A novel fully automated method for mitral regurgitant orifice area quantification

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A B S T R A C T
Background: Effective regurgitant orifice area (EROA) in mitral regurgitation (MR) is difficult to quantify. Clinically it is measured using the proximal isovelocity surface area (PISA) method, which is intrinsically not automatable, because it requires the operator to manually identify the mitral valve orifice. We introduce a new fully automated algorithm, (“AQURO”), which calculates EROA directly from echocardiographic colour M-mode data, without requiring operator input.

Methods: Multiple PISA measurements were compared to multiple AQURO measurements in twenty patients with MR. For PISA analysis, three mutually blinded observers measured EROA from the four stored video loops. For AQURO analysis, the software automatically processed the colour M-mode datasets and analysed the velocity field in the flow-convergence zone to extract EROA directly without any requirement for manual radius measurement.

Results: Reproducibility, measured by intraclass correlation (ICC), for PISA was 0.80, 0.83 and 0.83 (for 3 observers respectively). Reproducibility for AQURO was 0.97. Agreement between replicate measurements calculated using Bland-Altman standard deviation of difference (SDD) was 21,17 and 17mm² for the three respective observers viewing independent video loops using PISA. Agreement between replicate measurements for AQURO was 6, 5 and 7mm² for automated analysis of the three pairs of datasets.

Conclusions: By eliminating the need to identify the orifice location, AQURO avoids an important source of measurement variability. Compared with PISA, it also reduces the analysis time allowing analysis and averaging of data from significantly more beats, improving the consistency of EROA quantification. AQURO, being fully automated, is a simple, effective enhancement for EROA quantification using standard echocardiographic equipment.

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1. Introduction

Quantification of effective regurgitant orifice area (EROA) is an important aspect of evaluating mitral regurgitation (MR), but is difficult to achieve consistently in day-to-day clinical practice. The root cause of this difficulty is the intrinsic impossibility of automating the standard recommended technique, the proximal isovelocity surface area (PISA) method [1–3], because a human operator must measure the distance r between the flow convergence shell and the orifice. Both

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position of the orifice is known unambiguously. However, the exact location of the orifice is often difficult to identify. Can we quantify EROA without a human measuring the radius r?

In this study we explore a new technique, AQURO, which does not require manual measurement of r and can therefore be performed automatically, making it easy to obtain multiple independent measurements. It is based on an in-vitro study [12] arising from a simple rewriting of the conventional PISA mathematical equation. It uses a transformed slope of the velocity profile in the flow convergence zone to calculate orifice area without operator intervention. We compare AQURO with conventional PISA in subjects with known mitral regurgitation, in order to assess the validity of the technique for clinical application.

2. Method

2.1. Subjects

Twenty stable subjects with MR, identified from the echocardiography laboratory of Imperial College Healthcare NHS Trust, underwent trans thoracic echocardiography. Inclusion criteria were the presence of mild, moderate or severe MR as judged by a conventional clinical echocardiogram and a recognisable PISA in the 4-chamber apical view. Patients were excluded if they had moderate or severe disease of tricuspid or pulmonary valves (3 patients), any aortic valve disease graded mild or higher, a prosthetic aortic valve (2) or atrial fibrillation (4). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee and written informed consent was obtained.

2.2. Echocardiography

Echocardiographic data were acquired with the patient in the left lateral decubitus position using a Philips iE33 echocardiography system. Continuous wave (CW) Doppler, colour Doppler and colour M-mode images were acquired with simultaneous ECG, and stored digitally. Images were acquired in the apical view, using a 30° colour Doppler sector. CW Doppler velocity across the mitral valve was acquired co-axially with the regurgitant flow convergence region was visualized by colour Doppler velocity mapping. The beam was positioned along the centreline of the regurgitant orifice. Flow velocities were acquired as colour M-Mode images. For each AQURO measurement we used an average of 20 s of data (to create a fair comparison with PISA). Typically this time was spent acquiring 10 still frames of 2–3 beats each. Quadruplicate AQURO measurements (a total of 40 still frames per patient) were acquired with 55 cm/s aliasing velocity, which is the optimal velocity for AQURO analysis.

Software then automatically calculated EROA beat-by-beat. The program first identifies regurgitant areas for each image (Fig. 3a). Because of the movement of the mitral valve though systole it then shears the image to allow averaging of flow velocities at equivalent distances across the sequential lines of the colour M-mode image (Fig. 3b). It then calculates the rate at which velocity declines with increasing distance from the orifice along each scan line. The program converts colour pixel data to velocities using the colour scale bar, and then analyses all vertical scan lines of each beat. It plots \( \sqrt{V_r/V_f} \) against r for series of time points (Fig. 3c). The analysis distance in the r direction is fixed at 1 cm (chosen after pilot data analysis). The slope of the relationship between \( \sqrt{V_r/V_f} \) and r is expected to be linear near the valve. The program calculates the slopes of scan lines where this relationship is linear, rejecting scan lines where linearity is poor because they most likely reflect noisy instants or instants at the very beginning or end of systole; the number of scan lines actually used per beat was 28 ± 15. The software then calculates the average of the slopes of those lines, and hence the EROA, defined as \( \frac{2 \pi}{A_o} \) (Fig. 3d). The entire process is repeated for each beat and for all 10 colour M-Mode images in a single AQURO measurement. The average of all these individual \( \frac{2 \pi}{50} \) values is taken to be the single AQURO EROA from the 20 s of acquired data (typically 20–25 beats).

2.3. Proximal isovelocity surface area method

Currently, conventional PISA is the recommended method for MR quantification [1]. The PISA method is based on the continuity principle that flow converges toward the regurgitant orifice approximately symmetrically from all directions (at least near the orifice). Progressively closer to the orifice, blood must accelerate because the surface area of the notional hemisphere through which it passes becomes progressively smaller, while flow rate (in ml/min), equaling velocity × area, is conserved because blood is incompressible. The downwards aliasing velocity is typically chosen for Vr (velocity at distance r from the orifice), because it can be read directly from the colour bar on the scanner. The radius r is the distance from the orifice to the onset of aliasing. Velocity at the orifice \((V_f)\) is determined separately by continuous wave Doppler. The orifice area \((A_o)\) is then calculated (Fig. 1).

The flow convergence region was visualized by colour Doppler velocity mapping. The aliasing velocity was kept at 31.9 cm/s, suitable for PISA. Quadruplicate loops of 2 beats each were acquired (acquisition time = 5 s). Three operators spent an average of 15 s measuring the radius for each conventional PISA EROA measurement, blinded to each others’ findings. The operators were required to select the frame from which to take the measurements, as well as to choose the exact location of the orifice from where to measure r, and calculate EROA. The 4 EROAs took a total of ~80 s for acquisition and analysis.

2.4. AQURO method

It is not essential to measure the radius of a shell to calculate EROA with the flow convergence concept. The flow convergence pattern contains valuable information that could help calculate the EROA. The rate of increase of velocity with distance can replace the separate measurement of velocity and distance. Although this entails making more measurements, the whole method can be automated.

The origin of this method is a rewriting [12] of the conventional PISA mathematical equation so that, in the case of hemispheric isovelocity surfaces, the relationship between \( \sqrt{V_r/V_f} \) and r is linear with a slope \( \frac{\sqrt{V_r/V_f}}{2\pi} \), where \( V_f \) is the peak velocity at the regurgitant orifice (obtained from CW Doppler measurements), and \( V_r \) is the profile flow velocities obtained at distances r from the orifice. The EROA can be calculated directly from this slope (Fig. 2).

Just as for conventional PISA, the flow convergence region was imaged by colour Doppler flow mapping. The beam was positioned along the centreline of the regurgitant orifice. Flow velocities were acquired as colour M-Mode images. For each AQURO measurement, we used an average of 20 s of data (to create a fair comparison with PISA). Typically this time was spent acquiring 10 still frames of 2–3 beats each. Quadruplicate AQURO measurements (a total of 40 still frames per patient) were acquired with 55 cm/s aliasing velocity, which is the optimal velocity for AQURO analysis.

The intraclass correlation coefficient (ICC) of measurement (conventional PISA and AQURO) was used to analyse the quadruplicate measurements (conventional PISA and AQURO). It quantifies whether measurements differ between patients because of true difference between patients or random measurement noise (Fig. 4). The ICC value lies between 0 (all noise, no signal) and 1 (all signal, no noise).
We assessed agreement between replicate measurements for both the PISA and AQURO methods using Bland-Altman analysis [13] giving the mean difference and standard deviation of difference (SDD, a measurement of their disagreement). We chose to evaluate 3 replicate measures for each of the two methods. For PISA we therefore compared data from 1 pre-specified video loop from each observer. For AQURO we compared the EROA data from 3 separate pre-specified sets of data. Interobserver variability for conventional PISA was tested, by 3 operators independently measuring the same video loops.

3. Results

3.1. Patient characteristics

The twenty patients (9 male) had a mean age 73 years (SD 8). Aetiology of MR was degenerative valve disease (7 patients), prolapse (6), functional due to ischemic heart disease (1), and functional due to dilated cardiomyopathy (6). Severity of MR categorised by conventional PISA measurements was severe in 7, 8 and 2 patients (as assessed by observers 1, 2 and 3 respectively), moderate in 10, 6 and 8 (observers 1, 2 and 3 respectively), and mild in 3, 6 and 10 (observers 1, 2 and 3 respectively). The jet was central in 9, and eccentric in 11, predominantly anteriorly directed in 4 and posteriorly directed in 7.

3.2. Analysability

In all patients, within each 20-second session there were sufficient data acquired to calculate EROA, using both conventional PISA and AQURO.

3.3. Test–retest reproducibility of conventional PISA and AQURO, and agreement between the 2 techniques

Fig. 5 shows full disclosure of all measurements made on all patient datasets, by all PISA observers and by AQURO. The display shows the impact of different video loops (viewed by the same observer), and different observers (viewing the same video loop). The 3 observers viewed 4 loops each, giving 12 assessments of PISA EROA per patient: the range of EROAs is shown as a black bar. The 4 AQURO datasets (analysed automatically, no observer) also gave a range of EROAs (white bar).

Fig. 6 shows the variability between successive image sets for conventional PISA and AQURO. Because PISA requires an observer, it has separate values for between observer variability and (for each observer) within-observer variability.

3.4. Test–retest reproducibility of conventional PISA

Reproducibility of conventional PISA was measured using the ICC. ICC for conventional PISA measurements was 0.80, 0.83 and 0.83 for
each observer (Table 1). Agreements between conventional PISA measurements are shown in Table 2.

3.5. Test–retest reproducibility of AQURO

Reproducibility of AQURO, measured using the intraclass correlation coefficient, was 0.97 for AQURO measurements (Table 1). Table 2 shows the agreements between replicate AQURO measurements.

4. Discussion

This study presents and evaluates a new, fully automated algorithm for quantification of the effective mitral regurgitant orifice area, which does not require manual measurement of PISA radius. It uses the same principle as conventional PISA but calculates the EROA directly from colour M-mode echocardiographic images without human intervention. The AQURO method is found to be faster and have reproducibility at least as good as conventional PISA.

Fig. 5. EROA measurements calculated by 3 operators using conventional PISA and AQURO in all patients. Black bar: range of EROAs given by the 3 observers; white bar: range of EROAs given by AQURO.

Fig. 6. Within patient variability (SD) of EROA. Variability using AQURO is lower than variability using conventional PISA. PISA has separate values for between observer variability and (for each observer) within-observer variability.
The key advantage over conventional PISA is that eliminating the manual measurement of the PISA radius $r$ permits full automation, making multiple replicates easier to conduct, improving precision.

### 4.1. Why might AQURO have good reproducibility?

For conventional PISA to calculate EROA, three values are needed: peak CW, colour bar velocity, and PISA radius. For AQURO, the first two are the same but the third is velocity gradient. Although its algebraic expression \( \frac{d}{dx} \) may seem complex, it is simple for a machine to calculate, is more reproducible than PISA radius and, notably, does not require the radius $r$ to be measured by the operator. Mathematically, the information needed is similar for the two equations. But practically, the AQURO method is automatable and more reproducible.

### 4.2. Differences in time consumed

Acquisition plus analysis time was kept similar for both techniques at 20s. However, in the same time needed to acquire and analyse one conventional PISA measurement, the AQURO method obtained 10 colour-M-Mode images, ~20–25 analysable beats. Furthermore, there is no technical barrier to AQURO being computed in real time during acquisition.

### 4.3. Different image settings

AQURO requires different settings from conventional PISA. For conventional PISA, operators shift the colour baseline downward in the direction of the flow, to make the PISA large so that the radius can be measured with small percentage uncertainty. However, AQURO requires the opposite: a large range of non-aliased velocities in the flow convergence zone. To obtain this the colour baseline should be shifted upward on the colour velocity scale, so that there is a wide range of negative (away-from-ventricle) velocities on the colour-velocity map. The ultrasound signals and their hardware processing are identical (producing a 127.8 cm/s wide range of velocities); the difference is only whether this was colourized as $+55.9$ to 71.9, or $-31.9$ to 95.9. In an imagined future AQURO device, with direct access to velocities from the hardware, such adjustment of the zero point on the colour bar would not be necessary.

### 4.4. Limitations of both AQURO and conventional PISA

The isovelocity surface required for conventional PISA calculations is frequently non-hemispheric. Mathematical analysis has shown that even an idealised pointlike orifice in an infinite field, the vector

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**Table 1**

Conventional PISA and AQURO measurements of EROA and reproducibility between separate datasets of the methods.

<table>
<thead>
<tr>
<th>Patient</th>
<th>OBSERVER 1 PISA measurements of EROA (mm²)</th>
<th>OBSERVER 2 PISA measurements of EROA (mm²)</th>
<th>OBSERVER 3 PISA measurements of EROA (mm²)</th>
<th>Automated, no observer AQURO measurements of EROA (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#1</td>
<td>#2</td>
<td>#3</td>
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</table>

**Table 2**

Inter-observer agreement between PISA measurements analysed by 3 blinded observers (top) and agreement between replicate automated AQURO measurements (bottom).

<table>
<thead>
<tr>
<th>PISA</th>
<th>Observer 1 viewing Loop 1 versus Observer 2 viewing Loop 2</th>
<th>Observer 1 viewing Loop 1 versus Observer 3 viewing Loop 3</th>
<th>Observer 2 viewing Loop 2 versus Observer 3 viewing Loop 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.42</td>
<td>0.51</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean Difference (mm²)</td>
<td>−4</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>SD Difference (mm²)</td>
<td>21</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>AQURO</td>
<td>Set of measurement 1 versus Set of measurement 2</td>
<td>Set of measurement 1 versus Set of measurement 3</td>
<td>Set of measurement 2 versus Set of measurement 3</td>
</tr>
<tr>
<td>r</td>
<td>0.96</td>
<td>0.97</td>
<td>0.95</td>
</tr>
<tr>
<td>Mean Difference (mm²)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SD Difference (mm²)</td>
<td>6</td>
<td>5</td>
<td>7</td>
</tr>
</tbody>
</table>
nature of Doppler means that the isovelocity surface can never be a hemisphere but is a rounded ‘urchinoid’ [14,15].

Therefore to accurately measure regurgitant flow and EROA, the area of the surface should be calculated using the usual formula from a single measurement of \( r \) taken parallel to the direction of the flow. The beam should be on axis with the direction of the flow, with AQURO just as much with conventional PISA.

Just like PISA, AQURO requires colour images that produce a progressive decline in velocity pattern above the orifice to measure EROA, which means that the beam should pass through the vicinity of the orifice.

### 4.5. Exploration of discordant findings between AQURO and conventional PISA

There were some potentially informative outliers in our dataset. Although mean EROA was similar between AQURO and conventional PISA, two patients showed a marked discrepancy in one direction (patients 1 and 9) and one patient in the other direction (10).

In patients 1 and 9 some beats showed a smoother dataset with less evident noise than others. These smoother beats agreed relatively well with the conventional PISA, and the more noisy beats did not (Fig. 7).

If the noisier beats had been excluded the agreement between conventional PISA and AQURO would have been closer. However to avoid post-hoc distortion, all our results represent the full dataset without removal of noisy beats.

In patient 10, where AQURO reports lower values of EROA than conventional PISA, there were two adjacent jets. The operator acquiring the AQURO data appears to have focused on the smaller jet, while the PISA observers focussed on the larger jet (Fig. 8).

### 4.6. Study limitations

This study only compares two methods for evaluating EROA by echocardiography: one widely recommended but not possible to
automate (PISA) and another novel but readily automated (AQURO). EROA is not a complete evaluation of mitral regurgitation: assessment of colour jet area, left ventricular size, pulmonary pressures, pulmonary vein systolic flow reversal, quantitative Doppler or semi-quantitative angiography are also valuable and this study has no impact on how these measurements should be conducted. This study solely addresses the problem that conventional PISA, although recommended, is considered sufficiently time-consuming by many routine clinical practitioners that it is only used on infrequent occasions, thereby limiting both benefits of its utilisation and the experience needed to perform it efficiently.

The study does not attempt to compare AQURO EROAs with a gold standard or “true” EROA because there is no universally accepted clinical gold standard of EROA. Although more advanced techniques such as MRI exist, this study is not proposing to replace an echocardiograph with an MRI scanner, but rather to provide better tools for application in standard echocardiography. The study examines reproducibility (between beats and between observers) because although good reproducibility does not necessarily mean correct measurement, a poor reproducibility definitely produces incorrect measurements.

The flow-convergence assumptions behind evaluation of EROA are not universally valid. In particular, if the regurgitant orifice shape is not simple (e.g. crescent-like, slit-like or with two jets) or there are special configurations of regurgitant jet, then both AQURO and PISA would experience the same error. Thus AQURO only provides a way of automating EROA determination based on the flow-convergence principle (not automatable with PISA) but does not eliminate the fundamental weaknesses of the flow-convergence assumptions.

Although the number of patients studied was not large, it was sufficient to answer the intended question of the feasibility of automatic quantification of EROA in patients with mitral regurgitation, and to evaluate its inter-beat and inter-observer reproducibility in comparison to conventional PISA.

In 3 of the 20 patients studied, AQURO appears to have given incorrect values. In two of these, a future incarnation of AQURO which concentrated on the least noisy beats would further improve reliability. In the third, improvements of AQURO alone could not help because the operator acquired the data from the smaller of two effective orifices. Specific training on AQURO might alleviate this. The data presented in this manuscript are unabridged.

5. Conclusion

AQURO is a fully automated method for calculating EROA in mitral regurgitation, which eliminates the need to manually measure the distance to the orifice, thereby improving consistency of EROA estimations. AQURO is at least as reproducible as the conventional PISA method, quicker to acquire and could potentially operate in real time during acquisition. It is a simple, effective enhancement for the EROA quantification using standard 2D echocardiographic equipment.

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