

IMPACT OF A GEOMETRIC CORRECTION FOR PROXIMAL FLOW CONSTRAINT ON THE ASSESSMENT OF MITRAL REGURGITATION SEVERITY USING THE PROXIMAL FLOW CONVERGENCE METHOD

JEONG YOON JANG, MD¹, JOON-WON KANG, MD², DONG HYUN YANG, MD², SAHMIN LEE, MD², BYUNG JOO SUN, MD³, DAE-HEE KIM, MD², JONG-MIN SONG, MD², DUK-HYUN KANG, MD², AND JAE-KWAN SONG, MD²

¹DIVISION OF CARDIOLOGY, DEPARTMENT OF INTERNAL MEDICINE, GYEONGSANG NATIONAL UNIVERSITY SCHOOL OF MEDICINE, GYEONGSANG NATIONAL UNIVERSITY CHANGWON HOSPITAL, CHANGWON, KOREA

²CARDIAC IMAGING CENTER, ASAN MEDICAL CENTER HEART INSTITUTE, UNIVERSITY OF ULSAN COLLEGE OF MEDICINE, SEOUL, KOREA

³DIVISION OF CARDIOLOGY, DEPARTMENT OF INTERNAL MEDICINE, CHUNGNAM NATIONAL UNIVERSITY HOSPITAL, DAEJEON, KOREA

BACKGROUND: Overestimation of the severity of mitral regurgitation (MR) by the proximal isovelocity surface area (PISA) method has been reported. We sought to test whether angle correction (AC) of the constrained flow field is helpful to eliminate overestimation in patients with eccentric MR.

METHODS: In a total of 33 patients with MR due to prolapse or flail mitral valve, both echocardiography and cardiac magnetic resonance image (CMR) were performed to calculate regurgitant volume (RV). In addition to RV by conventional PISA (RV_{PISA}), convergence angle (α) was measured from 2-dimensional Doppler color flow maps and RV was corrected by multiplying by $\alpha/180$ (RV_{AC}). RV measured by CMR (RV_{CMR}) was used as a gold standard, which was calculated by the difference between total stroke volume measured by planimetry of the short axis slices and aortic stroke volume by phase-contrast image.

RESULTS: The correlation between RV_{CMR} and RV by echocardiography was modest [RV_{CMR} vs. RV_{PISA} ($r = 0.712, p < 0.001$) and RV_{CMR} vs. RV_{AC} ($r = 0.766, p < 0.001$)]. However, RV_{PISA} showed significant overestimation ($RV_{PISA} - RV_{CMR} = 50.6 \pm 40.6$ mL vs. $RV_{AC} - RV_{CMR} = 7.7 \pm 23.4$ mL, $p < 0.001$). The overall accuracy of RV_{PISA} for diagnosis of severe MR, defined as $RV \geq 60$ mL, was 57.6% (19/33), whereas it increased to 84.8% (28/33) by using RV_{AC} ($p = 0.028$).

CONCLUSION: Conventional PISA method tends to provide falsely large RV in patients with eccentric MR and a simple geometric AC of the proximal constraint flow largely eliminates overestimation.

KEY WORDS: Mitral regurgitation · Regurgitant volume · Proximal flow convergence · Echocardiography · Cardiac magnetic resonance image.

INTRODUCTION

Quantitative assessment of the severity of mitral regurgitation (MR) is critical for both diagnosis of severe MR and clinical decision making of the optimal timing of surgical intervention.¹⁾ Two-dimensional (2D) echocardiography remains a

key diagnostic modality and quantitation using the proximal isovelocity surface area (PISA) in the flow convergence region has been established to calculate regurgitant volume (RV) and effective regurgitant orifice area.¹⁻⁴⁾ Because of complex spatial and dynamic flow patterns across the mitral valve (MV), the

• Received: January 16, 2018 • Revised: February 25, 2018 • Accepted: February 26, 2018

• Address for Correspondence: Jae-Kwan Song, Cardiac Imaging Center, Asan Medical Center Heart Institute, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea Tel: +82-2-3010-3155, Fax: +82-2-486-5918, E-mail: jksong@amc.seoul.kr

• This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

PISA method based on the geometric assumptions can generate errors in quantification of MR severity.⁵⁻⁷⁾ Among them, overestimation of MR severity by echocardiographic PISA technique has been reported recently, and the role of echocardiographic assessment of MR severity has been seriously questioned.⁸⁾ In the early introductory stage of PISA technique, clinicians already found that PISA provided falsely larger RV, especially in patients with prolapse or flail MV characterized by eccentric MR jet.⁹⁻¹²⁾ Myxomatous degenerative change of the MV including prolapse and flail leaflets is the most common etiology of MR requiring MV surgery in most countries. Thus, whether echocardiographic PISA technique can serve as a reliable method for accurate quantitative assessment of MR severity remains a challenging issue. A simple geometric correction using the flow convergence angle in patients with eccentric MR has been suggested to overcome overestimation of the conventional PISA method,⁹⁾ but it has not been successfully incorporated in routine clinical practice. The aim of this study was to evaluate whether the angle correction (AC) of the constrained flow field may be useful for accurate quantitative assessment of MR using echocardiographic PISA technique. To test our hypothesis, both echocardiography and cardiac magnetic resonance image (CMR) were performed in patients with prolapse or flail MV. We selectively included patients with myxomatous degeneration and CMR was used as a gold standard method of MR quantification.

METHODS

STUDY PATIENTS

Consecutive patients aged more than 18 years referred for echocardiographic examination at the Asan Medical Center were prospectively included if they showed eccentric MR from prolapsed or failed MV in echocardiography. Exclusion criteria included patients with pronounced multiple jets (≥ 2 large jets), MR from infective endocarditis, functional MR, presence of mitral stenosis or aortic valve disease of any severity, intracardiac shunt, poor echocardiographic window resulting in inadequate image quality, and atrial fibrillation or other arrhythmias that would lead to suboptimal analysis. This study was approved by the Institutional Review Board of Asan Medical Center (AMC 2013-0058), and all patients were required to provide written informed consent before participation.

ECHOCARDIOGRAPHIC ASSESSMENT OF MR

Comprehensive 2D and Doppler echocardiographic examinations were performed in all patients. We followed the standards and techniques recommended by the American Society of Echocardiography.¹⁰⁾ PISA was determined by measuring proximal flow convergence by lowering imaging depth and reducing the Nyquist limit at mid-systole. Various views were used for optimal visualization of the PISA. Baseline shift was used to adjust the aliasing velocity around 40 cm/s. RV by PISA method

(RV_{PISA}) was calculated as effective orifice area by PISA multiplied by the MR velocity-time integral as per current guidelines. The regurgitant velocity-time integral was determined by tracing the contour of the regurgitant jet obtained by continuous-wave Doppler (Fig. 1A). The geometric convergence angle (α°) was determined to be the minimum angle between two sides of the proximal flow field obtained from two or more views, while the constraining angle was defined as $180^\circ - \alpha^\circ$.⁹⁾ Based on the observed α° (Fig. 1B), a corrected RV was calculated from a formula: $RV_{AC} = RV_{PISA} \times (\alpha^\circ/180^\circ)$.⁹⁾

QUANTIFICATION OF MR SEVERITY WITH CMR

CMR was performed using a 1.5 T CMR scanner (Magnetom Avanto, Siemens, Erlangen, Germany) with a phase array cardiac coil. A three-lead vector cardiogram was applied for retrospective electrocardiogram-gating scan. For evaluation of left ventricular (LV) stroke volume, cine images using steady state free precession technique was obtained in the short-axis and three long-axis (2-, 3-, 4-chamber) views of the LV. The short axis images covered from the LV apex to the mitral annular plane. Typical parameters of the cine image were 8-mm slice thickness (2-mm slice gap), 30 phases per R-R interval, repetition time of 43.2 ms, echo time of 1.5 ms, generalized auto-calibrating partially parallel acquisitions acceleration factor of 2, a field of view of 273×340 mm², and matrix of 224×180 pixels. For evaluation of aortic flow, breath-held, through-plane phase-contrast flow imaging was performed at the level of ascending aorta (2-4 cm above the aortic valve) with following scan parameters: repetition time, 39.2 ms; echo time, 2.6 ms;

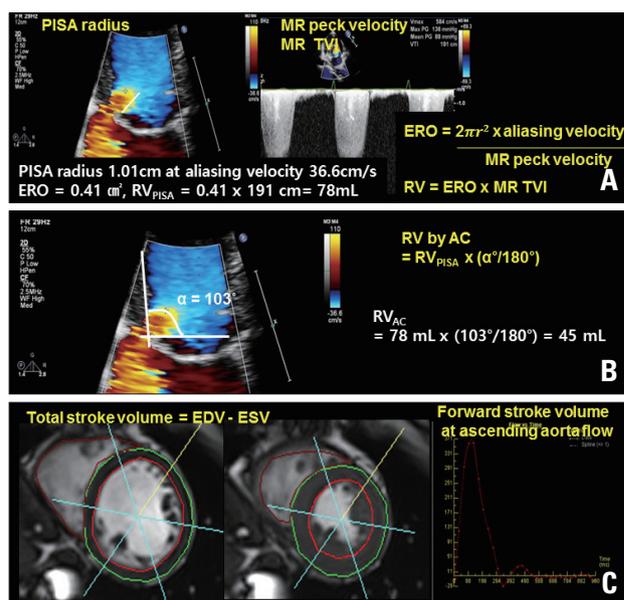


Fig. 1. A representative case showing the measurement of the RV using the conventional PISA method (A), the angle-corrected PISA (B), and cardiac magnetic resonance image (C). PISA: proximal isovelocity surface area, RV: regurgitant volume, AC: angle correction, MR: mitral regurgitation, EDV: end-diastolic volume, ESV: end-systolic volume, ERO: effective regurgitant orifice, TVI: time-velocity integral.

flip angle, 30°; number of average, 1; 30 phases per R-R interval; in-plane spatial resolution, 1.5 × 1.5 mm; slice thickness, 6.0 mm; and scan time, 10–15 sec. A maximum velocity started at 150 cm/sec and the maximum velocity was increased by 20 cm/sec if aliasing occurred. Blinded CMR measurements were performed by two experienced radiologists in consensus. Quantification of LV end-systolic and end-diastolic volumes was performed on the short-axis cine images after semi-automatic segmentation of the epicardial and endocardial borders. Papillary muscles were included with the LV chamber. LV stroke volume was obtained by subtracting LV end-systolic volume from LV end-diastolic volume. By tracing the borders of the aorta on flow image, aortic antegrade flow was measured. The RV using CMR (RV_{CMR}) was calculated by

Table 1. Baseline characteristics of participants

Variables	Values
Demographic	
Age, years	52 ± 9
Male gender, n (%)	27 (82)
Body surface area, m ²	1.73 ± 0.18
Underlying medical illness	
Hypertension, n (%)	13 (39)
Diabetes mellitus, n (%)	2 (6)
Echocardiographic variables	
LV end-systolic dimension, mm	34 ± 4
LV end-diastolic dimension, mm	54 ± 5
LV end-systolic volume, mL	53 ± 22
LV end-diastolic volume, mL	167 ± 39
LV ejection fraction, %	69 ± 7
PISA radius, cm	1.1 ± 0.3 (0.8–1.2)
PISA angle, °	102 ± 10 (95–111)

LV: left ventricular, PISA: proximal isovelocity surface area

the difference between LV stroke volume and antegrade aortic volumes (Fig. 1C). All patients underwent CMR in same day of 2D echocardiography.

STATISTICAL ANALYSIS

Categorical variables are presented as numbers and percentages, and were compared using Chi square and Fisher's exact test. Continuous variables are expressed as mean ± standard deviation, and were compared using Student's t-test. We used the Fisher's Z transformation to assess the significance of the difference between the two correlation coefficients found in two independent samples. To test the intra- and inter-observer reproducibility of convergence angle, the intraclass correlation coefficient (ICC) was used. The kappa statistic was used to assess agreement in categorizing MR severity. MR severity was classified using calculated RV: mild MR ($RV < 30$ mL), moderate MR (RV of 30–59 mL), and severe MR ($RV \geq 60$ mL). All reported p values were two-sided, and a value of $p < 0.05$ was considered statistically significant. SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA), was used for all statistical analyses.

RESULTS

BASELINE CHARACTERISTICS

A total of 33 patients (mean age 52 ± 9 years) with MR due to prolapse or flail MV was included. Baseline characteristics of the patients are summarized in Table 1. Male comprised more than 80% of the subjects ($n = 27$, 82%). Other medical illness included hypertension ($n = 13$, 39%) and diabetes mellitus ($n = 2$, 6%). All patients except one showed normal LV ejection fraction (69 ± 7%). CMR and echocardiography were done on the same day in all patients. PISA radius and angle were 1.1 ± 0.3 cm (0.8–1.2 cm) and 102° ± 10° (95°–111°),

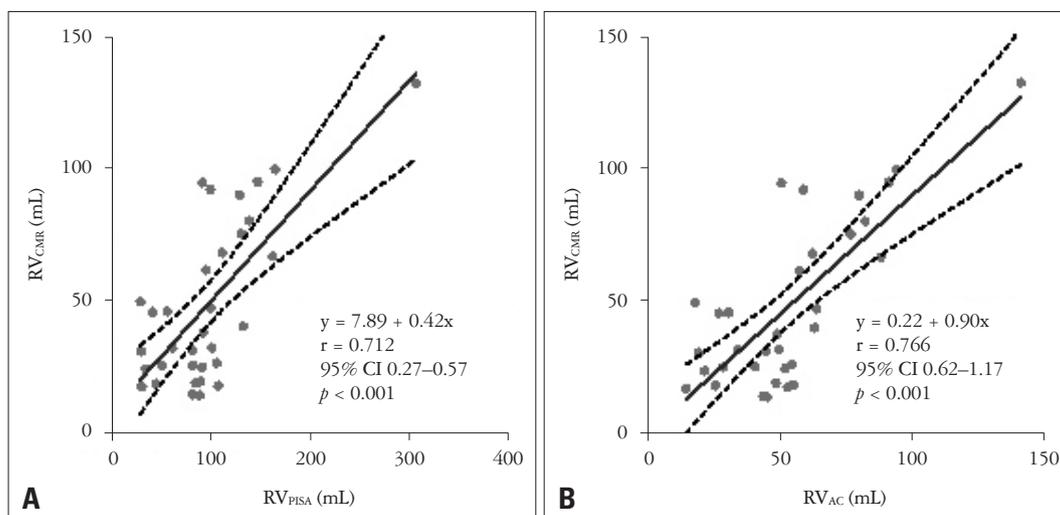


Fig. 2. Quantitative comparison of RV as determined by CMR (RV_{CMR}) and echocardiography before (RV_{PISA}) (A) and after the AC of the PISA method (RV_{AC}) (B). CMR: cardiac magnetic resonance image, RV: regurgitant volume, PISA: proximal isovelocity surface area, AC: angle correction, CI: confidence interval.

respectively. The interobserver and intraobserver reproducibility for convergence angle were good as expressed by intraclass correlation (ICC = 0.854 and 95% confidence interval: 0.70 to 0.93 and ICC = 0.907, 95% confidence interval: 0.81 to 0.95, respectively).

COMPARISON BETWEEN ECHOCARDIOGRAPHY AND CMR

The mean RVs obtained by conventional PISA, PISA with AC, and CMR were 96 ± 53 mL, 54 ± 27 mL, and 48 ± 31 mL, respectively. A quantitative comparison of RV by echocardiography and CMR is shown in Fig. 2, revealing a modest correlation. The difference of RV between the conventional PISA and CMR method was 50.6 ± 40.6 mL, which was significantly decreased after AC (7.7 ± 23.4 mL, $p < 0.001$) (Fig. 3).

CONCORDANCE BETWEEN ECHOCARDIOGRAPHY AND CMR

Table 2 and Fig. 4 show a comparison of categorical assessment of MR severity between echocardiography and CMR. The overall agreement between CMR and the conventional PISA was 39.4% (13/33), which did not change significantly after the AC [51.5% (17/33), $p = 0.32$]. However, the overestimation of MR severity by the conventional PISA method decreased significantly after the AC [54.5% (18/33) vs. 30.3% (10/33), $p = 0.046$]. If patients were classified as having severe or non-severe MR, the concordance or the overall accuracy improved from 57.6% (19/33) to 84.8% (28/33, $p = 0.028$) after the AC. The sensitivity and specificity for the diagnosis of severe MR using the conventional PISA method were 100% (11/11) and 36.4% (8/22), respectively. The sensitivity and specificity of the PISA method after the AC were 72.7% (8/11)

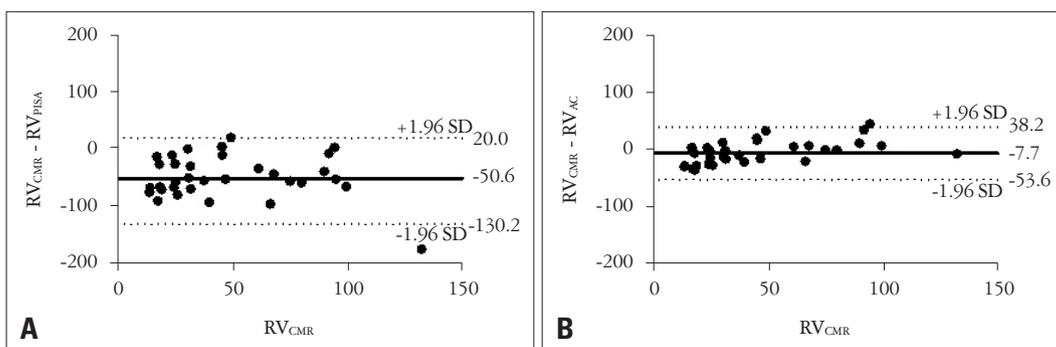


Fig. 3. Bland-Altman plot showing the difference of RV as determined by CMR (RV_{CMR}) and echocardiography before (RV_{PISA}) (A) and after the AC of the PISA method (RV_{AC}) (B). CMR: cardiac magnetic resonance image, RV: regurgitant volume, PISA: proximal isovelocity surface area, AC: angle correction.

Table 2. Comparison of numbers for each grade of MR severity: CMR vs. conventional PISA and CMR vs. $PISA_{AC}$

PISA	CMR				PISA _{AC}	CMR			
	Mild	Moderate	Severe	Total		Mild	Moderate	Severe	Total
Mild	0	2	0	2	Mild	4	3	0	7
Moderate	4	2	0	6	Moderate	8	5	3	16
Severe	8	6	11	25	Severe	0	2	8	10
Total	12	10	11	33	Total	12	10	11	33

MR: mitral regurgitation, CMR: cardiac magnetic resonance image, PISA: proximal isovelocity surface area, AC: angle correction

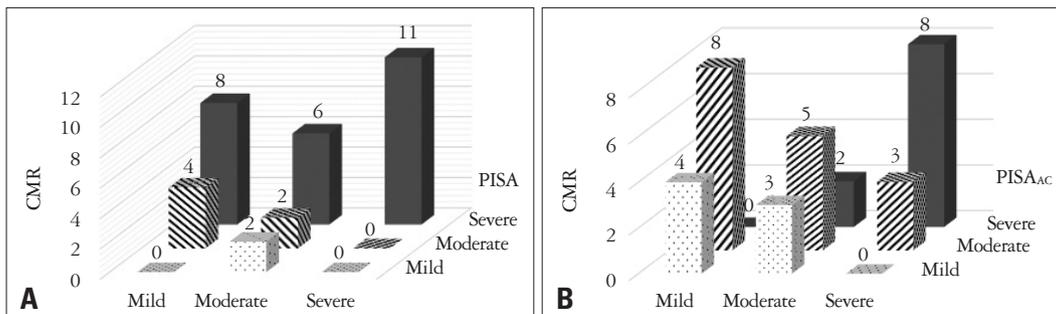


Fig. 4. Comparison of mitral regurgitation severity: CMR vs. conventional PISA (A) and CMR vs. angle-corrected PISA (B). CMR: cardiac magnetic resonance image, PISA: proximal isovelocity surface area, AC: angle correction.

and 90.9% (20/22), respectively, resulting in significant improvement of the specificity ($p = 0.002$).

DISCUSSION

In this study, we have confirmed only a modest agreement between echocardiography and CMR in the assessment of MR severity. Of 25 patients with a diagnosis of severe MR by the conventional PISA method, 14 (56%) had non-severe MR by CMR, suggesting substantial discordance. The discordance or overestimation by the conventional PISA method can be effectively eliminated by simple geographic correction of the proximal flow field and AC should be routinely done in patients with characteristic eccentric MR.

This is not the first to report overestimation of MR severity by the conventional PISA method in the evaluation of MR severity resulting in varying degrees of discordance between CMR and echocardiography.⁸⁾¹³⁻¹⁵⁾ As Doppler echocardiography is the most widely applied technique to assess the severity of MR, some investigators proposed altering thresholds for grading MR severity by MRI just to ensure concordance between the two modalities.¹³⁾ In the most recently published paper,⁸⁾ the authors hypothesized that post-surgical LV remodeling is related solely to the severity of MR before surgery based on the observation of tight coupling between RV and LV end-diastolic volume in patients with chronic, isolated MR.¹⁶⁾¹⁷⁾ They showed that there was a strong correlation between post-surgical LV remodeling and MR severity assessed by CMR ($r = 0.85$, $p < 0.001$), whereas no correlation between post-surgical LV remodeling and MR assessed by the conventional PISA method ($r = 0.32$, $p = 0.1$).⁸⁾ Their data with established CMR accuracy to determine RV suggest that CMR is more accurate than echocardiographic PISA technique in assessing the severity of MR. Although the authors suggest that CMR should be done before the clinical decision to undergo MV surgery,⁸⁾¹⁸⁾ routine application of both echocardiography and CMR is quite challenging in real world clinical practice. As we have shown that a simple application of the AC during the PISA method can effectively eliminate the overestimation of the conventional PISA method and improve the overall accuracy of the diagnosis of severe MR, this AC correction can be a very cost effective and practical way with high feasibility. In the previous study by Pu et al.,⁹⁾ the convergence angle of the proximal flow in MR was reported to be $119^\circ \pm 17^\circ$ and that of our study was $102^\circ \pm 10^\circ$. The previous study was characterized by heterogeneity of the study subjects including significant numbers of patients with central [34% (29/85)] or ischemic MR [19% (16/85)], whereas our study included only patients with eccentric MR due to prolapse or chordae rupture. Further investigations are necessary to evaluate whether underlying etiology of MR determines the convergence angle of the proximal flow.

Recently, 3D echocardiography has been proposed as an advanced technology to overcome the inherent limitations of 2D PISA technique including geometric assumption of the proximal

flow convergence region.¹⁹⁻²²⁾ Moreover, automated calculation of the intracardiac flow using the real time full volume color Doppler has been reported to be useful for accurate MR assessment.¹⁹⁾²⁰⁾ However, even with application of the 3D technique, angle dependence of color Doppler flow mapping still remains an inherent limitation, which makes it almost impossible to calculate the true surface area of the proximal flow convergence region.²³⁾²⁴⁾ Additionally, relatively low voxel rate of the current automated flow calculation program using the real time full volume color Doppler is another challenging issue.²³⁾²⁴⁾ Clinical usefulness of direct measurement of the regurgitant orifice area rather than flow rate or RV using the 3D data need to be further evaluated.²⁵⁾ Finally, direct comparison of AC of 2D PISA measurement with 3D echocardiographic measurement needs to be tested.

LIMITATIONS

There were several limitations in this study. First, this study is based on a single-center clinical experience including a relatively small number of patients. Moreover, we selectively included patients with prolapse or flail MV characterized by eccentric MR. Thus, the frequency of overestimation or discordant rate cannot be generalized to all patients with different etiologies. However, we believe this selective enrollment can also be an advantage of our study, as prolapse or flail MV is the most common cause of primary MR requiring the MV surgery. The previous studies included MR patients with different etiologies including both primary and functional MR¹⁹⁾²¹⁾²²⁾ and thus their analysis was mainly focused on the agreement of the techniques. They could not assess the diagnostic performance of each method for accurate diagnosis of severe MR, as the cutoff values of RV for diagnosis of severe MR are different according to the underlying etiology of MR.³⁾⁴⁾ We believe our data provide more meaningful information because of homogeneity of the subjects. Our contention needs to be tested by other investigators. The second argument is that experienced echocardiographers assess MR severity on the basis of a comprehensive approach that integrates several well-recognized and distinct criteria, including the size of the color flow jet, the width of the vena contracta, and the PISA-derived RV.²⁴⁾²⁶⁾ Thus, calculation of RV is not the only way for diagnosis of severe MR and thus somebody may argue that the potential clinical impact of the AC for accurate assessment of MR severity may not be considerable.²⁴⁾ However, we selected patients with eccentric MR, in which measurement of distal color jet and vena contracta has well documented to be very hard and thus quantitative measurement of RV is expected to play more important role.

CLINICAL IMPLICATIONS

Echocardiography is a cost-effective, readily available and well-established investigative tool for assessment of MR severity and the PISA method remains a main method for MR quantification. Along with an understanding of the inherent limita-

tions of the 2D PISA method, a simple geometric correction of the proximal flow field, the AC, can eliminate the overestimation of RV and prevent discordant grading, especially in patients with prolapse or flail MV characterized by eccentric MR.

• Acknowledgements

This study was supported by a research fund from Korean Society of Echocardiography.

REFERENCES

1. Thavendiranathan P, Phelan D, Collier P, Thomas JD, Flamm SD, Marwick TH. *Quantitative assessment of mitral regurgitation: how best to do it.* *JACC Cardiovasc Imaging* 2012;5:1161-75.
2. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, Hagendorff A, Monin JL, Badano L, Zamorano JL; European Association of Echocardiography. *European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease).* *Eur J Echocardiogr* 2010;11:307-32.
3. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M; ESC Committee for Practice Guidelines (CPG); Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS). *Guidelines on the management of valvular heart disease (version 2012): the joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS).* *Eur J Cardiothorac Surg* 2012;42:S1-44.
4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O’Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD; ACC/AHA Task Force Members. *2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* *Circulation* 2014;129:2440-92.
5. Moraldo M, Cecaro F, Shun-Shin M, Pabari PA, Davies JE, Xu XY, Hughes AD, Manisty C, Francis DP. *Evidence-based recommendations for PISA measurements in mitral regurgitation: systematic review, clinical and in-vitro study.* *Int J Cardiol* 2013;168:1220-8.
6. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, Pennell DJ. *Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable?* *Eur Heart J* 2000;21:1387-96.
7. Biner S, Rafique A, Rafi F, Tolstrup K, Noorani O, Shiota T, Gurudevan S, Siegel RJ. *Reproducibility of proximal isovelocity surface area, vena contracta, and regurgitant jet area for assessment of mitral regurgitation severity.* *JACC Cardiovasc Imaging* 2010;3:235-43.
8. Uretsky S, Gillam L, Lang R, Chaudhry FA, Argulian E, Supariwala A, Gurrarn S, Jain K, Subero M, Jang JJ, Cohen R, Wolff SD. *Discordance between echocardiography and MRI in the assessment of mitral regurgitation severity: a prospective multicenter trial.* *J Am Coll Cardiol* 2015;65:1078-88.
9. Pu M, Vandervoort PM, Griffin BP, Leung DY, Stewart WJ, Cosgrove DM 3rd, Thomas JD. *Quantification of mitral regurgitation by the proximal convergence method using transesophageal echocardiography. Clinical validation of a geometric correction for proximal flow constraint.* *Circulation* 1995;92:2169-77.

10. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. *Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography.* *J Am Soc Echocardiogr* 2003;16:777-802.
11. Chen C, Koschyk D, Brockhoff C, Heik S, Hamm C, Bleifeld W, Kupper W. *Noninvasive estimation of regurgitant flow rate and volume in patients with mitral regurgitation by Doppler color mapping of accelerating flow field.* *J Am Coll Cardiol* 1993;21:374-83.
12. Enriquez-Sarano M, Sinak LJ, Tajik AJ, Bailey KR, Seward JB. *Changes in effective regurgitant orifice throughout systole in patients with mitral valve prolapse. A clinical study using the proximal isovelocity surface area method.* *Circulation* 1995;92:2951-8.
13. Gelfand EV, Hughes S, Hauser TH, Yeon SB, Goepfert L, Kissinger KV, Rofsky NM, Manning WJ. *Severity of mitral and aortic regurgitation as assessed by cardiovascular magnetic resonance: optimizing correlation with Doppler echocardiography.* *J Cardiovasc Magn Reson* 2006;8:503-7.
14. Kizilbash AM, Hundley WG, Willett DL, Franco F, Peshock RM, Grayburn PA. *Comparison of quantitative Doppler with magnetic resonance imaging for assessment of the severity of mitral regurgitation.* *Am J Cardiol* 1998;81:792-5.
15. Cawley PJ, Hamilton-Craig C, Owens DS, Krieger EV, Strugnell WE, Mitsumori L, D’Jang CL, Schwaegler RG, Nguyen KQ, Nguyen B, Maki JH, Otto CM. *Prospective comparison of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography.* *Circ Cardiovasc Imaging* 2013;6:48-57.
16. Uretsky S, Supariwala A, Nidadovolu P, Khokhar SS, Comeau C, Shubayev O, Campanile F, Wolff SD. *Quantification of left ventricular remodeling in response to isolated aortic or mitral regurgitation.* *J Cardiovasc Magn Reson* 2010;12:32.
17. Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, Smith PK, Hung JW, Blackstone EH, Puskas JD, Argenziano M, Gammie JS, Mack M, Ascheim DD, Bagiella E, Moquete EG, Ferguson TB, Horvath KA, Geller NL, Miller MA, Woo YJ, D’Alessandro DA, Ailawadi G, Dagenais F, Gardner TJ, O’Gara PT, Michler RE, Kron IL; CTSN. *Mitral-valve repair versus replacement for severe ischemic mitral regurgitation.* *N Engl J Med* 2014;370:23-32.
18. Myerson SG, d’Arcy J, Christiansen JP, Dobson LE, Mohiaddin R, Francis JM, Prendergast B, Greenwood JP, Karamitsos TD, Neubauer S. *Determination of clinical outcome in mitral regurgitation with cardiovascular magnetic resonance quantification.* *Circulation* 2016;133:2287-96.
19. Son JW, Chang HJ, Lee JK, Chung HJ, Song RY, Kim YJ, Datta S, Heo R, Shin SH, Cho IJ, Shim CY, Hong GR, Chung N. *Automated quantification of mitral regurgitation by three dimensional real time full volume color Doppler transthoracic echocardiography: a validation with cardiac magnetic resonance imaging and comparison with two dimensional quantitative methods.* *J Cardiovasc Ultrasound* 2013;21:81-9.
20. Thavendiranathan P, Liu S, Datta S, Walls M, Nitinunu A, Van Houten T, Tomson NA, Vidmar L, Georgescu B, Wang Y, Srinivasan S, De Michelis N, Raman SV, Ryan T, Vannan MA. *Automated quantification of mitral inflow and aortic outflow stroke volumes by three-dimensional real-time volume color-flow Doppler transthoracic echocardiography: comparison with pulsed-wave Doppler and cardiac magnetic resonance imaging.* *J Am Soc Echocardiogr* 2012;25:56-65.
21. Choi J, Heo R, Hong GR, Chang HJ, Sung JM, Shin SH, Cho IJ, Shim CY, Chung N. *Differential effect of 3-dimensional color Doppler echocardiography for the quantification of mitral regurgitation according to the severity and characteristics.* *Circ Cardiovasc Imaging* 2014;7:535-44.
22. Heo R, Son JW, Ó Hartaigh B, Chang HJ, Kim YJ, Datta S, Cho IJ, Shim CY, Hong GR, Ha JW, Chung N. *Clinical implications of three-*

- dimensional real-time color Doppler transthoracic echocardiography in quantifying mitral regurgitation: a comparison with conventional two-dimensional methods.* *J Am Soc Echocardiogr* 2017;30:393-403.e7.
23. Thavendiranathan P, Liu S, Datta S, Rajagopalan S, Ryan T, Igo SR, Jackson MS, Little SH, De Michelis N, Vannan MA. *Quantification of chronic functional mitral regurgitation by automated 3-dimensional peak and integrated proximal isovelocity surface area and stroke volume techniques using real-time 3-dimensional volume color Doppler echocardiography: in vitro and clinical validation.* *Circ Cardiovasc Imaging* 2013;6:125-33.
 24. Buck T, Plicht B. *Real-time three-dimensional echocardiographic assessment of severity of mitral regurgitation using proximal isovelocity surface area and vena contracta area method. Lessons we learned and clinical implications.* *Curr Cardiovasc Imaging Rep* 2015;8:38.
 25. Hamada S, Altiok E, Frick M, Almalla M, Becker M, Marx N, Hoffmann R. *Comparison of accuracy of mitral valve regurgitation volume determined by three-dimensional transesophageal echocardiography versus cardiac magnetic resonance imaging.* *Am J Cardiol* 2012;110:1015-20.
 26. Thomas L, Foster E, Hoffman JI, Schiller NB. *The mitral regurgitation index: an echocardiographic guide to severity.* *J Am Coll Cardiol* 1999;33:2016-22.