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EXPERIMENTAL PAPER

A novel method for the assessment of the accuracy of computing laminar flow stroke volumes using a real-time 3D ultrasound system: In vitro studies

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Abstract *Aims:* Laminar flow stroke volume (SV) quantification in the ascending aorta or pulmonary artery can provide a measure for determining cardiac output (CO). Comparing flows across different valves can also compute shunt volumes and regurgitant fractions. Quantification methods for 3D color Doppler laminar flow volumes have been developed using reconstructive 3D, but these are cumbersome and time-consuming both in acquisition and measurement. Our study evaluated newly developed color Doppler mapping with real-time live 3D echo to test velocity, spatial and temporal resolution for computing SV.
Methods and results: Five rubber tubes (diameters = 3.0, 2.25, 2.0, 1.9, 1.7 cm), a freshly dissected porcine aorta (Ao) and a pulmonary artery (PA) (both 2–3 cm diameter) were connected to a pulsatile pump in a water bath. Different SV, from 10 to 80 ml/beat, were studied at pump rates of 40–60 bpm in this phantom model with flow quantified by timed collection. The Nyquist limit was set between 43 and 100 cm/s and frame rate ranged from 14 to 23/s. ECG triggered 3D color Doppler volumes were acquired with a 2–4 MHz probe. The digital scan line data from the 3D volumes, with retained velocity assignments, was exported and analyzed offline by MatLab custom software. Close correlations were found between 3D

Abbreviations: SV, stroke volume; CO, cardiac output; Ao, aorta; PA, pulmonary artery; ACM, automatic cardiac output measurement.

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calculated SV and reference data for all tubes ($r = 0.98$, $y = 1.14x - 1.69$, SEE = 2.82 ml/beat, $p < 0.0001$). Both Ao and PA flows were also highly correlated with the reference measurements (PA: $r = 0.98$, SEE = 3.17 ml/beat; Ao: $r = 0.99$, SEE = 3.20 ml/beat).
Conclusions: Real-time 3D color Doppler method could provide an efficient, accurate and reliable method for clinical evaluation and quantification of flow volumes in patients.

Introduction

Cardiac output is an important indicator of cardiac function.[1–3] To date, conventional invasive methods such as pulmonary artery thermodilution are still used for cardiac output measurement but results can be erroneous in the presence of cardiac shunts or tricuspid valve insufficiency.[4,5] Also, the invasive nature of the catheters limits its use to certain groups of patients due to the risk of complications.[6,7]

Noninvasive quantification of laminar flow stroke volume in cardiac inflow and outflow tracts and great vessels can provide measurement of cardiac output and is very important in assessing cardiac functions in all patient groups. Moreover, comparing flows across arteries or valves will allow computation of shunt flows and quantifying regurgitation in patients with congenital heart defects and valvular lesions.[8,9]

Various noninvasive methods for the quantification of blood flow such as magnetic resonance imaging (MRI),[10,11] two-dimensional echocardiography (2DE) M-mode and spectral Doppler combined methods have been widely used in clinical practice in the past few decades.[1,7,12,13] Phase encoded MRI is an accurate method for quantifying flow across valves, inflow and outflow tracts and lacks the angle dependency and signal attenuation limitations encountered by Doppler ultrasound. However, clinical cardiac MRI usage is limited by long acquisition times, patient access during scanning and cost constraints. 2D M-mode and spectral Doppler method has been used widely in clinical settings since the 1980s due to the favorable portability, short acquisition time and cost effectiveness.[14,15] It uses M-mode echo to determine the cross section area of the lumen assumed to be circle then multiplies the velocity time integral obtained from spectral Doppler to calculate flow volume. However, inherent Doppler angle dependency problems, spatially changing velocity profiles as well as geometric assumptions of circular shape of flow cross section have combined to yield somewhat marginal accuracy in studies for quantifying flow volume in patients.[16,17] The digital color Doppler based 2D automatic cardiac output (ACM) measurement method we studied previously used spatial and temporal integration of the color Doppler velocity profile across the ventricular outflow tract throughout systole for measuring cardiac output.[18,19] It was based on flow data obtained parallel to the flow and within a single two-dimensional plane but assumption of axial or hemi-axial symmetrical flow limited its accuracy especially when the outflow tract was dynamically expanding or changing shape.[20,21]

Reconstructed 3D color Doppler flow methods were developed based on the direct measurement of the dynamic flow cross section projected on a Gaussian surface from reconstructed multiple 2D slices. These methods eliminate some of the problems encountered by 2DE methods and allow full characterization of complex, dynamic flow velocity profiles. Nonetheless, most of the 3D reconstruction methods were time consuming because they needed 30—40 triggered heart beats to rotate 360° for volume acquisition, which often lead to misalignment and they required complicated offline reconstruction for volume calculation and visualization.[17,22–25]

In comparison, the currently available live 3D system provides quick 3D volume acquisition (seven triggered heart beats with total sweep angle of 30°) and instant spatial visualization of flow and cardiac structures, which will greatly enhance the use of 3D for clinical diagnosis. The aim of our present study is to evaluate the accuracy and reliability of the live 3D digital color Doppler technique for quantifying laminar flow volume in rubber tubes and dissected pig aorta and pulmonary artery models.

Methods

Dynamic flow model

A pulsatile pump (Harvard Apparatus, Model 1423, South Natick, MA) with adjustable

(10—100 ml/beat) output volume/cycle, forward versus reverse flow ratio of 50/50 and ECG signal as well as the inlet and outlet valves was connected via stiff plastic tubes (internal diameter: 17 mm, cross sectional area: 2.27 cm^2) to the study models that will be connected to and circulated in water with a 1% (by weight) corn starch mix to mimic the blood (Fig. 1) content. This apparatus was suspended in a water bath.

Rubber tube model

Five different rubber tubes (20 cm length with inner diameter = 3.0, 2.25, 2.0, 1.9, 1.7 cm) with approximately the same wall thickness (3 mm) were connected to the pulsatile pump and studied separately. To eliminate the shadowing generated by the tube wall, rubber tubes were connected with a thin (0.5 mm) rubber tube segment approximately 15 cm in length as an echo window. Five to six different SV (20—80 ml/beat) were examined at pump rates of 40 bpm for each tube. A graduate cylinder and a stopwatch were used for the reference SV, which were averaged from 3 measurements.

Dissected fresh pig aorta and pulmonary artery

A freshly dissected segment (3—2 cm in radial diameter from proximal to distal) of the aorta and the pulmonary artery including the bifurcation from a 40 kg pig were also studied separately using the same pump system. Different SV (10—80 ml/beat for the Ao and 20—70 ml/beat for the PA) were studied at pump rates of 50—60 bpm.

Echocardiography and data acquisition

Ultrasound scanning was performed using the Philips Live 3D 7500 SONOS system (Philips Medical Systems, Andover, MA) interfaced with a 2—4 MHz xMatrix™ probe. The designated rubber tube was imaged parallel to the flow direction through the adjacent thin portion of the tube so the echo volume (pyramidal angle in high density: $30^\circ \times 30^\circ$) would cover the flow region. Images were optimized by adjusting the Nyquist limit (43—100 cm/s), color gain and wall filters to eliminate random color in areas without flow, as well as maximizing frame rate to 14—23/s and selecting highest density. A pseudo ECG generated from the pump was used to trigger the 3D acquisition through a sweep that contains seven sequential subsegments to form the 3D volume ($30^\circ \times 30^\circ$ pyramid) containing the anatomical structure and Doppler flow information (Fig. 2). At the end of the acquisition, the instant 3D visualization on the system allowed viewing of the acquired 3D volume including structures and color Doppler flow information in any desired cutting plane (Fig. 3). The acquisition time varies depending on the pump's cycle rate (summation of the seven alternate cycles). Scan line data for 3D volume with Doppler velocity assignments was exported and analyzed offline by MatLab custom software solution (written by Karl Thiele, Philips Medical

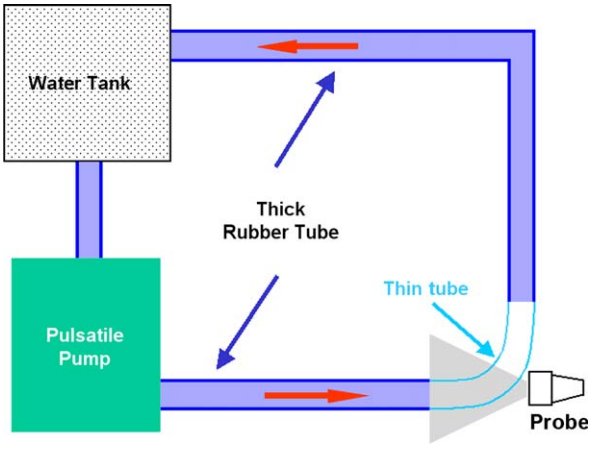

Figure 1 Diagram of the flow phantom. The imaging window was selected towards the junction of the thick and thin tube.

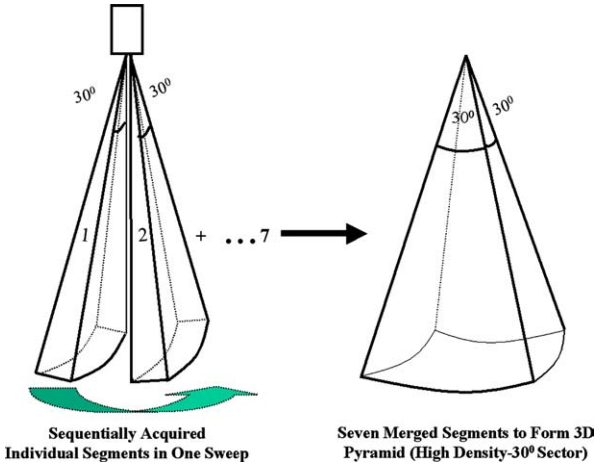

Figure 2 A schematic of the 3D volume acquisition. Left panel: a sweep contains seven (30°/7) individual segments triggered by ECG; right panel: a finished 3D volume (the pyramid) that contains the color flow and cardiac structure.

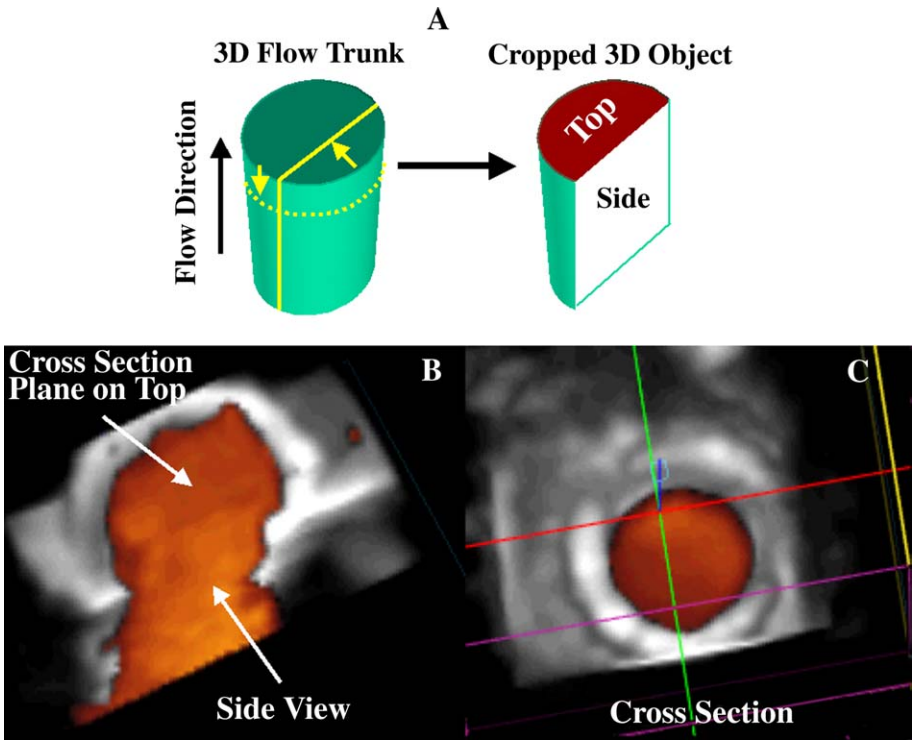

Figure 3 3D color Doppler views of the flow trunk at different cutting planes from tube model. Panel A: schematic of 3D flow volume before and after crop, yellow lines and arrows indicate the crop depth and directions from side (solid) and top (dot). Panel B: same view as panel A that cropped (top and side) from the 3D flow volume shows longitudinal view and partial cross section view of the flow. Panel C: cropped from the top shows a full cross section perpendicular to flow direction.

Systems). Using this program, frame by frame tracing that had been used in our previous 3D methods[22–25] was eliminated.

Measurement

3D digital scan line data sets were transferred to a PC work station and imported into the custom MatLab software database. Flow information was automatically cut into 6 slices along the flow direction when opening the data. A user defined flow boundary was selected from one of the six slices that contains velocity information in two orthogonal planes, which were shown automatically after the first boundary was selected (Fig. 4). Manually input information of frame rate and Nyquist limit were also needed. The program would compute and show the stroke volume curve and flow rate—time curve over time from the input data (Fig. 5). SV was calculated by selecting time phase from the flow rate—time curve (Fig. 5, right panel) after defining the depth of region of interest (Fig. 5, left panel). The result was shown automatically in Fig. 5, left panel, at the end. The total calculation time was usually less than 1 min. The algorithm of this calculation is based on the views that had been obtained perpendicular to the direction of flow with velocity vector being projected on a Gaussian surface for SV computation as an integration of velocity encoded color pixel intensity, area and time. Instantaneous flow rate is equal to velocity encoded color pixel intensity multiplied by pixel area for a frame.[22,23,25] $SV = Q \times t$, where Q = flow rate (ml/s); t = time (s).

Interobserver variability

To determine the reproducibility, two individual examiners performed measurements separately in 10 randomly selected data sets, blinded to each other's results and the reference data.

Statistical analysis

Data is expressed as mean $\pm$ SD. Linear regression was used for 3D tube data (5 tubes combined together) correlated with reference stroke volumes; aorta and pulmonary artery volumes were individually correlated with the reference stroke volumes. The Bland-Altman method was used for testing the agreement between the 3D and reference data as well as the two observer's

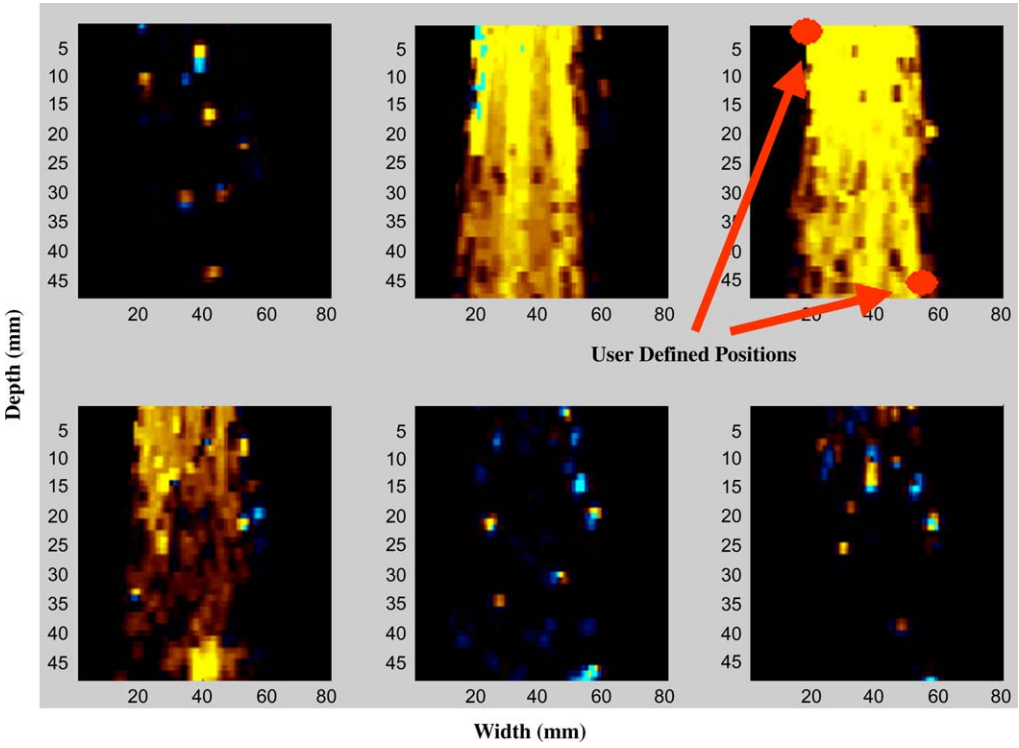

Figure 4 Six parallel slices were shown when the data were opened. This figure showed one of the orthogonal planes with user defined boundaries (red dots) of flow. The upper left panel and bottom right panel are slices that are outside the data range.

measurement results. A value of $p < 0.05$ was considered to be statistically significant.

Results

Tube models

3D stroke volumes obtained through the tube models at different pump settings were combined together and correlated with reference data. Mean difference between reference and 3D obtained SV was 3.64 ± 3.24 ml/beat; mean percentage difference was $9.51 \pm 7.72\%$. There was an excellent correlation between the 3D calculated SV and reference data: $r = 0.98$, $y = 1.14x - 1.69$, SEE $= 2.82$ ml/beat, $p < 0.0001$ was obtained (Fig. 6, left panel). Very good agreement between the 3D SV calculation and reference data was obtained by the Bland-Altman method (Fig. 6, right panel). The green lines in the figure are the regression lines that show bias or trend from the agreement plot. In Fig. 6, this indicated a linear

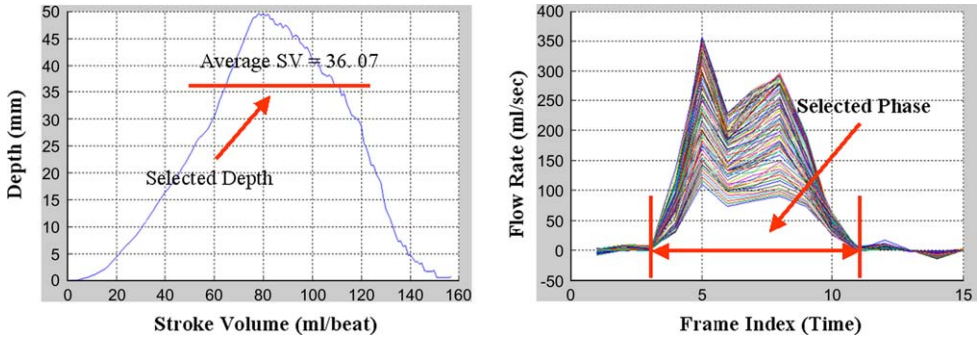

Figure 5 MatLab calculation of laminar flow stroke volume after selection of user defined region of interest. Left panel: SV curve over time, red line is user defined depth for SV calculation; right panel: red line indicating user selected phase from flow rate curve for SV calculation. The average SV will be calculated and shown on left panel.

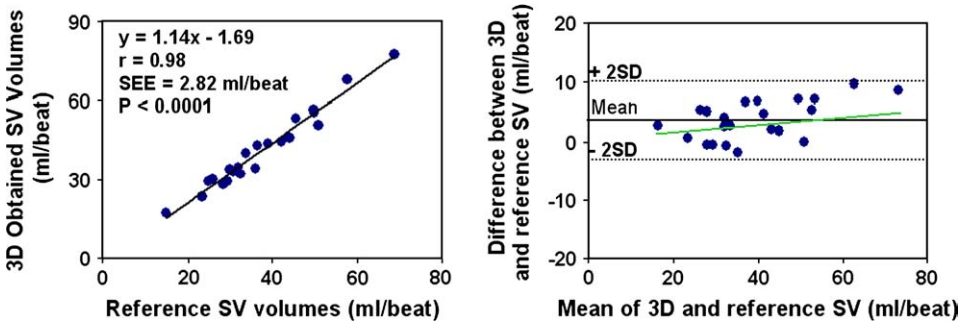

Figure 6 Left panel: linear regression between 3D method obtained stroke volumes and reference data for 5 tubes; right panel: level of agreement 3D and reference method as per Bland-Altman, the green line is the regression line of the agreement.

trend of overestimation, which gradually increased from low stroke volume to higher stroke volumes.

Pig aorta and pulmonary artery segments

3D color Doppler derived SVs were closely correlated to the reference data for both Ao and PA. For the Ao: mean difference was 3.13 ± 3.89 ml/beat and percentage difference was $6.85 \pm 13.77\%$; for the PA: mean difference was 4.93 ± 3.51 ml/beat and percentage difference was $10.04 \pm 9.38\%$. 3D derived SV volumes also correlated very well with the reference SV volumes: Ao, $r = 0.98$, $y = 1.11x - 1.55$, SEE = 3.17 ml/beat, $p < 0.0001$; PA: $r = 0.99$, $y = 1.11x + 0.45$, $p = 0.0002$, SEE = 3.20 ml/beat (Fig. 7, left: upper = Ao; lower = PA). Very good agreement between the 3D SV calculation and reference data was obtained by the Bland-Altman method (Fig. 7, right; upper = Ao; lower = PA). The green regression lines also showed increasing overestimation for both Ao and PA model.

Interobserver variability

Each of the two separate research staff who measured the data obtained excellent correlation between the 3D method and the reference method: $r = 0.97$, $y = 1.16x - 2.88$, $p < 0.0001$ versus $r = 0.98$, $y = 1.06x + 0.72$, $p < 0.0001$. Also,

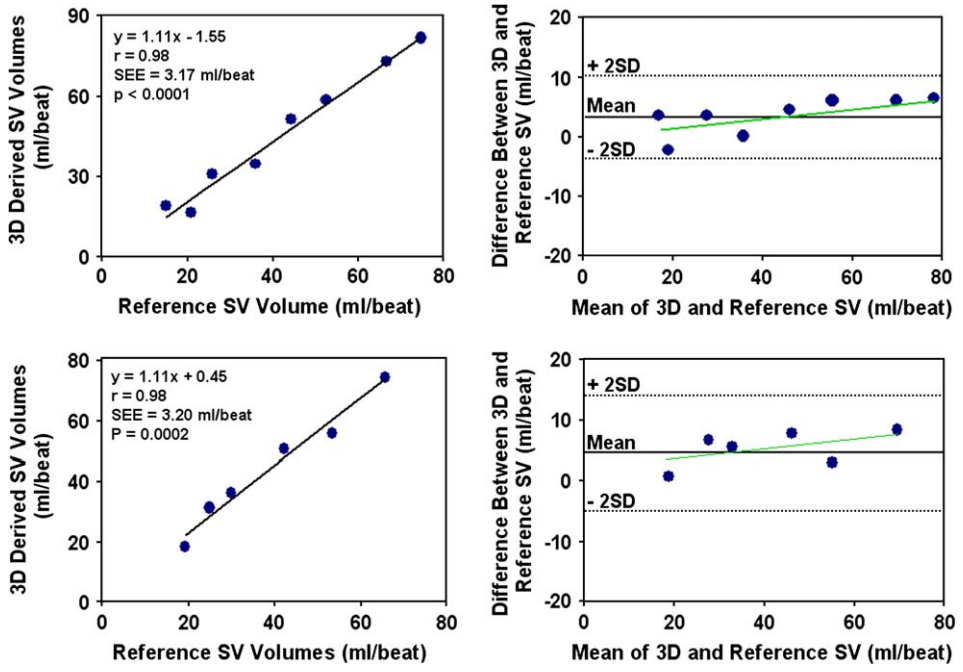

Figure 7 Left panel (upper, Ao; lower, PA): linear regression between 3D method derived stroke volumes and reference data; right panel (upper, Ao; lower, PA): level of agreement 3D and reference method as per Bland-Altman. The green lines indicate the regression of the agreement plot.

excellent agreement was found between the two examiners in which 95% of all the points fall in the range (mean $\pm$ 2SD) of 5.87 to -5.93 ml/beat.

Discussion

Echocardiography is a powerful tool for noninvasive evaluation of cardiac structure and function. It is quick, cost effective and generally accurate for diagnosis and management decision making related to a wide range of cardiac problems. However, the widely employed 2D echo and spectral Doppler methods for estimating cardiac output have not proved accurate for use due to the inherent Doppler angle dependency and geometric assumptions of the circular flow cross sectional area.[16,17,21] 3D color Doppler flow volume methods allow direct measurement of the instantaneous flow cross section and velocity which has the potential to overcome the problems that are encountered by the 2D method.

Previous 3D laminar flow volume measurement

Quantification of real-time color Doppler laminar flow volume has been studied previously using rotational reconstruction method. It acquires data parallel to the flow direction to minimize Doppler angle dependency and reconstructs the 3D stroke volume by integration of the raw digital scan line velocity information from multiple 2D images. It then projects the individual velocity vectors within the selected out flow tract or vessel cross section onto a Gaussian surface.[17,21,25] Thus, the measurement of the flow cross section is directly derived from the velocity data in the entire lumen and no geometric assumption is necessary. Accurate laminar flow volume derived by these 3D methods has been previously reported by our group and others.[17,22–25] Yet, these methods were cumbersome and time consuming due to the rotational acquisition over 30–40 cardiac cycles and the lengthy offline reconstruction that did not allow visualization of the 3D volume instantly. In addition, a fixed position of the transducer over such a long time would often cause misalignment from movement and respiration activity. The volumetric real-time 3D imaging system developed at Duke University (Model 1, Volumetric Medical Imaging, Durham, NC) was the first system with the function of real time display of the 3D anatomy and allowed navigation through any plane within the 3D volume. However, while left and right ventricle cavity volumes could be computed, the color Doppler quality was limited and forward or regurgitation flow volumes were not quantifiable.[8,9]

Current 3D method for laminar flow volume measurement

In our study, a pyramidal volume containing seven subpyramidal volumes was acquired by ECG trigger with the scan direction parallel to the flow. The integrated 3D volume (entire pyramid) can be visualized immediately on the ultrasound system and can be cropped at any desired cutting plane within the 3D object. The offline computation of flow volume from velocity profiles across a curved 3D surface in a plane generally perpendicular to the flow is then performed with our custom software using raw scan line data. This calculation principle is similar to previous 3D studies. The major advantages of this method as compared with previous 3D methods are the short acquisition time (seven alternate heart beats) and instant visualization of the live 3D imaging after the acquisition, which is important for clinical quantification and quality control. Short acquisition time also reduces the likelihood of the probe movement during the exam as compared with the rotational methods. In addition, advanced transducer technology enables better resolution for both tissue and color Doppler imaging to enhance the ability of boundary detection for lumen, cavity and flow. Furthermore, our tube 3D method derived flow stroke volume showed similar correlation coefficient and narrower range of mean differences in the agreement test while compared with our previous 3D tube study reported by Irvine et al.[17]

Limitations

In this initial study, we did not compare the 3D derived SV with the routine clinical 2D and spectral Doppler methods. However, we have started to compare both 2D and 3D methods in our clinical studies to phase encoded MRI.

Secondly, due to the Doppler angle dependency, this method of laminar flow computation still needs to obtain Doppler information parallel to the flow direction to minimize the loss of velocity information. Our phantom model made it easy to get good quality images as compared to the clinical environment, whereas some patients may not have good windows to facilitate aligning scan directions parallel to the flow.

Thirdly, the acquisition combines seven gated 3D subvolumes consecutively obtained from a fixed probe position, and minimizing respiratory movement during acquisition was important.

The offline measurement requirement for this method could limit its clinical use even though the calculation time is relatively short. Moreover, aliased flow may cause inaccurate measurement using current software, even when baseline shift was used prior to the calculation. In our in vitro tube results, as well as the biologic great arteries from pig, however, overestimation gradually increased from low stroke volumes to higher stroke volumes, as shown in our agreement test. This could be because, at higher stroke volumes, aliasing could not be fully eliminated. Also, color versus tissue balance was sometimes difficult to optimize during high flows in pulsatile tubes.

In the future, we believe, these limitations could be overcome by further technical evolution and refinement of the real-time 3D scanning and the development of semiautomatic but interactive computation programs for measuring flow rate and stroke volume.

We have ongoing animal experiments and clinical studies, which will further investigate the applicability and accuracy of this 3D method. The results will be compared to electromagnetic flow meters in animals and phase encoded MRI in patients.

Conclusions

The live 3D color Doppler method provides an efficient and accurate quantification of laminar flow volumes and thus cardiac output, which is very important for evaluation of cardiac function in clinical practice.

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