Comparison of Echocardiographic Methods in Assessing Severity of Mitral Regurgitation in Patients with Mitral Valve Prolapse

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Background and aim of the study: **Mitral regurgitation (MR) shows different characteristics in mitral valve prolapse (MVP); hence, it is important to assess MR severity accurately in these patients. The study aim was to compare Doppler echocardiographic methods in making such assessment.**

Methods: **Forty-seven patients with confirmed MVP and at least moderate mitral insufficiency, as established by Doppler echocardiography, were studied. Quantitative Doppler was used as the reference standard method. Color Doppler mapping was used to determine regurgitant jet area (JA/LAA), flow convergence (EROA-PISA) and vena contracta width (VCW). Systolic pulmonary venous flow reversal (SPVFR) and mitral E-wave velocity were also monitored.**

Results: **Univariate analysis showed severe MR to be significantly correlated to age, presence of atrial fibrillation, left ventricular systolic and diastolic diameter, left atrial diameter, mitral E velocity, JA/LAA, VCW, EROA-PISA and the presence of SPVFR. On multivariate analysis, the strongest determinants of severe MR were EROA-PISA, VCW and E velocity. The greatest area under the receiver-operator curve for diagnosing severe MR was observed with EROA-PISA. The 45-mm² threshold of EROA-PISA had the highest risk ratio of severe MR with a high sum of sensitivity and specificity. However, the JA/LAA had the lowest risk ratio and negative predictive value for severe MR.**

Conclusion: **PISA, VCW, E velocity and SPVFR measurements may be used to evaluate MR severity semi-quantitatively in patients with MVP; however, the ratio of JA/LAA appears to be a less reliable method in this respect.**

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Mitral valve prolapse (MVP), or myxomatous mitral valve disease, is the most common condition causing mitral regurgitation (MR) necessitating surgical correction (1-3). MR is the most frequent hemodynamic complication in patients with MVP, and unfavorably affects the prognosis (4-6). Moreover, notable rates of sudden death have been observed in patients with severe MR without risk factors (7). Consequently, the monitoring of patients for the development and progression of MR is important in assessing and treating MVP.

In the past, a variety of color and spectral Doppler echocardiographic methods have been used to monitor MR severity (8-15). The pathophysiology of MR differs in the presence of MVP. Under normal conditions, most of the regurgitant volume is ejected early (16,17), and a parallel decrease in left ventricular volume and regurgitant orifice area occurs throughout systole (18,19). In MVP, however, a progressive increase in regurgitant orifice area occurs during systole (20). The regurgitant jet in MVP is almost always eccentric, unless there is a prolapse at the central portion of the anterior leaflet or middle scallop of the posterior leaflet, or both (21).

As MR in MVP demonstrates different characteristics, it is of great importance to assess the severity of the condition accurately in these patients. To the present authors' knowledge, this is the first study conducted to compare echocardiographic methods when assessing MR severity in the presence of MVP.

Clinical material and methods

Patients

Forty-seven patients (20 men, 27 women; mean age 32 ± 20 years; range: 8 to 72 years) with confirmed

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MVP and at least moderate mitral insufficiency, as established using Doppler echocardiography, were studied. Among these patients, eight (17%) had a flail leaflet, 36 (77%) were in sinus rhythm, and 11 (23%) had atrial fibrillation (AF) at the time of the study. Thirty patients had a holosystolic murmur, while 17 had mid to late systolic murmur on auscultation. Floppy mitral valve was the underlying pathology in the studied patients. Patients with potential causes of secondary MVP, such as rheumatic mitral valve disease, atrial septal defect, coronary artery disease with prior myocardial infarction, significant pericardial effusion, cardiomyopathy, left ventricular systolic dysfunction and any patient with additional valvular heart disease were excluded. Of the 47 patients with MVP, 37 (79%) had a prolapse of the anterior leaflet, and 10 (21%) had a prolapse of the posterior leaflet. Mitral regurgitation was eccentric in all patients.

In addition, 30 patients (12 women, 18 men; mean age 28 ± 7 years) without MR and a cardiac shunt underwent quantitative Doppler measurements prospectively to assess the accuracy of stroke volume measurements.

During these studies, recommendations provided by the Helsinki Declaration for guidance of physicians in biomedical research involving human subjects were followed; informed consent was obtained from each patient.

Echocardiography

Transthoracic echocardiography was performed by one of the authors (who was blinded to patient clinical data) using a Hewlett-Packard Sonos 1500 instrument (Hewlett-Packard, Andover, MA, USA) fitted with a 2.5 MHz phased-array transducer. Recordings were taken with patients positioned in the left lateral decubitus position. The mean of five consecutive measurements from a good quality tracing was taken for each parameter. M-mode traces were recorded at 50 mm/s. Simultaneous electrocardiographic recordings were also taken. Measurements of left ventricle diameter, left ventricular ejection fraction and left atrium diameter at end-ventricular systole were obtained according to established standards (22). Diagnosis of MVP (annular overshoot of leaflets >2 mm in long-axis views) (23) and of flail segment (24) were based on recommended criteria.

Reference method (Quantitative Doppler study)

Quantitative Doppler assessment was performed as previously described (8,9). Mitral stroke volume was determined using the method proposed by Ascah et al. (9). This method assumes that the mitral annulus is an ellipse, the area of which is calculated using the mitral annular diameters obtained from apical two- and four-chamber views. Mitral stroke volume was calculated as the product of this area and the time-velocity integral (TVI) of the mitral annular Doppler tracing. Similarly, the aortic stroke volume was calculated as the product of the area of the left ventricular outflow tract and the TVI of the aortic annular Doppler tracing (8,9). The following parameters were calculated using the related formulae:

1. Regurgitant volume (RV, cm^3) of MR = (mitral stroke volume) - (aortic stroke volume)
2. Regurgitant fraction (RF, %) = RV/(mitral stroke volume)

The criterion for severe MR was taken as a RF ≥50% (25).

Other Doppler studies

From an apical four-chamber view, the area of the regurgitant mitral jet relative to the size of the left atrium (JA/LAA) (10) was measured using color-flow imaging. The RV and effective regurgitant orifice area (EROA) were calculated by the proximal isovelocity surface area (PISA) using color-flow imaging obtained from the apical four-chamber view (11). Vena contracta width (VCW), which is the narrowest portion of the MR jet downstream from the orifice, was measured either from parasternal or apical long-axis views using color-flow (12).

From the apical four-chamber view, the pulsed Doppler beam was placed 0.5-1 cm distal to the junction of the left atrium and right and left pulmonary vein, and flows were recorded. Systolic pulmonary venous flow reversal (SPVFR) was considered to be an

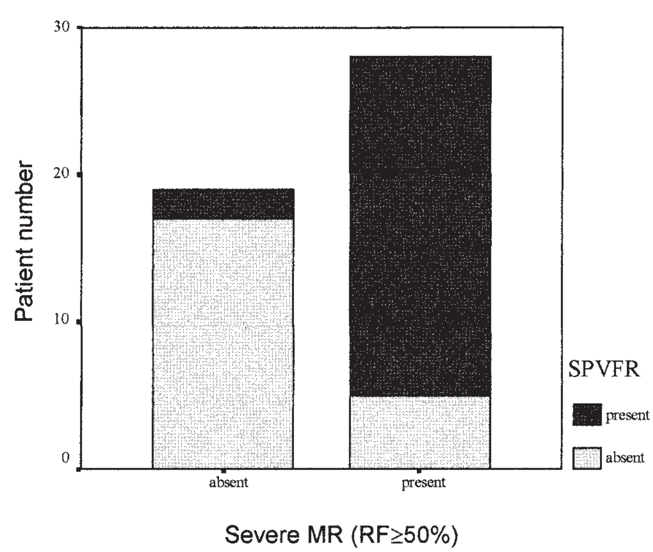

Figure 1: Relationship between severe mitral regurgitation (MR) and systolic pulmonary vein flow reversal (SPVFR).

Table I: Patients clinical, echocardiographic and hemodynamic findings based on severity of mitral regurgitation (MR).

Parameter	RF <50% (n = 19)	RF ≥50% (n = 28)	p-value*	r†	p-value†
Age (years)	22 ± 8	39 ± 22	0.001	0.32	<0.05
Females (n)	19 (68)	14 (50)	NS	0.18	NS
Heart rate (beat/min)	90 ± 13	86 ± 17	NS	-0.25	NS
AF (n)	1 (5)	10 (34)	0.016	0.35	<0.05
LVDD (mm)	55 ± 4	64 ± 5	<0.001	0.68	<0.001
LVSD (mm)	35 ± 5	39 ± 5	0.004	0.35	<0.05
EF (%)	67 ± 7	66 ± 8	NS	-0.09	NS
LAD (mm)	43 ± 8	58 ± 11	<0.001	0.60	<0.001
E velocity (cm/s)‡	144 ± 22	194 ± 24	<0.001	0.73	<0.001
JA/LAA (%)	28 ± 7	35 ± 11	0.006	0.36	<0.05
VCW (mm)‡	4.1 ± 0.6	7.3 ± 0.2	<0.001	0.83	<0.001
SPVFR (n)	2 (11)	23 (82)	<0.001	0.70	<0.001
EROA-PISA (mm^2)‡	26 ± 7	105 ± 40	<0.001	0.85	<0.001
RV-PISA (cm^3)	37 ± 15	143 ± 51	<0.001	0.84	<0.001
RV-QD (cm^3)	32 ± 9	85 ± 19	<0.001	-	-
III/IV MR (n)	1 (7)	28 (100)	<0.001	0.95	<0.001

Values are mean ± SD.
Values in parentheses are percentages.
*Severe MR (RF ≥50%) versus non-severe MR (RF <50%).
†Severe MR and the relationship with variables.
‡Strongest predictors of severe MR.
AF: Atrial fibrillation; EF: Ejection fraction; EROA-PISA: Effective regurgitant orifice area calculated by PISA; JA/LAA: Ratio of jet area to left atrial area; LAD: Left atrial diameter; LVDD: Left ventricular diastolic diameter; LVSD: Left ventricular systolic diameter; NS: Not significant; QD: Quantitative Doppler; RF: Regurgitant fraction; RV: Regurgitant volume; SPVFR: Systolic pulmonary vein flow reversal; VCW: Vena contracta width.

index of severe MR (13). Mitral inflow E velocity was also obtained by pulsed-wave (PW) Doppler echocardiography from the apical four-chamber view by placing the sample volume at the tips of the mitral leaflets (14,15).

Angiography

Among the 47 patients, 43 underwent cardiac catheterization.. Left ventriculography was performed using a 7 Fr pigtail catheter in the 30° right oblique position. The injection of contrast medium was carried out using a pump speed of 14 ml/s and a volume of 35-40 ml. The severity of MR was graded according to the classification of Sellers et al. (26), from I (mild) to IV (severe). Angiographically, grade III and IV MR was considered as severe. The angiograms were interpreted by consensus of two observers who were blinded to the results of the echocardiographic examination.

Statistical analysis

Numerical values were reported as mean ± SD. In the comparison of groups, Student's *t*-test was performed for numerical values, and a chi-square test for non-numerical values. A Spearman linear regression analysis was performed to analyze the correlation of variables with severe MR. Variables which correlated with severe MR were subjected to logistic multivariate analysis in order to identify the determinants of severe MR. For Doppler parameters, the highest risk ratio values were used to identify the threshold showing severe MR. Sensitivity, specificity and predictive values were calculated based on these threshold values. To compare the value of Doppler parameters in assessing severe MR, an ROC analysis was performed. In reproducibility measurements, Bland-Altman and Kappa analyses were used for numerical and nominal variables, respectively. The SPSS 7.5 statistical software package was used to carry out statistical calculations. A p-value <0.05 was considered to be statistically significant.

Results

Comparisons between groups (severe MR versus non-severe MR)

Twenty-eight (60%) patients had severe MR (RF ≥50%). The frequency of SPVFR in patients with non-severe MR was lower than in those with severe MR (11% versus 82%, p <0.001) (Table I: Fig. 1). The presence of AF was more frequent in patients with severe MR (34% versus 5%, p = 0.016). The left atrium and ventricle diameters were larger in patients with severe

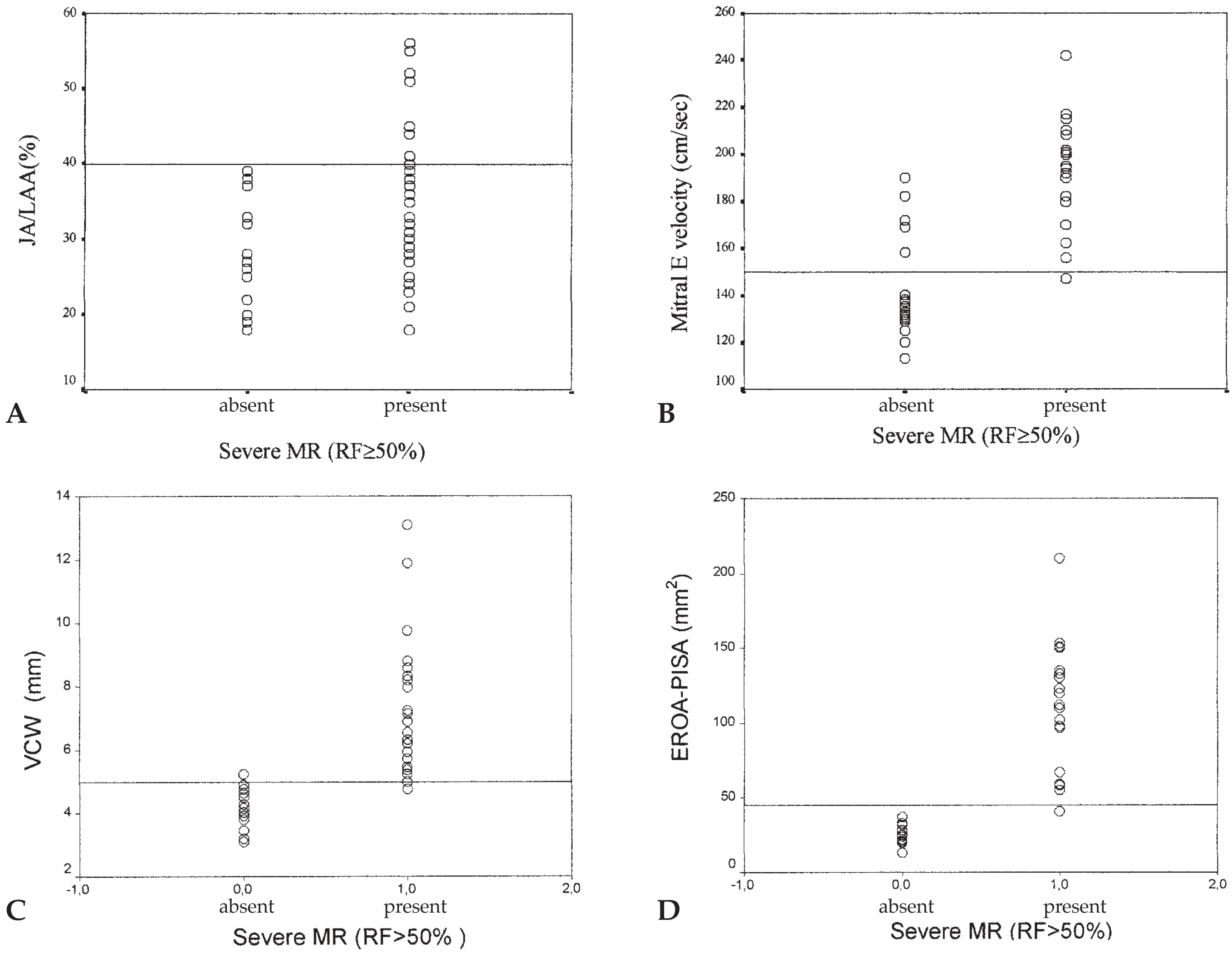

Figure 2: a) Relationship between the ratio of jet area/left atrial area (JA/LAA) and severe mitral regurgitation (MR). b): Relationship between severe MR and mitral diastolic E velocity. c) Use of vena contracta width (VCW) in detecting severe MR. d) Relationship of severe MR to effective regurgitant orifice area (EROA-PISA).

MR. The ratio of jet area to left atrium area (Fig. 2a), mitral E velocity (Fig. 2b), VCW of MR (Fig. 2c) and EROA calculated by the PISA method (Fig. 2d) were each higher in patients with severe MR.

Determinants of severe MR

On univariate analysis, severe MR was significantly correlated to age, the presence of AF, left ventricular systolic and diastolic diameters, left atrial diameter, mitral E velocity, JA/LAA, VCW, EROA-PISA and the presence of SPVFR (Table I). The strongest determinants of severe MR were found to be EROA-PISA, VCW and E velocity on multivariate analysis.

Diagnostic values of Doppler echocardiography

The greatest area under the ROC for diagnosing severe MR was observed with EROA-PISA (Fig. 3). The 45-mm^2 threshold of EROA-PISA had the highest risk ratio (20) of severe MR with a high sum of sensitivity and specificity (Table II). However, the JA/LAA had the lowest risk ratio and negative predictive value for severe MR.

Catheterization findings

Of 43 patients who underwent left ventriculography, 14 (33%) had grade II MR, nine (21%) grade III, and 20 (46%) grade IV. Thus, 29 (67%) patients had grade III or IV MR. The presence of grade III/IV MR showed statistically significant correlations with VCW ($r = 0.80$, $p < 0.001$), EROA-PISA ($r = 0.80$, $p < 0.001$), the presence of SPVFR ($r = 0.75$, $p < 0.001$), mitral E velocity ($r = 0.72$, $p < 0.001$) and JA/LAA ($r = 0.45$, $p = 0.002$).

Reproducibility of measurements

There was a good agreement between the aortic (69 ± 20 cm^3) and mitral (71 ± 24 cm^3) stroke volumes as

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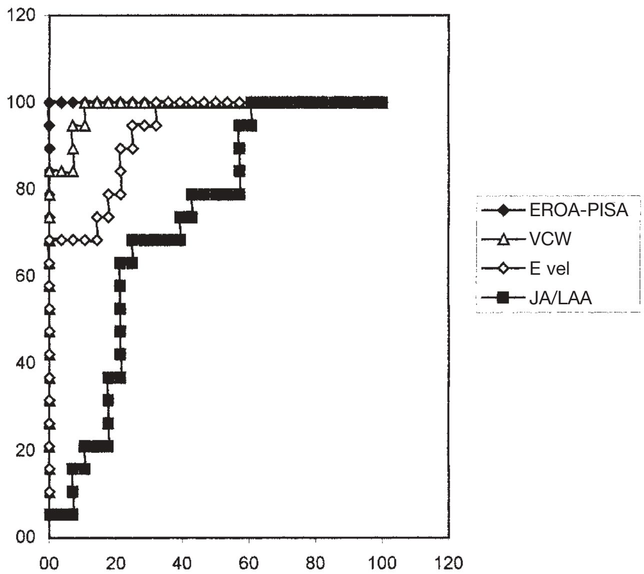

Figure 3: Receiver operating curves (ROC) showing the relationship of vena contracta width (VCW), E velocity, effective regurgitant orifice area (EROA-PISA) and ratio of jet area/left atrial area (JA/LAA) to severe mitral regurgitation (MR).

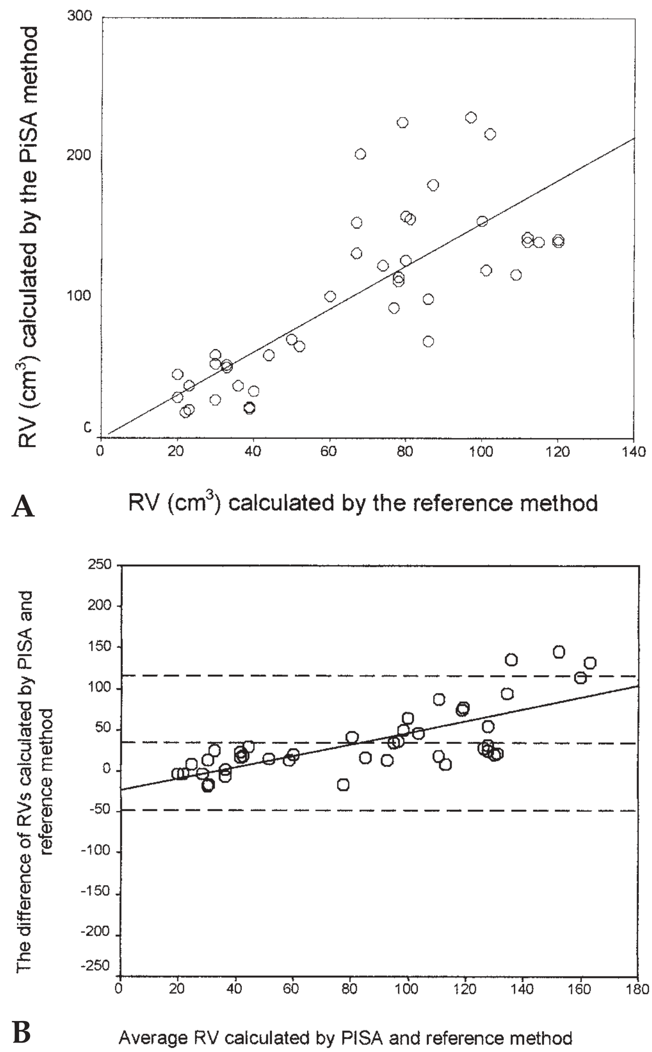

Figure 4: a) Relationship of regurgitant volume (RV) calculated by the reference and PISA methods. b) Differences in RV calculated by the reference and PISA methods.

calculated by the quantitative Doppler method in the normal group ($r = 0.96$, $p < 0.001$; mean difference 2.25 ± 7.45 cm^3, SEE = 1.41 cm^3 and $p = 0.12$). The pseudo mitral RF, calculated from two stroke volumes, was $1.95 \pm 7.9\%$ (minimum -13%, maximum 15%). In addition, there was an excellent agreement between echocardiographic severe MR (RF ≥50%) and angiographic severe MR (grade III/IV MR) (Kappa = 0.95, $p < 0.001$).

The inter-observer variabilities of Doppler parameters were evaluated in 15 randomly selected patients using the videotape records. There were excellent inter-observer agreements observed for the presence of SPVFR (Kappa = 1, $p < 0.001$), and measurements of VCW ($r = 0.96$, $p < 0.001$; mean difference 0.2 ± 0.3 mm, SEE 0.1 mm, $p = 0.77$), R diameter ($r = 0.93$, $p < 0.001$;

Table II: Diagnostic value of Doppler echocardiography in detecting severe mitral regurgitation (MR).

Parameter	Cut-off value	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)	RR
JA/LAA (%)	40	71	100	49	100	51	1.96
SPVFR	-	82	89	81	92	85	4
E velocity (cm/s)	150	93	68	87	81	83	6.23
VCW (mm)	5	93	95	90	96	94	9.6
EROA-PISA (mm^2)	45	96	100	95	100	98	20

E velocity: Mitral early diastolic flow velocity; EROA-PISA: Effective regurgitant orifice area calculated by PISA; JA/LAA: Ratio of jet area to left atrial area; NPV: Negative predictive value; PPV: Positive predictive value; RR: Risk ratio; SPVFR: Systolic pulmonary vein flow reversal; VCW: Vena contracta width.

mean difference 0.2 ± 0.4 mm, SEE 0.1 mm, $p = 0.8$), mitral E velocity ($r = 0.98$, $p <0.001$; mean difference -2.53 ± 7.20 cm/s, SEE 1.86 cm/s, $p = 0.19$), regurgitant jet area ($r = 0.94$, $p <0.001$; mean difference -0.25 ± 1.68 cm^2, SEE 0.43 cm^2, $p = 0.58$) or left atrial area ($r = 0.89$, $p <0.001$; mean difference 0.31 ± 4.25 cm^2, SEE 1.1 cm^2, $p = 0.78$).

Although the RV obtained using the PISA method correlated well with that obtained with the reference method ($r = 0.96$, $p <0.001$) (Fig. 4a), those values obtained with the PISA method were systematically overestimated (Fig. 4b).

Discussion

The results of the present study showed that, despite the overestimation of RV by PISA, the method can be used to assess the severity of MR due to MVP. Vena contracta width, E velocity and SPVFR can also be used to evaluate MR severity in patients with MVP, but JA/LAA appeared not to be a reliable method.

EROA by the PISA method in detecting severe MR

Although EROA showed excellent agreement with the reference method, RV was overestimated in the present study. In MVP, a progressive increase in EROA occurs during systole; this variability may lead to an overestimation of EROA and RV by use of the PISA method (3,20,27). Any deterioration in orifice geometry may cause the isovelocity surfaces to flatten out, and an overestimation of EROA occurs (28,29). On such an occasion, the geometric convergence angle should be determined and corrected (28). Indeed, without this angle correction, EROA may be overestimated (28), as in the present study. Despite these limitations, an EROA ≥45 mm^2 was predictive of severe MR, at least semi-quantitatively.

VCW in severe MR

According to the multivariate analysis, another powerful predictor of severe MR was VCW, and this showed good agreement with the reference method. Whereas the flow convergence method requires certain pitfalls to be avoided, the measurement of VCW is independent of hemodynamics and orifice geometry (30). The measurement of VCW is relatively simple and quick, but the fact that VCW values of 3 to 5 mm show both severe and moderate MR represents a limitation for this method (12). However, this appeared not to influence the present results as the number of patients in this situation was small.

Mitral E velocity in severe MR

Mitral E velocity was another strong predictor of severe MR. Early diastolic mitral inflow velocity relates directly to the instantaneous pressure gradient between the left atrium and left ventricle. The added RV increases the left atrium-to-left ventricle gradient, which in turn increases the early mitral inflow velocity (E wave). The peak E-wave velocity normally ranges from 60 to 130 cm/s (31). According to the present results, a mitral peak E-wave velocity ≥150 cm/s was predictive of severe MR, with 93% sensitivity and 84% specificity. Indeed, the present data were in agreement with previous studies in which E-wave velocity was shown as a reliable tool in predicting severe MR (14,15). Mitral E velocity by pulsed-wave Doppler is easy to measure, and is independent of the regurgitant orifice and jet morphology. Therefore, this method seems widely applicable in clinical practice as a simple technique to screen patients with MVP and severe MR. One problem is that E velocity may be influenced adversely by left ventricular dysfunction (14,15) and aortic regurgitation (32), both of which were excluded in the present study. In this setting, additional methods would be necessary to clarify the valvular lesion severity.

SPVFR in severe MR

It has been reported previously that pulmonary vein flow tracing obtained by transthoracic echocardiography (TTE) can be used to detect severe MR of various etiologies (13,33). The results of the present study show that SPVFR has a good sensitivity (82%), specificity (89%) and accuracy (85%) for diagnosing severe MR. Enriquez-Sarano et al. (33) reported that SPVFR has a low sensitivity and correlation for severe MR caused by different mitral valvular lesions. With the evaluation of both pulmonary veins, Eren et al. found a far better sensitivity for SPVFR in indicating severe MR (13), and the present results were in agreement with those of the latter authors. Enriquez-Sarano et al. (33) also reported that eccentric jets alter pulmonary venous systolic flow, regardless of the degree of MR, by its local effect on the pulmonary vein orifices. Because the regurgitant jet is usually eccentric in patients with MVP, this could be a limitation in assessing MR severity by using the presence of SPVFR. However, Eren et al. (13) noted that most of the SPVFR occurred in the pulmonary vein opposite to that in which the jet was directed. Thus, the formation of SPVFR cannot be explained only by a local effect of eccentric jets. In addition, Pieper et al. (34) reported a good relationship between severe MR and SPVFR for eccentric jets by using only the right pulmonary vein.

The presence of AF may be a limitation for SPVFR in indicating severe MR (35). It has been shown that the systolic component of pulmonary venous flow decreases in AF because of a deterioration in elasticity of the left atrium (36). Thus, SPVFR can easily be present in the pulmonary vein in patients with AF, but without severe MR. This limitation does not appear to have affected the present study however, because 10 of the 11 patients with AF had SPVFR and severe MR.

JA/LAA ratio and severe MR

In the present study, the ratio of JA/LAA proved only weakly reliable in detecting severe MR in patients with MVP. This may be explained by the fact that the jet area tends markedly to underestimate MR severity in eccentric jets (37). Even in studies including patients with central jets, the ratio of JA/LAA was shown not to be a good method for assessing MR severity (12). Moreover, jet area can be affected by technical factors (38), as well as by significant inter-observer variability when measuring this parameter (39). In order to overcome these limitations in the present study, care was taken such that optimal device settings were used, and consequently the inter-observer variability was low.

Accuracy of the reference method

Although the present reference method has certain technical limitations, its validity had been proven by its use in previous studies (10,20,22,27). Furthermore, in the present study there was a good agreement between the aortic and mitral stroke volumes calculated by the reference method in the normal group, and the pseudo mitral RF was also within an acceptable range. An excellent correlation was also found between angiographically detected severe MR (III/IV degree) and severe MR (RF ≥50%) measured with the reference method (Kappa = 0.95, p <0.001). Moreover, simultaneous measurement of the Doppler parameters assessing MR severity may increase the accuracy of the present results.

Study limitations

The main study limitation was that although patients were subdivided into groups of severe or non-severe MR, the methods used for the assessment were most likely inadequate, and further studies are required in this respect. From a different viewpoint, there is a general trend to consider patients with MVP and severe MR as the best surgical candidates for early surgery (40). Therefore, it seems more important to detect patients with MVP and severe MR rather than to classify patients with less severe MR.

In conclusion, PISA, VCW, E velocity and SPVFR may be applicable as a technique for evaluating MR severity semi-quantitatively in patients with MVP, whilst the ratio of JA/LAA appears not to be a reliable method for this purpose.

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