Left Ventricular Early Inflow–Outflow Index: A Novel Echocardiographic Indicator of Mitral Regurgitation Severity

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***Background*—**No gold standard currently exists for quantification of mitral regurgitation (MR) severity. Classification by echocardiography is based on integrative criteria using color and spectral Doppler and anatomic measurements. We hypothesized that a simple Doppler left ventricular early inflow–outflow index (LVEIO), based on flow velocity into the left ventricle (LV) in diastole and ejected from the LV in systole, would add incrementally to current diagnostic criteria. LVEIO was calculated by dividing the mitral E-wave velocity by the LV outflow velocity time integral.

***Methods and Results*—**Transthoracic echocardiography reports from Montefiore Medical Center and its referring clinics from July 1, 2011, to December 31, 2011 (n=11 235) were reviewed. The MR severity reported by a cardiologist certified by the National Board of Echocardiography was used as a reference standard. Studies reporting moderate or severe MR (n=550) were reanalyzed to measure effective regurgitant orifice area by the proximal isovelocity surface area method, vena contracta width, MR jet area, and left-sided chamber volumes. LVEIO was 9.3±3.9, 7.0±3.2, and 4.2±1.7 among those with severe, moderate, and insignificant MR, respectively (ANOVA $P<0.001$). By receiver operating characteristic analysis, area under the curve for LVEIO was 0.92 for severe MR. Those with LVEIO ≥8 were likely to have severe MR (likelihood ratio 26.5), whereas those with LVEIO ≤4 were unlikely to have severe MR (likelihood ratio 0.11). LVEIO performed better in those with normal LV ejection fraction (≥50%) compared with those with reduced LV ejection fraction (<50%) (area under the curve 0.92 versus 0.80, $P<0.001$). By multivariate logistic regression analysis, LVEIO was independently associated with severe MR when compared with vena contracta width, MR jet area, and effective regurgitant orifice area measured by the proximal isovelocity surface area method.

***Conclusion*—**LVEIO is a simple-to-use echocardiographic parameter that accurately identifies severe MR, particularly in patients with normal LV ejection fraction. **(*J Am Heart Assoc.* 2015;4:e000781 doi: 10.1161/JAHA.113.000781)**

Key Words: echocardiography • imaging • mitral valve • regurgitation

No gold standard currently exists for the quantification of mitral regurgitation (MR) severity. The American Society of Echocardiography (ASE) guidelines outline a number of validated parameters for grading MR severity, including vena contracta (VC) width, color flow jet area, and effective regurgitant orifice area (ERO) measured by the proximal isovelocity surface area method (PISA)[1]; however, an integrative approach is recommended because of the limitations specific to each parameter.

The ASE guidelines include the regurgitant volume method as an alternative way to quantify MR severity. With this method, the left ventricular (LV) inflow volume during diastole is quantified using the mitral orifice area estimated from the mitral annulus diameter in conjunction with the spectral Doppler measurement of mitral inflow velocity integrated over the diastolic filling period (Figure). The LV systolic stroke volume is subtracted from the inflow volume to estimate the regurgitant volume. Some limitations of this technique impede widespread clinical use. The mitral orifice area is difficult to estimate accurately from a single linear measurement of its diameter owing to its irregular shape. In addition, measurement of the mitral inflow spectral Doppler tracing is time consuming.[2] Consequently, we sought to simplify this technique and harness its strengths by focusing on the more reproducible Doppler tracing measurements and removing the less reproducible anatomic measurements. We simplified the technique by using a single-point measurement of the early diastolic filling velocity (instead of a tracing of the entire mitral inflow profile), because the first value is more routinely reported on clinical echocardiographic reports, and by using

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Received December 31, 2013; accepted March 5, 2015.

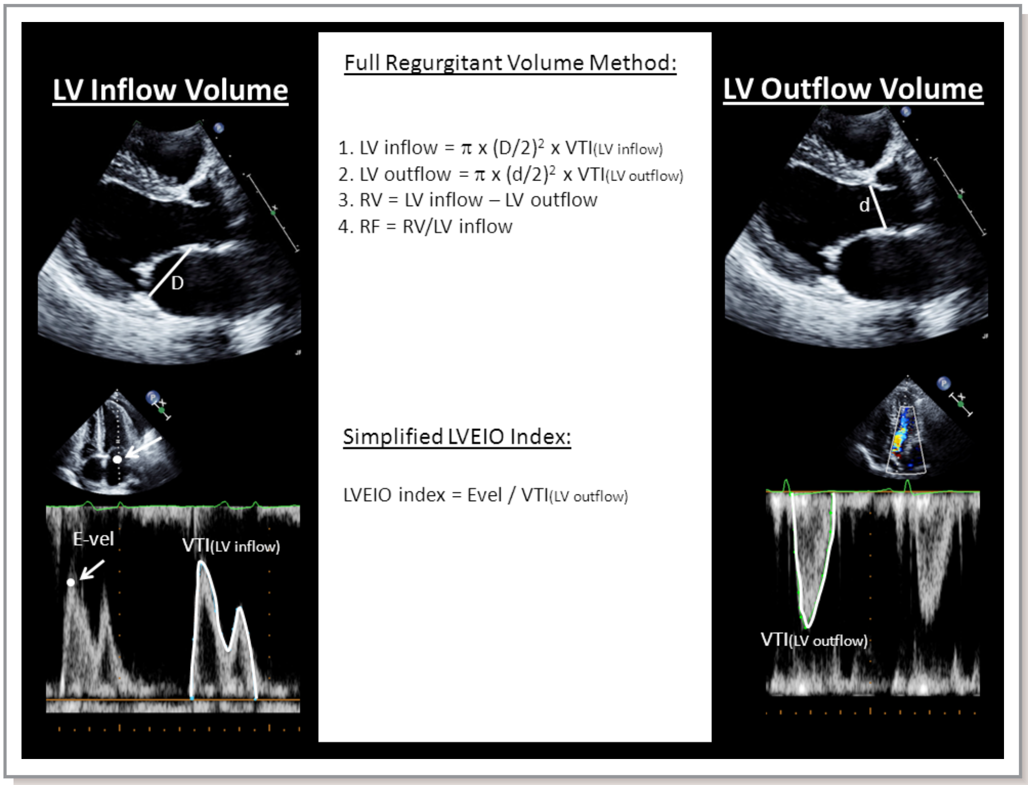

Figure. Measurements used by the regurgitant volume method and LVEIO. The index is a simplification of the regurgitant volume method and uses only a single-point measurement of early diastolic filling velocity (E-vel) and LV outflow velocity integrated over the systolic ejection period (LV VTI). d indicates diameter of left ventricular outflow tract; D, diameter of mitral annulus; E-vel, E-wave velocity; LV, left ventricular; LVEIO, left ventricular early inflow–outflow index; RF, regurgitant fraction; RV, regurgitant volume; VTI, velocity time integral.

the LV outflow velocity integrated over the systolic ejection period. In this way, we conceived the LV early inflow–outflow index (LVEIO). We hypothesized that this index would accurately identify severe MR, adding incrementally to current diagnostic criteria, and would be useful for clinical practice (Figure).

Methods

Study Sample and Design

The cardiology database Apollo (Lumedx) was queried for transthoracic echocardiograms (TTEs) routinely performed at Montefiore Medical Center and its referring clinics from July 1, 2011, to December 31, 2011 (n=11 235). TTEs reported to show moderate or severe aortic valve regurgitation (AR; n=25) were excluded. TTEs reported to show any mitral stenosis (n=131), prior mitral valve surgery (n=180), atrial septal defect (n=4), ventricular septal defect (n=6), or LV assist device (n=139) were excluded. TTEs with inadequate or missing LV inflow or outflow Doppler recordings were excluded (n=4486). ASE recommends an integrative approach to grading the severity of MR based on multiple parameters. This approach is used to minimize the effects of technical or measurement errors that are inherent to each quantitative method. The integration of the individual quantitative measures allows MR to be semiquantitatively categorized as mild, moderate, or severe. The clinical echocardiographic reports at our institution in the study period were generated by 11 cardiologists who are board certified by the National Board of Echocardiography and who routinely use the ASE integrative criteria for grading MR severity. Because there is no true gold standard for grading MR severity, the integrative assessment was used as a reference standard for this study. The remaining 6264 TTEs reported no or mild MR (n=5714), moderate MR (n=301), and severe MR (n=249). All studies reporting moderate MR (n=301) or severe MR (n=249) were reanalyzed to measure VS width, MR jet area, ERO by PISA, LVEIO, and left-sided chamber volumes. The examinations were performed using a Sonos 7500 or an IE-33 ultrasound system (Philips), and TTEs were digitally archived on a long-term storage server (Centricity; General Electric). All TTEs were reanalyzed by a single investigator (M.L.) using a Centricity Cardiology CA1000 v2.0 (General Electric) workstation. No TTEs with moderate or severe MR were excluded from reanalysis, and the quality of echocardiographic image acquisition for each TTE was graded as adequate, suboptimal, or inadequate. The study was approved by the institutional review board of Albert Einstein College of Medicine.

Evaluation of MR

All echocardiographic measures of MR severity were performed in accordance with the ASE guidelines.[1] VC was measured at the narrowest portion of the regurgitant jet at or just downstream from the regurgitant orifice from a magnified parasternal long-axis view. Regurgitant jet area was measured at its maximum from the apical 4-chamber view. The PISA radius was measured from a magnified apical 4-chamber view with color Doppler in which the flow convergence region had a hemispheric shape, and the color baseline was shifted to achieve a Nyquist limit (aliasing velocity) of 35 cm/s in the direction of regurgitant flow. The ERO was calculated using the following formula:

$$\mathrm{ERO} = (2\pi r^2 \cdot V_a)/V_{max}$$

The value r is the measured PISA radius, V_a is the aliasing velocity of the proximal flow convergence, and V_{max} is the peak velocity of the regurgitant jet measured by continuous-wave Doppler. The mitral early inflow (E-wave) velocity was measured from the pulse-wave Doppler recording at the tips of the mitral leaflets. LV outflow velocity time integral (VTI) was traced from the pulse-wave Doppler recording at the LV outflow tract. LVEIO was calculated using the following formula:

$$\mathrm{LVEIO} = \text{E-wave velocity}/\text{LV VTI}$$

Chamber Volume and Diastolic Function

The left atrial end-systolic volume was measured using the biplane method of discs (modified Simpson's rule) from the apical 2- and 4-chamber views. The LV end-diastolic and end-systolic volumes were measured using the biplane method of discs (modified Simpson's rule) from the apical 2- and 4-chamber views. Chamber volumes were indexed to body surface area.[3] LV ejection fraction (LVEF) was calculated from the measured end-diastolic and end-systolic volumes. Study subjects were considered to have diastolic dysfunction if the lateral mitral annular tissue velocity was <10 cm/s and the ratio of early mitral inflow to the annular tissue velocity (E/Em) was >8.[4]

Staistical Analysis

Statistical analysis was performed using Stata software v9.2. Comparison of means was performed using the 2-sample *t* test. Comparison of categorical data was performed using the chi-square test. *P* values were considered significant if $P<0.05$. Multivariate logistic regression analysis was performed to examine associations between severe MR and VC width, MR jet area, E-wave velocity, left atrial volume index, end-diastolic volume index, and LVEIO. Receiver operating characteristic analysis was performed to evaluate the accuracy of LVEIO and traditional parameters to detect severe MR. Likelihood ratios were calculated from the measured sensitivity and specificity of various cutoff points of LVEIO between 4 and 9 to find values with potential clinical utility for ruling in or ruling out severe MR. Cuzick's method was used to test for linear trend in MR variables across groups of MR severity. This method is a nonparametric test based on the Wilcoxon rank-sum test.[5]

To study measurement reproducibility, another investigator who was blinded to the original measurement remeasured E-wave velocity, LV VTI, and LVEIO in 20 consecutive study patients with moderate or severe MR. Agreement between readers was excellent. E-wave velocity was measured as 103.9±29.7 and 103.5±29.8 cm/s (intraclass coefficient 0.98), LV VTI was 14.2±4.5 and 14.4±4.8 cm (intraclass coefficient 0.87), and LVEIO was 8.2±3.7 and 7.9±3.1 (intraclass coefficient 0.88).

Results

Study Sample by MR Grade

Patient demographics and echocardiographic measurements of MR severity stratified by MR grade are summarized in Table 1. Patients with at least moderate (grade ≥2) MR were older ($P<0.001$), had lower body mass index ($P<0.001$), and had lower LVEF ($P<0.001$) than those with no or mild (grade 0/1) MR. Within the group with at least moderate MR, the etiology for MR was considered to be functional (n=202), leaflet/chordal calcification (n=156), multifactorial (n=122), prolapse (n=44), endocarditis (n=13), rheumatic without MS (n=8), and systolic anterior motion of the mitral valve (n=5) (ANOVA $P<0.001$). Patients in all groups were more often female, but there was no significant difference in sex between MR groups.

Significant linear trends were demonstrated for left atrial volume index, end-diastolic volume index, E-wave velocity, LV VTI, MR jet area, VC width, and ERO across groups of increasing MR severity (Table 1). Within each group of MR severity, the values found for each parameter were consistent with the ASE guidelines for grading MR.[1]

LVEIO

Linear increase in LVEIO was also noted across groups of increasing MR severity ($P<0.001$) (Table 1). Using receiver

Table 1. Patient Demographics and Echocardiographic Measures of MR Severity Stratified by MR Grade

	MR Grade				*P* Value
	0/1 (n=5714)	2 (n=301)	3 (n=111)	4 (n=138)	
Demographics					
Age, y	62.0±16.9	72.0±15.5	70.5±14.0	66.9±18.6	<0.001*
Male, %	43	45	47	47	0.220†
BMI	30.1±7.9	28.0±6.2	27.9±6.3	27.9±7.7	<0.001*
Anatomic measures					
LVEF, %	59.4±11.5	44.2±16.4	37.4±16.1	42.2±17.8	<0.001*
LVEF<50%, %	12	51	62	52	<0.001†
LAVI	31.1±12.3	42.3±15.3	47.4±18.8	54.3±26.2	<0.001‡
EDVI	54.1±20.7	74.7±28.9	87.4±28.3	90.1±49.3	<0.001‡
Color and spectral Doppler measures					
E-wave, cm/s	82.2±24.7	106.4±29.5	118.8±36.8	127.1±32.7	<0.001‡
LV VTI, cm	20.8±5.4	17.0±5.7	15.5±5.5	14.6±5.7	<0.001‡
LVEIO	4.2±1.7	7.0±3.2	8.6±3.9	9.7±3.8	<0.001‡
VC width, mm	—	4.0±1.2	5.8±1.7	6.6±2.4	<0.001‡
Jet area, cm^2	—	6.1±2.6	8.7±3.4	10.3±6.1	<0.001‡
ERO, cm^2	—	0.20±0.08	0.30±0.13	0.42±0.42	<0.001‡

MR grade: 0/1, none/mild; 2, moderate; 3, moderate to severe; 4, severe. BMI indicates body mass index; EDVI, end-diastolic volume index; ERO, effective regurgitant orifice area; LAVI, left atrial volume index; LV VTI, left ventricular velocity time integral; LVEF, left ventricular ejection fraction; LVEIO, left ventricular early inflow–outflow index; MR, mitral regurgitation; VC, vena contracta.
*Two-sample *t* test was used to compare means between those with no or mild (grade 0/1) MR and those with at least moderate (grade ≥2) MR.
†Chi-square test was used to compare categorical data between those with no or mild (grade 0/1) MR and those with at least moderate (grade ≥2) MR.
‡Cuzick's method was used to test for linear trend of MR variable across groups of MR grade.

operating characteristic analysis, the area under the curve of each parameter for the detection of severe MR (grades 3 and 4) is shown in Table 2. LVEIO was a significantly better discriminator of severe MR compared with E-wave velocity alone (area under the curve 0.92 [95% CI 0.90 to 0.93] versus 0.84 [95% CI 0.81 to 0.86]; $P<0.001$). Direct comparison of LVEIO to ERO, VC width, and MR area was not possible because these parameters were measured only in studies with at least moderate MR and adequate imaging. In the subgroup with reduced LVEF, most parameters performed less well for discriminating severe MR. In patients with diastolic dysfunction, area under the curve for E-wave velocity for the detection of severe MR was slightly worse but not for the other MR parameters.

Results of multivariate logistic regression analysis for predictors of severe MR (grades 3 and 4) are shown in Table 3. Quantitative measures of MR severity were dichotomized according to their recommended cutoff points.[1] LVEIO ≥8, VC width ≥0.7 cm, MR jet area >10 cm^2, and ERO ≥0.4 cm^2 were each independent predictors of severe MR. Use of LVEIO improved classification of MR severity compared with each of the other traditional echocardiographic findings alone (Table 4).

Discussion

The results of our study demonstrate that LVEIO is independently associated with severe MR and compares favorably with traditional diagnostic parameters, including VC width, regurgitant jet area, and ERO by PISA.

Although this study is the first to examine LVEIO as an echocardiographic indicator of MR severity, LVEIO is adapted from the regurgitant volume method. In this method, the regurgitant volume is calculated from the difference between the stroke volume at the mitral annulus in diastole and the stroke volume at the LV outflow tract in systole.[6,7] A key weakness of this method is the need for anatomic measurements. Several studies have shown that the regurgitant volume method significantly overestimates MR severity because it oversimplifies the calculation of cross-sectional area by using monoplanar anatomic measurements and assuming that the mitral annulus and LV outflow tract are circular when, in fact, they are oval.[8–10] LVEIO omits geometric error inherent to the regurgitant volume method.

Most other methods for quantification of MR rely heavily on color Doppler imaging and depend on subjectively selected single-frame measurements, which capture only a snapshot of

Table 2. AUC by ROC Analysis of LVEIO and Traditional Parameters for Discrimination of Severe MR (From Nonsevere MR)

	Full Study Cohort (n=6264)	Reduced LVEF (n=960)	Diastolic Dysfunction (n=2972)
LVEIO	0.92 (0.90 to 0.93)	0.80 (0.77 to 0.84)*	0.90 (0.88 to 0.93)
E-wave velocity	0.84 (0.81 to 0.86)†	0.78 (0.73 to 0.81)*	0.81 (0.77 to 0.84)*
VC width	0.83 (0.80 to 0.87)	0.83 (0.78 to 0.88)*	0.83 (0.79 to 0.87)
ERO	0.81 (0.75 to 0.86)	0.76 (0.68 to 0.84)*	0.83 (0.76 to 0.89)
LV VTI	0.79 (0.72 to 0.84)	0.64 (0.58 to 0.70)*	0.82 (0.77 to 0.87)
Jet area	0.76 (0.72 to 0.80)	0.76 (0.71 to 0.82)	0.77 (0.72 to 0.82)

Data are shown as AUC (95% CI). AUC was recalculated in subgroups with reduced LVEF and with diastolic dysfunction. For both subgroups, comparison testing was performed for AUC of those in the subgroup compared with those not in the subgroup. AUC indicates area under the curve; ERO, effective regurgitant orifice area; LV VTI, left ventricular velocity time integral; LVEF, left ventricular ejection fraction; LVEIO, left ventricular early inflow–outflow index; MR, mitral regurgitation; ROC, receiver operating characteristic; VC, vena contracta.
*$P<0.05$ for comparison between those with reduced LVEF and those with normal LVEF and for comparison between those with diastolic dysfunction and those without diastolic dysfunction.
†$P<0.05$ for comparison of AUC of LVEIO and AUC of E-wave velocity for severe MR. MR measurements available for VC width (n=495), ERO (n=305), and jet area (n=499). The remaining parameters were available for the entire study cohort.

Table 3. Association of Various Color and Spectral Doppler Measurements and Severe MR by Multivariate Logistic Regression Analysis

	OR	95% CI	*P* Value
LVEIO ≥8	1.8	1.2 to 2.8	0.005
VC width ≥0.7 cm	90.3	12.3 to 665.4	<0.001
Jet area >10 cm^2	5.1	3.0 to 8.9	<0.001
ERO ≥0.4 cm^2	21.7	4.9 to 95.7	<0.001

Each finding was independently associated with severe MR. ERO indicates effective regurgitant orifice area; LVEIO, left ventricular early inflow–outflow index; MR, mitral regurgitation; OR, odds ratio; VC, vena contracta.

Table 4. Net Reclassification Improvement Calculated for the Addition of LVEIO to Prediction of Severe MR by Each of the Listed Echocardiographic Parameters

	E-Wave Velocity	LVOT VTI	VC Width	Jet Area	ERO
Net reclassification improvement	1.04	0.76	0.34	0.35	0.44
P value	<0.001	<0.001	<0.001	<0.001	<0.001

ERO indicates effective regurgitant orifice area; LVEIO, left ventricular early inflow–outflow index; LVOT VTI, LV outflow tract velocity time integral; MR, mitral regurgitation; VC, vena contracta.

MR and fail to fully characterize its dynamic nature throughout systole.[11] Because the regurgitant flow rate and regurgitant orifice geometry both vary throughout systole, both of these factors are sources of error when assessing MR severity by jet area, VC width, or ERO by PISA.[12,13] In addition, the etiology of MR (degenerative versus functional), jet direction (central versus eccentric), number of jets, orifice geometry, instrument settings (eg, transducer frequency, color gain, Nyquist limit), and quality of image acquisition, including adequate visualization of the regurgitant orifice, all influence the ability of color Doppler methods to accurately assess MR severity.[11,14–21] Biner et al questioned the reliability of color Doppler–based parameters of MR severity and, consequently, advocated the integration of more reliable, non–color Doppler parameters, such as mitral inflow pattern, in the assessment of MR severity.[22,23] In our study, we demonstrated that the discriminating power of LVEIO not only was impressive, with an area under the curve of 0.92, but also surpassed that of mitral early inflow velocity alone.

LVEIO has several important limitations. The discriminating power of LVEIO was lower among those with reduced LVEF compared with those with normal LVEF. As expected, reduced LVEF is associated with lower stroke volume and, consequently, lower LV VTI. Reduced LVEF is also associated with clinical congestive heart failure, increased left atrial pressure, and accordingly increased E-wave velocity. Consequently, LVEIO is expected to be higher in patients with reduced LVEF, even if MR is mild or absent. Another explanation for the reduced performance of LVEIO in this group is that ventricular dilatation may alter the size of the LV inflow and outflow in a disparate manner, thereby altering the velocity profiles across each site. Despite this, we found that LVEIO still had reasonable discriminating power in this group.

In conclusion, LVEIO is a simple, accurate, and independent echocardiographic predictor of severe MR that adds incrementally to traditional methods for grading MR severity. Accurate quantification and classification of MR severity is critical for clinical decision making and timing of surgical intervention; therefore, incorporation of LVEIO into the integrative approach for grading MR severity should be considered.

Disclosures

None.

References

1. 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. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777–802.
2. Ray S. The echocardiographic assessment of functional mitral regurgitation. *Eur J Echocardiogr*. 2010;11:i11–i17.
3. Ristow B, Ali S, Na B, Turakhia MP, Whooley MA, Schiller NB. Predicting heart failure hospitalization and mortality by quantitative echocardiography: is body surface area the indexing method of choice? The Heart and Soul Study. *J Am Soc Echocardiogr*. 2010;23:406–413.
4. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Otto AS, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009;22:107–133.
5. Cuzick J. A Wilcoxon-type test for trend. *Stat Med*. 1985;4:87–89.
6. Rokey R, Sterling LL, Zoghbi WA, Sartori MP, Limacher MC, Kuo LC, Quinones MA. Determination of regurgitant fraction in isolated mitral or aortic regurgitation by pulsed Doppler two-dimensional echocardiography. *J Am Coll Cardiol*. 1986;7:1273–1278.
7. Enriquez-Sarano M, Bailey KR, Seward JB, Tajik AJ, Krohn MJ, Mays JM. Quantitative Doppler assessment of valvular regurgitation. *Circulation*. 1993;87:841–848.
8. Doddamani S, Bello R, Friedman MA, Banerjee A, Bowers JH Jr, Kim B, Vennalaganti PR, Ostfeld RJ, Gordon GM, Malhotra D, Spevack DM. Demonstration of left ventricular outflow tract eccentricity by real time 3D echocardiography: implications for the determination of aortic valve area. *Echocardiography*. 2007;24:860–866.
9. Doddamani S, Grushko MJ, Makaryus AN, Jain VR, Bello R, Friedman MA, Ostfeld RJ, Malhotra D, Boxt LM, Haramati L, Spevack DM. Demonstration of left ventricular outflow tract eccentricity by 64-slice multi-detector CT. *Int J Cardiovasc Imaging*. 2009;25:175–181.
10. Ren B, de Groot-de Laat LE, McGhie J, Vletter WB, ten Cate FJ, Geleijnse ML. Geometric errors of the pulsed-wave Doppler flow method in quantifying degenerative mitral valve regurgitation: a three-dimensional echocardiography study. *J Am Soc Echocardiogr*. 2013;26:261–269.
11. Grayburn PA, Bhella P. Grading severity of mitral regurgitation by echocardiography: science or art? *JACC Cardiovasc Imaging*. 2010;3:244–246.
12. Buck T, Plicht B, Kahlert P, Schenk IM, Hunold P, Erbel R. Effect of dynamic flow rate and orifice area on mitral regurgitation strove volume quantification using the proximal isovelocity surface area method. *J Am Coll Cardiol*. 2008;52:767–778.
13. Hall SA, Brickner ME, Willett DL, Irani WN, Afridi I, Grayburn PA. Assessment of mitral regurgitation severity by Doppler color flow mapping of the vena contracta. *Circulation*. 1997;95:636–642.
14. Chen C, Thomas J, Anconina J, Harrigan P, Mueller L, Picard M, Levine R, Wayman A. Impact of impinging wall jet on color Doppler quantification of mitral regurgitation. *Circulation*. 1991;84:712–720.
15. Enriquez-Sarano M, Tajik A, Bailey K, Seward J. Color flow imaging compared with quantitative Doppler assessment of severity of mitral regurgitation: influence of eccentricity of jet and mechanism of regurgitation. *J Am Coll Cardiol*. 1993;21:1211–1219.
16. Sahn DJ. Instrumentation and physical factors related to visualization of stenotic and regurgitant jets by Doppler color flow mapping. *J Am Coll Cardiol*. 1988;12:1354–1365.
17. Enriquez-Sarano M, Miller FA Jr, Hayes SN, Bailey KR, Tajik AJ, Seward JB. Effective mitral regurgitant orifice area: clinical use and pitfalls of the proximal isovelocity surface area method. *J Am Coll Cardiol*. 1995;25:703–709.
18. Simpson IA, Shiota T, Gharib M, Sahn DJ. Current status of flow convergence for clinical applications: is it a leaning tower of "PISA"? *J Am Coll Cardiol*. 1996;27:504–509.
19. 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;92:2951–2958.
20. Roberts BJ, Grayburn PA. Color flow imaging of the vena contracta in mitral regurgitation: technical considerations. *J Am Soc Echocardiogr*. 2003;16:1002–1006.
21. Grayburn PA. How to measure severity of mitral regurgitation. *Heart*. 2008;94:376–383.
22. Biner S, Rafique A, Rafii F, Tolstrup K, Noorani M, 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;3:235–243.
23. Thomas L, Foster E, Schiller NB. Peak mitral inflow velocity predicts mitral regurgitation severity. *J Am Coll Cardiol*. 1988;31:174–179.