppler beam [30] hampered the method. Alignment between the Doppler beam and flow in the LVOT may be difficult with underestimation of flow velocities as a possible consequence. One approach to compensate for this was to detect the highest velocities and use these in the measurement of VTI.

Blood flow measured by Doppler gives velocities relative to the ultrasonic probe. In order to get correct velocity values, representing the flow through the valve, the movement of the valve plane should be taken into account [31-33]. The missing volume, due to the aortic annulus movement during systole, was not added to the conventional 2D PW Doppler method. Similarly, the relative velocity of mitral blood flow is the sum of the blood flow velocity and the rate of mitral annulus recoil toward the atrium. As the mitral annulus moves in the opposite direction of inflow the inflow will be underestimated using a fixed measure surface.

Several methods have been proposed to deal with some of these issues. The Automated Cardiac Output Method (ACM) introduced a method less sensitive to the variations in the blood flow velocity profile and the angle dependency of the

Doppler beam [34, 35]. Volumetric flow can be measured independently of the angle between the ultrasound beam and blood flow by integration of velocity vectors perpendicular to a surface [36, 37]. This principle has been applied to one- [34], two- [36] and multiplane methods [32, 38]. However, the multiplane method were limited by long acquisition time and the fact that the rotational probe must be kept stable during the recording to avoid geometrical artefacts in the reconstruction of 3D volumes.

Both Doppler colour flow and MRI studies have been conducted to illuminate the uncertainty regarding the blood flow velocity distribution in aortic and mitral flow. However, recordings from only one or two cross sectional planes were limitations to the ultrasound colour flow studies [12, 14, 23]. Magnetic Resonance Imaging (MRI) techniques have also been described, but these techniques were limited by costs, immobile equipment, long acquisition time, limited temporal resolution, fixed measure volumes as well as contraindications to the procedure [17, 28, 39].

Due to the methodological difficulties mentioned above, the following projects were initiated:

Aims of the study:

- To develop a new 2D colour flow method to evaluate the instantaneous cross sectional velocity profile variability in the left ventricular outlet tract of patients with atrial fibrillation. This was not possible in 3D, as data from a number of heart cycles of regular R-R interval lengths were required for the construction of 3D volumes.

- To develop a 3D ultrasound method with short acquisition time, improved temporal resolution, no angle dependency of the Doppler beam, no assumptions of the velocity profile or flow area and where flow velocities were corrected for the movement of the valve plane.
- To validate this freehand 3D color flow method in calculations of CO in mitral and aortic flow.
- To study the blood flow velocity distributions in mitral and aortic blood flow by using the new 3D ultrasound method. By using a single sample volume in Doppler measurements of the VTI, potential errors may be introduced in calculations of stroke volumes. We wanted to assess this error.

Subjects and Methods:

Subjects:

All subjects gave informed consent to participate in the studies. The institutional committee on human research approved the studies that were in accordance with the Helsinki declaration.

In paper I, nine patients with fibrillation and no significant heart valve disease or other structural heart disease were consecutively included before elective DC cardioversion at the department of cardiology, University hospital of Trondheim, Norway. 7 men and 2 women of mean age 62 (range 41 to 75) were included.

In paper II, one male subject was used to exemplify the potential of the 3D method.

In paper III-V, the same subjects were studied. Recordings from 24 subjects, 16 men and 8 women with no history of cardiac disease were acquired prior to evaluation of the 3D reconstruction. All were in sinus rhythm. Median age was 26,5 (range19-48). In paper III, 18 subjects were included in method A and C. In method B, 17 subjects were included. Calculations of CO in 19 subjects were included in the comparison between 3D mitral flow vs. flow in the LVOT measured by 2DPW Doppler. In the comparison between 3D mitral vs. 3D aortic flow 15 subjects were included. In paper IV 19 subjects where included, and in paper V 17 subjects were included

Equipment:

A digital ultrasonographic scanner (System Five, GE Vingmed Ultrasound, Horten, Norway) with a 2.5 MHz phased array transducer was used for all echocardiographic measurements. Recordings of tissue images were obtained by second harmonic imaging mode with a transducer transmit frequency of 1.7 MHz. For colour flow imaging the centre frequency of the transmitted pulse was 2.5 MHz. In paper II-V, a magnetic locating device (Flock of Birds, Ascension Technology Corporation, Burlington, VT, USA) continuously recorded the spatial position and orientation of the transducer during the recording. Digital raw ultrasound data were transferred to an external standard personal computer, and scan conversion and further processing were performed with a prototype version of the EchoPAC-3D software (GE Vingmed Ultrasound, Horten, Norway) and MATLAB (The Mathworks inc. USA). In paper I, all post processing were done in MATLAB.

Data acquisition:

In paper I, a prototype data acquisition technique was used that gave increased frame rate (≥90 frames/s). Three subsequent heartbeats with different R-R interval lengths in the Electrocardiogram (ECG) were recorded in apical five-chamber view and apical long axis view. The sector angle was set to a minimum and the region of interest (ROI) minimised, but large enough to cover the flow region, to obtain as high frame rates as possible. In paper II-V, the transducer was tilted in a fanlike manner from the posterior wall toward the anterior or vice versa during 10-20 cardiac cycles to cover the entire flow area. For each frame, the sensor position co-ordinates, the digital ultrasound data and the ECG signal were stored in the digital replay memory.

Data processing.

In paper I, a line was drawn across the distal LVOT. Angle corrected blood flow velocities perpendicular to this line were plotted as a function of time and visualised as colour M mode. Aliased velocities were baseline shifted. The instantaneous cross sectional velocity profile was reconstructed by plotting blood flow velocities against time and position along the diameter of LVOT. Further, any skew was described as the ratio of the maximum velocity to the mean at peak flow. The ratio of the maximum VTI to the mean VTI was calculated. Further, the position of the maximum velocity and the maximum VTI along the cross sectional line was noted. Finally we calculated the part of the line crossing the LVOT in which values between maximum VTI and maximum

VTI -20% were detected. Two subsequent heart cycles of different R-R interval lengths were compared.

In paper II-V, frames with the same temporal delays relative to the R-wave in the ECG signal were used to reconstruct 3D volumes throughout the cardiac cycle (Figure 1). Blood flow velocity vectors perpendicular to a surface, and thus aligned with the ultrasound beam, were extracted from the 3D data and reconstructed in 2D slices. In paper III (method A and B), the level was fixed at a constant depth throughout systole, i.e. at the level of the septal insertion of the aortic valve identified in start systole in method A and 0.5 cm proximal to the annulus in method B. In paper II, III (method C) and V the surface tracked the annulus throughout the systole. In paper III-IV the surface was positioned at the mid-level of the medial part of the mitral valve, i.e. approximately 1 cm proximal to the mitral ring, and tracked the mitral valve plane throughout diastole. The E and A wave in mitral blood flow were treated separately. The velocity of the movement of the AV plane was calculated and added to the blood flow velocities. In this way we compensated for the possible underestimation of blood flow velocities due to the movement of the AV valve pane.

In the 2D slice, a region of interest was manually defined to exclude velocities from nearby flow or structures. The tissue and Doppler signals were filtered, and aliased blood flow velocities baseline shifted according to Berg et al [33]. The velocity vectors in the ROI were integrated over time giving the total blood flow in paper II and III. By spatial integration of the flow velocity component over a surface perpendicular to the ultrasound beam, angle independence of the Doppler beam was achieved. A larger flow area compensated the

underestimation of the Doppler derived blood flow velocities. In paper IV and V the ratio maximum VTI to the mean VTI was calculated. Similarly, the ratio of the maximum to the mean velocity at peak flow was compared. Further the location of maximum velocity and mean velocities in each slice were visualised. In paper V, the location of the maximum and mean VTI was visualised. The location of the mean VTI was visualised by averaging VTIs throughout the systole. This image was superposed on an image of the surrounding tissue. The tissue slices were averaged throughout the systole to constitute the anatomical frame around flow.

Statistical analysis:

In paper I, two subsequent heart cycles of different R-R interval lengths were compared using two tailed paired t-test.

In paper III, all results were evaluated according to Bland and Altman i.e. one compared the difference between two methods with the average of the same two [40]. Paired t-test was used to compare difference in heart rate and the mean difference between the 3D methods and the 2D PW Doppler method. Statistical data were calculated in SPSS for Windows Version 8.0.0-10.05.

Results:

Paper I:

The data indicated a non-uniform velocity distribution with the highest velocities and VTI located in the centre of the LVOT and toward the intraventricular

septum. The maximum VTI overestimated the mean VTI by approximately 40% in both planes. At peak flow, the maximum velocity overestimated the mean velocity by approximately 50 % in the apical long axis view and approximately 60 % in the five-chamber view .The line from the septum to the middle part of LVOT covered VTI values from maximum to 20% below. There were no significant differences at the 5 % level between the two heartbeats in any of the calculated variables except from difference in R-R interval lengths.

Paper II:

The data were acquired rapidly during 10-20 heartbeats using a freehand system. The data were recorded at high frame rate, up to 104 frames/s (temporal resolution less than 10 ms). The jitter artefact was ± 4.8 ms. 3D data were sampled from a fixed surface at the same level as the 2D PW Doppler method and the CO was calculated: 4.5 l/min vs. 4.0 l/min. By using a moving surface the estimate was 5.5 l/min.

Paper III:

Aortic flow:

The range of agreement between method A and the 2D PW Doppler method was 0,2 ± 1,7 l/min (mean ± 2SD). Between method B and the 2D PW Doppler method it was 0,3 ± 1,5 l/min (mean ± 2SD) and between method C and the 2D PW Doppler method 0,7 ± 1,7 l/min (mean ± 2SD).

According to analysis in the 10 first recordings in method C the missing volume corresponded to 9 % of CO (95% CI (0,4 to 0,5) l/min)).

Intra-observer: The coefficient of repeatability was 0,6 l/min. One clear outlier was excluded. Inter-observer: The coefficient of repeatability was 0,9 l/min.

Mitral flow:

The range of agreement between 3D mitral and 3D aortic flow was 0.04 ± 1.32 l/min (mean of differences ± 2 SD), and between 3D mitral blood flow and the 2D PW Doppler method in the LVOT it was 0.88 ± 1.64 l/min (mean of differences ± 2 SD).

The volume due to movement of the AV valve plane during diastole constituted 11% of the total volume. There was a significant difference in mean CO between 3D mitral flow and flow in the LVOT obtained by the 2D PW Doppler method. P=0,001 and 95%CI (0,4 to 1,24). By excluding the volume represented by the movement of the AV valve plane, the mean difference was non-significant. P=0,17 and 95%CI (-0,13 to 0,65).

Intra-observer: The coefficient of variability was 0,4 l/min, with no bias. One clear outlier was omitted.

Inter-observer: The coefficient of variability was 0,7 l/min. One clear outlier was omitted (the same as in the intra-observer study).

Paper IV:

The velocity profiles were variably skewed. The mean ratio of the VTI to the mean VTI was 1,3 (range 1,1 to 1,6). By assuming that the mean VTI is the correct estimate in volumetric calculations using Doppler, the use of the

maximum VTI would lead to errors ranging from 10 to 60 % with an average of 30 %. At the time of peak flow the mean ratio of the maximum to the mean velocity was 1,5 (range 1,2 to 2,6).

Paper V:

The mean ratio of the maximum systolic VTI to the mean VTI was 1,4 (range 1,2 to 1,5). At the time of systolic peak flow the mean ratio of the maximum velocity to the mean velocity was 1,5 (range 1,1 to 2,0).

The mean VTI was located along the brim of the annulus while the maximum VTI was most often located toward the septum. The location of the maximum velocity and the mean velocity at the same time was followed in each 2D slice throughout systole. Most often the maximum velocity at peak flow and the maximum VTI were located toward the septum.

Discussion:

We have described a new Doppler method to evaluate the instantaneous cross sectional velocity profile variability in the left ventricular outlet tract of patients with atrial fibrillation. This is the first time cross sectional velocity profiles in the LVOT of patients with atrial fibrillation has been described. Previous studies were based on interpolation of colour flow velocity samples from several heartbeats with regular R-R interval lengths to construct the instantaneous cross sectional velocity profile. Due to the high frame rates in our study (range 90 to 115) frames/s it was possible to display the cross sectional velocity profile during recording of one heart cycle. According to our results, by using a single

sample volume to measure the maximum VTI, a considerable overestimation of stroke volumes may be the result. This confirmed previous studies conducted in healthy subjects with sinus rhythm [14]. We found no significant difference in the calculated measures in two consecutive heartbeats of different R-R interval lengths. Thus, according to our results, measurements from heartbeats of different R-R interval lengths can be averaged without moving the pulsed wave sample volume along the diameter of the LVOT.

Further, the blood flow velocity distribution in the mitral flow channel (paper IV) and aortic annulus (paper V) was described using a new dynamic 3D method. Our results confirm earlier 2D ultrasound studies [12-14,23] and MRI studies [17, 28] that described the velocity profile as skewed. According to our results, the use of a single sample volume in Doppler measurements of the maximum VTI, errors ranging from 20 to 50 % may be introduced in calculations of stroke volumes in the aortic annulus and 10 to 60 % in the mitral flow channel. Although, there were differences in the upper range of the results, our results basically confirmed previous ultrasound studies. However, our 3D method had several advantages compared to previous 2D and multiplane ultrasound studies. In general, 3D data sets have been generated by gated acquisition of multiple 2D-scan planes. The 2D data were recorded during rotation, translation or tilting of the transducer [41] (Figure 3a-c). This was done by using motorised movements or by freehand techniques. The 2D scan planes were reorganised into 3D volumes according to their relative position in the ECG signal (Figure 1). To ensure the accuracy in 3D reconstruction in freehand systems, different locating devices have been proposed, mechanical, acoustical, optical or

electromagnetic systems. Real-time 3D has also been described [42]. By using a 2D phased array matrix it was possible to interrogate a pyramidal scan volume during one heart cycle. However limited frame rate severely restricted the quality of colour flow imaging. In paper II-V, a 3D freehand technique was used. The probe was tilted in order to acquire data from several 2D-scan planes for reconstruction into 3D volumes. A magnetic position system continuously recorded the spatial position and orientation of the probe. This enabled manual correction to optimise acoustic access during the recording. The acquisition of data was fast. The transducer was tilted transthoracically during 10-20 heart cycles. Raw digital data were obtained at high frame rate and analysed off-line in all our studies (I-V). By transferring and analysing raw digital ultrasound data, exact Doppler measurements were accessible as opposed to videobased systems and we were not limited by the video frame rate (PAL standard, 25 frames/second). Several attempts have been made to visualise blood flow since the introduction of 3D ultrasound imaging [43-45]. In most studies, the video signals were used, which made quantitative analyses difficult, as re-digitisation of the colour encoding may not reflect the original blood flow velocities. High frame rates were desirable due to several reasons: Better temporal resolution in recordings of rapidly moving structures and blood flow and less jitter artefacts in the reconstruction of 3D volumes. The jitter artefact was defined as timing error between two consecutive slices due to lack of synchronisation between the ECG trigger and the image sampling (Figure 2) [46]. Finally, high frame rate ensured less effect of the sweep time delay in the colour flow image update.

We applied a moving surface of measurement that tracked the flow apparatus in our method. In order to get correct velocity values, representing the flow through the valve, the movement of the aortic annulus or the mitral valve should be taken into account. In paper II-V, the blood flow velocities were calculated relative to the moving spherical surface, and true blood flow velocities through the aortic annulus or mitral valve were obtained. Kim et al calculated this underestimation to be 7 % of cardiac output [32]. In our study this volume constituted 11 % of CO in healthy subjects in mitral flow. This was also a relevant problem in the aortic flow quantification as described in paper II and III. This volume constituted 9 % of CO in healthy subjects according to our results in paper III.

Several authors have described volumetric methods that were not hampered by the angle dependence of the Doppler beam [32, 34, 36-38, 47]. By spatial integration of the flow velocity component over a surface perpendicular to the ultrasound beam, angle independence of the Doppler beam was achieved. A larger flow area compensated the underestimation of the Doppler derived blood flow velocities. Since all recorded blood flow velocities were integrated in measurement of volumetric flow, no assumption about the velocity profile or effective flow area was needed. We applied this principle to a freehand 3D method. This principle is applicable to 3D data sets acquired by the use of rotational, tilting or translational movements.

Quantitative multiplane colour flow studies of mitral blood flow [32, 38] and mitral regurgitation jets [48, 49] has been described previously. The majority of these methods were trans-oesophageal, which limited the use in follow up of

patients. The acquisition time was long and by using rotational probes it was essential to keep the position of the transducer stable to avoid artefacts in the 3D reconstruction.

A problem in validation of new cardiac output methods is the lack of a "gold standard". To our knowledge there is no gold standard in the calculation of cardiac output. Invasive methods have traditionally been used for comparison, but these methods are also hampered by assumptions [50]. Further, it would seem unethical to subject healthy individuals to invasive procedures due to the associated risk. We chose to compare our 3D CO measurements with a conventional 2D PW Doppler method that has been used by several groups and is the standard method in our hospital. The statistical method proposed by Bland and Altman that was used in our study was designed for such comparisons [40].

The freehand 3D ultrasound imaging technique has been highly accurate in calculations of volumes in water filled balloons [46]. By applying the method to volumetric measurements of both mitral- and aortic flow in subjects without valve regurgitation, a close agreement would favour the accuracy of the method. The 3D methods showed good agreement and no bias. The observed bias between the 3D methods and 2D PW Doppler were larger. This may be due to several factors. The missing volume, due to the movement of the aortic annulus during systole and AV plane during diastole, was not added to the 2D PW method. Another possible reason for the observed bias is the angle dependency of the 2D PW Doppler method.

Limitations:

The results in paper I must be interpreted cautiously as only a limited number of patients were included in the study. Thus, there is a possibility of having made a type II statistical error.

The cross section velocity profile was recorded in two orthogonal planes. A complete three-dimensional velocity profile was not studied.

In paper II -IV, all recordings in our studies were performed before any evaluations of the 3D reconstruction were done. If the 3D reconstruction had been evaluated on line, or off-line immediately after the recording, a higher rate of success would probably have been achieved as a new and presumably better recording could replace a corrupted recording. Due to limited access between the ribs it may be difficult to cover the region of interest. Combination of several 3D scans may solve this problem. Leotta et al described a freehand 3D method in witch multiple scans of tissue images of the left ventricle were combined to calculate stroke volumes [51].

The 3D method used in paper II-V was not suited to investigate persons with irregular R-R interval lengths, as this would corrupt the 3D reconstruction. Subjects who are unable to hold their breath for a short period of time will be excluded, as a minimum of time is required to cover the region of interest. Although the acquisition time was short, post processing was time consuming. The total time needed to acquire and process data from mitral flow was approximately 20 minutes altogether.

In paper I, II and IV, the velocity profile was only close to instantaneous due to sweep time delay in the colour flow image, but this error was limited by the high

frame rate. The change in recorded blood flow velocities from one side of the sector to the other would be maximum 0.1 m/s at 100 frames per s and 0.17 m/s at 57 frames/s with a blood flow acceleration of 10 m/s^2. However, the VTI was unaffected by this. In paper V, the position of the maximum VTI and mean VTI were assessed subjectively as they were only visualised.

As in all Doppler studies, machine settings influence the analysis. By varying tissue gain, reject, compress and tissue priority to their extremes, overestimates in CO relative to the initial setting were maximum 67 %. However, such adjustments were obviously wrong as tissue velocity signals were interpreted as flow or vice versa. Nevertheless, some of the variability in our measurements of CO may be attributed to adjustment problems. The algorithm to baseline shift aliased velocities (II-V) lead to some loss of low blood flow velocities. To avoid aliasing it is important to increase the pulse repetition frequency.

Ferro-magnetic materials affect the magnetic position sensor system, and movement from the subject during recording may introduce 3D reconstruction artefacts.

Finally, in paper II- V only young healthy volunteers were included, and one should be careful in generalising the feasibility of the method in all clinical settings.

Further work:

Transoesophageal 3D colour flow methods have been described to calculate the regurgitate jet volume of patients with mitral regurgitation [44, 45, 48, 49]. Potential clinical applications of the described freehand 3D method in this thesis

is quantification of regurgitant flow in mitral regurgitation. Doppler regurgitatant fraction and volume can be calculated by comparing mitral and aortic forward stroke volumes or cardiac output. Assumptions about jet size are avoided. Methods measuring jet area mapped with colour Doppler measure not only the velocities of blood moving from one chamber to another but also the motion of the blood that is entrained and displaced on its path.

However, calculations of regurgitate fraction or volume will not replace the need of standard echocardiographic measurements as the compensatory changes as chamber size, compliance and mass is not detected by a quantitative flow measure.

3D ultrasound methods have not become an everyday clinical tool in cardiology yet. This is due to the complexity in data acquisition and post processing. However, further development in real-time 3D may solve some of these obstacles in order to ease the use and quality of 3D ultrasound imaging.

Conclusion:

In this thesis, we have discussed and illustrated a variety of problems regarding 2D PW methods in calculations of CO and proposed and validated a freehand 3D method that solves some of these difficulties.

A 2D colour flow method was described and applied to studies of the instantaneous cross section velocity profile of patients with atrial fibrillation. The velocity profiles were skewed with the maximum velocity and VTI most often located in the middle of the LVOT and toward the septum. The maximum VTI overestimated the mean VTI by approximately 40 %.

No differences existed in these measures in two consecutive heartbeats of different R-R interval lengths. Thus, according to our results measurements from heartbeats of different R-R interval lengths can be averaged without moving the pulsed wave sample volume along the diameter of the LVOT.

The velocity profiles in human aortic- and mitral blood flow were described by using a new a freehand 3D colour flow imaging method. Blood flow velocity vectors were measured through a moving sample surface that followed the valve apparatus throughout the systole and diastole. Raw ultrasound data were obtained at high frame rate. The blood flow velocity profile was non-uniform. By using a single sample volume in Doppler measurements of the maximum VTI, errors ranging from 10 to 50 % may be introduced in calculations of stroke volumes in aortic flow and 10 to 60 % in mitral flow.

The 3D method was applied to measurements of volumetric aortic and mitral flow. The range of agreement between 3D mitral and 3D aortic blood flow was good with a bias of no more than 0,04 l/min. The 3D data had the same temporal resolution as the original 2D data. The method was angle independent, no assumptions about the flow geometry were made and the measured flow through the LVOT and mitral orifice was correctly measured with respect to the movement of the valve plane relative to the probe.

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Figure legends:

Figure 1.

3D reconstruction.

For each 2D frame, the sensor position co-ordinates, the digital ultrasound data and the ECG signal were stored in the digital replay memory.

In EchoPAC-3D, frames with the same temporal delays relative to the R-wave in the ECG signal were used to reconstruct 3D volumes throughout the cardiac cycle.

Figure 2.

Jitter artefact.

The reconstruction jitter is due to the lack of synchronisation between the scanner frame sampling and the ECG. Thus, in this example, the 2D frames in a 3D volume are 11 ms apart in a given time step.

Figure 3 a-c:

3D data aqusition.

3D data set may be generated by acquisition of multiple 2D scan planes.

a. Rotation

b. Tilting

c. Translation

Errata:

Paper III.

Page 207:

Mitral flow, the last sentence should be:

"In EchoPAC-3D, the start of the heart cycle was set to 300 ms **after** the R wave in the ECG", not **before** as stated in the article.

Page 210:

Reference # 16 should not have been mentioned here. This reference should have been mentioned after reference #5, at page 204

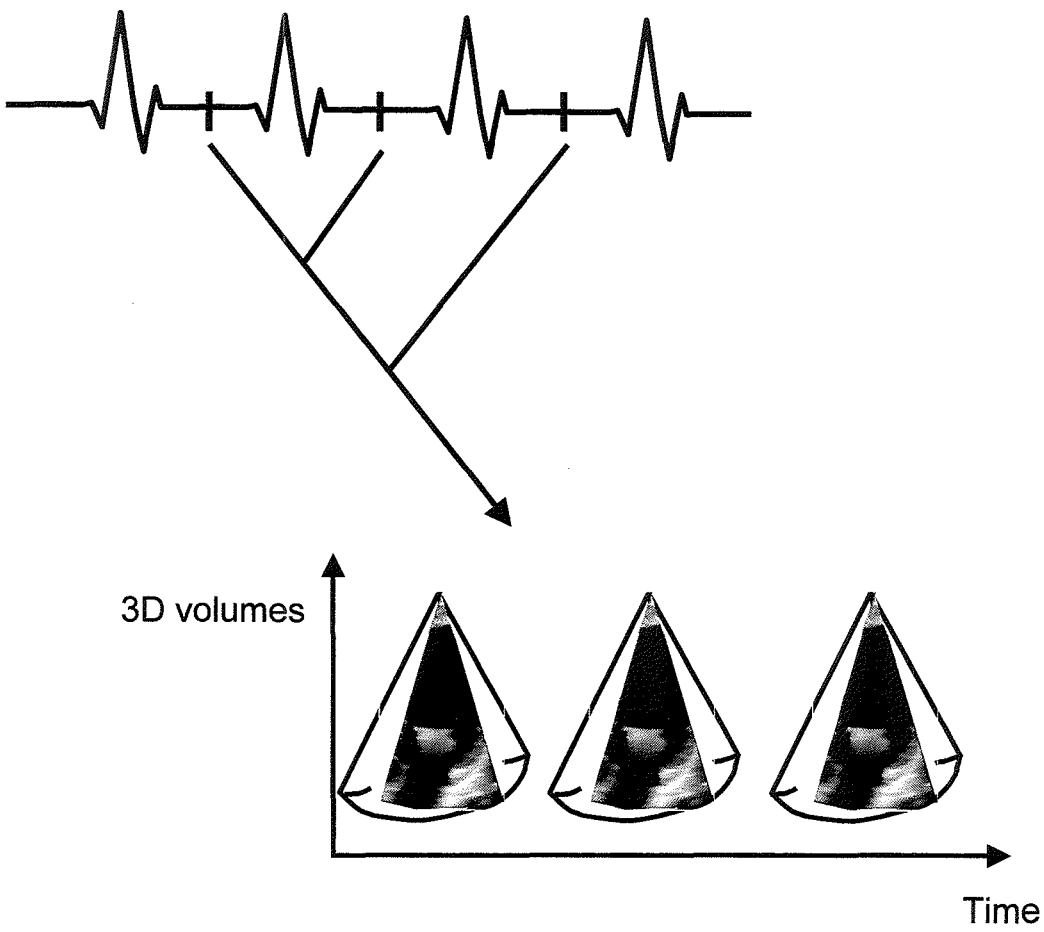

Figure 1

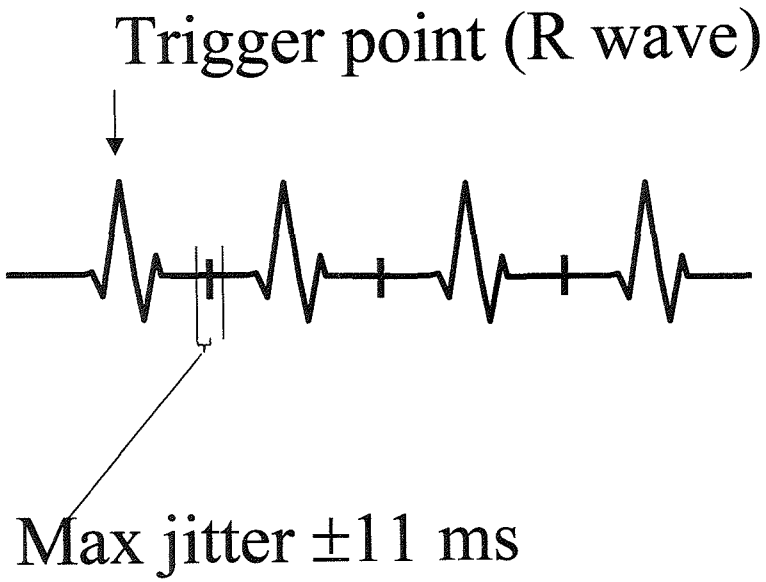

Figure 2

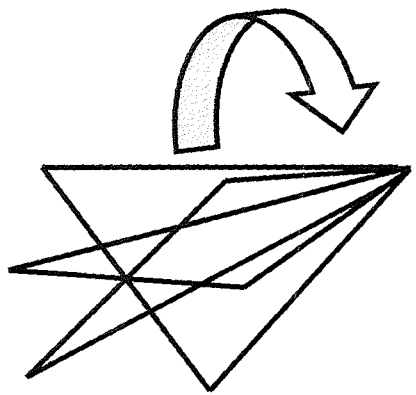

Figure 3a. Rotation

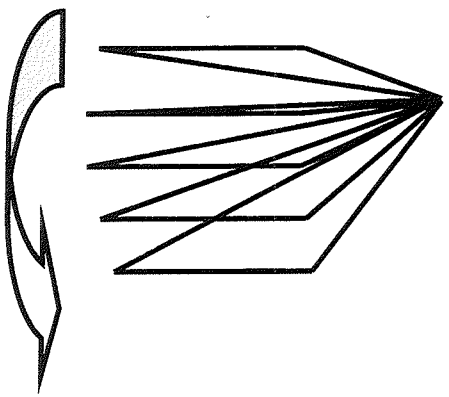

Figure 3b. Tilting

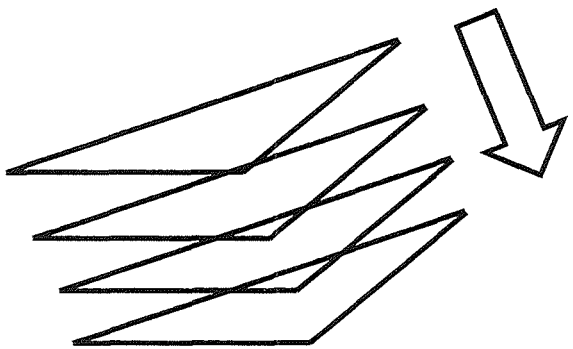

Figure 3 c. Translation

Paper I

A New Method Describing Cross-Sectional Blood Flow Velocity Profiles in the Left Ventricular Outflow Tract of Patients with Atrial Fibrillation with the Use of High-Frame Rate 2-Dimensional Color Flow Imaging

Bjørn Olav Haugen, MD, Steinar Bjærum, MSc, Stein Olav Samstad, MD, PhD, Terje Skjærpe MD, PhD, and Hans Torp, DrTechn, *Trondheim, Norway*

A new Doppler method was developed to evaluate the instantaneous cross-sectional velocity profile variability in the left ventricular outlet tract in patients with atrial fibrillation. Blood flow velocities acquired at a high frame rate (>90 frames/s) from a single heart cycle were used to display the velocity profile. In 9 patients, 2 heart cycles with different R-R interval lengths were recorded in color flow mode in a transthoracic apical 5-chamber and long-axis view. Raw digital ultrasound data were analyzed with an external personal computer. The data indicated a variable skew in the profiles with the highest velocities and velocity-time integral (VTI) most often located in the center and toward the septum. The maximum VTI overestimated the mean VTI by approximately 40%. No significant difference existed between the two heartbeats. Thus the VTI can be averaged from heartbeats of different R-R lengths in atrial fibrillation. (J Am Soc Echocardiogr 2001;14: 50-6.)

INTRODUCTION

Stroke volumes can be calculated from echocardiographic measurements of the velocity-time integral (VTI) in the left ventricular outflow tract (LVOT) and the subvalvular diameter, assuming a circular outflow tract and a flat velocity profile.[1] However, several reports have shown a nonuniform velocity profile in the LVOT in persons in sinus rhythm.[2-4] These studies assumed constant R-R intervals, and no beat-to-beat variability of the velocity profile. With these assumptions, one velocity profile was calculated by interpolation of color flow velocity samples from several heartbeats. The previous method cannot be used in patients with irregular heart rhythm, and to our knowledge, no data exist on the possible beat-to-beat variability of the velocity profile in the LVOT in such patients. To calculate cardiac output from echocardiographic measurements of stroke volume, the VTI must be averaged from 5 to 10 heartbeats to compensate for the variability in blood flow.[1] If the profile is skewed, and the skew changes from stroke to stroke in an unpredictable manner, another uncertainty and limitation are introduced in the pulsed wave Doppler technique.

We have developed a new method that uses blood flow velocity estimates acquired at a high frame rate (≥90 frames/s) from one heart cycle. A similar method has been applied in studies of the instantaneous cross-sectional velocity profile in the mitral blood flow of persons in sinus rhythm.[5]

The purpose of our study was to develop a fast and easy method to study the instantaneous cross-sectional blood flow velocity profile in the LVOT in patients with atrial fibrillation. The method was

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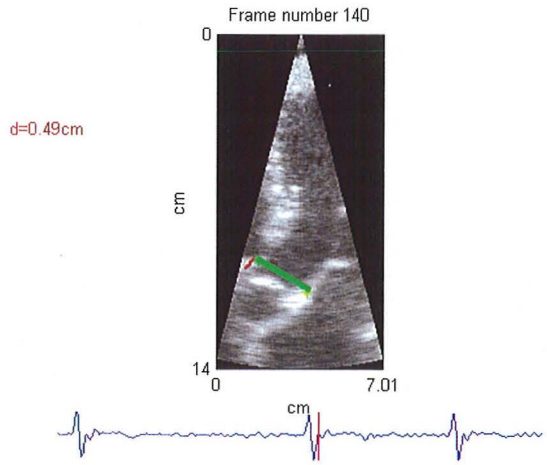

Figure 1 A line across the left ventricular outflow tract was drawn 0.5 cm proximal to the insertion of the aortic valve, and cross-sectional velocities were extracted from this line.

applied to 9 patients, and velocity profiles from 2 consecutive heartbeats of different R-R interval lengths were compared to assess any possible differences in the velocity profile.

METHODS

Informed, written consent was obtained from each subject in accordance with the regional ethical committee on human research.

Subjects

Nine patients with atrial fibrillation and no significant heart valve disease or other structural heart disease were consecutively included before elective DC cardioversion at the department of cardiology, University Hospital of Trondheim, Norway. The group comprised 7 men and 2 women (mean age 62 years, range 41 to 75). The mean heart rate was 88 bpm (range 65 to 110).

Equipment

A digital ultrasonographic scanner (System Five, GE Vingmed Ultrasound, Horten, Norway) with a 2.5-MHz phased-array transducer was used for all echocardiographic measurements. Digital image data were transferred to an external personal computer and analyzed with MATLAB (The MathWorks, Inc, Natick, Mass) software. To obtain the information needed from 1 heartbeat to construct the instantaneous cross-sectional velocity profile, we used software developed for high-frame rate imaging as described below.

Instrument Setting

Recordings of tissue images were obtained in second harmonic imaging mode with a transducer transmittal frequency of 1.7 MHz. For color flow imaging, the center frequency of the transmitted pulse was 2.5 MHz. The radial sample volume length was 0.8 mm.

Data Acquisition

The subjects were examined in the left lateral decubital position. To reduce cardiac movement, the recordings were done in held end-expiration. Ultrasonographic data were acquired in an apical 5-chamber view and an apical long-axis view. To get as high a frame rate as possible during recordings of aortic blood flow, a prototype data acquisition technique was used, which provided an increased frame rate with a moderate decrease in spatial resolution. The sector angle was set to a minimum, and the region of interest was minimized to cover the LVOT to obtain a rate of ≥90 frames/s, and a time delay less than 6 ms over the flow sector was achieved. Thus, from a single heartbeat, blood flow velocities from various positions within the LVOT were recorded with a resolution better than 6 ms at each point.

We scrolled the replay memory in the digital ultrasonographic scanner to find the longest R-R interval. The subsequent R-R interval was short. The digital image data from

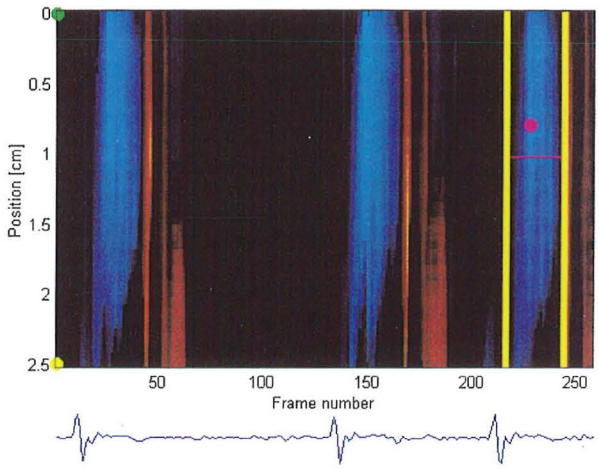

Figure 2 Cross-sectional blood flow velocities encoded as color flow from the left ventricular outflow tract obtained in a 5-chamber view in a patient with atrial fibrillation. The *blue area limited by yellow lines* represents the systolic period. The *green marker* is located at the septum. The *yellow marker* is located laterally. The *pink marker* is located at the point of maximum velocity, and the *pink line* represents the maximum velocity-time integral.

the 3 subsequent heartbeats corresponding to these 2 R-R intervals were transferred from the ultrasonographic scanner to an external personal computer.

Data Processing

For each sample volume, the flow information was encoded in a 16-bit "word." This data format ensures adequate resolution for both the power and velocity estimates. The data were visualized and processed with the use of software written in the MATLAB language. By performing angle correction, flow velocities perpendicular to arbitrary lines in the image could be plotted as a function of time. Detection of large discontinuities in the velocity estimates enabled correction for aliasing caused by high estimates. This way, the color flow data could be used in the quantitative analysis of the flow pattern through the aortic valve.

Tissue priority and flow gain were adjusted to ensure that the flow was within the anatomic borders. The systolic periods from 2 subsequent heartbeats were studied. Measurements were obtained for the R-R interval, defined as the time from the previous heartbeat to the one studied. A line across the LVOT was drawn 0.5 to 1 cm proximal to the insertion of the aortic valve (Figure 1), and cross-sectional velocities were extracted from this line and visualized with color M-mode echocardiography (Figure 2). The line was fixed and did not track the tissue during systole. Blood flow velocities from any given time interval (in our setting, during systole) were analyzed by extracting the data as illustrated in Figure 2. The following heartbeat was treated in the same manner.

The instantaneous cross-sectional velocity profile was reconstructed by plotting blood flow velocities against time and position along the diameter of the LVOT (Figure 3). Figure 4 shows the velocity profile from 2 heartbeats of different R-R interval lengths (long and short). As a quantitative assessment of the velocity distribution, any possible skew was described by comparing the ratios of the maximum VTI to the mean velocity integral, and the maximum velocity to the mean velocity. Furthermore, the position of the maximum velocity and the maximum VTI along the cross-sectional line was noted. Finally, we calculated the part of the line that crossed the LVOT in which values between the maximum VTI and maximum VTI - 20% were detected (Figure 5).

Statistical Analysis

Data from 2 different heartbeats were compared with the paired t test (null hypothesis: there is no difference between the 2 heartbeats; alternate hypothesis: there is a difference). The level of significance was chosen at $P < .05$.

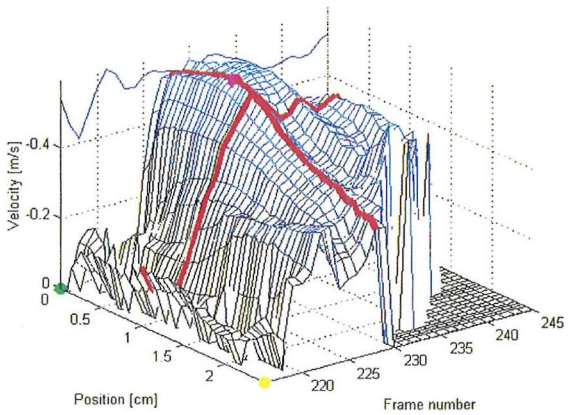

Figure 3 The instantaneous cross-sectional velocity profile in systole limited by *yellow lines* in Figure 2. The *red line crossing the picture along the axis-marked position* represents time of maximum velocity. The *pink marker* represents the maximum velocity. The *red line along the axis-marked frame number* represents the position of maximum velocity-time integral.

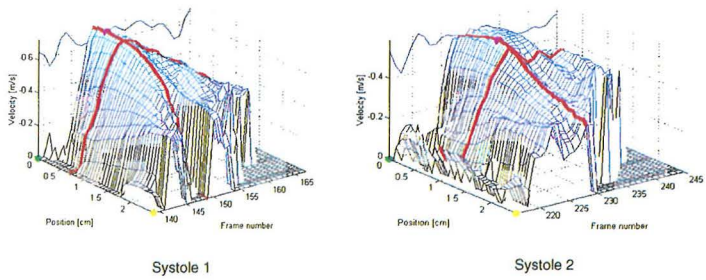

Figure 4 The instantaneous cross-sectional velocity profiles from 2 heartbeats with different R-R interval lengths in a patient with atrial fibrillation. Blood flow velocities are plotted against time and position along the diameter of the left ventricular outflow tract. The highest blood flow velocities are located toward the intraventricular septum.

RESULTS

The data indicated a nonuniform velocity distribution with the highest velocities and VTI located in the center of the LVOT and toward the intraventricular septum. The maximum VTI overestimated the mean VTI by approximately 40% in both planes. At peak flow, the maximum velocity overestimated the mean velocity by approximately 50% in the apical long-axis view and by about 60% in the 5-chamber view. The line from the septum to the middle part of the LVOT covered VTI values from maximum to 20% below maximum.

No significant difference was found at the 5% level between the 2 heartbeats in any of the calculated variables, except the difference in R-R interval length. However, the ratios of the maximum velocity/mean velocity recorded in the apical long-axis view showed a difference of $P = .05$, close to significance.

Tables 1 through 4 present the data from the recordings of 2 different heartbeats obtained in 2 orthogonal planes, a 5-chamber view, and the apical long-axis view. The recordings were obtained at a high frame rate (mean 100 frames/s, range 90 to 115). The mean time resolution was 10 ms (range 8.7 to 11 ms).

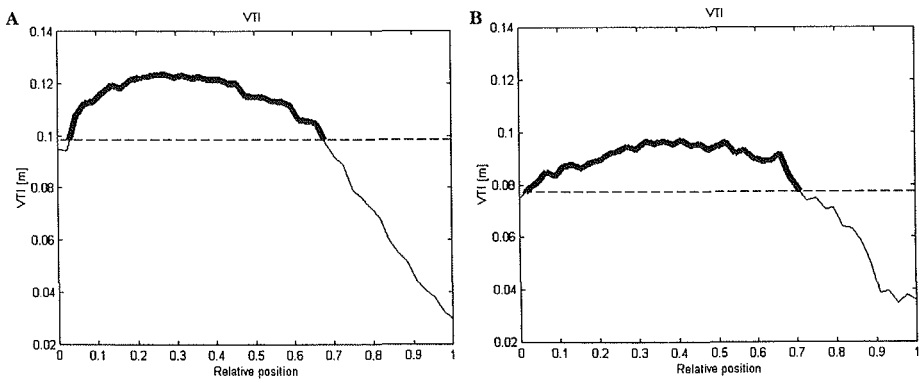

Figure 5 The relative length of *(VTI max to VTI max – 20%)/Total diameter.* Five-chamber view. The *x-axis* represents the line across the left ventricular outflow tract. *Point 0* is located at the septum and *1* at the lateral end. The *bold part of the curve* is the interval *VTI max to VTI max – 20%.* **A,** Heartbeat 1. The relative length of (VTI max to VTI max – 20%)/Total diameter = 0.65. **B,** Heartbeat 2. The relative length of (VTI max to VTI max – 20%)/Total diameter = 0.69. *VTI,* velocity-time integral.

Table 1 The recordings from two different heartbeats in 9 patients with atrial fibrillation (apical long-axis view)

	Heartbeat 1	Heartbeat 2	95% CI difference in mean	*P* value
R-R length (s)	0.93	0.59	0.21 to 0.48	.0001
Length of (VTI max to VTI max – 20%)/Total line	0.56	0.44	–0.03 to 0.25	.1
Max VTI/Mean VTI	1.38	1.49	–0.61 to 0.38	.62
Max V/Mean V	1.37	1.67	–0.59 to –0.01	.05

In calculations of the relative length of (VTI max to VTI max – 20%)/Total line, point 0 is localized to the anterior, and 1 is located at the posterior end. *R-R,* Time interval between two R complexes in the electrocardiogram; *VTI,* velocity-time integral; *V,* velocity; *max,* maximum.

Table 2 The recordings from two different heartbeats in 9 patients with atrial fibrillation (5-chamber view)

	Heartbeat 1	Heartbeat 2	95% CI difference in mean	*P* value
R-R length (s)	0.94	0.61	0.18 to 0.47	.001
Length of (VTI max to VTI max – 20%)/Total line	0.56	0.63	–0.16 to 0.06	.07
Max VTI/Mean VTI	1.32	1.42	–0.06 to 0.24	.19
Max V/Mean V	1.8	1.32	–0.59 to 1.53	.33

In calculations of the length of (VTI max to VTI max – 20%)/Total line, point 0 is located at the septum and 1 at the lateral end. *R-R,* Time interval between two R complexes in the electrocardiogram; *VTI,* velocity-time integral; *V,* velocity.

DISCUSSION

In this study, we have presented a fast and easy method to describe instantaneous cross-sectional blood flow velocity profiles in the LVOT of patients with atrial fibrillation. At 90 frames/s and above, the time resolution was better than 11 ms. The influence of the sweep time delay was strongly reduced and therefore disregarded in our study. Thus, it was possible to display the instantaneous velocity profile from the recording of a single heart cycle. Because we compared 2 heartbeats, any possible influence in the skew caused by sweep time delay would influence both heartbeats. This was a more feasible method than previous methods in which color flow velocity samples from several heartbeats with regular R-R intervals were interpolated to construct the instantaneous cross-sectional velocity profile.[2-4,6,7]

In conventional pulsed wave Doppler techniques, 5 to 10 heartbeats are averaged in patients with atrial fibrillation to ensure a reliable measure of cardiac output. We did not find any significant difference in the

Table 3 The recordings from two different heartbeats in 9 patients with atrial fibrillation

Relative position of the maximum velocity along the line crossing the LVOT	Heartbeat 1	Heartbeat 2	95% CI difference in mean	*P* value
Five-chamber view	0.43	0.41	−0.26 to 0.19	.74
Apical long-axis view	0.35	0.53	−0.09 to 0.33	.24

In the relative position of the maximum velocity, point 0 is located at the septal/anterior end, and 1 is located at the lateral/posterior end. *LVOT,* Left ventricular outflow tract.

Table 4 The recordings from two different heartbeats in 9 patients with atrial fibrillation

Relative position of the maximum VTI along the line crossing the LVOT	Heartbeat 1	Heartbeat 2	95% CI difference in mean	*P* value
Five-camber view	0.44	0.47	−0.24 to 0.19	.76
Apical long-axis view	0.34	0.44	−0.28 to 0.07	.22

In the relative position of the maximum VTI, point 0 is localized at the septal/anterior end, and 1 is located at the lateral/posterior end. *LVOT,* Left ventricular outflow tract; *VTI,* velocity-time integral.

blood flow velocity profile in 2 consecutive heartbeats of different R-R interval lengths. One potential implication of this finding is that when measuring blood flow velocities with the pulsed Doppler technique, the sample volume can be fixed in the same position along the diameter of the LVOT during the recording. The maximum VTI has been described in 2 settings: the relative position of maximum VTI, and the part of the line that crosses the LVOT in which values between maximum VTI and maximum VTI - 20% were measured. The maximum VTI was a robust parameter as opposed to the mean VTI because of less dependence of the high pass filter limit. Furthermore, the maximum VTI was less sensitive to poor differentiation of tissue and blood flow velocities. The mean VTI was measured for comparison with previous works. The Doppler sample volume is fixed during recording of blood flow velocities, but the heart is moving.

Thus, the introduction of the parameter *Length of (VTI max to VTI max - 20%)/total line* illustrates that the acceptance of a potential variation of 20% in the calculation of stroke volume likely enables the sample volume to actually detect these velocities along the diameter. If this distance is short, it would be difficult to detect blood flow velocities within this range, and the estimate of the VTI would be less precise. As shown in Tables 1 and 2, the line from the septum to the middle part of the LVOT covers VTI values from the maximum to 20% below the maximum. The skew in the velocity profile has been described in patients in sinus rhythm as previously mentioned and must be kept in mind when sampling blood flow velocities with the use of the pulsed Doppler technique.

Study Limitations

The results describing the velocity profiles must be interpreted cautiously because a limited number of patients were included in this study. Each patient analysis was limited to 2 cardiac cycles. However, we scrolled the replay memory in the digital ultrasonographic scanner to find the longest R-R interval. The subsequent R-R interval was significantly shorter. Thus, the probability of detecting differences in the velocity profile was maximized.

The cross-sectional velocity profile was recorded in 2 orthogonal planes; thus a complete 3-dimensional velocity profile was not studied. It is not possible to generalize our findings to all patients with atrial fibrillation, as they might represent a selected group.

Conclusion

We have developed a fast and easy method that enables the study of the instantaneous cross-sectional velocity profile in patients with atrial fibrillation. The velocity profiles were skewed with the maximum velocity and VTI most often located in the middle of the LVOT and toward the septum. The maximum VTI overestimated the mean VTI by approximately 40%.

No differences existed in these measures in 2 consecutive heartbeats of different R-R interval lengths. Thus, according to our results, measurements from heartbeats of different R-R interval lengths can be averaged without moving the pulsed wave sample volume along the diameter of the LVOT.

The authors would like to thank Stig Arild Slørdahl, MD, PhD, with the Department of Physiology and Biomedical Engineering, Norwegian University of Science and Technology, Trondheim, for reviewing our manuscript.

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Paper II

Volumetric Blood Flow Measurement with the Use of Dynamic 3-Dimensional Ultrasound Color Flow Imaging

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We describe a new method for measuring blood volume flow with the use of freehand dynamic 3-dimensional echocardiography. During 10 to 20 cardiac cycles, the ultrasonographic probe was slowly tilted while its spatial position was continuously recorded with a magnetic position sensor system. The ultrasonographic data were acquired in color flow imaging mode, and the separate raw digital tissue and Doppler data were transferred to an external personal computer for postprocessing. From each time step in the reconstructed 3-dimensional data, one cross-sectional slice was extracted with the measured and recorded velocity vector components perpendicular to the slice. The volume flow rate through these slices was found by integrating the velocity vector components, and was independent of the angle between the actual flow direction and the measured velocity vector. Allowing the extracted surface to move according to the movement of anatomic structures, an estimate of the flow through the cardiac valves was achieved. The temporal resolution was preserved in the 3-dimensional reconstruction, and with a frame rate of up to 104 frames/s, the reconstruction jitter artifacts were reduced. Examples of in vivo blood volume flow measurement are given, showing the possibilities of measuring the cardiac output and analyzing blood flow velocity profiles. (J Am Soc Echocardiogr 2000;13:393-402.)

INTRODUCTION

Ultrasound Doppler is a widely used clinical tool for estimating blood volume flow and cardiac output. In the most commonly used technique, the velocity in the Doppler spectrum is traced during systole, and the integral of this curve is multiplied by the aortic area defined by the diameter, as measured by B-mode ultrasonography (ultrasound). This calculates the stroke volume. One such method was proposed by Skjærpe[1] and consists of measuring the blood velocity by pulsed wave (PW) Doppler in the distal left ventricular outflow tract (LVOT). The modal velocity in the Doppler spectrum is traced during systole, and the diameter is measured in the LVOT close to the insertion of the aortic valves. This technique assumes a nearly flat velocity profile, which may not reflect the actual flow distribution. It is also sensitive to errors in the Doppler sample volume placement, the tracing of the spectrum, and the diameter measurement.

A different approach with the use of 2-dimensional (2D) color flow imaging (CFI) was described by Tsujino et al.[2] In this method, a line is placed across the flow region, and the flow volume is calculated from the corresponding velocity profile. Shiota et al[3] applied this method to quantification of aortic regurgitation.

The aortic blood flow measurement method as described, which uses the PW Doppler technique, is based on a Doppler sample volume placed at a constant depth throughout the cardiac cycle. This probably leads to an underestimation of the stroke volume because the blood flow is only measured during systole when the aortic annulus moves in the opposite direction. The movement of the annulus relative to the measurement position describes a blood volume that ideally could be measured during diastole when the annulus moves back the same distance, together with the corresponding blood pool. This blood volume is lost because of the low sensitivity of the PW Doppler technique.

Since the introduction of 3-dimensional (3D) ultrasound, several attempts have been made to visualize

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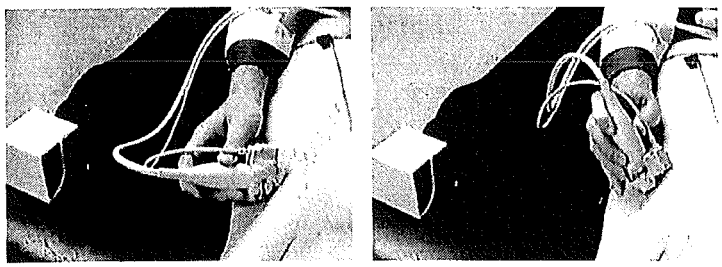

Figure 1 The probe was slowly tilted from the start to the end position during 10 to 20 cardiac cycles through the left ventricle from an apical position, covering the left ventricular outflow tract. The patient must not breathe or move during data acquisition.

blood volume flow from 3D data containing Doppler measurements. An early attempt by Miyagi et al[4] showed the possibility of creating 3D color flow images from the umbilical cord. Picot et al[5] described a 3D color flow system for visualizing the carotid artery. Visualizations of dynamic 3D intracardiac color flow jets have also been performed.[6,7]

Most methods presented so far have been based on the video output signal from the ultrasound scanner. This makes it difficult to do quantitative analysis of the flow data because the color values from the video signal are the result of mapping from the original Doppler frequencies. This mapping includes processing to give optimal visualization of the flow and is not necessarily optimal for flow quantization.

The video data also suffer from poor temporal resolution (25 frames/s for the PAL [phase alteration by line] video standard). This causes reconstruction jitter artifacts caused by the lack of synchronization between the electrocardiogram (ECG) signal and the video signal sampling. As a result, the reconstructed data will consist of neighboring image frames deviating up to 20 ms relative to the ECG trigger position. With the limited temporal resolution in the ultrasound scanner itself, this error will increase because the ultrasound image sampling and the video grabbing are not synchronized. This jitter introduces errors when the 3D color flow data are used quantitatively. In addition, low temporal resolution may undersample the flow velocities.

Most of the work presented on quantitative 3D flow has been performed in vitro. Guo et al[8] described how flow through a test phantom could be quantified with 3D color Doppler. However, when measuring Doppler frequencies in the heart in vivo, additional problems arise because of the moving heart walls. Recently, the possibility of calculating regurgitant jet volume has been demonstrated.[9,10]

The purpose of our work was to develop a new method for calculating the cardiac blood volume flow in vivo with the use of 3D color Doppler data acquired with a freehand position sensor. The raw digital data from the scanner were captured at high frame rates.

The development of dynamic 3D echocardiography has made it possible to reconstruct 3D cardiac sequences of separate tissue and color flow data with no loss of temporal resolution and with small spatial reconstruction errors.[11] The volume flow algorithm was based on an angle-independent measurement method.[12,13] The general idea was to extract the measured velocity vector components that were perpendicular to a cross-sectional slice through the flow tract and estimate the volume flow independent of the flow direction. Haugen et al[14] validated the method in vivo, and one example showing the possibilities of blood volume flow measurements is given in our article.

MATERIALS AND METHODS

Data Acquisition

Raw digital data were acquired with the use of a System Five (GE Vingmed Ultrasound, Horten, Norway) ultrasound scanner with a 2.5-MHz phased-array transducer. The spatial position and orientation of the probe were continuously recorded with a position sensor system (Flock of Birds, Ascension Technology Corp, Burlington, Vt), consisting of a magnetic field transmitter and a sensor (receiver), which was mounted directly on the probe. The transmitter and the sensor were both coupled to an electronic control unit, and the sensor had to be located inside the magnetic field of the transmitter. The operating range of the sensor was 25 to 60 cm from the transmitter. The control unit was

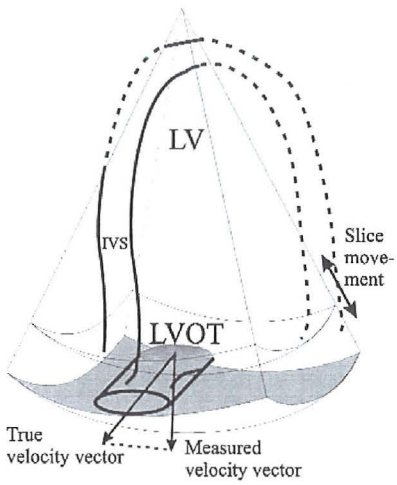

Figure 2 The reconstructed volume at one time instance; the volume contains part of the left ventricle *(LV)*, the intraventricular septum *(IVS)* at left, and the left ventricle outflow tract *(LVOT)*. The measured velocity vector components are perpendicular to the extracted surface.

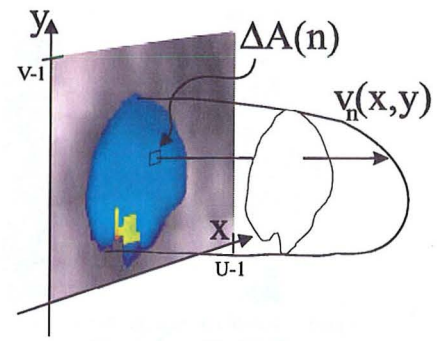

Figure 3 The 3-dimensional flow profile at time n consists of a set of discrete vector components $v_n(x, y)$ representing the velocity in the area ΔA.

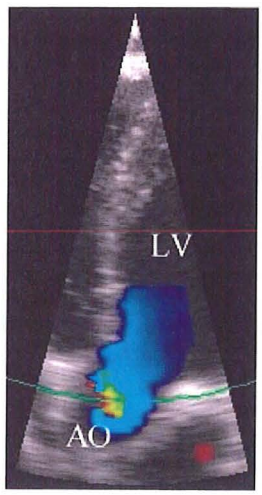

Figure 4 Midsystolic outflow from the left ventricle *(LV)* through the aortic outlet *(AO)*. The *green curve* indicates the intersection with the cross-sectional slice passing through the annulus.

coupled directly to the scanner. The sensor position coordinates were stored in the digital replay memory together with the corresponding image frames and all other relevant scanner parameters including the ECG signal.

The data were acquired with frame rates up to 104 frames/s in CFI mode. From a transthoracic apical position, the probe was tilted slowly during held end-expiration (Figure 1). Typically, one complete scan lasted 10 to 20 cardiac cycles. The raw digital ultrasound data, consisting of separate 8-bit tissue values and 16-bit color flow values, were transferred to an external personal computer for 3D reconstruction.

Volume Flow Measurement Data

To reconstruct volumetric data from each consecutive time step, the raw scan line data from the 2D scan planes were reorganized according to their position in the cardiac cycle with the use of a prototype version of the EchoPAC-3D software (GE Vingmed Ultrasound). The data from the first scan plane in each cycle (defined by the ECG) were used to build up the first volume, and data from the second scan plane, the second volume, and so on.[11]

One 2D slice was extracted from the 3D data for all the different time steps (Figure 2). Both the raw tissue and the Doppler values were resampled on this surface. Because the ultrasonic beam was perpendicular to this surface at all points, the measured blood flow velocity component was perpendicular to the surface. The position of this surface was then given only by the depth, which was manually positioned during a review of the 3D data.

The probable underestimation of the aortic outflow as a result of the moving annulus was avoided by using the described cross-sectional surface. The blood volume that passed through the same anatomic structure (eg, the aortic annulus) was calculated. The surface was manually positioned at the desired depth at start- and end-systole.

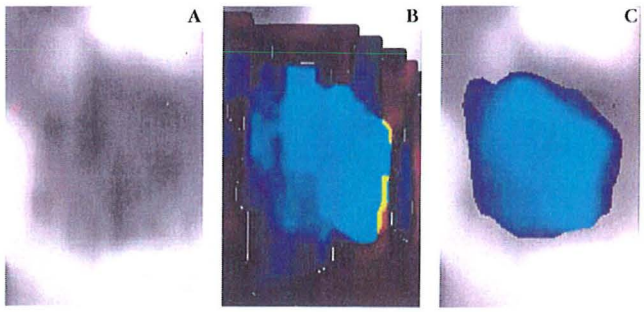

Figure 5 One slice through the 3-dimensional data in the distal left ventricular outflow tract during the aortic outflow in systole. **A,** The raw tissue data. **B,** The corresponding raw Doppler values. The negative velocities (away from the probe) are coded in *blue*. The *red* and *dark colors* are positive velocities (toward the probe). **C,** Combination of the filtered, separate tissue and Doppler values. Note that the colors represent the velocity vector components perpendicular to the image plane.

Between these positions, the surface depths were interpolated, resulting in a surface that followed the movement of the selected structure. The velocity of this movement was recorded and added to the blood velocity.

The extracted surface data were represented by two $U \times V \times N$ matrixes for the raw tissue values and the Doppler values, where $U \times V$ was the size of the surface, and N was the number of time steps. The Doppler values were the pulse-to-pulse complex autocorrelation function values for zero and unity lags, $R(0)$ and $R(1)$, respectively. These values were used to estimate the signal power, $P = R(0)$, and the center frequency, $w = \arg R(1) \in [-\pi, \pi]$.[15] The Doppler frequency w was proportional to the blood flow velocity used in the volume flow calculations. Further processing on these autocorrelation function values was performed using MATLAB (MathWorks Inc, Natick, Mass).

Region of Interest

Inside the Doppler flow region in the extracted slice, flow was detected from several sources. To prevent unwanted velocities from being used in the volume flow calculations, a region of interest was manually indicated in the data. For the aortic outflow, one region of interest was defined in the start-systolic frame and one in the end-systolic frame. Interpolation was performed for the frames in between. These contours were not used as the exact flow border definition, but only to exclude surrounding blood flow. This also reduces the errors from drop-out effects occurring when low-gain tissue causes blood flow to be incorrectly detected.

Spatial and Temporal Signal Smoothing

To smooth the data and reduce the variance, the values $R(0)$ and the complex $R(1)$ were filtered with a spatial average filter mask. The filter size depended on the amount of oversampling in the reconstructed 2D slice. The tissue values were detected with a higher spatial resolution than the Doppler values in the original scan plane (azimuth direction). During the resampling, the elevation resolution was set approximately equal to the original azimuth tissue resolution and equal for both the tissue and the Doppler values. The spatial Doppler filter size was adjusted so that it was close to the original Doppler sampling density. The data were then smoothed in the temporal direction by averaging each value with the values from the previous and the next time step. Finally, spatial interpolation was performed. The tissue values were filtered and interpolated accordingly.

Baseline Shift

Aliasing of the Doppler frequency is common for the highest velocities during the aortic outflow. These values can be baseline shifted (unwrapped) to give the correct velocity value. In areas where high velocity blood flow meets slowly moving tissue, the filtering and interpolation of the aliased velocity values introduce velocity estimate errors. We corrected for this effect by first baseline shifting the aliased values, then dividing the complex $R(1)$-argument by 2 before doing the filtering and interpolation, and adjusting the Nyquist velocity accordingly.

Volume Flow Calculation

All velocity vectors in the resampled cross-sectional surface were the components along the ultrasound beams. These vector components were perpendicular to the surface. By integrating all velocities across the surface, it was possible to calculate the total blood volume flow independent of the angle between the ultrasound beam and the

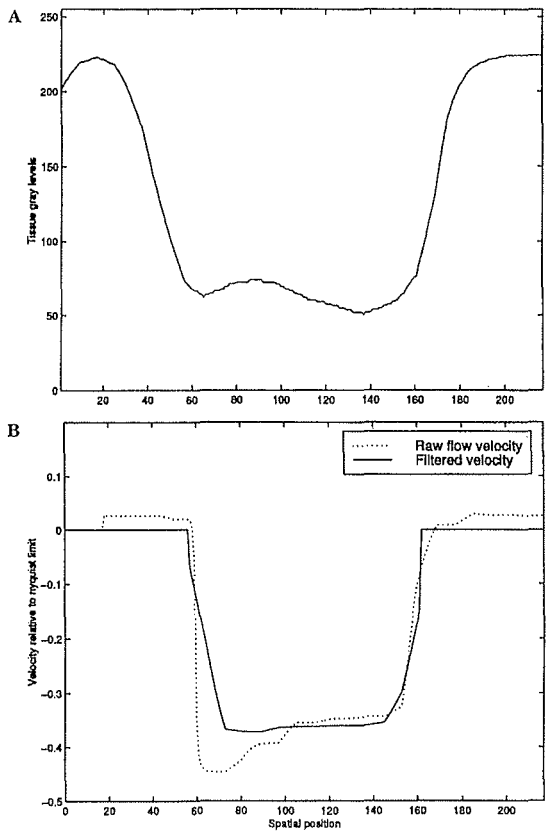

Figure 6 Plots of one vertical line in Figure 5. **A,** The gray-level tissue values. **B,** The raw flow data velocity *(dotted line)*, and the filtered flow values *(solid line)*. Nyquist limit: −0.5.

flow direction. The magnitude of the velocity vector component at each position (x, y) at time n was given by

$$v_n(x, y) = v_{nyq} \cdot w_n(x, y)/\pi - v_n^{surf},\ n \in [0, N-1],\ x, y \in U \times V \quad (1)$$

Here, v_n was corrected for the velocity of the cross-sectional surface v_n^{surf}. N is the number of time steps, and v_{nyq} is the Nyquist velocity (Figure 3).

The instantaneous blood volume flow (the flow rate) through the region $U \times V$ at time n, was given by

$$q(n) = \sum_{k=0}^{U-1} \sum_{l=0}^{V-1} \Delta A(n) \cdot v_n(k, l) \quad (2)$$

where ΔA is the area occupied by one velocity vector component. The size of this area was time dependent because the surface was allowed to move; it was given by the Doppler resampling resolution, which decreased with the distance from the probe. The velocity v_n was different from zero only when blood was detected.

The total blood volume flow was found by integrating the blood volume flow curve

$$Q = \sum_{t=0}^{N-1} q(t)\Delta t \quad (3)$$

where Δt is the temporal resolution. When N equaled the length of the cardiac cycle, Q was the stroke volume (SV).

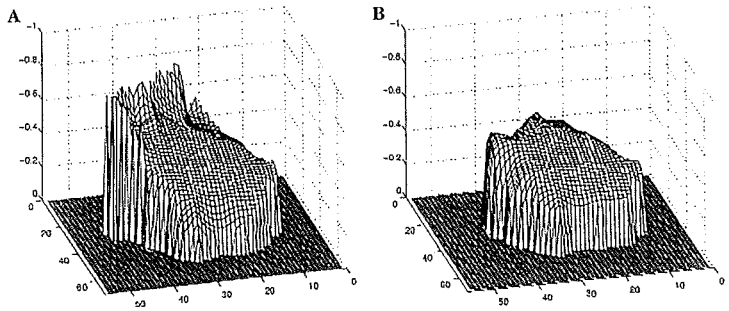

Figure 7 Mesh plots of aortic flow velocity profile with aliased velocities near the tissue border. The height of the mesh is proportional to the blood velocity. A, Overestimated border velocities. B, Border values decreased toward zero velocity by using the corrected baseline shift algorithm.

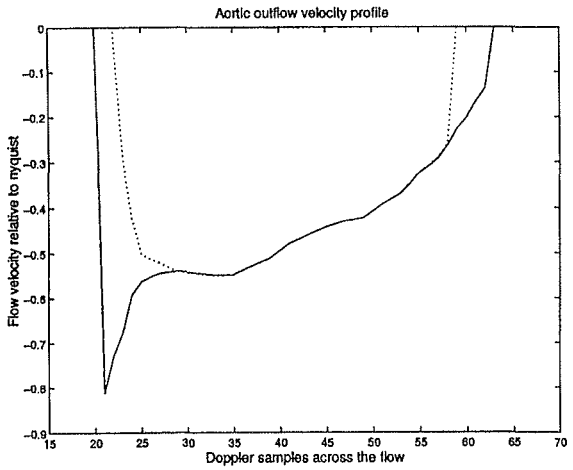

Figure 8 Plot of one line through the data in Figure 7. The *solid curve* is the profile with the overestimated border values, and the *dotted curve* is the corrected profile that decreases toward zero. Nyquist limit: −0.5.

The cardiac output (CO) was then the SV multiplied by the heart rate: $CO = SV \cdot HR$.

In Vivo Volume Flow

Dynamic 3D data from the aortic outlet were collected from a healthy volunteer without evidence of cardiac disease. We also calculated the CO by using the routine method as described by Skjærpe.[1]

After transferring the raw digital ultrasound data from the scanner to the external computer, the instantaneous blood volume flow and the cardiac output were calculated from 2 different cross-sectional surface positions. First, the surface was placed in the aortic annulus, moving along with this structure throughout systole. Then the surface was placed 0.5 cm above the annulus in start-systole and kept at that depth throughout systole (Figure 4). The last approach made a direct comparison with the PW Doppler method possible.

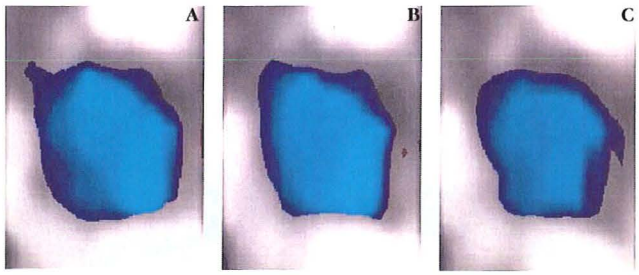

Figure 9 Three consecutive slices of aortic outflow with a time resolution of 9.6 ms.

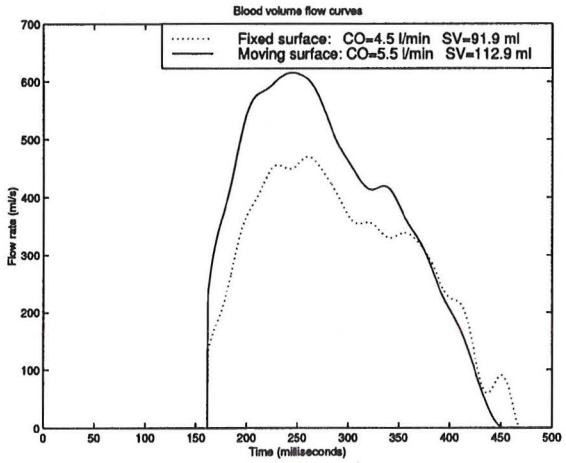

Figure 10 In vivo blood volume flow curves from 2 different measurements, showing the aortic outflow during systole. Moving surface *(solid line)* and fixed surface *(dashed line)*. *CO*, Cardiac output; *SV*, stroke volume.

RESULTS

Raw Data 3D Reconstruction

After filtering the separate raw tissue and Doppler data, the different velocities were color encoded and mixed with the gray-level tissue values. This produced a color overlay image similar to normal 2D CFI (Figure 5). This tissue/flow arbitration depended on the power of the signals. The moving myocardial tissue created positive Doppler frequencies (dark red), which were ignored after arbitration because of low signal power. The effect of filtering and arbitration is also shown in Figure 6, in which one line through the data was plotted. The clutter filter removed signals with low frequency. This missing blood flow was seen near the tissue border (Figure 5).

Interpolation and filtering of raw Doppler data containing aliased blood velocities and tissue velocities resulted in over-estimated flow border values. With the corrected baseline shift algorithm, this error was reduced (Figures 7 and 8).

Successful acquisition and reconstruction of 3D color flow data were achieved with temporal resolution of less than 10 ms (Figure 9). With a frame rate of 104 frames/s, the 3D data contained a total of 120

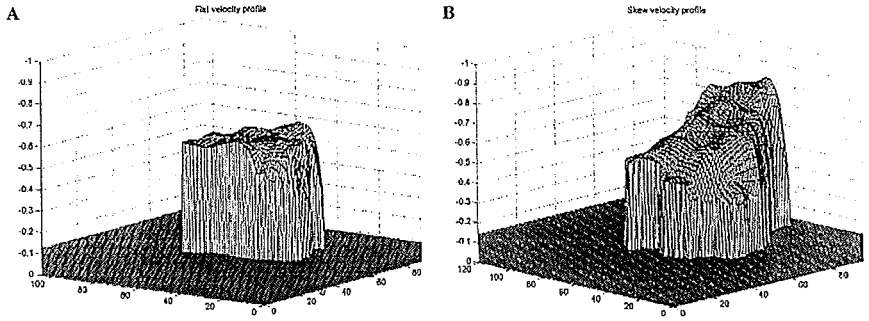

Figure 11 Two velocity profiles in 2 different persons from the aortic outflow in the peak systole with different characteristics. The velocity scale was defined with the Nyquist velocity at −0.5. **A,** Flat profile. **B,** Skew profile with higher velocities toward the intraventricular septum.

time steps through the cardiac cycle. There were 31 volumes with color flow data during systole. With this time resolution, the maximal timing error (jitter) between two consecutive slices in one 3D volume was 4.8 ms.

Aortic Blood Volume Flow

The instantaneous blood volume flow was calculated from both the moving and the fixed surfaces (Figure 10). The fixed surface was placed in the same position as the sample volume from the PW Doppler method, giving comparable flow volume estimates. With the fixed surface, the CO was 4.5 L/min (SV = 91.9 mL), whereas with the PW Doppler estimates, the CO was 4.0 L/min (SV = 87.0 mL). The moving surface resulted in a greater flow volume (CO = 5.5 L/min and SV = 112.9 mL). In this case, the average velocity of the surface was used. The blood flow volume represented by the movement of the annulus corresponded to 11% of the cardiac output.

We found that the velocity profiles in different persons had different shapes (Figure 11), indicating that the form of the profile was subject to individual variability.

DISCUSSION

Measurement of cardiac blood volume flow by the conventional Doppler method is an established clinical procedure.[1] It is easy to perform and gives an estimate of the cardiac output. There are, however, several shortcomings to this method. The Doppler velocity is measured from within a small sample volume, and the cardiac output estimate is sensitive to the placement of this volume.[16] The method assumes a flat velocity profile, but it has been shown that the flow velocity distribution in the aorta may have different characteristics that can influence the velocity estimates of this method.[17] This was also illustrated by the 3D reconstructions in our study. In addition, the method is sensitive to errors in the tracing of the Doppler spectrum.

Several techniques have been proposed to improve volume flow estimation on the basis of the principle of integrating velocity vectors across a surface. Sun et al[13] estimated the volume flow rate by surface integration of velocity vectors from 2 rotated planes. Poulsen and Kim[12] showed a similar method that used several rotated planes and was tested in an in vitro model. This method was also applied in vivo.[18] Common for these methods was that the volume flow was estimated independently of the angle between the ultrasound beam and the blood flow. We also used this approach, but unlike the previously presented methods, our method used a full 3D data set consisting of raw digital color flow data to estimate and visualize the blood flow. By using high frame rates, it was not necessary to average the flow measurements from several consecutive cardiac cycles, as described earlier.[12,18] There were, however, still limitations to the accuracy with which we could measure the blood flow because of errors from Doppler velocity estimation, aliasing, and 3D reconstruction.

The Doppler frequency shift from the backscattered ultrasound signal contains information from both moving blood and tissue (clutter). The separation of blood and tissue moving at equal velocities was not possible, so this clutter filtering resulted in a loss of blood signals with low velocity. Too low a cutoff frequency for filtering clutter gave a bias in the estimate toward zero velocity.

Aliased velocities were overestimated at the border between the tissue and the blood. This occurred when the unwrapped velocity values were averaged with slowly moving tissue velocity values. Correct unwrapping of the aliased velocities is difficult, especially when flow in 2 directions occurs simultaneously. In our calculations, however, we considered only flow in one direction at the time, making a baseline shift possible.

It has been shown that the reconstruction errors for this freehand technique were smaller than the resolution of the original ultrasound beam.[11] The jitter artifacts in the 3D reconstruction were at most 10 ms when the frame rate was 50 frames/s. This introduced errors in the volume flow estimates; these errors were reduced by increasing the frame rate. As shown, it was possible to reconstruct 3D color flow data with a frame rate of 104 frames/s, reducing the jitter to a maximum of 4.8 ms.

For gated 3D ultrasound, movement of the patient during acquisition results in reconstruction errors. In our study, this error was reduced by the short acquisition time (10 to 20 seconds).

Poor detection of the myocardial tissue introduced uncertainty in the flow region definition and resulted in volume flow estimation errors. It was important to tilt the probe sufficiently to totally cover the flow and surrounding tissue area.

The method has been evaluated in vivo in 18 persons by comparison with the 2D PW Doppler method,[14] and has shown good agreement with a mean difference of 0.3 L/min with the use of a fixed surface and 0.7 L/min with a moving surface. These results confirm the tendency given by the patient example in our study. Because the raw data were used in the reconstructions, and because the cross-sectional surface was clearly placed in relation to anatomic structures, one potential of this method is greater independence of the examiner than is possible with the ordinary PW Doppler method.

Limitations

The acquisition method presented here required regular heart rhythm during the scanning. Even though the scan time is short, there may not be sufficient time to cover the area of interest for patients who are unable to hold their breath. In addition, the acoustic window must provide sufficient access to cover the whole flow region.

Conclusion

The method presented here enables calculation of blood volume flow versus time throughout the cardiac cycle in vivo with freehand 3D ultrasound with the use of raw digital tissue and Doppler data. The 3D reconstructed flow data had the same temporal resolution as the original 2D data. As many as 104 frames/s were achieved, reducing to less than 5 ms the reconstruction jitter artifacts, which were small compared with the physiologic beat-to-beat variations. The blood volume flow through the LVOT was correctly measured with respect to the movement of the aortic annulus relative to the probe. The method was angle independent, and no assumption of the flow geometry was made. In addition, blood flow velocity profiles could be analyzed throughout the cardiac cycle.

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Paper III

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Measurement of Volumetric Mitral and Aortic Blood Flow Based on a new Freehand Three-dimensional Colour Flow Imaging Method. An *in vivo* Validation

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Aims: To validate a new three-dimensional (3D) colour flow method used to calculate cardiac output (CO) in aortic and mitral blood flow.

Methods: The transducer was freely tilted transthoracically using a magnetic locating device recording its spatial position. Raw digital ultrasound data were recorded in healthy subjects during 10–20 heartbeats at a high frame rate ranging from 41 to 66 frames/s and analysed off-line with no loss in temporal resolution. Blood flow velocities aligned with the ultrasound beam were integrated across a moving spherical surface to calculate volumetric flow.

Results: The range of agreement between the 3D mitral and 3D aortic method was 0·04 ± 1·32 l/min (mean ± 2 standard deviations). The range of agreement between 3D aortic flow and the two-dimensional (2D) pulsed wave Doppler method (2D PW) in the left ventricular outflow tract (LVOT) was 0·7 ± 1·7 l/min, while the range of agreement between 3D mitral flow and the 2D PW method was 0·88 ± 1·64 l/min.

Conclusion: The 3D methods agreed well. The 3D volumetric flow overestimated the 2D PW method, as expected, and the range of agreement was wide. The common pitfalls in pulsed wave ultrasound methods to calculate CO were avoided, as the 3D method was angle-independent, no assumptions about the velocity profile were made, and a moving sample surface was applied. The acquisition of data was fast and easy and high temporal resolution was achieved.

(Eur J Echocardiography 2000; 1: 204–212)

Key Words: three-dimensional colour flow; volumetric; cardiac output; high frame rate; freehand; ultrasound.

Introduction

Stroke volumes in the distal left ventricular outflow tract can be calculated from two-dimensional (2D) echocardiographic measurements of the subvalvular diameter and the velocity time integral (VTI). These calculations assume a flat velocity profile and a circular outflow tract (LVOT)[1]. Several studies have shown non-uniform velocity profiles in the LVOT[2–4]. The 2D pulsed wave (PW) Doppler method is angle-dependent and measurement of the angle between the Doppler beam and the blood flow is difficult[1]. Further, blood flow velocities are sampled at a fixed depth throughout the cardiac cycle. The aortic annulus moves in the opposite direction during the systole and the resulting missing volume is not added to the stroke volume. Finally, calculation of the subvalvular diameter assumes a circular shape and errors in diameter measurements are squared.

Non-invasive measurements of mitral blood flow also have a number of difficulties; the biphasic diastolic filling, variation of effective flow area, the non-uniformity of the blood flow velocity profile[5] and the diastolic movement of the AV plane[6].

Several methods have been proposed to deal with some of these issues. The automated cardiac output method (ACM) introduced a method less sensitive to the

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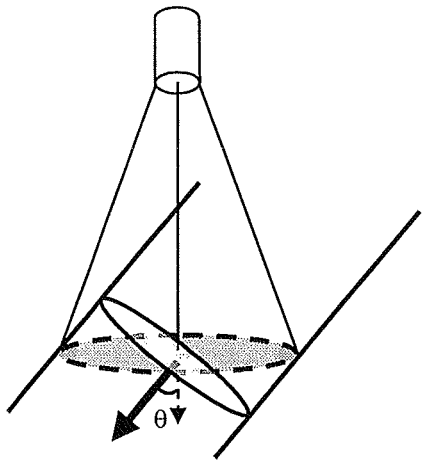


Figure 1. The angle independence was based on the following principle: due to misalignment between the Doppler beam (– – –arrow) and blood flow (—arrow) by an angle (θ), the recorded velocity (– – –arrow) was under-estimated by cos (θ). Further, if the measure surface (– – –) was misaligned with the LVOT (—) by an angle (θ), the surface would appear wider by a factor of 1/cos (θ). Thus, the overestimation of the measure surface cancelled out the underestimation of blood flow velocities. Velocity vectors perpendicular to a spherical sampling surface and equidistant to the transducer were computed.

variations in the blood flow velocity profile and the angle dependency of the Doppler beam[7,8].

An angle-independent multiplane method to measure volumetric flow has also been described by Poulsen *et al.*[9]. The principle of the angle independence of the Doppler beam is illustrated in Figure 1.

Kim *et al.* have validated this concept by comparing measurements of volumetric mitral flow using multiplane colour Doppler imaging to thermodilution[10] and MRI[11].

We used a new freehand 3D-colour flow imaging method that has recently been described[12,13]. The purpose of this study was to compare calculations of CO by using the 3D-colour flow method at the mitral flow area with measurements in the aortic annulus. Three-dimensional aortic and mitral volumetric flow was also compared to the conventional echocardiographic method (2D PW) in the LVOT.

Methods

Equipment

A digital ultrasound scanner (System Five, GE Vingmed Ultrasound, Horten, Norway) with a 2·5 MHz phased array transducer was used for all echocardiographic measurements. A magnetic locating device (Flock of Birds, Ascension Technology Corporation, Burlington, VT, U.S.A.) continuously recorded the spatial position and orientation of the transducer during the recording. This system consisted of a tramsmitter that generated a magnetic field. The transmitter was located 25–60 cm from the sensor, which was mounted on the transducer. These elements were connected to a control unit, which in turn was connected directly to the scanner. The control unit recorded the position of the sensor and the spatial position of each recorded frame, which was stored in the digital replay memory of the scanner. Digital raw ultrasound data were transferred to an external standard PC (Pentium II processor, 256 MB RAM). Scanconverting and further processing were performed with a prototype version of the EchoPAC-3D software (GE Vingmed Ultrasound, Horten, Norway)[14] and MATLAB (The MathWorks, Inc., U.S.A.).

Data Acquisition and Processing

Recordings of tissue were obtained by second harmonic imaging mode with a transmit frequency of 1·7 MHz. For colour flow imaging, the centre frequency of the transmitted pulse was 2·5 MHz.

The subjects were examined in the left lateral decubitus position. The subject rested 15 min before blood flow velocities were recorded. Prior to the 3D recordings, CO was measured by the 2D PW Doppler method. The diameter of the aortic annulus was measured close to the insertion of the aortic valve visualized in a parasternal long axis view. Blood flow velocities were obtained from the centre of LVOT as described by Rossvoll *et al.*[2]. Modal velocities were traced in the Doppler spectrum and the velocities under the curve were integrated giving the velocity time integral (VTI). CO was calculated by averaging three to five heartbeats.

To reduce cardiac movement while acquiring 3D data, recordings were done in passive-held end expiration. Images and velocities were acquired from the transthoracic apical position in the five-chamber view. The sector angle was set to a minimum and the colour flow sector was minimized to obtain as high a frame rate as possible, but large enough to cover the LVOT or the mitral valve. The transducer was tilted in a fanlike manner from the posterior wall toward the anterior, or vice versa, during 10–20 cardiac cycles to cover the entire flow area. For each frame, the sensor position co-ordinates, the digital ultrasound data and the ECG signal were stored in the digital replay memory. In EchoPAC-3D, frames with the same temporal delays relative to the R-wave in the ECG signal were used to reconstruct 3D volumes throughout the cardiac cycle. Typically, an aortic recording obtained at 59 frames/s and heart rate of 61 beats per minute resulted in 17

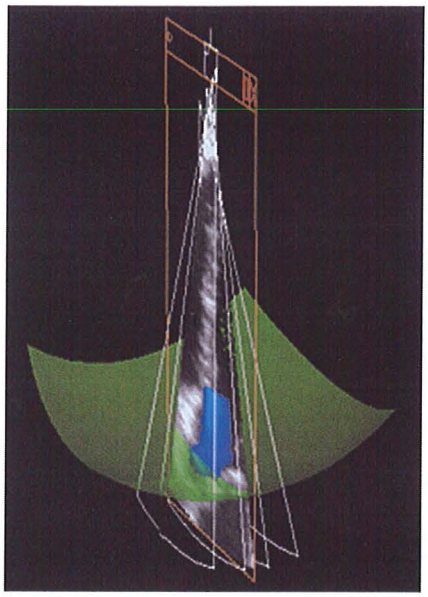


Figure 2. A five-chamber view and colour flow in the LVOT. The white sectors represent additional slices within a 3D volume. The green area represents a spherical cross-sectional level of measurement. All measured blood flow velocity vectors are perpendicular to this area.

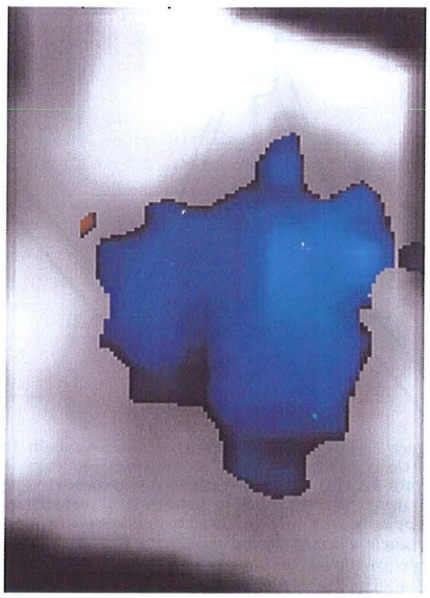


Figure 3. Cross-sectional view of aortic flow velocities perpendicular to the green area in Figure 2 encoded as colour flow.

volumes during a systole and a mitral recording 12 3D-volumes during diastole obtained at 46 frames/s.

Aortic Flow

A spherical cross-sectional surface (Fig. 2) was positioned at the level of the septal insertion of the aortic valve identified in start systole and kept at this depth throughout the systole (method A). Velocity vectors perpendicular to the surface and thus aligned with the ultrasound beam were extracted from the 3D data and reorganized into 2D slices (Fig. 3) for consecutive time intervals. In the same manner, a spherical surface 0·5 cm proximal to the annulus was applied (method B).

In addition, we placed a spherical surface at the level of the annulus in the start systole and end systole. By interpolating levels between these extremes, the spherical surface tracked the aortic annulus throughout systole. The velocity of this movement was calculated and added to the blood flow velocities. This was done by measuring the movement of the aortic annulus during systole and the corresponding time interval (method C). In this way we compensated for the underestimation of blood flow velocities, since the annulus moves in the opposite direction of the fixed PW measure point during systole.

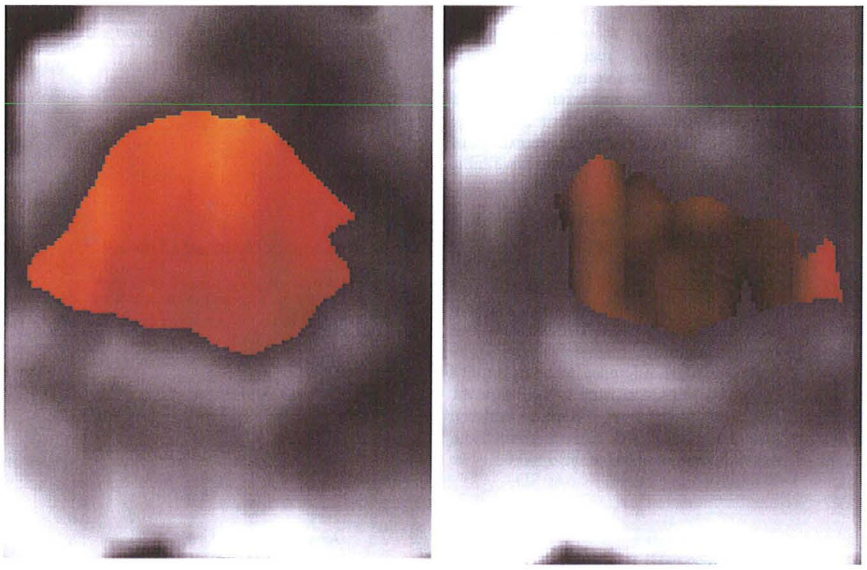
In the 2D slice reconstruction (Fig. 3) we defined a region of interest (ROI) at the onset of systole and at the end systole, interpolating the slices in between, thus enabling us to remove blood flow velocities from surrounding vessels. In the MATLAB program the tissue and Doppler signals were filtered, and aliased blood flow velocities baseline shifted according to Berg *et al.*[13]. All velocity vectors perpendicular to the cross-sectional surface in each time step were integrated, giving the total blood flow.

Median frame rate in the 18 3D recordings was 59 (range 45–66) frames/s. Median temporal resolution was 17 (range 15–22) ms. The jitter artefact, defined as timing error between two consecutive slices due to lack of synchronization between the ECG trigger and the image sampling, ranged from 7·6 to 11 ms.

To investigate the repeatability of analyses, we conducted an intra-observer study. We repeated the CO calculations from the first 12 recordings at the fixed level of the aortic annulus in MATLAB twice. An inter-observer study was also performed in MATLAB in the 10 first subjects.

Mitral Flow

The method was modified to enable volumetric calculations of the biphasic mitral flow. In EchoPAC-3D, the



(A) (B)

Figure 4. Cross-sectional view of blood flow velocities in mitral flow perpendicular to the spherical moving sample surface, encoded as colour flow. (A) The E wave of diastolic flow; (B) The A wave of diastolic flow.

start of the heart cycle was set to 300 ms before the R wave in the ECG. A measure surface was positioned at the mid-level of the medial part of the mitral valve, i.e. ~1 cm proximal to the mitral ring, and tracked the mitral valve throughout diastole. The E and A waves in mitral blood flow were treated separately. The movement of the mitral valve plane during the E wave was not uniform, and to compensate for this a surface was manually placed at the start, middle and end of the E wave. The surface depths were interpolated to enable movement of the surface. The start of the early wave of mitral flow was determined by the valve opening and ended at the end of the annulus movement with partly valve closure and no visible colour flow. A similar procedure was repeated during the atrial systole; the only difference was that the surface depths were interpolated between start and end of atrial flow. The first and the last frame with visible colour flow determined the atrial systole. Blood flow velocity vectors were extracted from the 3D data and reconstructed in 2D slices, as illustrated in Figure 4A and 4B. In MATLAB, the velocity of the valve movement was added to these vectors and were integrated over time to calculate volumetric flow.

Median frame rate was 46 (range 41–47) frames/s. The temporal resolution was median 22 (range 21–24) ms and jitter artefact was median 11 (range 10·5–12) ms.

An intra- and interobserver analysis was conducted by repeating analysis of the first 11 recordings obtained by 3D mitral colour flow imaging in MATLAB twice.

Subjects

Recordings were acquired from 24 subjects, 16 men and eight women with no history of cardiac disease. Median age was 26·5 (range 19–48) years. All volunteers were in sinus rhythm and gave informed consent to participate in the study. The institutional committee on human research approved that the study was in accordance with the Helsinki declaration.

Aortic Recordings

One of the subjects was excluded due to unstable electrocardiogram (ECG) and five due to poor 3D image quality. Thus, recordings from 18 were analysed to calculate CO. In addition, in one of the subjects analysis of velocity vectors from a fixed surface at the level of the aortic annulus were excluded prior to CO calculation in MATLAB, due to poor 3D-image quality.

Mitral Recordings

Three-dimensional mitral flow reconstruction was possible in 19 individuals and was compared to pulsed Doppler in the LVOT. The rest was excluded due to unstable electrocardiogram (ECG) or poor 3D image quality. Due to mismatch in successful 3D recordings of mitral flow vs. aortic, only 15 recordings were available for this comparison.

Statistics

The results were evaluated according to Bland and Altman, i.e. the difference between the two methods were compared with the average of the same two[15]. The results were given as mean of differences ± two standard deviations (SD). Paired *t*-test was used to compare the difference in heart rate and the mean difference between the 3D methods and the 2 PW Doppler method. The level of significance was chosen at $P<0{\cdot}05$. The coefficient of variability was defined as two SD.

Results

Aortic Flow

The range of agreement between method A and the 2D PW Doppler method was 0·2 ± 1·7 l/min (mean ± 2 SD). Between method B and the 2D PW Doppler method it was 0·3 ± 1·5 l/min (mean ± 2 SD), and between method C and the 2D PW Doppler method 0·7 ± 1·7 l/min (mean ± 2 SD). Plots of the difference between the methods and their mean are presented in Figure 5a–c. According to analysis, in the 10 first recordings in method C the missing volume corresponded to 9% of CO (95% CI: 0·4–0·5) l/min).

There was no difference in heart rate during the recordings. Median heart rate during 2D PW Doppler recording was 63 beats/min. Median heart rate during 3D recordings was 61 beats/min. 95% confidence interval for the difference in heart rate was (−5·1–2·3).

Intra-observer: the coefficient of repeatability was 0·6 l/min. One clear outlier was excluded (mean difference of −2 l/min). Inter-observer: the coefficient of repeatability was 0·9 l/min.

Mitral Flow

The range of agreement between 3D mitral and 3D aortic flow was 0·04 ± 1·32 l/min (mean differences ± 2 SD), and between 3D mitral blood flow and the 2D PW Doppler method in the LVOT it was 0·88 ± 1·64 l/min (mean of differences ± 2 SD).

Plots of the difference between the methods and their mean are presented in Figure 6a and 6b.

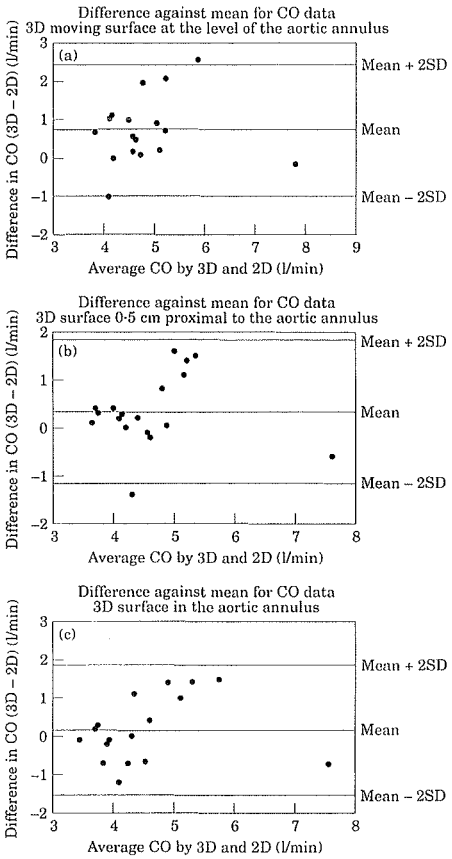


Figure 5(a–c). Difference against mean for CO data. 3D compared to the 2D PW Doppler method (2D). Reference lines are mean of difference and mean ± two SD. (a) Three-dimensional moving surface following the aortic annulus compared to the 2D PW Doppler method. (0·7 ± 1·7) l/min, $n=18$ (there are two identical values in the plot). (b) Three-dimensional surface 0·5 cm proximal to the aortic annulus compared to the 2D PW Doppler method. (0·3 ± 1·5) l/min, $n=18$. (c) Three-dimensional surface in the level of the aortic annulus compared to the 2D PW Doppler method. (0·2 ± 1·7 l/min, $n=17$.

The volume due to movement of the valve plane during diastole constituted 11% of the total volume. An example of conventional 2D PW Doppler from the LVOT compared to 3D aortic and mitral flow with and without the volume represented by the valve plane movement is presented in Table 1. There was a significant difference in mean CO between 3D mitral

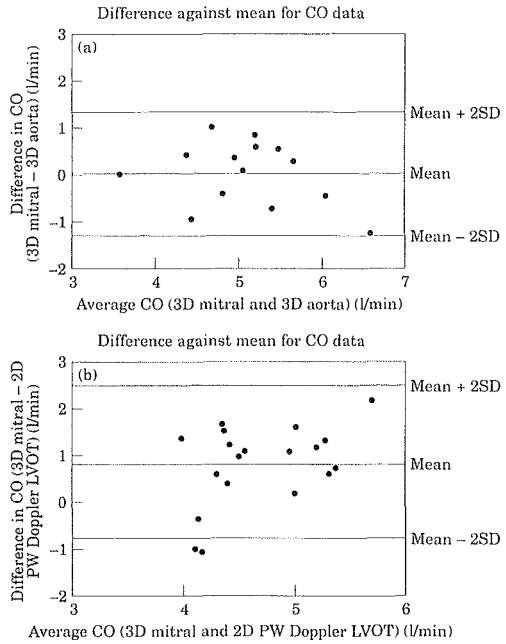


Figure 6. (a) Differences against mean for CO data. Three-dimensional mitral flow compared to 3D aortic annulus flow. Reference lines are mean of differences and mean ± two SD. The range of agreement was 0·04 ± 1·32 l/min (mean of differences ± 2 SD). $n=15$. (b) Difference against mean for CO data. Three-dimensional mitral flow compared to the 2D PW Doppler method. The range of agreement was 0·88 ± 1·64 l/min (mean of differences ± 2 SD). $n=19$.

flow and flow in the LVOT obtained by the 2D PW Doppler method. $P=0·001$ and 95% CI (0·4 to 1·24). By excluding the volume represented by the movement of the valve plane, the mean difference was non-significant: $P=0·17$ and 95% CI −0·13 to 0·65.

There was no significant difference in heart rate between the recordings of 3D mitral- and 3D aortic flow: $P=0·44$ and 95% CI −6·6 to 0·98.

Table 1. An example of conventional 2D PW Doppler from the LVOT compared to 3D aortic and mitral flow with and without the volume represented by the valve plane movement*.

2D PW Doppler in the LVOT	4·6 l/min
3D mitral flow with correction*	5·8 l/min
3D mitral without correction*	5·1 l/min
3D aortic flow with correction*	5·5 l/min
3D aortic flow without correction*	5·1 l/min

There was a significant difference in heart rate between the recordings of 3D mitral flow and the 2D PW Doppler method in the LVOT: $P=0·03$ and 95% CI −7·6 to −0·5.

Intra-observer: the coefficient of variability was 0·4 l/min, with no bias. One clear outlier was omitted. Inter-observer: the coefficient of variability was 0·7 l/min. One clear outlier was omitted (the same as in the intra-observer study).

Discussion

In this study, a transthoracic 3D-colour flow method, using a moving sampling surface, has been used to measure volumetric aortic and mitral flow. The 3D method has several advantages compared to the conventional 2D PW Doppler method. The 3D method is angle-independent, and assumptions about geometry or the blood flow velocity profile are not necessary.

Possible errors in measuring a correct subvalvular diameter are avoided. The acquisition time was short, approx. 20 s, and by using digital raw data acquired at high frame rate, better temporal resolution than video based 3D systems is ensured[12]. By using a magnetic locating device combined with high frame rate imaging, allowing the transducer to be freely tilted over the region of interest during acquisition of digital raw ultrasound data, a full 3D dataset was obtained. The 3D freehand method using the Bird system enables manual correction during a recording to maintain optimal acoustic accesses.

The only significant bias was observed, as expected, where the 3D-measure surface followed the aortic annulus or the AV plane and comparisons were made with the 2D PW method. The missing volume due to the aortic annulus movement during systole was not added to the 2D method. This volume constituted 9% of the CO according to our results. Similarly, the relative velocity of mitral blood flow is the sum of the blood flow velocity and the rate of mitral annulus recoil toward the atrium. As the mitral annulus moves in the opposite direction of inflow, the inflow will be underestimated using a fixed measure surface. Several investigators have commented on this limitation to previous ultrasound methods[6,10,16]. Kim *et al.* calculated this underestimation to be 7% of cardiac output[10]. In our study it was 11% in healthy subjects. In fact, 11% of the total 16% in mean difference between the 3D mitral flow and the 2D PW method in the LVOT can be explained by the volume represented by the movement of the valve plane. By excluding this volume, there was no significant bias between 3D mitral vs 2D PW Doppler estimates of CO.

Another possible reason for the observed bias is the angle dependency of the 2D PW Doppler method.

A problem in validation of new cardiac output methods is the lack of a 'gold standard'. We chose to compare our 3D CO measurements with a conventional 2D PW Doppler method that is used by several groups and is the standard method in our hospital. The precision of this method has been described previously[17,18]. A range of agreements similar to our results has been reported in studies validating the 2D PW Doppler method in the LVOT vs. thermodilution[19]. The freehand 3D-ultrasound imaging technique has been highly accurate in calculations of volumes in water filled balloons[12] but has not been tested in roller pump models. However, by applying the method to volumetric measurements of both mitral and aortic flow in subjects without valve regurgitation, a close agreement would favour the accuracy of the method. Our method yielded a range of agreement between 3D mitral flow and 3D aortic flow of $0{\cdot}04 \pm 1{\cdot}32$ l/min (mean of differences $\pm$ 2 SD).

A number of 2D ultrasound methods have been proposed to measure volumetric flow[1,22,23]. However, all made assumptions about the effective flow area and the velocity profile that exhibit significant interindividual variations[5]. Further, in the previous methods fixed sample volumes were used. Lewis *et al.* used PW Doppler in the mitral annulus vs. PW Doppler in the LVOT which yielded a range of agreement in CO measurements of $0{\cdot}14 \pm 1{\cdot}28$ l/min (mean of differences $\pm$ 2 SD) in healthy individuals (based on data from Table 1, $n=24$ patients without valve regurgitation)[23].

Several investigators have reported good results by integrating velocity vectors perpendicular to a spherical surface, a principle that we have applied to a 3D freehand method. Tsujino *et al.*[20] described the principle and applied it to large vessel phantoms. Sun *et al.*[21] applied this principle to the human LVOT *in vivo* in two orthogonal planes and found that measurements correlated well with the Fick oxygen method.

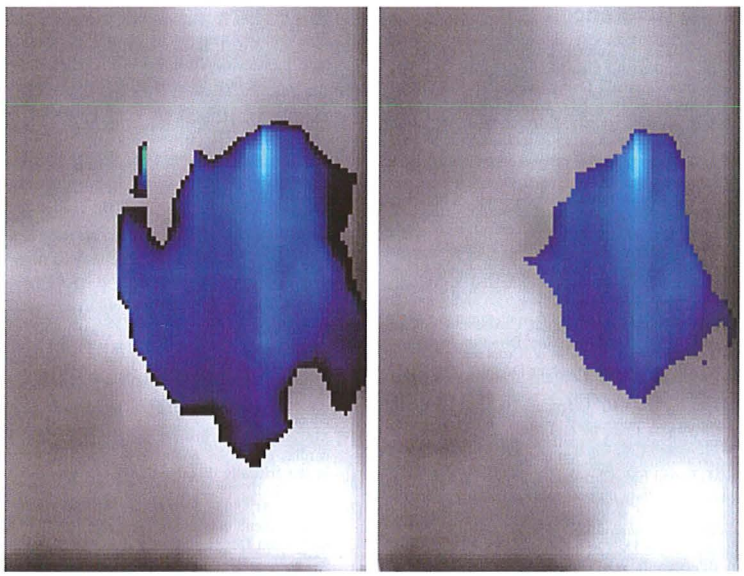
The ACM introduced a method less sensitive to angle errors and assumptions of the velocity profile but the sample volume remained fixed throughout diastole, as in the other mentioned methods. Further, recordings were obtained from two- and four-chamber views and averaged[8]. Van Camp *et al.*[24] used the ACM. Their study yielded a range of agreement between mitral flow and flow in the LVOT of $-0{\cdot}26 \pm 1{\cdot}26$ l/min (mean of differences $\pm$ 2 SD) using two imaging planes. Sun *et al.* reported a higher agreement between mitral and aortic flow using the ACM method: $-0{\cdot}09 \pm 0{\cdot}84$ l/min (mean of differences $\pm$ 2 SD)[8].

As mentioned previously, Kim and Paulsen proposed an angle-independent multiplane colour flow method in which blood flow velocities were integrated across a spherical surface similar to our method. They used rotating stepper motor probes and asynchronous sampling of blood flow acquired at low frame rate[10,11]. The probe must be kept at the same position during the recording to avoid artefacts in the reconstruction of the 3D volumes. In one study they compared a multiplane method in mitral flow to MRI in the aorta ascendens in healthy individuals. The range of agreement was $0{\cdot}21 \pm 0{\cdot}83$ l/min (mean of differences $\pm$ 2 SD)[11].

Limitations

All the recordings in our study were acquired before any evaluations of the 3D reconstruction were done. Thus, if the 3D reconstruction had been evaluated on-line, or off-line immediately after scanning each subject, a higher rate of success would have been achieved as a new, and presumably better, recording could replace the corrupted recording. It may be difficult to cover the region of interest due to limited access between the ribs. Combination of several 3D scans may solve this problem.

Colour flow can be adjusted by various machine settings. By varying tissue gain, reject, compress and tissue priority to their extremes, overestimates in CO relative to the initial setting were maximum 67%. However, such adjustments were obviously wrong, as tissue velocity signals were interpreted as flow, or vice versa, as shown in Figure 7. Nevertheless, some of the variability



(A) (B)

Figure 7. By changing tissue priority, variations in CO up to 67% were registered. However, as illustrated in (A), flow virtually flooded the surrounding tissue and was obviously wrong, compared to (B) that was used in the study.

in our measurements of CO may be attributed to adjustment problems. The proposed algorithm to unwrap aliased velocities by Berg *et al.*[13] led to some loss of low blood flow velocities. To avoid aliasing, it is important to increase the pulse repetition frequency.

The method was not suitable to investigate persons with irregular RR intervals, such as atrial fibrillation, as this would corrupt the 3D reconstruction. Selecting the RR intervals of interest during the recording may solve this problem. However, this was not a major limitation to our study, as only one of the dropouts in our study was due to unstable ECG. Subjects who are unable to hold their breath for a short period of time will be excluded, as a minimum of time is required to cover the region of interest.

Although the acquisition time was short, post-processing was time-consuming. Storage on the image replay buffer took around 1 min and transfer of raw data approx. 30 seconds. In the most time-consuming method in the aortic recordings (method C), 3D reconstruction in EchoPAC 3D and processing in MATLAB to calculate CO took 10 min. Acquisition and data processing of mitral blood flow took approx. 20 min altogether. As a tool for research this is fast enough, but as a clinical tool on-line applications are required. However, the method is well suited for further automization with on-line measurement of CO.

Finally, this study was conducted on young healthy volunteers, and one should be careful in generalizing the feasibility of the method in all clinical settings.

Conclusion

The range of agreement between 3D mitral and 3D aortic blood flow was good, with a bias of no more than 0·04 l/min. The common pitfalls in pulsed wave ultrasound methods to calculate CO were avoided, as the 3D method was angle-independent, no assumptions about the velocity profile were made, and a moving sample surface was applied. The acquisition of data was fast and easy and high temporal resolution was achieved.

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Paper IV

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Velocity Profiles in Mitral Blood Flow Based on Three-dimensional Freehand Colour Flow Imaging Acquired at High Frame Rate

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Aims: To describe the mitral blood flow velocity distribution, we applied a freehand dynamic three-dimensional (3D) colour flow method using a moving sample surface that followed the mitral apparatus during diastole.

Methods: Nineteen healthy volunteers were studied. The ultrasound data were captured from 10–20 heartbeats at high frame rate (mean 46 frames/s) while freely tilting the transducer in an apical position. A magnetic position sensor system recorded the spatial position and orientation of the probe. Blood flow velocities were integrated across a spherical surface. In volumetric blood flow measurements this would yield angle independence of the Doppler beam. Raw digital data were analysed off-line with no loss of temporal resolution.

Results: The ratio of the maximum velocity time integral (VTI) to the mean VTI was mean 1·3 (range 1·1–1·6). At the time of peak flow the ratio of the maximum to the mean velocity was mean 1·5 (range 1·2–2·6).

Conclusion: The blood flow velocity profile was non-uniform. By using a single sample volume in Doppler measurements of the maximum VTI errors ranging from 10 to 60% may be introduced in calculations of stroke volumes.

(Eur J Echocardiography 2000; 1: 252–256)

Key Words: three-dimensional colour flow; velocity profiles; high frame rate; freehand; ultrasound.

Introduction

Both Doppler colour flow and MRI studies have been conducted to illuminate the uncertainty regarding the blood flow velocity distribution in mitral flow. According to these studies, mitral blood flow does not pass through the mitral orifice with spatially homogenous velocities, i.e. the velocity profile is not flat[1–3]. The skew compromises the use of pulsed Doppler in measurements of volumetric flow. However, recordings from only one plane and a fixed sample level relative to the transducer limited the colour flow studies. Furthermore, only velocity profiles from the early mitral blood flow (E wave) were studied. Low temporal resolution, a fixed level of measurement and long acquisition time limited the MRI study.

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A new freehand three-dimensional (3D) colour flow imaging method using digital raw ultrasound data acquired at high frame rates has recently been presented[4–7]. The purpose of this study was to use a modification of this method to describe the velocity profile in the biphasic mitral blood flow. A spherical sampling surface that tracked the mitral valve throughout the diastole was applied in measurements of blood flow velocities. By using a single sample volume in Doppler measurements of the maximum velocity time integral (VTI), potential errors may be introduced in calculations of stroke volumes. We wanted to assess this potential error.

Methods

Subjects

All subjects gave informed consent to participate. The study was in accordance with the regional committee on

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human research and the Helsinki declaration. Twenty-four subjects were included in the study. Mean age was 27·8 (range 19–48) years. Five were exluded due to poor quality of 3D reconstruction or unstable electrocadiogram.

Equipment

The 3D-colour flow method has been described in detail elsewhere and has been applied to calculation of cardiac output in the aorta and mitral valve[4–6]. In this study, modifications were made to enable calculation of a variety of parameters used to describe the blood flow velocity distribution, such as the maximum velocity, the mean velocity, the visualization of these, and calculation of the maximum VTI and the mean VTI. A digital ultrasound scanner (System Five, GE Vingmed Ultrasound, Horten, Norway) with a 2·5 MHz phased array transducer and a magnetic locating device (Flock of Birds, Ascension Technology Corporation, Burlington, VT, U.S.A.) were used for data acquisition. Post-processing of data was performed on an external standard PC with a prototype version of the EchoPAC-3D software (GE Vingmed Ultrasound, Horten, Norway)[7] and MATLAB (The MathWorks, Inc., U.S.A.).

Data Acquisition

The subjects were examined lying in the left lateral position. The recordings were made in passively held expiration. In an apical view, the transducer was tilted in a fanlike manner during 10–20 heartbeats to cover the entire mitral flow area.

Data Processing

In EchoPAC-3D, the start of the heart cycle was set to 300 ms after the R wave in the ECG in order to encompass the entire diastole. The temporal resolution of the 2D data defined as the inverse value of frame rate was preserved in the 3D dataset and ranged from 22 to 24 ms corresponding to a maximum temporal jitter of ± 11–12 ms between the scan planes in the 3D volumes. A spherical cross-sectional surface was positioned at the mid-level of the medial part of the mitral valve and tracked the mitral valve throughout diastole. The E wave and atrial blood flow (A wave) were treated separately. Blood flow measured by Doppler gave velocities relative to the ultrasonic probe. In order to get correct velocity values, representing the flow through the valve, the movement of the mitral valve should be taken into account. In MATLAB, the blood flow velocities were calculated relative to the moving spherical surface and true blood flow velocities through the mitral valve were obtained. The b-mode and colour Doppler signals were filtered separately, and aliased blood flow velocities baseline shifted according to Berg *et al.*[5]. In this way a distribution of the blood velocity component perpendicular to a spherical surface close to the mitral valve was obtained at any time instant through the cardiac cycle. By integrating this velocity distribution over the surface, instantaneous volume flow was obtained independent of the Doppler beam angle.

As a quantitative assessment of the velocity distribution, the ratio of the maximum velocity (max V) to the mean velocity (mean V) at peak flow described any possible skew. Further, the location of maximum velocity and mean velocities in each slice were visualized (Fig. 1).

To assess the sensitivity of sample-volume position in PW-Doppler measurement, the VTI was calculated at each point of the spherical surface covering the mitral orifice. The time interval for integration could be manually adjusted by the operator to select diastolic E wave, A wave, or the whole cardiac cycle. Integration of VTI over the surface gives the total volume passing through the mitral valve during the integration time interval. The ratio of the maximum VTI to the mean VTI was compared and illustrates the potential error by measuring the maximum VTI with Doppler from a single sample volume in calculations of stroke volumes.

Results

The velocity profiles were variably skewed. The ratio of the maximum VTI to the mean VTI was mean 1·3 (range 1·1–1·6). By assuming that the mean VTI is the correct estimate in volumetric calculations using Doppler, the use of the maximum VTI would lead to errors ranging from 10 to 60%, with an average of 30%. At the time of peak flow the ratio of the maximum to the mean velocity was mean 1·5 (range 1·2 to 2·6). The data are presented in Table 1.

The location of the mean velocity and maximum velocity was followed throughout diastole, as illustrated in Figure 1. Most often the maximum velocities at peak flow were located anteriorly (Fig. 2).

Discussion

In this study, the mitral blood flow velocity profile in humans has been described using a new 3D colour flow method with a moving sampling surface that tracked the mitral flow channel throughout the diastole. The 3D data were captured in a fast and easy manner by using a freehand magnetic locating device. Raw digital data were acquired at high frame rates that improved temporal resolution. The velocity profiles yielded a variably skew with the highest velocities located anteriorly. Measurements of the maximum VTI would overestimate calculations of stroke volumes as described in previous studies.

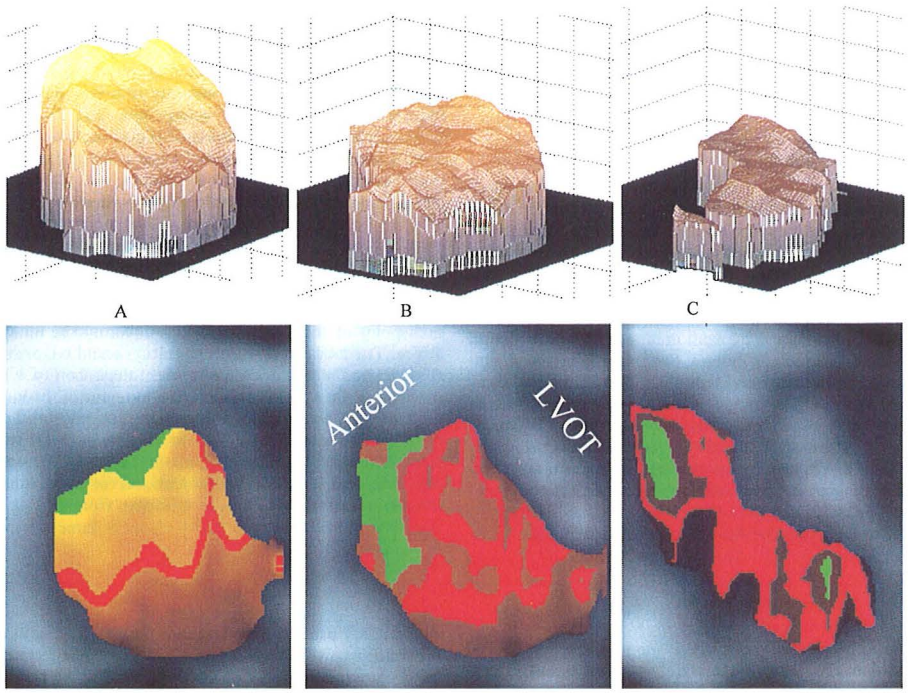

Figure 1. Examples of three-dimensional velocity profiles from peak flow in early diastole, late in the E wave and during the A wave. The height of the profiles is proportional to blood flow velocities. The corresponding 2D slice is located below each profile. LVOT=left ventricular outflow tract. Colour codes: red=mean velocity; green=maximum velocity.

The first study that described the mitral velocity profile was conducted invasively in dogs, using the Pitot principle[8]. At the level of the mitral annulus the profile was flat, i.e. plug flow. At the valve outlet, a skew was described in mid and late diastole.

The initial studies regarding the skew in the mitral velocity profile in humans were based on ultrasound colour flow imaging from only one plane[1,2]. Samstad *et al.*[2] found that the maximum VTI in the E wave overestimated the mean VTI by 45% and a wide inter-individual variability (20–120%) in normal subjects. Thus, the assumption that mitral blood flow is plug flow was no longer valid. However, the A wave was not included in this study and a fixed level of measurement was used as opposed to our 3D method. The highest velocities were located anteriorly, as confirmed by our findings. The skew at peak flow, described as maximum velocity/mean velocity at peak flow, was similar in both studies, 1·6 (range 1·4–2·2) *vs.* 1·5 (range 1·2–2·6). The maximum VTI/mean VTI was less in our study, 1·3 (range 1·1–1·6). The reason for this difference may be due to several factors, such as differences in the study population, recordings from only one plane in the conducted 2D study, and errors due to transducer movement and fixed sample volumes.

A pulsed wave Doppler technique has been applied in studies of mitral velocity profiles in pigs[9]. A skewed profile at the level of the annulus and leaflet tips was described and the importance of these findings in calculations of cardiac output was illuminated. However, the method was hampered by several factors. It was invasive, as the probe was placed onto the epicard and the acquisition time was long, 30–40 min *vs.* approx. 20 s in our study. Finally, when using this rotational method it is vital to maintain a stable position during recording to avoid reconstruction artifacts. Preliminary results from 2D colour flow imaging using frame rates of 80–90 frames/s have been presented. Biphasic flow was studied and the findings were similar to ours, but were limited by recordings from only one plane[10].

Real-time 3D imaging is a promising tool for acquisition of ultrasound data. Although the acquisition time is

Table 1. Quantitative assessment of the blood flow velocity distribution.

Subject	Max V	Mean V	Max V/Mean V	Max VTI	Mean VTI	Max VTI/Mean VTI
1	77·1	57·9	1·3	13·4	10·6	1·3
2	76·1	56·3	1·4	14·1	11·0	1·3
3	84·9	43·1	2·0	11·0	7·7	1·4
4	81·7	68·6	1·2	12·0	10·2	1·2
5	87·7	55·2	1·6	15·3	12·4	1·2
6	80·1	58·7	1·4	14·6	11·4	1·3
7	78·3	63·0	1·2	6·9	5·8	1·2
8	77·9	44·7	1·7	13·5	12·0	1·1
9	83·5	51·9	1·6	12·3	9·4	1·3
10	83·0	57·1	1·5	12·8	9·8	1·3
11	64·7	44·6	1·5	10·2	8·3	1·2
12	98·0	67·0	1·5	10·1	7·6	1·3
13	110·4	63·2	1·7	12·0	8·3	1·4
14	59·8	45·5	1·3	11·1	9·0	1·2
15	51·1	39·2	1·3	11·6	9·3	1·2
16	123·9	99·9	1·2	25·6	16·0	1·6
17	98·3	38·2	2·6	21·9	14·1	1·6
18	77·8	61·1	1·3	15·8	12·8	1·2
19	67·1	54·9	1·2	16·3	13·0	1·3
Average	82·2	56·3	1·5	13·7	10·4	1·3
Min	51·1	38·2	1·2	6·9	5·8	1·1
Max	123·9	99·9	2·6	25·6	16·0	1·6

V = velocity, VTI = velocity time integral. Mean V = mean velocity at time of peak flow.

short, the technique which is based on 2D phased array matrix is still hampered by limited spatial and temporal resolution[11]. Another technique, based on fast rotating phased array probe for real-time 3D acquisition, has recently been described by Djoa *et al.*[12]. High frame rate combined with fast rotation of the probe resulted in 16 3D tissue volumes/s. To our knowledge, the methods have not yet been applied to quantitative analysis of flow.

Detailed complete cross-sectional velocity profiles have been described by MRI. Kupari *et al.*[3] found marked spatial inhomogeneity in normal humans that confirmed the results from the ultrasound studies. The maximum velocity was in the anterior annulus in the E wave shifting posteromedially in late diastole. However, the temporal resolution was limited, 30–40 ms as opposed to 22–24 ms in our 3D dataset. Furthermore, the sample volumes were fixed. Finally, the acquisition time was long, up to 256 heart cycles *vs.* 10–20 in our study. Fujimoto *et al.*[13] described a skew with the highest velocities located to the septal side. They concluded that this skew was of minor importance. However, the temporal resolution was low, up to 50 ms, and they may have missed the peak values in the E wave. Others have described the mitral velocity profile using MRI with improved temporal resolution (28 ± 4 ms (SD))[14,15]. However, only velocities across one diameter were studied. Houlind *et al.*[13] confirmed the variable skew in the E wave that would compromise calculations of flow from single point velocity measurements. Kim *et al.*[14] described the profile as flat in the mitral orifice and slightly skewed at the level of the mitral valve tips, with the maximum velocities located posteriorly.

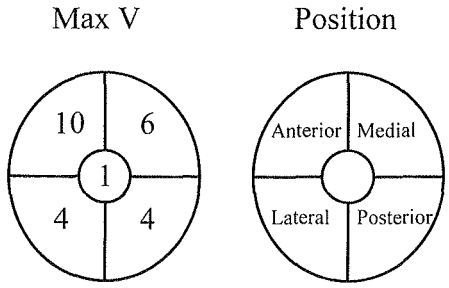

Figure 2. The appearance of maximum velocities (Max V) at peak flow in each of the five areas in the flow region was counted and summarized. Number of subjects = 19.

Study Limitations

Five subjects were excluded due to unstable ECG or poor 3D reconstruction. This was discovered during post-processing of the data, which was conducted after all data from all subjects were acquired. Thus, by evaluating the 3D reconstruction immediately after the recording, a new recording can be acquired to replace the corrupted one.

The described method is not suitable in for subjects with irregular heart rhythm or those unable to hold their breath for a short period of time. Limitations in detection and accuracy of the blood flow estimate due to jitter artefact and aliasing are discussed elsewhere[4].

Conclusion

In summary, we have described the velocity profile in human mitral blood flow by using a new freehand 3D-colour flow imaging method. Blood flow velocity vectors were measured through a moving sample surface that followed the mitral apparatus throughout the diastole. Raw ultrasound data were obtained at high frame rate and analysed, which yielded a better temporal resolution.

A non-uniform blood flow velocity profile was found. By using a single sample volume in Doppler measurements of the maximum VTI, errors ranging from 10 to 60% may be introduced in calculations of stroke volumes.

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Paper V

Blood flow velocity profiles in the aortic annulus: A three-dimensional freehand color flow imaging study.

Short title: Haugen. 3D-velocity profiles in the aortic annulus.

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Abstract:

Background: The use of a single sample volume in Doppler measurements of the velocity time integral (VTI) may introduce errors in calculations of stroke volumes, shunts, regurgitate fractions and aortic valve area. To study the blood flow velocity distribution and assess this potential error, we used a dynamic three-dimensional (3D) color flow imaging method.

Methods and results: 17 healthy volunteers were studied. The ultrasound data were captured from 10-20 heartbeats at high frame rate (mean 57 frames/s) while freely tilting the transducer in the apical position. A magnetic position sensor system recorded the spatial position and orientation of the probe. The raw digital ultrasound data were analyzed off-line with no loss of temporal resolution. Blood flow velocities were integrated across a spherical surface that tracked the aortic annulus during systole.

The mean ratio of the systolic maximum to the systolic mean VTI was 1,4 (range 1,2 to 1,5). At the time of systolic peak flow the mean ratio of the maximum to the mean velocity was 1,5 (range 1,1 to 2,0).

Conclusion: The blood flow velocity profile was non-uniform and generally skewed towards the septum. By using a single sample volume in Doppler measurements of the VTI errors ranging from 20 to 50 % may be introduced in calculations of stroke volumes.

Key words: velocity profiles, three-dimensional, high frame rate

Introduction:

Knowledge of the velocity distribution in the aortic annulus is of great importance to the clinician due to several reasons: The pulsed wave Doppler technique in measurement of stroke volumes assumes a flat profile [1]. Errors can be introduced as the sampled velocities over- or underestimate the mean velocity time integral. This technique is applied to calculation of stroke volumes in the left ventricular outflow tract (LVOT), the pulmonal artery and mitral orifice and will affect calculations of shunts [2] and regurgitate fractions [3,4] as well. Further, any error in measurement of velocities in the LVOT will influence calculations of the aortic valve area in aortic stenosis when using the equation of continuity [5].

Invasive techniques such as perivascular pulsed wave (PW) ultrasound Doppler [6], intraluminal PW ultrasound Doppler [7,8] and hot-film anometry [9] as well as MRI [10-12] have been used in studies of velocity profiles in the ascending aorta. Non-invasive ultrasound [13-16] and MRI [17] have been used in studies of the velocity profile in the LVOT and the aortic annulus and have shown that the profile in the distal left ventricular outflow tract and the aortic annulus is skewed with the highest velocities located toward the septum. However, recordings from only one or two cross sectional planes were limitations to the ultrasound color flow studies. Further, blood flow measured by Doppler gives velocities relative to the direction of the ultrasound beam propagation. In order to get correct velocity values, representing the flow through the valve, the movement of the annulus should be taken into account. Similarly, low temporal resolution, a fixed level of measurement and long acquisition time were

limitations to the MRI study [17]. We wanted to apply a freehand three-dimensional (3D) color flow imaging method [18-19] using digital raw ultrasound data acquired at high frames rate to assess the blood flow velocity distribution in the aortic annulus. Blood flow velocities were measured through a spherical surface that followed the movement of the aortic annulus during systole.

Methods:

Subjects:

Twenty-four subjects, 16 men and 8 women with no history of cardiac disease were included in the study. Mean age was 27,8 (range19-48) years. All the recordings were acquired before the quality was evaluated off-line. Seven subjects were excluded. One was excluded due to unstable electrocardiogram (ECG) and 6 due to poor 3D-image quality. All subjects had sinus rhythm. The regional committee on human research approved the study that complied with the Declaration of Helsinki. All subjects gave informed consent to participate.

Equipment:

A digital ultrasound scanner (System Five, GE Vingmed Ultrasound, Horten, Norway) with a 2.5 MHz phased array transducer and a magnetic locating device (Flock of Birds, Ascension Technology Corporation, Burlington, VT, USA) were used for data acquisition. The Flock of Birds tracked the spatial position and orientation of the transducer during the recording. Further

processing was performed in an external standard PC with a prototype version of the EchoPAC-3D software [20](GE Vingmed Ultrasound, Horten, Norway) and MATLAB (The MathWorks, Inc.USA). This new 3D high frame rate color flow imaging technique has been described in detail in previous studies [18,19,22].

Data acquisition:

The subjects were examined in the left lateral recumbent position. Each subject rested 15 minutes before blood flow velocities were recorded. The recordings were made in suspended end-expiration to reduce cardiac movement while acquiring 3D data.

Recordings of tissue were done in second harmonic imaging mode with a transmit frequency of 1.7 MHz. In color flow imaging mode the center frequency of the transmitted pulse was 2,5 MHz.

High frame rate was achieved by minimizing the tissue- and color flow sector. Mean frame rate in the 17 three-dimensional recordings was 57 (range 45 - 66) frames/s.

The transducer was tilted from the posterior towards the anterior wall during 10-20 cardiac cycles. In this manner, the entire aortic annulus was intended to be covered. Each frame was stored with the corresponding position co-ordinates and the ECG signal in the digital replay memory of the ultrasound scanner.

Data processing:

Raw digital ultrasound data were transferred to a PC and analyzed off-line.

Corresponding frames relative to the R-wave in the ECG were used to construct 3D volumes. In a five-chamber view the aortic valve was identified and a spherical cross sectional surface was positioned at the level of the septal part of the valve. This surface followed the movement of the aortic annulus throughout systole. In MATLAB, the blood flow velocities were calculated relative to the moving spherical surface, and true blood flow velocities through the annulus were obtained. Velocity vectors perpendicular to the surface, aligned with the ultrasound beam, were extracted from the 3D data and reconstructed in 2D slices as illustrated in fig 1. The tissue and Doppler signals were filtered, and aliased blood flow velocities baseline shifted according to Berg et al. [19].
As a quantitative assessment of the velocity distribution, any possible skew was described by the ratio maximum velocity time integral (VTI) to the systolic mean VTI. The maximum velocity systolic peak flow was measured and compared to the mean velocity at the same time. Further the location of maximum velocity and mean velocities in each 2D slice were visualized as shown in fig 1. Finally, the location of the maximum and mean VTI was visualized as shown in fig 2c.

Results:

The mean ratio of the maximum systolic to the mean VTI was 1,4 (range 1,2 to 1,5). At the time of systolic peak flow the mean ratio of the maximum to the mean velocity was 1,5 (range 1,1 to 2,0).
The results are presented in table 1. The mean VTI was located along the brim of the annulus while the maximum VTI was most often located toward the septum, as illustrated in fig 2. The velocity profile is visualized as a mesh plot

and as color flow in 2D slices extracted from the 3D data set. The location of the maximum velocity and the mean velocity at the same time was followed in each 2D slice throughout systole, as illustrated in fig 1. Most often the maximum velocity at peak flow and the maximum VTI were located toward the septum (fig 3).

Discussion:

This study shows the possibility to describe the 3D-velocity profile with ultrasound in the aortic annulus with a moving sampling surface. Several investigators have commented on this limitation to previous ultrasound methods. Kim et al [21] calculated this underestimation to be 7 % of cardiac output in mitral blood flow. In calculations of volumetric flow in the aorta, blood flow velocities are also underestimated since the annulus moves in the opposite direction relative to a fixed measure point during systole. This volume corresponded to 9 % of CO (95% CI (0,4 to 0,5) l/min) in healthy individuals [22] . Another advantage of our new method is a better temporal resolution than reported by Kupari et al [17], i.e. 15-22 ms in our study vs. 30-40 ms, which will enhance the quality of the measurements.

Our study also confirms earlier 2D ultrasound studies that described the velocity profile as skewed in the aortic annulus, as shown by the fact that the mean ratio of the maximum to the mean velocity at the time of peak flow was 1,5. The described ratio was higher than previous color flow methods from healthy subjects [13-14]. One explanation might be that the sample surface in our study was spherical and not necessarily perpendicular to the aortic root axis as

opposed to the previously mentioned color flow studies. In systole, blood flow velocities might be detected earlier in the lateral part of the annulus than towards the septum. Further, due to the sweep time delay, the change in recorded blood flow velocities from one side of the sector to the other would be maximum 0.17 m/s at 57 frames/s and blood flow acceleration of 10 m/s^2. However, the VTI is unaffected by this and the ratio of the maximum VTI to the mean found in our study was similar to the study by Zhou at al [14].

The maximum velocities and VTIs were most often located toward the septum and these findings confirm previous studies [13,14,17]. The mean VTI was located along the brim of aortic annulus. The reason for the somehow peripherally location of the mean VTI was that blood flow velocities decreased sharply toward zero close to the arterial wall. The blurring of the tissue border in the 2D-slice reconstruction of the mean VTI enhanced the impression of a location in the periphery (fig 2 c). This was due to movement of the anatomical structures and some change in shape during the cardiac cycle (fig 2 a,b). Several slices were averaged to illustrate the position of the mean VTI.

This study does not implicate changes in the current practice regarding the traditionally Pulsed Wave Doppler technique [1] as a spherical measure surface that tracked the annulus throughout systole was applied in our study. These methods are not directly comparable, but our results must be taken into account when calculations of stroke volumes are based on recordings with pulsed wave Doppler from a single sample volume. Previous studies have concluded that blood flow velocities in the center of the annulus should be measured with PW Doppler. However, the Doppler sample volume is fixed

during recording of blood flow velocities, but the heart is moving. Thus, the PW Doppler volume is not really recorded from one particular position in the annulus. According to our results, the mean VTI is located along the brim of the annulus and the ratio maximum VTI/mean VTI illustrate the range of possible errors due to blood flow measurements in calculations of stroke volumes based on the 2D PW Doppler method.

Several ultrasound methods have been proposed to deal with the problems related to a skewed and non-uniform velocity profile in volumetric calculations. Spatio-temporal integration of blood flow velocities is a way to avoid this obstacle. Kim et al applied a transthoracically multiplane method in calculations of volumetric mitral blood flow in humans and showed close agreement with MRI in the aorta ascendens [23]. Preliminary reports using digital color Doppler acquired with multiplane transesophagal probes in volumetric calculations in vitro or in vivo in open chest animals have recently been presented [24-27]. These methods showed close correlation with electromagnetic flow probes. Our 3D-color flow method has also been validated in calculations of volumetric flow [22]. The common pitfalls in pulsed wave ultrasound methods to calculate CO were avoided, as the 3D method was angle independent, no assumptions about the velocity profile were made and a moving sample surface was applied. The acquisition of data was fast and easy and high temporal resolution was achieved. These studies suggest that 3D-color flow imaging may turn out to be a valuable clinical tool in calculation of cardiac output and regurgitatant fractions.

However, our study was limited by several factors:

It may be difficult to cover the entire region of interest due to a limited acoustic window. The method is not suited to investigate subjects with irregular heart rhythm such as atrial fibrillation or those unable to hold their breath for a short period of time. The velocity profile was only close to instantaneous due to sweep time delay in the color flow image, but this error was limited by the high frame rate.

In conclusion, we have described the three-dimensional velocity profile in the aortic annulus based on a new dynamic 3D-color flow method. High frame rate improved the temporal resolution and blood flow velocities were measured through a spherical surface that followed the annulus throughout systole. The blood flow velocity profile was non-uniform. The maximum velocity and VTI was located toward the septum and the mean VTI was located along the brim of the aortic annulus. By using a single sample volume in Doppler measurements of the maximum VTI errors ranging from 20 to 50 % may be introduced in calculations of stroke volumes.

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Figure legends:

Fig 1. Examples of three-dimensional velocity profiles from early systole, peak flow and late systole. The profiles are visualized as a mesh plot and encoded as color flow in 2D slices extracted from the 3D data. The height of the mesh plot is proportional to blood flow velocities. The corresponding 2D slice is located below each mesh. Red = mean velocity. Green = maximum velocity. RV= right ventricle. LV= left ventricle.

Fig 2. An example of the location of the mean (red) and max VTI (green) within the annulus (c). The tissue slices were averaged to constitute the anatomical frame around the mean and max VTI. Two tissue slices from early (a) and late systole (b) are shown to explain the blurring of tissue in the averaged slice (c). This was due to movement of the anatomical structures during the systole. RV= right ventricle. LV= left ventricle. AO= aortic annulus.

Fig 3. The appearance of maximum velocities (Max V) at peak flow and maximum VTIs (Max VTI) in each of the five areas in the annulus was counted and summarized. Number of subjects =17.

Subject No	Max Velocity cm/s	Mean Velocity cm/s	Max Velocity /Mean Velocity	Max Velocity Time Integral cm	Mean Velocity Time Integral cm	Max Velocity Time Integral /Mean Velocity Time Integral
1	123,3	91,0	1,4	19,6	15,3	1,3
2	97,9	60,9	1,6	20,4	13,8	1,5
3	80,8	60,6	1,3	17,8	14,1	1,3
4	128,0	95,0	1,3	32,1	23,0	1,4
5	124,3	86,2	1,4	23,6	18,8	1,3
6	115,3	80,0	1,4	22,9	16,5	1,4
7	131,6	91,2	1,4	27,1	19,3	1,4
8	99,4	74,1	1,3	19,8	15,2	1,3
9	113,6	57,6	2,0	21,1	14,0	1,5
10	79,7	47,7	1,7	19,0	12,9	1,5
11	103,9	82,2	1,3	21,8	17,8	1,2
12	105,1	80,6	1,3	24,0	18,7	1,3
13	110,7	88,1	1,3	24,3	18,0	1,4
14	111,6	71,0	1,6	27,6	19,7	1,4
15	110,2	97,0	1,1	27,2	21,9	1,2
16	108,2	71,4	1,5	19,7	14,4	1,4
17	114,1	64,6	1,8	28,3	18,7	1,5
Average	109,3	76,4	1,5	23,3	17,2	1,4
Max	131,6	97,0	2,0	32,1	23,0	1,5
Min	79,7	47,7	1,1	17,8	12,9	1,2

Table 1.Quantitative assessment of the blood flow velocity distribution

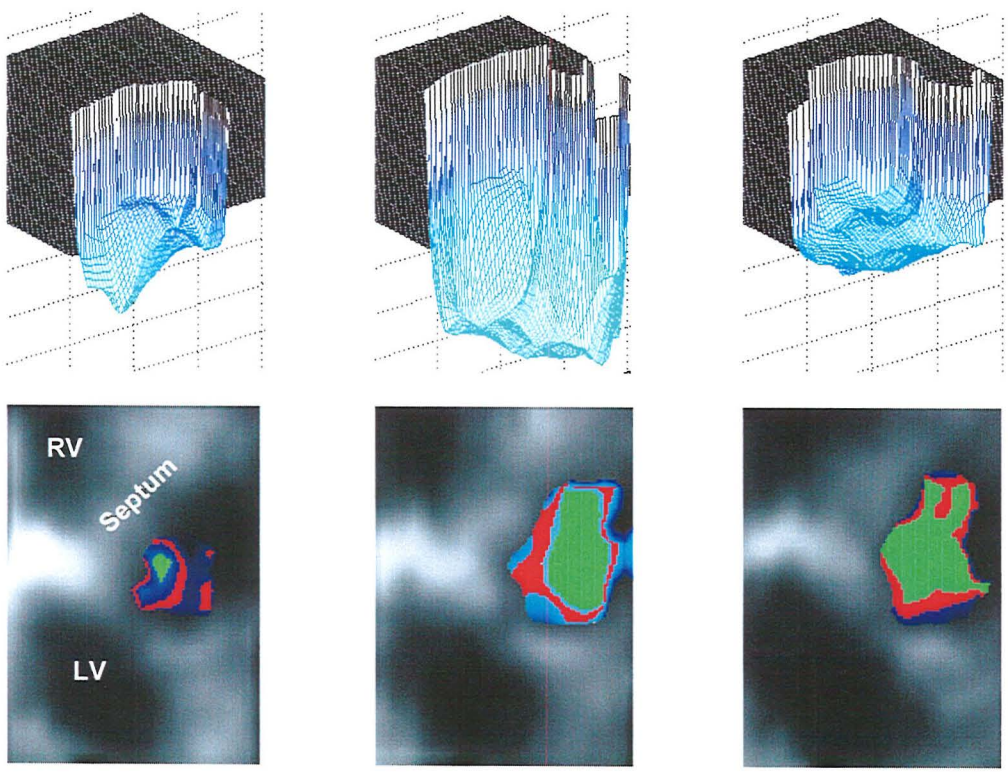

Fig 1

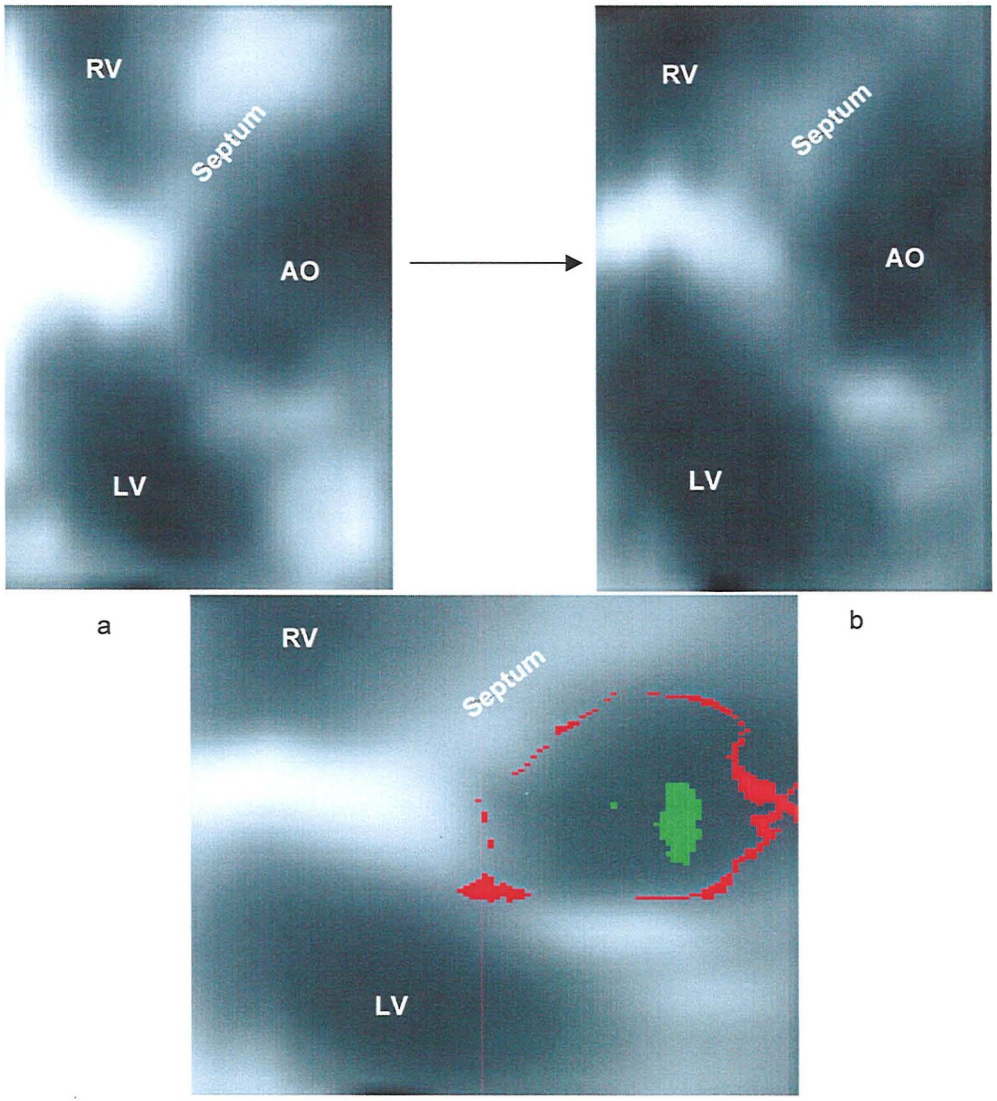

Fig 2

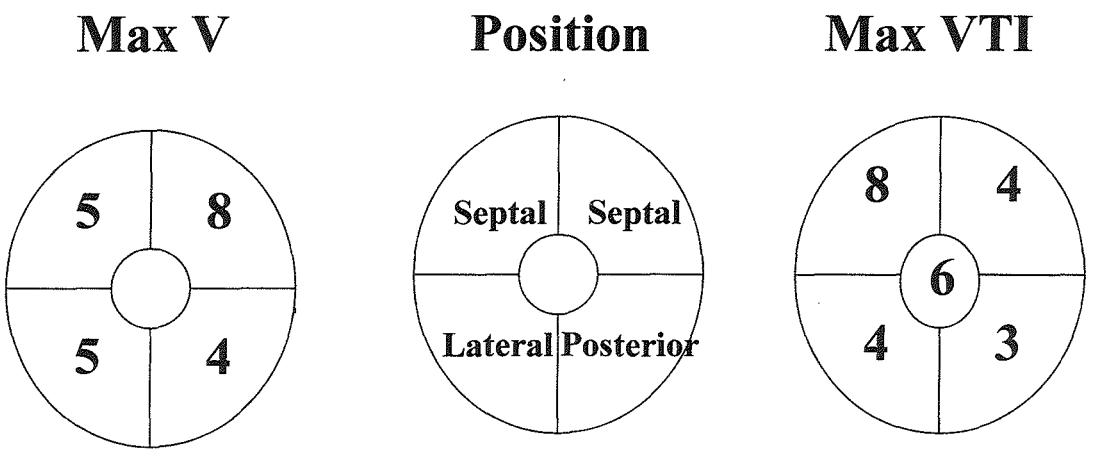
Max V
5
8
5
4
Position
Septal
Septal
Lateral
Posterior
Max VTI
8
4
6
4
3

Fig 3

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