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In Vitro Validation of Real-Time Three-Dimensional Color Doppler Echocardiography for Direct Measurement of Proximal Isovelocity Surface Area in Mitral Regurgitation

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Abstract

The 2-dimensional (2D) color Doppler (2D-CD) proximal isovelocity surface area (PISA) method assumes a hemispheric flow convergence zone to estimate transvalvular flow. Recently developed 3-dimensional (3D)-CD can directly visualize PISA shape and surface area without geometric assumptions. To validate a novel method to directly measure PISA using real-time 3D-CD echocardiography, a circulatory loop with an ultrasound imaging chamber was created to model mitral regurgitation (MR). Thirty-two different regurgitant flow conditions were tested using symmetric and asymmetric flow orifices. Three-dimensional-PISA was reconstructed from a hand-held real-time 3D-CD data set. Regurgitant volume was derived using both 2D-CD and 3D-CD PISA methods, and each was compared against a flowmeter standard. The circulatory loop achieved regurgitant volume within the clinical range of MR (11 to 84 ml). Three-dimensional-PISA geometry reflected the 2D geometry of the regurgitant orifice. Correlation between the 2D-PISA method regurgitant volume and actual regurgitant volume was significant ($r^2 = 0.47$, $p < 0.001$). Mean 2D-PISA regurgitant volume underestimate was 19.1 ± 25 ml (2 SDs). For the 3D-PISA method, correlation with actual regurgitant volume was significant ($r^2 = 0.92$, $p < 0.001$), with a mean regurgitant volume underestimate of 2.7 ± 10 ml (2 SDs). The 3D-PISA method showed less regurgitant volume underestimation for all orifice shapes and regurgitant volumes tested. In conclusion, in an in vitro model of MR, 3D-CD was used to directly measure PISA without geometric assumption. Compared with conventional 2D-PISA, regurgitant volume was more accurate when derived from 3D-PISA across symmetric and asymmetric orifices within a broad range of hemodynamic flow conditions.

Accurate quantitation of regurgitant volume is an ongoing challenge in the assessment of patients with valvular heart disease. The flow convergence or proximal isovelocity surface area (PISA) method is derived from the principle that as blood approaches a regurgitant orifice, its velocity increases, forming concentric shells of increasing velocity and decreasing surface area.^{1,2} This surface area (PISA) can be estimated during 2-dimensional (2D) color Doppler (CD) echocardiography (2D-CD) assuming a hemispheric distribution of velocity vectors proximal to the regurgitant orifice. Under the principle of flow continuity, the severity of valve dysfunction can be quantified using PISA to determine the effective regurgitant orifice area and regurgitant volume.³

The weakness of this 2D-PISA method was exposed in both clinical and in vitro studies that showed consistent underestimation of actual regurgitant volume.⁴⁻⁶ This limitation is imposed by the 2D nature of conventional imaging systems because the true shape of the isovelocity surface may not be hemispheric.^{4,7-11} Real-time 3-dimensional (3D)-CD echocardiography is a relatively new technology that can provide spatial information about the actual 3D shape of the PISA zone using a handheld ultrasound system. Here, we report the validation of a method to assess regurgitant volume based on real-time 3D-PISA imaging in an in vitro model of mitral regurgitation (MR).

Methods

A pulsatile circulatory loop was created using a variable-speed bellows pump (Baylor College of Medicine, Houston, Texas) and connecting tubing with prosthetic valves ensuring unidirectional flow to a compliance chamber and fluid reservoir. The circuit was designed to achieve up to 7-L/min forward flow assessed using a calibrated ultrasonic flowmeter (Transonic Systems, Ithaca, New York). Fluid viscosity was similar to blood (30% glycerin, 70% water) with 1% corn starch added as ultrasound scattering particles.¹² All experiments were performed at a pump frequency of 60 cycles/min. By increasing downstream resistance, pulsatile flow was driven into a separate regurgitant loop incorporating an imaging chamber with 2 acrylic cylinders partitioned by a divider plate containing a geometric orifice. High-fidelity pressure transducers (Merit Medical, South Jordan, Utah) were positioned on either side of the divider plate to record peak chamber pressure and the transorifice pressure gradient. Incorporated into the imaging chamber were ultrasound windows at standard anatomic position and distance to the orifice (Figure 1).

The central regurgitant orifice was interchangeable, allowing different flow volumes to be tested through orifices of varying size and shape. The orifices tested were designed to assess PISA characteristics through idealized flow convergence conditions using small simple shapes, as well as through areas of increasing size and geometric complexity to more closely model clinical MR. Regurgitant volumes were chosen to approximate hemodynamic conditions of clinical MR (10 to 80 ml/beat). In all, we assessed 8 different pulsatile regurgitant volumes through each of the 4 rigid orifices differing in size and shape as a 0.15-cm² circle, 0.39-cm² circle, 0.35-cm² rectangle, and 0.4-cm² arc.

Two-dimensional-CD and continuous-wave Doppler data across the model orifice were acquired from an “apical” view equivalent parallel to the regurgitant flow using a commercial ultrasound scanner (Sonos 7500, Philips Medical Systems, Bothell, Washington) with a 2- to 4-MHz transducer and digitally transferred to an offline quantitative station (DigiView, Digisonics Inc, Houston, Texas). For each test orifice and flow condition, 3 continuous-wave Doppler signals across the regurgitant orifice were optimized, digitally acquired, and averaged. Two-dimensional-PISA optimization included adjusting the Nyquist limit and shifting the baseline of the CD aliasing velocity to achieve the largest hemispheric flow convergence contour. The 2D-CD frame rate was 28 Hz at a constant Doppler scan depth of 12 cm. Measurements were performed offline and blinded to flow measurements, regurgitant orifice characteristics, and 3D data. Two-dimensional-PISA was derived with a hemispheric assumption as $2\pi r^2$, where r is the largest flow convergent radius during regurgitant flow. Effective regurgitant orifice area was derived as (PISA $\times$ aliasing velocity)/peak MR velocity, and regurgitant volume was derived as effective regurgitant orifice area $\times$ TVI_{MR}, where TVI is the time-velocity integral of the transorifice continuous-wave Doppler spectrum.³

Without changing flow conditions or scan depth, an X4 transducer (Philips Medical Systems) was held at the apical-equivalent window to digitally acquire 3D Doppler data

immediately after the 2D Doppler study. Three-dimensional-CD images were optimized using real-time assessment of PISA size and shape for each test orifice and flow condition (Figure 2). Three-dimensional-CD frame rate was 15 Hz. Digital images were stored on compact disc for later review and analysis.

We used a custom novel computer program specifically developed for 3D-PISA reconstruction and surface area determination (Echoview, TomTec Imaging, Germany). Measurements were performed blinded to flow measurements, regurgitant orifice characteristics, and 2D data. At a known aliasing velocity, 8 equidistant radial planes of the largest PISA zone during regurgitant flow were manually traced. These data were used to reconstruct the total surface area of the converging isovelocity zone (Figure 3). Doppler angle correction was not performed. Three-dimensional-PISA was used to derive effective regurgitant orifice area as $(3D-PISA \times \text{aliasing velocity})/\text{peak MR velocity}$. Three-dimensional-PISA regurgitant volume was derived as 3D-effective regurgitant orifice area multiplied by TVI_{MR} .

Linear regression analysis was used to assess the strength of the relation between 2D-PISA and 3D-PISA estimate of regurgitant volume compared with a gold standard regurgitant volume measured using an ultrasonic flowmeter. The Bland-Altman method was used to show the potential clinical impact of using either of the 2 diagnostic test methods.¹³ Graphed data indicate mean test value $\pm$ 2 SDs and measurement bias. Intraclass correlation coefficient was calculated to assess interobserver variability in measuring regurgitant volume. Paired Student's *t* test or Mann-Whitney rank-sum test was used to test for differences between measures (version 3.0.1, SigmaStat, San Jose, California). A *p* value <0.05 was considered statistically significant.

Results

A circulatory loop able to generate pulsatile flow with transorifice pressure gradients within the range of clinical MR was created. Peak transorifice pressure gradients averaged 117 mm Hg (range 40 to 245). Peak Doppler velocity across the regurgitant orifice averaged 560 cm/s (range 307 to 793). The quality of the in vitro PISA zone image was excellent for both 2D-CD and 3D-CD (Figure 2). We modeled 8 flow volumes through each of 4 different orifices for a total of 32 different flow conditions. Three-dimensional-PISA was measured for all flow conditions with a typical reconstruction time of 8 to 10 minutes.

In reconstructing the 3D-PISA zone, we observed that the 3D geometry of the flow convergence zone reflected the regurgitant orifice geometry. PISA shape was hemispheric, or hemispheroidal, only when regurgitant flow was modeled through a circular orifice. When regurgitant flow was modeled through the rectangle or arc-shaped orifice, the reconstructed PISA zone was nonhemispheric, with convergence flow mirroring the rectangular or arc shape orifices. Figure 4 shows 3D-PISA reconstructions in regurgitations through a circular and arc-shaped orifice.

The flow model contained anatomic regurgitant orifices ranging from 0.15 to 0.40 cm² (mean 0.32). Using the 2D-PISA method, the derived effective regurgitant orifice area was smaller (mean 0.08 cm², range 0.03 to 0.19, *p* <0.001). Significant correlation was observed between 2D-PISA-derived effective regurgitant orifice area and actual orifice area (*r* = 0.47, *p* <0.001). Using the 3D-PISA method, the derived effective regurgitant orifice area was larger than observed with 2D-PISA, but smaller than actual orifice area (mean 0.16 cm², range 0.06 to 0.28, *p* <0.001 vs 2D-effective regurgitant orifice area, *p* <0.001 vs actual orifice area). Good correlation was observed between 3D-PISA-derived effective regurgitant orifice area and actual orifice area (*r* = 0.88, *p* <0.001).

Mean regurgitant volume using a flow meter for all flow conditions tested was 43 ml (range 11 to 84). Regurgitant volume derived using the 2D-PISA method was significantly smaller than by flowmeter (mean 19.9 ml, range 3.7 to 63.5, $p < 0.001$). Significant correlation was observed between 2D-PISA and actual regurgitant volumes ($r^2 = 0.47$, $p < 0.001$; Figure 5). However, the regression equation indicated a consistent significant underestimation of regurgitant volume using the 2D-PISA method (2D-PISA regurgitant volume = $1.6 + 0.5$ actual regurgitant volume). For all orifice shapes tested, the 2D-PISA method was associated with significant underestimation of actual regurgitant volume. Figures 6 and 7 show the relation of derived regurgitant volume with actual regurgitant volume for each regurgitant orifice shape and size. The magnitude of 2D-PISA regurgitant volume underestimation increased as orifices with larger area and asymmetric shape were modeled. Using the 2D-PISA method, mean underestimate of regurgitant volume was 19.1 ± 25 ml (2 SDs). In addition, there was a bias toward increased relative underestimation of actual regurgitant volume as larger volumes were modeled through the asymmetric (rectangle and arc) orifices (Figure 5).

Mean actual regurgitant volume for all flow conditions tested was 43 ml (range 11 to 84). The derived regurgitant volume by the 3D-PISA method was smaller (mean 36 ml, range 11 to 62, $p < 0.001$). For all orifice shapes tested, the 3D-PISA regurgitant volume measure was more accurate than the 2D-PISA method compared with the flow meter standard. Linear regression showed a correlation with actual regurgitant volume with little underestimation and uniform clustering of data around the regression line (3D-PISA regurgitant volume = $2.1 + 0.9$ actual regurgitant volume, $r^2 = 0.92$, $p < 0.001$). As shown in Figure 5, Bland-Altman analysis showed that the mean regurgitant volume underestimate using the 3D-PISA method was 2.7 ± 10 ml (2 SDs). Irrespective of the size and shape of the regurgitant orifice tested, the 3D-CD PISA method did not show a bias to regurgitant volume underestimation as greater flow volumes were modeled.

A second interpreter (BP) performed blinded repeated measurement of a subset (25%) of 3D-PISA and regurgitant volume derivation to assess interobserver variability. Good interobserver agreement for 3D-PISA measures was shown, with an intraclass correlation coefficient of 0.93.

Discussion

We created an in vitro model of MR to test a novel method of regurgitant volume estimation using real-time 3D-CD echocardiography and 3D reconstruction to measure PISA without geometric shape assumption. The conventional 2D-PISA method was associated with underestimation of regurgitant volume, particularly with asymmetric regurgitant orifices and large regurgitant volumes. In contrast, the 3D-PISA method was more accurate in estimating regurgitant volume for all regurgitant shapes tested and did not deteriorate as larger regurgitant volumes were modeled.

In recommended quantitative measures, the derivation of effective regurgitant orifice area and regurgitant volume from the proximal flow convergence zone are concepts familiar to many echocardiographers.³ Use of the PISA method to assess regurgitation severity is attractive because unlike other echocardiographic parameters, it is less dependent on instrumentation settings and complex hemodynamic factors that effect the spatial jet distribution in the receiving chamber.^{7,14} Of quantitative Doppler parameters, the PISA method is a more robust measure of regurgitant flow than an index such as CD jet area that can be highly influenced by the transvalvular pressure gradient and direction of the regurgitant velocity vector.¹⁵

Despite this promise, the PISA method has failed to become a routine tool in many clinical echocardiography centers. The most valid criticism of the method focuses on the assumption that the converging isovelocity zone is hemispheric. It was shown that the concept of a converging zone of hemispheric shape is true for a pinhole regurgitant orifice with circular shape, but this assumption may not represent flow conditions of clinical MR.^{16,17} Studies suggested that the proximal flow convergence zone is dynamic and changes from laminar flow in the mid-ventricle to a hemispheroidal flow as lateral forces entrain it toward the orifice to a truly hemispheric flow field and ultimately to a flattened convergent zone nearest to the regurgitant orifice.¹⁶ Previous studies using in vitro models showed significant underestimation of regurgitant volume using a 2D-PISA method.^{10–12} In short, use of simple geometric models involving axial symmetry (hemispheric or hemielliptic) for PISA calculations introduces a potentially significant error into the calculation of regurgitant flow.

In this study, the 2D-PISA method performed best when modeling regurgitant volumes through circular orifices. As shown in Figures 6 and 7, regression slope and mean underestimation were similar for 2D-PISA regurgitant volume estimates through either the small (0.15 cm²) or large (0.39 cm²) circular orifice. The assumption of a hemispheric flow convergence zone is likely most valid under these idealized flow conditions. When regurgitant flow was modeled through asymmetric orifices, the assumption of a hemispheric 2D-PISA became increasingly less valid (Figure 4). This assumption of hemispheric flow may underestimate the converging isovelocity surface area and regurgitant volume derived from the PISA estimation. This error is compounded as larger actual regurgitant volume is modeled, leading to the poor performance of the 2D-PISA method in estimating regurgitant volume through asymmetric orifices with relatively large flow rates. As shown in Figure 5, the 2D-PISA method consistently underestimated actual regurgitant volume for almost all flow conditions tested, and degree of regurgitant volume underestimation was largest for experiments modeling larger flow volumes through asymmetric orifices.

A second limitation of the 2D-PISA method is in accurate determination of the hemisphere radius.¹⁸ This measure from the isovelocity shell to regurgitant orifice can be technically challenging and difficult to reproduce. This limitation is important because this radial measure (r) is squared to derive the isovelocity surface area ($PISA = 2\pi r^2$). It is likely that as the size of the flow convergence zone increases, so does the magnitude of error in determination of flow convergence radius. In contrast, the 3D-PISA method requires manual tracing of the isovelocity shell and identification of the relatively large lower boundary of the flow convergence zone (orifice plate or mitral leaflet) and not the regurgitant orifice itself.

Application of 3D-CD to the quantification of regurgitant flow is a natural extension to the 2D-CD method. Important previous work by others^{4,5,10,11} using an in vitro model with a fixed transesophageal probe showed that custom software can be used to reconstruct a 3D flow convergence surface area from serial 2D images and that derived orifice area and regurgitant volume are accurate. Coisne et al⁵ showed that the 2D-PISA method underestimated regurgitant volume by 44%, whereas the 3D-PISA method underestimated actual flow rates by only 3%.

In this study, we show for the first time that real-time 3D-CD echocardiography from a handheld transducer can be used for accurate quantification of regurgitant flow across a broad spectrum of flow conditions. When 3D-PISA was measured directly using offline analysis, the derived 3D-PISA regurgitant volumes were more accurate than the corresponding 2D-PISA-derived volume for all orifice shapes and flow rates tested. Mean 3D-PISA regurgitant volume underestimate of actual regurgitant volume was small (~3 ml).

Additionally, the confidence interval around the 3D-PISA regurgitant volume measure was better than the corresponding 2D-PISA range (10 vs 25 ml, respectively).

In developing our MR model, we optimized the size of the imaging flow chamber, location of the ultrasound windows, and regurgitant volumes tested to model transthoracic imaging of clinical MR. As a simplified model, the interchangeable plates of the regurgitant orifices were flat, whereas actual mitral valve regurgitant flow usually achieves a flow convergence arc $>180^\circ$. In addition, we did not explore what, if any, effect various pump rates would have on the accuracy of 2D-CD or 3D-CD estimates of regurgitant flow. We predict that any effect on diagnostic accuracy would be similar for either Doppler method. Finally, the time required for offline 3D-PISA measurement was considerable. Although the time required for 3D-PISA regurgitant volume derivation improved with operator experience, it would still likely prohibit widespread clinical application. Having validated the measurement concept, the next logical step would be to streamline the reconstruction and measurement process with a fully or semi-automated software application package. The described 3D-PISA measurement and regurgitant volume derivation methods will be applied to patients with MR to evaluate its clinical utility as a noninvasive measure of regurgitant volume.

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Figure 1.
MR flow model.

Figure 2. Comparison of (A) 2D and (B) real-time 3D-CD imaging of PISA in a circular orifice model.

Figure 3. Illustration of the method of 3D-PISA reconstruction performed by tracing 8 equidistant radial planes of equal velocity through the flow convergence.

Figure 4. The complex geometry of 3D-PISA is influenced by the shape of the flow orifice. For a (A) circular and (B) arc-shaped flow orifice (*left panel*,) the corresponding 3D-PISA are shown: (*center panel*) 3D-PISA is viewed from above and (*right panel*) 3D-PISA viewed from the side.

Figure 5. Correlation between actual regurgitant volume (RV) and RV derived from the (A) 2D-PISA or (B) 3D-PISA method. Bland-Altman depiction of RV measurement bias using the (C) 2D-PISA or (D) 3D-PISA method.

Figure 6. Correlation between actual regurgitant volume and regurgitant volume derived from the PISA method for flow through a symmetric orifice. Small circular orifice (A) 2D-PISA and (B) 3D-PISA method and large circular orifice (C) 2D-PISA and (D) 3D-PISA method correlations.

Figure 7. Correlation between actual regurgitant volume and regurgitant volume derived using the PISA method for flow through an asymmetric orifice. Rectangular-slot orifice (A) 2D-PISA and (B) 3D-PISA method and arc-shaped orifice (C) 2D-PISA and (D) 3D-PISA method correlations.