FULL LENGTH ARTICLE

Radius of proximal isovelocity surface area in the assessment of rheumatic mitral stenosis: Connecting flow to anatomy and hemodynamics

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Background: **Echocardiographic assessment of left atrial pressure (LAP) in mitral stenosis (MS) is controversial. We sought to examine the role of the radius of the proximal isovelocity surface area (PISA-r) in the assessment of the hemodynamic status of MS after fixing the aliasing velocity (Val).**

Methods and results: **We studied 42 candidates of balloon mitral valvuloplasty (BMV), for whom pre-BMV echocardiography was done and LAP invasively measured before dilatation. PISA-r was calculated after fixing aliasing velocity to 33 cm/s. In addition, the ratio IVRT/Te′–E was also measured, where IVRT was isovolumic relaxation time, and Te′–E was the time difference between the onset of mitral flow E-wave and mitral annular early diastolic velocity. IVRT/Te′–E and PISA-r showed a strong correlation with LAP (r = −0.715 and −0.637, all $p < 0.001$) and with right-sided pressures. In addition, PISA-r correlated with mitral valve area by planimetry method (MVA) and with left ventricular outflow tract stroke volume (r = 0.66 and 0.71, all $p < 0.001$). Receiver operator characteristic curve (ROC-curve) showed that PISA-r was not inferior to IVRT/Te′–E in differentiating LAP ⩾25 from <25 mmHg.**

Conclusion: **Provided that Val is set to a constant of 33 cm/s, PISA-r can assess the hemodynamic status of MS, and seems a simple alternative to the tedious IVRT/Te′–E for estimation of LAP.**

Keywords: Mitral stenosis, Mitral valve area, Left atrial pressure, Proximal isovelocity surface area

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Introduction

Symptoms of mitral stenosis (MS) are believed to be due to the building up of pressures behind the stenosed valve leading to increased left atrial pressure (LAP) and pulmonary pressures [1]. Changes in LAP are not only dependent on the anatomic severity of MS but also on various other factors such as mitral valve resistance, left atrial size and compliance [2–5].

Echocardiographic assessment of LAP in MS is difficult as most echocardiographic determinants of LAP become inaccurate [3]. Reportedly, the time interval variable IVRT/Te'–E can estimate LAP in MS, where IVRT is isovolumic relaxation time (IVRT) and Te'–E is the time difference between the upstroke of the tissue Doppler early mitral annular velocity and the Doppler early mitral inflow velocity [6].

Proximal isovelocity surface area (PISA) is an application of the continuity equation that reportedly can assess mitral valve area (MVA) using the following equation:

$$\text{MVA} = \text{PISA-flow}/\text{Vmax}$$

PISA flow in this equation can be calculated using the equation:

$$\text{PISA-flow} = \text{PISA surface area} \times \text{aliasing velocity} \times \text{angle correction}$$

That is, PISA-flow = $2\pi \times \text{PISA-r}^2 \times \text{Val} \times \alpha/180$, where PISA-r is the radius of the PISA cap in centimeters, Val is the aliasing velocity in cm/s, and α is the angle between mitral valve leaflets in degrees [7–12]. Several simplifications of the PISA equation have been suggested [13–16]. We have recently suggested that fixing α to 100 degrees and Val to 33 cm/s would not affect the accuracy of PISA and would leave only one parameter, PISA-r, apparently the most important in the PISA flow equation [17], allowing for a chance to study the effects of MS on the size of the PISA cap, determined by the PISA-r.

Accordingly, we sought to study the value of PISA-r in the echocardiographic assessments of patients with MS, after fixing the Val to 33 cm/s.

Abbreviations

MS	mitral stenosis
BMV	Balloon mitral valvuloplasty
MVA	mitral valve area by planimetry method
PISA-r	radius of proximal isovelocity surface area cap
PG	pressure gradient
LAVmax	maximal left atrial volume
LAVmin	minimal left atrial volume
Cn	net atrio-ventricular compliance
IVRT	isovolumic relaxation time
Te'–E	time difference between the onset of mitral annular e' and mitral flow E-wave
DFT	diastolic filling time
LAP	left atrial pressure
mPAP	mean pulmonary artery pressure
RVSP	right ventricular systolic pressure
Cath. PG	invasively measured LA-LV mean pressure gradient
Af	atrial fibrillation
TDI	tissue Doppler imaging
ΔP	pressure gradient

Methods

Study population

In the period between August 2013 and June 2014, we recruited 45 consecutive rheumatic MS patients referred to our echocardiography laboratory for pre-balloon mitral valvuloplasty (BMV) assessment. The study protocol was approved by the research committee of our institution, and all patients gave informed consent consistent with this protocol. Three patients (7%) were excluded from all subsequent analyses because of suboptimal images from poor echocardiographic windows. Accordingly, the patient study group consisted of 42 patients.

Invasive measurements

Fluoroscopically verified cardiac pressures, particularly left atrial pressure (LAP), pulmonary artery pressure (mPAP), and systolic right ventricular pressure (sRVP), and mean LA-LV pressure gradient (Cath.PG) was measured before balloon inflations during BMV. Pressures were obtained at end expiration with the zero-level set at the mid-axillary line and representing the average of five cardiac cycles.

Echocardiography

Echocardiographic examinations were done immediately before BMV. All echocardiographic studies were acquired with a commercially available echocardiography system using a 2.5 MHz multi-frequency phased array transducer (Vivid 5 or 7; GE Vingmed Ultrasound AS, Horten, Norway). The LV ejection fraction was assessed using the biplane Simpson's method by manual tracing of the digital images. Maximum and minimum left atrial volume (LAVmax, LAVmin) were assessed using the biplane area length method. Left atrial stroke volume (LA-SV) was calculated as the difference between LAVmax and LAVmin.

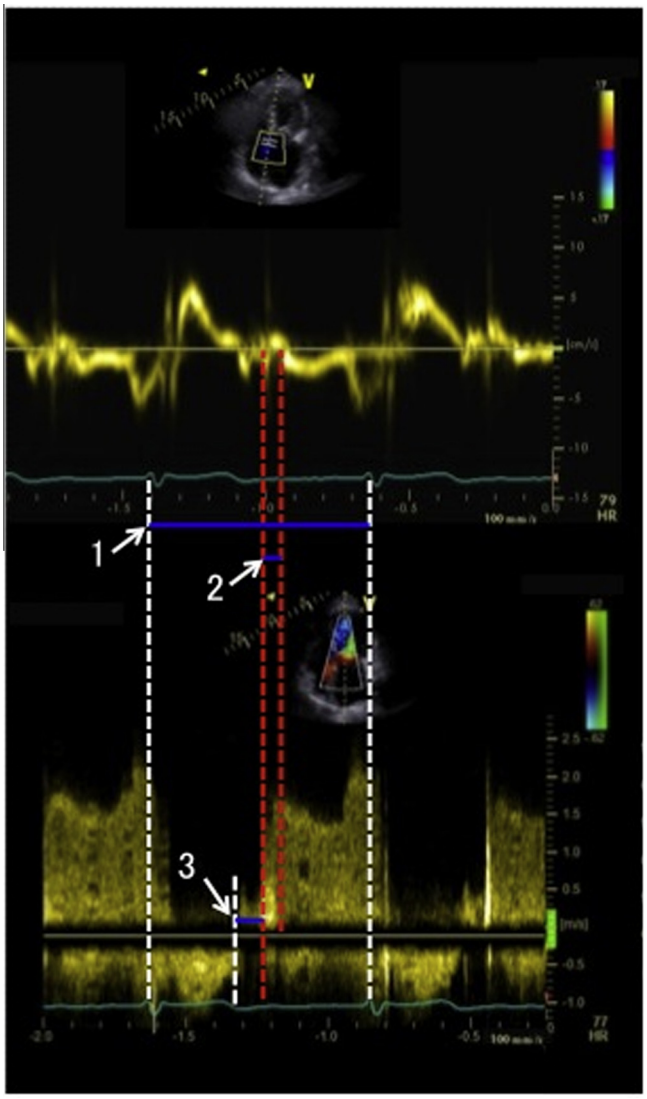

Figure 1. Method of calculating IVRT/Te'–E as a measure of LAP in MS patients. Upper panel shows septal mitral annular tissue Doppler velocities, and lower panel shows mitral flow velocities contaminated by aortic valve velocity recorded by continuous Doppler. The cardiac cycles with the closest possible electrocardiographic R-R intervals are first identified in both panels (dashed white line, and arrow and solid blue line number 1). Times to onset of mitral annular e' wave (Te') and times to onset of mitral E wave (T-E) are then measured from the top of the electrocardiographic R-wave previous to the selected cycle, and to the upstroke of each wave (dashed red lines). Difference between Te' and TE is then calculated as Te'–E (arrow and solid blue line number 2). Isovolumic relaxation time is then measured as the time spent from the end of aortic valve flow to the upstroke of the mitral E-wave (arrow and solid blue line number 3).

The mean trans-valvular pressure gradient (PG) was calculated with the modified Bernoulli equation. Left ventricular outflow tract stroke volume (LVOT-SV) was measured in 30 patients using the continuity equation as follows: (SV in ml = 0.785 $\times$ LVOTd^2 $\times$ LVOT-VTI), where LVOTd is the left ventricular outflow tract diameter in cm, and LVOT-VTI is the velocity time integral of the left ventricular outflow tract in cm. Mitral valve resistance (MVR) was calculated as (MVR = 1333 $\times$ Cath-PG/Q), where Cath-PG is the invasively measured mean pressure gradient, and Q is the mitral valve flow rate calculated as LVOT-SV divided by diastolic filling period [18]. Finally, net atrioventricular compliance (Cn) was calculated in ml/mmHg, using the equation: Cn = 1270 $\times$ MVA/E-wave deceleration slope [19–21]. Two experienced echocardiographers working separately reviewed all echocardiographic data, and all measurements were made in $\geqslant$3 consecutive cardiac cycles, and in $\geqslant$5 cycles if the patient's rhythm was atrial fibrillation. The average values were used for the final analyses.

Measurement of mitral valve area (MVA)

From the parasternal LV basal short-axis view, the smallest orifice of the mitral valve was

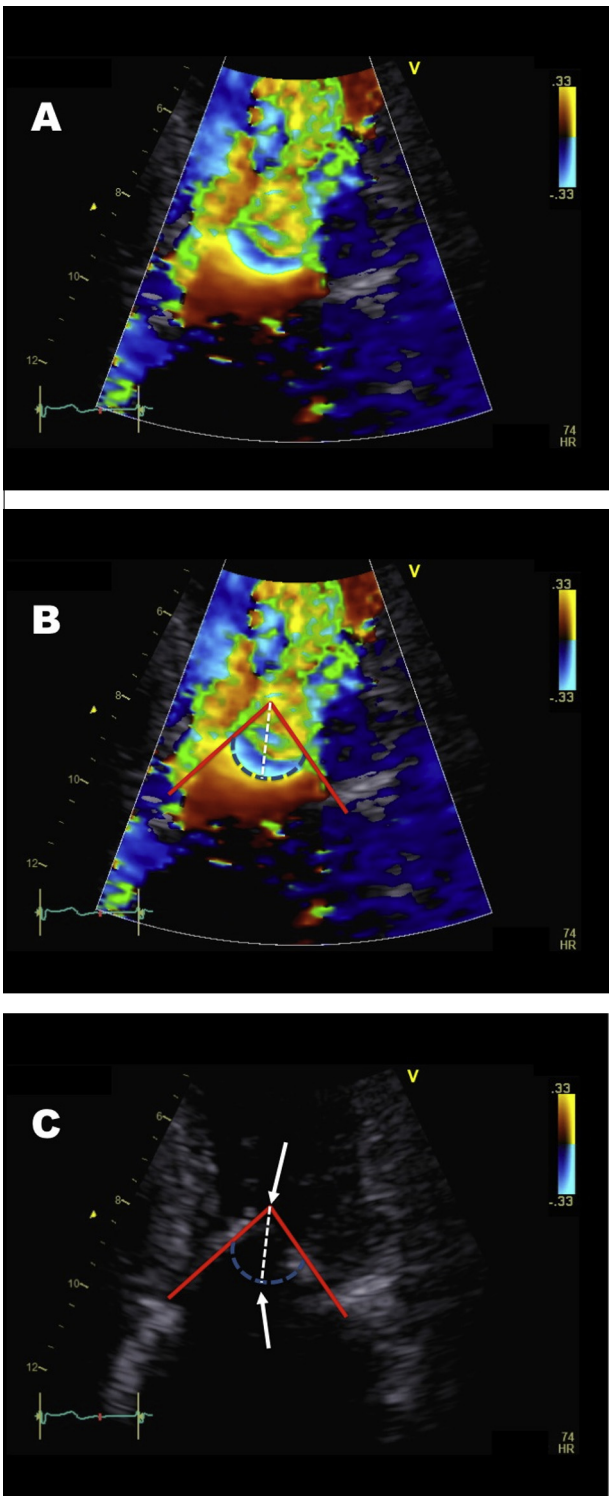

Figure 2. PISA-r measurement. A: the blue cap of the forward PISA flow above the mitral valve in early diastole. B: method of measuring PISA-r using imaginary lines from mitral leaflets (solid straight red line), and the red-blue aliasing border (curved dashed blue line). PISA radius is then measured between the apex of the triangle formed by the mitral leaflets (upper arrow) and the aliasing line (dashed straight white line), parallel to the mitral flow. C: Same image with color Doppler turned off to show boundaries of measurements.

identified by scanning from the left atrium in the direction of the LV apex. The gain settings were adjusted until the lowest level was determined, at which the circumference of the mitral orifice was still visible. After identification of the frame with the mitral valve orifice at its maximal opening in early diastole, MVA was measured by planimetry of its contours. The anatomic severity of MS was defined as mild if MVA was >1.5 cm^2, moderate if MVA was >1.0 and ⩽1.5 cm^2, and severe if MVA was ⩽1.0 cm^2.

The time interval variable IVRT/Te'–E: (Fig. 1)

The ratio IVRT/Te'–E was calculated as an echocardiographic estimate of left atrial pressure (LAP), where IVRT was isovolumic relaxation time, Te'–E was time difference between the onset of mitral annular motion during early diastole (Te') and onset of the upslope of mitral flow velocity during early diastole (T-E). Calculation of this variable was excluded if instantaneous onset of both mitral annular motion and mitral flow was encountered, i.e., Te'–E = zero. It is important to note that all possible care was paid to measure Te' and T-E from the two corresponding cardiac cycles with the closest possible electrocardiographic R-R wave interval.

Proximal isovelocity surface area radius (PISA-r) (Fig. 2)

Color flow Doppler was applied on the mitral position and the aliasing velocity (Val) was selected by shifting down the frequency to 33 cm/s, followed by zooming the PISA flow, and the cine loop was moved to obtain the largest PISA cap radius (PISA-r) in early diastole. PISA-r was then measured as the maximum distance between the apex of the triangle formed by both mitral leaflets at one end (defined as the point at which imaginary lines passing at the inner side of both leaflets would meet below the mitral valve with the color Doppler turned off), and the first line of aliasing at the other end (defined by the change of the color from red to blue).

To assess intra- and inter-observer variability for PISA-r, ten patients were randomly selected, for whom PISA-r was re-measured by the same operator (A.M.S.O.) and another operator (M.A.A.) in a different setting, blinded to the first measurements.

Statistical analysis

Nominal data were expressed as number (%). Continuous data were expressed as mean ± SD and were compared between groups using

student t-test. Correlation analyses were performed using linear regression and expressed as Pearson correlation coefficients. Receiver operator characteristics curve (ROC-curve) was used to identify the ability of the PISA-r and IVRT/Te'–E to predict LAP. Intra- and inter-class variability for PISA-r was expressed as mean ± SD and interclass correlation coefficient. The p-value $\leqslant 0.05$ was considered statistically significant. All analyses were performed with commercially available software (SPSS version 21.0, SPSS, Inc., Chicago, IL, USA). The authors had full access to the data and take full responsibility for their integrity.

Results

Table 1 summarizes the basic demographic and clinical data for all patients. Mean age was 36.3 ± 13.4 years, 29 patients (69%) were females and 12 (29%) had atrial fibrillation (Af). The mean invasively measured left atrial pressure (LAP) was 29.4 ± 6.4 mmHg.

The intra-observer variability for PISA-r was 0.03 ± 0.074 mm with interclass correlation coefficient of 0.9, $p < 0.001$, and the inter-observer variability for PISA-r was 0.06 ± 0.08 mm and the interclass correlation coefficients were 0.88, $p < 0.001$.

Concerns about timing variables

There was no significant difference between mean R-R interval in tissue Doppler imaging (TDI)-derived mitral annular images and the mean R-R interval in mitral flow images (717 ± 143 vs. 726 ± 140 ms, p = 0.170). The mean difference between both R-R intervals was 24.4 ± 31 ms. R-R interval difference was zero

Table 1. Basic clinical and echocardiographic data for all patients.

	All patients (n = 42)
Age (years)	36.3 ± 13.4
Sex (male/female) n(%)	13(31)/29(69)
Rhythm (sinus/atrial fibrillation)	30(71)/12(29)
Ejection fraction (%)	61.5 ± 4
Mitral stenosis (moderate/severe)	19(45)/23(55)
Mitral regurgitation (trivial to mild/moderate/severe)	37(88)/5(12)/0(0)
Tricuspid regurgitation (trivial to mild/moderate/severe)	28(66)/7(17)/7(17)
MVA (cm^2)	0.99 ± 0.25
PISA-r (cm)	1.32 ± 0.15
PG (mmHg)	12.1 ± 5.7
LAVmax (ml)	119 ± 40
LAVmin (ml)	81.9 ± 37.1
d-LAV (ml)	39.7 ± 12.7
Cn (ml/mmHg)	2.88 ± 1.3
LAVmax/Cn (mmHg)	51.8 ± 31.9
LAVmin/Cn (mmHg)	35 ± 24
d-LAV/Cn (mmHg)	16.7 ± 9.6
LVOT-SV (ml)*	59.7 ± 13.7
IVRT (ms)	84 ± 28.7
Mitral flow R-R interval (msec)	727 ± 140
Mitral annular velocity R-R interval (msec)	718 ± 143
R-R interval difference	24.4 ± 31
Te'–E (ms)	67 ± 28
IVRT/Te'–E**	1.21 ± 0.45*
DFT (sec)	0.443 ± 0.133
Mean LAP (mmHg)	29.4 ± 6.4
mPAP (mmHg)	40.7 ± 14.7
RVSP (mmHg)	56.4 ± 18.6
Mean aortic pressure (mmHg)	95.2 ± 13.3
Cath-PG (mmHg)	15.9 ± 7
Heart rate (beat/min)	84.2 ± 16.8

Categorical variables were expressed as n(%), and continuous variables were expressed as mean ± SD. MVA, mitral valve area by planimetry method; PISA-r, radius of the PISA cap; PG, pressure gradient; LAVmax, maximal left atrial volume; LAVmin, minimal left atrial volume; Cn, net atrioventricular compliance; IVRT, isovolumic relaxation time; Te'–E, time difference between the onset of mitral annular e' and mitral flow E-wave; DFT, diastolic filling time; LAP, left atrial pressure; mPAP, mean pulmonary artery pressure; RVSP, right ventricular systolic pressure; Cath-PG, invasively measured LA-LV mean pressure gradient.

* calculated in 30 patients.

** calculated in 34 patients.

Table 2. Correlations with left atrial pressure for patients who underwent BMV.

	Linear regression		Multivariate regression Adjusted $r^2 = 0.668$		
	r	p	beta	p	95% CI
PISA-r (cm)	−0.637	<0.001	−0.404	0.009	−30.5 to −4.9
IVRT/Te′–E*	−0.715	<0.001	−0.539	0.001	−11.2 to −3.3
PG (mmHg)	0.149	0.371	—	—	—
LAVmax (ml)	0.220	0.219	—	—	—
LAVmin (ml)	0.209	0.260	—	—	—
d-LAV (ml)	0.312	0.093	—	—	—
Cn (ml/mmHg)	0.055	0.764	—	—	—
LAVmax/Cn (mmHg)**	0.562	0.001	0.022	0.873	–0.052 to 0.061
LAVmin/Cn (mmHg)**	0.529	0.003	—	—	—
d-LAV/Cn (mmHg)**	0.538	0.003	—	—	—
MVA (cm2)	0.376	0.02	0.05	0.807	−8.6 to 11

Abbreviations as in Table 1.
* only 34 cases.
** shows strong co-linearity.

milliseconds in eight (19%) patients (i.e. identical cardiac cycle length), all were in sinus rhythm. R-R interval difference was less than or equal to 25 (10.8 ± 6.5) milliseconds in 24 (48%) patients (considered acceptable), 17 (71%) of them were in sinus rhythm and only seven (29%) had Af. However, R-R interval was more than 25 (64 ± 35) milliseconds in ten (24%) of the patients (considered unacceptably different R-R intervals), five (50%) of whom had Af and five (50%) had sinus rhythm.

The upstroke of mitral annular e′ and mitral flow E-wave was simultaneous in eight (19%) cases, thus the ratio IVRT/$T_{e'–E}$ was only possible in 34 (81%) patients (1.21 ± 0.45), because the value $T_{e'–E}$ in the other eight patients was equal to zero, making the calculation of the ratio impossible.

It is worth noting that while IVRT/Te′–E was only possible in 34 patients, PISA-r could be measured in all patients (1.32 ± 0.15 cm).

Correlations with left atrial pressure: (Table 2, Fig. 3)

Interestingly, PISA-r showed a strong correlation with LAP (r = –0.637, $p < 0.001$; Table 2, Fig. 3-A). In addition, and as expected, it was found that the ratio IVRT/Te′–E correlated strongly with the invasively measured LAP (r = –0.715, $p < 0.001$; Table 2, Fig. 3-B). Importantly, both PISA-r and IVRT/Te′–E correlated significantly with LAP in patients with sinus (r = 0.81, 0.83, both $p < 0.001$), as well as Af (r = 0.63, 0.86, $p = 0.027$, 0.003), and in patients with moderate MS (r = 0.77, 0.819, both $p < 0.001$) as well as severe MS (r = 0.75, 0.824, both $p < 0.001$).

MVA also correlated weakly with LAP, while PG, LAVmax, LAVmin, LA-SV, and Cn did not correlate with LAP. When LA volumes were indexed by Cn in the ratios LAVmax/Cn, LAVmin/Cn, and LA-SV/Cn, they all showed significant correlations with LAP. Multivariate regression model was initiated to compare correlations with LAP for PISA-r, IVRT/Te′–E, MVA,

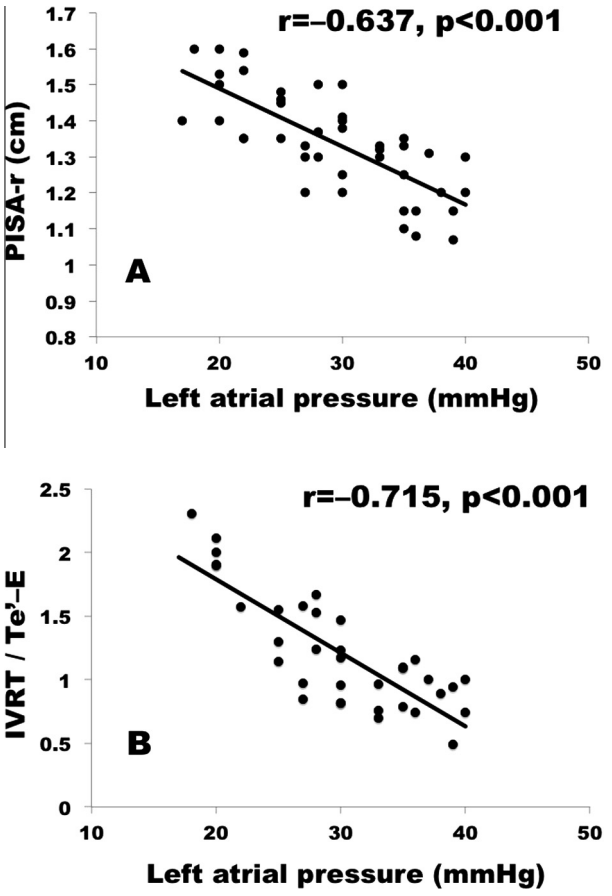

Figure 3. Dot plots for correlations with LAP (A) vs. IVRT/Te′–E; and (B) vs. PISA-r.

Table 3. Correlations with right-sided pressures.

	SV (ml)		mPAP (mmHg)		RVSP (mmHg)	
	r	p	r	p	r	p
PISA-r (cm)	0.66	<0.001	0.630	<0.001	0.55	<0.001
IVRT/Te'–E*	0.31	0.129	0.651	0.001	0.405	0.021
MVA	0.753	<0.001	0.64	<0.001	0.717	<0.001
Cn (ml/mmHg)	0.54	0.007	0.259	0.221	0.497	0.003
PG (mmHg)	0.29	0.133	0.481	<0.001	0.612	<0.001
LAVmax (ml)	0.261	0.229	0.036	0.877	0.086	0.722
LAVmin (ml)	0.303	0.170	0.097	0.692	0.072	0.714
LA-SV (ml)	0.066	0.775	0.064	0.802	0.012	0.951
LAVmax/Cn (mmHg)	0.705	<0.001	0.677	0.002	0.651	<0.001
LAVmin/Cn (mmHg)	0.684	0.001	0.686	0.002	0.636	<0.001
LA-SV/Cn (mmHg)	0.670	0.001	0.552	0.018	0.569	<0.001

Abbreviations as in Table 1.
* only 34 cases.

and LAVmax/Cn (LAVmin/Cn and LA-SV/Cn were not included in the model because of strong co-linearity with LAVmax/Cn, r = 0.98, 0.86, both $p < 0.001$), and it was found that PISA-r was not inferior to IVRT/Te'–E (Table 2), while MVA and LAVmax/Cn lost correlation.

Correlations with LVOT stroke volume

In 30 patients, LVOT-d was 2.26 ± 0.23 cm; LVOT-VTI was 15.2 ± 4.4 cm; and LVOT-SV was 59.7 ± 13.7 ml.

As expected in patients with mitral stenosis, SV correlated significantly with MVA (r = 0.753, $p < 0.001$, Table 3). SV also correlated significantly with Cn (r = 0.54, $p = 0.007$, Table 3). However, no correlations with SV were noticed in the case of PG, LAVmax, LAVmin, or LA-SV. However, again, when left atrial volume parameters were indexed against Cn, all ratios correlated significantly with LVOT-SV (Table 3).

Interestingly, PISA-r correlated with SV (r = 0.66, $p < 0.001$, Table 3), while IVRT/Te'–E failed to do so (0.31, $p = 0.129$, Table 3).

It is also important to note that, in addition to its correlations with LAP and SV, PISA-r correlated significantly with MVA (r = 0.71, $p < 0.001$). IVRT/Te'–E, on the other hand, as with LVOT-SV, failed to correlate with MVA (r = 0.245, $p = 0.139$).

Other correlates with MVA-PLN in our study were mean PG (r = 0.5, $p = 0.001$), and Cn (r = 0.64, $p < 0.001$).

Other correlations

Both PISA-r and IVRT/Te'–E correlated significantly with RVSP (r = 0.630, 0.651, $p < 0.001$, = 0.001, Table 3) and with mean PAP (r = 0.55, 0.405, $p < 0.001$, = 0.021, Table 3). Again, Cn, LAV, and PG did not correlate with mPAP or RVSP, while LAV parameters indexed to Cn correlated significantly with both.

Finally, neither PISA-r nor IVRT/Te'–E correlated with PG, or LAVmax, LAVmin, or LA-SV. PISA-r correlated with Cn (0.34, p = 0.04), while IVRT/Te'–E did not. After indexing LAV with Cn, both PISA-r and IVRT/Te'–E correlated significantly with LAVmax/Cn (r = 0.661, 0.49, $p < 0.001$, = 0.01), LAVmin/Cn (r = 0.603, 0.426, $p = 0.001$, 0.03), and LA-SV/Cn (r = 0.68, 0.56, $p < 0.001$, = 0.002), with all correlations being slightly better in the case of PISA-r.

Comparisons according to left atrial pressure

Next, patients were classified according to their LAP into 14 patients with LAP <25 mmHg, and 28 patients with LAP ⩾25 mmHg (Table 4). It was found that, compared to patients with LAP <25 mmHg, patients with LAP ⩾25 mmHg had significantly smaller PISA-r and IVRT/Te'–E, larger MVA, smaller LVOT-SV, larger LAVmax/cn, LAVmin/cn, and LA-SV/Cn, while PG and Cn were not different.

Correlations with mitral valve resistance

For the sake of measuring MVR, Cath-PG (14.8 ± 7 mmHg) in addition to diastolic filling time (0.433 ± 0.133 s) were measured. Cath-PG was significantly higher than the Doppler PG ($p = 0.04$), and they correlated only weakly (r = 0.34, $p = 0.06$).

The mean MVR was 390 ± 222 dynes · s · cm^{-5}. It was noticed PISA-r correlated significantly with MVR (−0.71, $p < 0.001$), MVA, and IVRT/Te'–E, and Cn also correlated with MVR but the correlations were weaker than that of PISA-r (r = −0.61, −0.51, −0.46 $p = 0.002$, 0.018, 0.035). PG, on the other hand, did not correlate with MVR

Table 4. Comparisons according to left atrial pressure.

	LAP < 25 mmHg (n = 28)	LAP ⩾ 25 mmHg (n = 14)	*p*-value
LAP (mmHg)	21.6 ± 2.6	33 ± 4.2	<0.001
MVA-PLN (cm^2)	1.1 ± 0.21	0.96 ± 0.25	0.007
PISA-r (cm)	1.47 ± 0.1	1.27 ± 0.11	<0.001
IVRT/Te'–E*	1.75 ± 0.39	1.03 ± 0.3	<0.001
SV (ml)	67.8 ± 17	56.3 ± 10.7	0.043
PG (mmHg)	11.5 ± 5.3	12.4 ± 5.9	0.653
LAVmax (ml)	102.5 ± 41.5	125.3 ± 39	0.149
LAVmin (ml)	68.4 ± 41	87.4 ± 34	0.197
LA-SV (ml)	34.1 ± 14.3	42 ± 11.6	0.117
Cn (ml/mmHg)	3.02 ± 1.2	2.8 ± 1.2	0.692
LAVmax/Cn (mmHg)	28.1 ± 10	60.8 ± 33	0.009
LAVmin/Cn (mmHg)	18.2 ± 11.4	41.5 ± 24.8	0.015
LA-SV/Cn (mmHg)	9.9 ± 4.3	19.3 ± 9.9	0.013

Abbreviations as in Table 1.
* only 34 cases (10 < 25 mmHg and 17 ⩾ 25 mmHg).

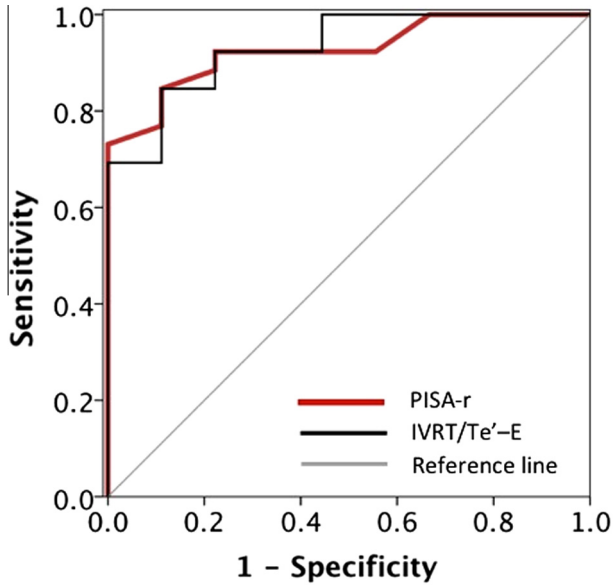

Figure 4. ROC-curve for detection of LAP ⩾25 mmHg as decided by PISA-r (red line), and IVRT/Te'–E (black line).

(r = 0.246, $p = 0.236$). By multivariate linear regression, PISA-r was the only variable that could independently predict MVR, while MVA, and IVRT/Te'–E, and Cn were excluded from the model due to loss of correlation (beta = −0.667, −0.141, −0.08, 0.01, $p = 0.001$, 0.749, 0.752, 0.98, respectively).

Ability to detect LAP ⩾25 mmHg

ROC-curve was initiated for PISA-r and IVRT/Te'–E to compare their ability to detect LAP ⩾25 mmHg. It was found that PISA-r and IVRT/Te'–E values of 1.39 cm and 1.27, respectively, were the best values to detect LAP ⩾25 mmHg with sensitivities of 89, 89% and specificities of 91, 83%, respectively (AUC: 0.955, 0.952, 95% CI: 0.896 to 0.999, 0.888 to 0.999, respectively, all $p < 0.001$, Fig. 4). Fig. 5 gives examples of PISA-r in two patients with LAP <25 (Fig. 5A) mmHg and with LAP ⩾25 mmHg (Fig. 5B).

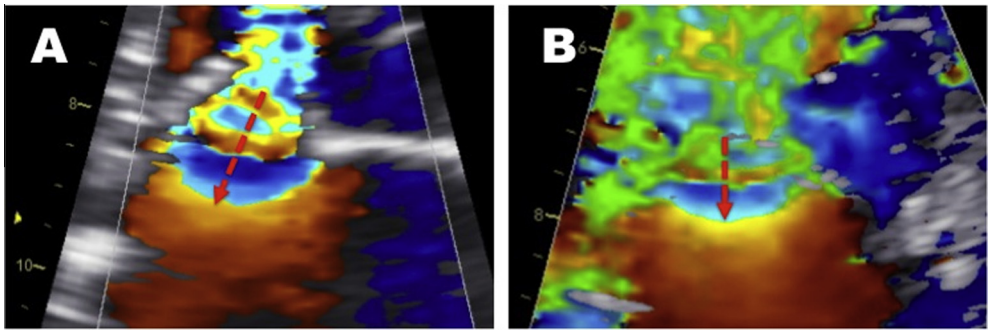

Figure 5. Examples of PISA-r in different MS severities and different LAP. (A) PISA-r = 1.5 cm, LAP = 20 mmHg, MVA = 1.33 cm^2; (B) PISA-r = 1.15 cm, LAP = 36, MVA = 0.6 cm^2.

Conventional methods of LAP assessment

The best conventional echocardiographic estimate of LAP is E/e'. However, this variable is known to be inaccurate in MS. In our study, the mean E/e' was 42.8 ± 18 and was significantly higher in patients with severe MS versus patients with moderate MS (21.4 ± 5.3 vs. 12.9 ± 2.9, p = 0.025) possibly because of the larger E-wave velocities expected in a more severe MS. However, E/e' was not different between patients with LAP ⩾25 mmHg and LAP <25 mmHg (42.6 ± 19.8 vs. 41 ± 14.7, $p = 0.679$), and there was no correlation between LAP and E/e' in our study (r = 0.116, $p = 0.52$). Thus, it seems that our study also proves that E/e' is an incorrect measure of LAP in patients with MS.

Discussion

Our study showed for the first time that in patients with significant MS, and after fixing the aliasing velocity, PISA-r correlates with and predicts LAP in a way that is not inferior to the time interval ratio IVRT/Te'–E. In addition, PISA-r, and not IVRT/Te'–E, was shown to correlate with LV stroke volume and mitral valve area.

Problems in echocardiographic assessment of MS

MVA and pressure gradient, despite being excellent representatives of MS severity, are unfortunately poor representatives of hemodynamics and actual chamber pressures [2,3,6]. For instance, changes in the LAP in patients with significant MS are the result of the combined effect of multiple factors such as MVA, MVR, left atrial size and cardiac chamber compliance [2–6]. This might explain the fact that in our study MVA correlated weakly, while pure left atrial variables and isolated Cn failed to correlate with LAP and right-sided pressures.

Echocardiographic assessment of LAP in MS is problematic because the significant increase in Doppler mitral flow velocities renders the conventional parameters (like E/e' and E/A) inaccurate and causes erroneous measurement of the actual mitral valve stroke volume (LV inflow volume) [3,22]. Depending on the left atrial stroke volume (that is, the difference between maximum and minimum LAV) in calculating mitral valve stroke volume suffers yet again from the effect of cardiac chamber compliance. In our study, we found that pure left atrial volumes could not correlate with LVOT stroke volume until Cn was taken into consideration. The combination of left atrial volume and Cn was shown to be a good representation of the hemodynamic status of patients with MS, but this calculation is complex.

Pressure-flow-resistance relationships

Physically, flow is also proportional to the ratio of pressure to resistance (F = P/R) [23,24]. Under ideal laminar flow conditions, in which vascular resistance is independent of flow and pressure, at any given flow across a heart valve, an increase in resistance increases the pressure gradient (ΔP). However, in turbulent flow the situation is different because turbulence decreases the flow at any given pressure and increases resistance to flow so that greater pressures are required than they would be in laminar flow [24,25]. It is also reported that in fixed stenosis, valve resistance is much more flow dependent than valve area. Thus, it seems that the flow dependent resistance of the valve in MS is more representative of hemodynamics than it would be of pressures or orifice area alone [18].

In most studies, as in ours, Doppler derived PG fails to correlate with LAP in the case of MS. In our opinion, this might be partially due to the simplified method used in calculating pressure gradient using the Bernoulli equation ($P = 4 \times V^2$) which neglects altered pressure-flow-resistance relationships in the case of a turbulent flow of a stenosed valve.

In our study, the above assumptions were proven true as PG failed to correlate with MVR, LVOT-SV, and this might explain why PG does not correlate with LAP in our study or in previous studies.

What does PISA-r really represent?

PISA, in its foundation, is an application of the continuity equation to measure flow [22,26]. Flow using the continuity equation is measured using the simple equation of [flow (ml) = area (cm^2) × velocity (cm/s)]. PISA flow, however, could be calculated using an application of this equation for the hemispherical convergence flow approaching the mitral valve [PISA flow (ml) = area of the hemispherical converging flow (cm^2) × aliasing velocity (cm/s)]; the area of the hemispherical convergence zone can be calculated as $2 \times 3.14 \times \text{PISA-r}^2$, and the aliasing velocity (Val) is the predefined velocity that determines the blue red interface of the convergence zone. However, because mitral valve in MS is conical in shape, the angle formed by both leaflets (α in degrees) should be used for correction as follows: [PISA flow (ml) = $2 \times 3.14 \times \text{PISA-r}^2 \times \text{Val} \times \alpha/180$], an equation that contains three unknowns, namely,

PISA-r, Val, and the angle α. This equation has been reported to be useful in calculating volume flow rate across the stenotic mitral valve [22]. Reportedly, angle α can be fixed in mitral stenosis to 100 degrees without affecting the equation [7,13]. In addition, in our current as well as previous studies, we used fixed Val without affecting the accuracy of PISA calculations [8,17]. This leaves us with only one unknown variable, PISA-r, which seems to be the actual determinant of the PISA flow. Thus, it seems that PISA-r is an estimate of the flow approaching and crossing the mitral valve (i.e. mitral valve stroke volume or LV inflow volume).

PISA-r, a measure of flow that connects anatomy and hemodynamics

The correlation noticed in our study between PISA-r and MVA-PLN, despite being promising was, however, not surprising. Prior attempts to fix the aliasing velocity might have suggested the potential association between PISA-r and MVA [10]. However, the surprising part of our study was the ability of PISA-r to correlate with LAP, and thus appears to be a parameter representing a combination of the anatomical and hemodynamic status of MS.

MVR is the physiologic rather than anatomic expression of stenosis because it incorporates both pressure gradient and flow data. From the PISA equation, and as can be deduced from the results of the current study, PISA-r is also the measure of flow (LVOT-SV) that can be used to assess anatomy (MVA-PLN). Interestingly, PISA-r was a very strong correlate and was the only independent predictor of MVR. Thus, it seems that PISA-r appropriately represents the pressure-flow-resistance relationship of a turbulent flow; because PISA-r is more flow-and-resistance dependent than other variables in the study.

Accordingly, PISA-r seems to represent the hemodynamic reflection of the anatomic severity of MS. IVRT/Te'–E, on the other hand represents only LAP, and MVA-PLN represents only the anatomic severity of MS.

Advantages of PISA-r over IVRT/Te'–E as an estimate of LAP in MS

The ratio IVRT/Te'–E, was reported to effectively estimate LAP in patients with MS [6], which was proven correct in our study. This method, however, is extremely tedious and time consuming due to the need to measure different time intervals in different cardiac cycles and the need to choose cardiac cycles with similar electrocardiographic R-R intervals. In our study, despite all due care, a considerable number of patients still showed inevitably unacceptable different R-R intervals. Encountering such problems, however, seems unavoidable.

Moreover, it is not uncommon to find simultaneous upstrokes of mitral annular e' and mitral flow E-wave, causing an impossible calculation due to a denominator value of zero. In our study, this precise problem was encountered in eight patients.

PISA-r, on the other hand, was possible in all patients. There was no need to measure various time intervals in different cardiac cycles, and, unlike IVRT/Te'–E, PISA-r also correlated with MVA and LVOT-SV.

Technical issues with PISA-r measurements

The shape of the PISA cap has been a source of debate [27,28]. A large part of this debate, however, arises from the use of PISA in MR, in which the shape of the orifice might vary from slit to rounded holes and from regular smooth to irregular orifices. From our experience, the shape of the orifice pertaining to rheumatic MS is usually regular and rarely a slit, but is typically a fish mouth or button hole, and so might still keep the role of the hemispheric model of PISA calculations.

It is important to keep in mind some technical issues while measuring PISA-r, as measurement of the radius can have great inter-observer variability, mainly because of difficulties with identifying the level of the center of the curvature of PISA. To solve this possible problem, here and in previous studies, we have suggested a specific reproducible method to measure PISA-r. First, it is important to specify the timing of the PISA-r measurement, as PISA flow changes through the diastolic period in a similar way to the Doppler recorder velocities (i.e. reaching peaks during early filling and atrial contraction). Thus, we chose to always measure PISA-r in its maximum early, and not in its late, diastolic peak, because the latter is lost in atrial fibrillation. Despite it being outside the scope of this study, it might be reasonable to note at this specific point and for the purposes of measuring MVA using PISA, that the simultaneous Vmax would be E-wave velocity (i.e. maximal early diastolic velocity). In addition, to identify the level from which measurement of the radius starts, we used the apex of the triangle formed by both leaflets in color Doppler turned off images (Fig. 2-B). After identifying this point, color is applied again to the image and PISA-r is drawn from this point to the curvature of the PISA cap, or the curved line that separates the red from blue

flow. However, care must be taken with the direction of the mitral forward flow while drawing the PISA-r, so that the line is kept centered and parallel to that flow as much as possible (Fig. 2-C).

Limitations

This study included a small number of patients. Future studies with larger patient populations are necessary to verify study findings. Although we used the planimetry method to derive MVA, it has some limitations in that it may be influenced by severe leaflet or subvalvular calcification, asymmetrical leaflet affection, imaging technique or poor image quality. The careful selection of patients in our study could have avoided most of these limitations. A major problem was the funnel-shaped structure that was seen in a significantly large number of patients who had symmetrical affection of both leaflets. To avoid this limitation, we measured the distance between the anterior and posterior mitral leaflets in the LV parasternal long-axis view in its narrowest area for these patients. When viewing the LV short axis, planimetry of the mitral valve was not performed until we ascertained that the level of measurement was the level with the smallest distance between anterior and posterior leaflets, closest to the smallest distance obtained from the LV parasternal long-axis view, and thus serving as the narrowest area possible by planimetry of the mitral orifice. Newly developed imaging modalities, such as three-dimensional echocardiography, magnetic resonance imaging or computed tomography may reduce the operator dependence of the planimetry method and overcome most of its limitations.

Conclusion

Fixing the aliasing velocity of the PISA equation in mitral stenosis shows that PISA-r might be a representation of LV inflow, which appears to cause PISA-r to effectively assess both the anatomic severity and its reflection on the hemodynamic status of patients with MS. PISA-r might be a useful alternative to the tedious IVRT/Te'–E in assessing LAP, and to the operator dependent planimetry in assessing MVA.

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