

Assessment of functional mitral regurgitation Severity by proximal isovelocity surface area using three-dimensional transthoracic echocardiography

ABSTRACT

Background: Accurate quantitative evaluation of MR severity remains challenging because limited scan plane orientation of 2D echocardiography does not provide direct measurement of the regurgitant lesion. Three-dimensional echocardiography which has grown up to a clinically accepted technique has been demonstrated to provide important information for flow quantification and, thus, is promising to overcome the major limitations of 2D-based methods.

Objectives: To assess the reliability of PISA measurement using real-time 3D color trans-thoracic echocardiographic imaging in clinical practice and to compare its derived EROA, regurgitant volume (Rvol) and regurgitant fraction with that obtained by 2D trans thoracic PISA.

Patients and methods: This cross sectional study, included 30 patients with at least moderate functional MR came for evaluation on clinical basis indications at Al-Hussein and Bab AL She'reya university hospitals during the period from November 2020 to July 2021. Two & three dimensional echocardiography was done to asses MR and calculate vena contracta width ,2D PISA and deived EORA and regurgitant volume . also calculation of 3D EROA using PISA method by 3D probe .

Results: There was a significant positive correlation between 2D EPISA and 3D EROA using PISA method and EROA, p value was 0.0001.with higher values for 3D EROA using PISA method when compared with 2D PISA in different degrees of MR as summarized in " The mean value of EROA by 2D PISA in moderate MR was 0.25 ± 0.042 cm² ,while it was 0.32 ± 0.059 cm² by 3D EROA using PISA method . While the mean value of EROA by 2D PISA in severe MR was 0.58 ± 0.14 cm², and it was 0.47 ± 0.049 cm² by 3D EROA" .also showed significant difference in different direction of MR jets especially in eccentric jet as shown by the mean value of EROA by 2D PISA in central MR was 0.41 ± 0.19 cm² ,while it was 0.41 ± 0.87 cm² by 3D method . While the mean value of EROA by 2D PISA in eccentric MR was 0.53 ± 0.21 cm², and it was 0.44 ± 0.096 cm² by 3D EROA using PISA method.

Conclusion: The use of 3D EROA using PISA method and simple calculation of a mean systolic regurgitation orifice area proved to be superior to 2D measures (VC, 2D-PISA) for distinguishing moderate from severe MR , evaluation, classification and grading of MR in a routine clinical cardiology setting. 3D EROA reduces assumptions and seemingly improves diagnostic value as compared with 2D-PISA

Keywords: Three dimensional (3D), PISA (proximal isovelocity surface area), EROA (effective regurgitant orifice area) , MR (mitral regurge)

Introduction

Valvular insufficiencies are among the most frequent heart diseases and mitral regurgitation (MR) is considered the most common valve disease of significant regurgitation (moderate to severe and severe) in the general population (**Nkomo VT et al.,2006**).

Two-dimensional (2D) echocardiography with colorDoppler is the standard method for noninvasive assessment of severity and etiology of MR (**Zoghbi WA et al.,2003**).

However, accurate quantitative evaluation of MR severity remains challenging because limited scan plane orientation of 2D echocardiography does not provide direct measurement of the regurgitant lesion (**Enriquez-Sarano M et al 2005**).

Three-dimensional echocardiography which has grown up to a clinically accepted technique has been demonstrated to provide important information for flow quantification and, thus, is promising to overcome the major limitations of 2D-based methods (**Buck T et al 2015**).

Effective regurgitant orifice area (EROA) calculation using the proximal isovelocity surface area (PISA) method has been well validated with in vitro and in vivo models (**Recusani F et al.,1991**).

Despite its usefulness, pitfalls and limitations of this technique are well recognized, the conventional two-dimensional (2D) PISA method is based on the assumption of hemispheric symmetry of PISA and when the EROA is nearly circular. However, PISA can be variable

depending on the instrument settings and the shape of the regurgitant orifice, which is reported in several recent studies to be non circular in most patients (**Kahlert P et al.,2008**).

Leading to a discrepancy between EROA calculated with hemispheric assumption and the actual area.

Three dimensional (3D) echocardiography can provide the actual geometry of the flow convergence (**Grayburn PA et al 2005**), so measurement of EROA with 3D color Doppler echocardiography does not require the use of geometric assumptions and should reduce the errors in calculating EROA present with the 2D method.

Early studies using 3D color Doppler datasets already demonstrated that the shape of PISA is not hemispheric but elongated towards a more hemielliptic shape in most cases, causing systematic underestimation of EROA and regurgitant flow measured by the hemispheric PISA method (**Iwakura K et al.,2006**), (**Yosefy C et al.,2007**), (**Matsumura Y et al.,2008**).

Yosefy et al., in 2007 found clinical important underestimation of the grade of MR severity in 45 % of patients.

Kahlert et al., in 2008 found only small underestimation of EROA from 3D based hemielliptic PISA and described underestimation of EROA by 2D hemispheric PISA to be strongly dependent on the asymmetry of PISA and etiology of MR.

The aim of the present study was to Assess the feasibility and reliability of PISA measurement using real-time 3D color trans-

thoracic echocardiographic imaging in clinical practice and to compare its derived EROA, regurgitant volume (Rvol) and regurgitant fraction with that obtained by 2D transthoracic PISA.

Patients and method

This cross sectional study, included 30 patients with at least moderate functional MR in the standard color Doppler evaluation and have ischemic and dilated cardiomyopathic changes with EF less than 40% and came for evaluation on clinical basis indications at Al-Hussein and Bab AL She'reya university hospitals during the period from November 2020 to July 2021.

Inclusion criteria: 1. Patients with at least moderate functional MR in the standard color Doppler evaluation. 2. Ischemic and dilated cardiomyopathic patients with EF less than 40%.

Exclusion criteria: Patients with previous mitral valve surgery or concomitant mitral valve stenosis and poor image quality for TTE were excluded .

The clinical information of study population was recorded, such as age, gender, and cardiovascular risk factors including smoking, hypertension, and diabetes for possible aetiology of MR. The clinical data, including heart rate (HR), and blood pressure was obtained .

Echocardiographic data were acquired with an ultrasound Vivid E9 system (GE Vingmed Ultrasound AS, Horten, Norway), which was equipped with two-dimensional 3.5-MHz transducer (M5S-D), three -dimensional 3.5-MHz transducer (4C-D).

All the patients were examined in the left lateral decubitus position. Echocardiographic images were acquired from the standard views (parasternal long-axis, parasternal short axis at level of the great vessels, apical four-chambers,

apical five-chambers and apical two-chambers). Recordings and calculations of different cardiac chambers and ejection fractions were made according to the recommendations of the American Society of Echocardiography.

Quantification of MR by using:

- a) Quantitative pulsed Doppler assessment of EROA was performed in all patients as an independent method for comparison of the 2D and 3D approaches.

Mitral inflow and aortic outflow were calculated as the time velocity integral of the mitral or aortic inflow multiplied by the cross sectional area of the mitral annulus ($2 \pi a b$) or aortic annulus ($2 \pi r^2$), where a is the mitral annular dimension in the four-chamber view, b is the mitral annular dimension in the apical two-chamber view, and r is the left ventricular outflow tract diameter in the parasternal long-axis view (1 cm proximal to the aortic annulus). Mitral Rvol was calculated as the difference between mitral and aortic forward stroke volumes, and EROA was calculated as Rvol divided by the time-velocity integral of the continuous wave Doppler MR signal .Regurgitant fraction was calculated as Rvol divided by the mitral stroke volume and expressed as a percentage.

b) Vena contracta width:

Vena contracta width (VCW) is defined as the narrowest width of the proximal jet measured at or in the immediate vicinity of the MR orifice at the leaflet tips

The vena contracta will be calculated as following:

- From Two orthogonal planes (apical two and apical four-chamber view).
- Mean VCW will be averaged.
- Optimize color gain/scale
- Reduce the color sector size and imaging depth to maximize frame rate
- Expand the selected zone (Zoom)
- Use the cine-loop to find the best frame for measurement
- Measure the smallest VC (immediately distal to the regurgitant orifice, perpendicular to the direction of the jet)
- The severity of MR will be graded on the basis of current recommendations as mild (< 0.3 cm), moderate (0.3 to 0.69 cm), or severe (≥ 0.7 cm). (**Jorge solis, et al., 2013**).
- In patients with asymmetric vena contracta shape a biplane measurement in a 2- and 4-chamber view with a biplane vena contracta width of >0.8 cm has been recommended to define severe MR (**Vahanian A et al 2012**).

c) The proximal isovelocity surface area (PISA) method:

A narrow color flow sector width and the least depth will be chosen to maximize image resolution.

- All patients will be studied in the apical four-chamber view.
with a color Doppler sector angle of 30° .

- The ventricular surface of the mitral leaflets will be carefully scanned to recognize the PISA that will be zoomed to facilitate analysis.

- We can optimize the appearance of the PISA by shifting the Nyquist limit from 23.0 to 48.0 cm/sec (mean 32.6 ± 7.6 cm/sec).

- The largest flow convergence region will be selected as coinciding with maximal regurgitant flow.

- The radius of PISA will be measured by tracing along the centerline of the region from the center of the regurgitant orifice as demarcated by the leaflets to the farthest boundary of the PISA.

$$PISA = 2\pi r^2$$

- The maximal velocity of the regurgitant jet and time velocity integral (TVI) will be determined by continuous-wave Doppler.

- EROA will be calculated using the following formula:

$$EROA = 2\pi \times (PISAr)^2 \times V_{aliasing} / V_{max}$$

where $V_{aliasing}$ is the aliasing velocity of PISA (cm/sec), and V_{max} is the maximal velocity of the continuous wave Doppler MR signal (cm/sec).

- 2D PISA regurgitant volume (Rvol) will be calculated as

$$Rvol = EROA \times MR-TVI.$$

- Regurgitant fraction (RF) will be calculated as

$$RF = Rvol / \text{mitral stroke volume (Msv)}.$$

expressed as a percentage (%).

d) The 3-dimensional transducer were used to obtain 3D measurements of EROA by following steps :

- Image optimization by reducing the color Doppler

aliasing velocity to a value between 20 and 40 cm/sec (mean, 34 ± 7 cm/sec).

- To maximize the volume frame rate of acquisition, depth must be optimized.

- To minimize the potential effect of low temporal resolution of 3D color Doppler imaging, both 3D modes will be obtained (Zoom and Full volumes). from consecutive cardiac cycles will be acquired in each patient, looking for the largest convergence zone.

- RT3DE datasets will be used to assess PISA width, length, and radius for the calculation of HE PISA by an HE formula.

$$\text{HE-PISA} = 2\pi ([rP(D1/2)(p+ rP(D2/2)p + (D1/2)p(D2/2)p]/3)1/p$$

Where r is the PISA radius, D1 is the PISA width and D2 is the PISA length and $p=1.6075$ (Ashikhmina E et al.,2015)

- 3D PISA-HE will be used to derive EROA as

$$\text{EROA} = (3D \text{ PISA-HE} \times \text{Valiasing}) / \text{peak MR velocity.}$$

- 3D PISA Rvol will be calculated as

$$\text{EROA} = 3D \text{ PISA} \times \text{MR TVI.}$$

Statistical analysis

All continuous variables were presented as mean \pm standard deviation. Categorical data were presented as frequencies and percentages (%). Comparisons of parametric values were performed by Student's t-test and χ^2 test, when appropriate. A 2-tailed P value <0.05 was considered significant. All Data were analyzed using Statistical Program for Social Science (SPSS) version 26.0. SPSS software (IBMCompany, North Castle, NY).

RESULTS

The mean age of the included patients was 53.3 ± 9.2 years, and included 11 men (36.6%) and 19 female (63.3%) with mean heart rate 80.4 ± 6.7 bpm. As regard echocardiographic data was shown in (Table1).

Comparison between 2D PISA and 3D EROA using PISA method

1) comparison between two value in whole patients

There was no statistically significant difference between two methods in detecting MR severity compared to EROA

2) Comparison in different degree of MR

The mean value of EROA by 2D PISA in moderate MR was $0.25 \pm 0.042 \text{ cm}^2$, while it was $0.32 \pm 0.059 \text{ cm}^2$ by 3D method.

While the mean value of EROA by 2D PISA in severe MR was $0.58 \pm 0.14 \text{ cm}^2$, and it was $0.47 \pm 0.049 \text{ cm}^2$ by 3D method..

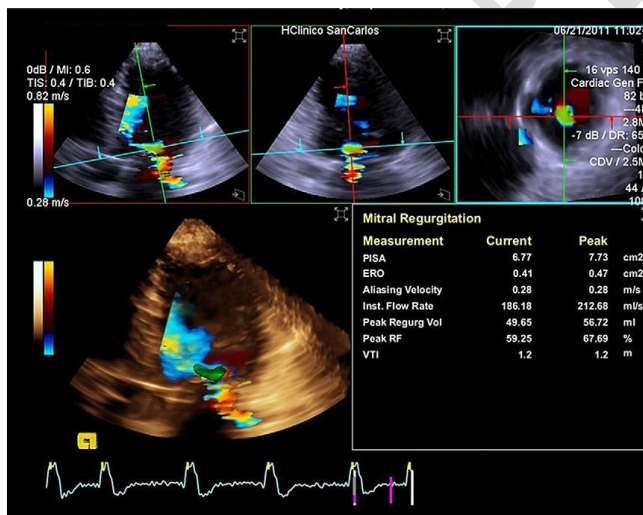


Figure 1 Example automatic 3D PISA extraction, visualized as green overlay on 3D color Doppler image (top three reference planes: left, four-chamber view; center, two-chamber view; right, short-axis view) and 3D-rendered PISA in the volume-rendered image (bottom left).

Table 1: echocardiographic data for assessment of MR					
Degree of MR	Echocardiographic parameter	Minimum	Maximum	Mean	Std. Deviation
Moderate MR	EROA	0.19	0.32	0.248	0.042
	VCW	0.35	0.61	0.48	0.076
	MR volume	30	54	40.64	6.8
	LA area	20	38	29.55	5.2
	3D PISA	0.25	0.42	0.32	0.058
	EF Simpson	31	40	36.91	2.91
	jet area	5.8	14.06	9.57	2.3
	Ratio of jet area to LA area	0.22	0.38	0.32	0.048
Severe MR	EROA	0.35	0.81	0.58	0.14
	VCW	0.5	1.0	0.80	0.14
	MR volume	50	120	87.58	21.58
	LA area	38	60	48.74	6.41
	3D PISA	0.42	0.58	0.47	0.049
	EF Simpson	28	40	35.74	3.82
	jet area	14.8	27.2	21.09	3.68
	Ratio of jet area to LA area	0.35	0.52	0.43	0.056

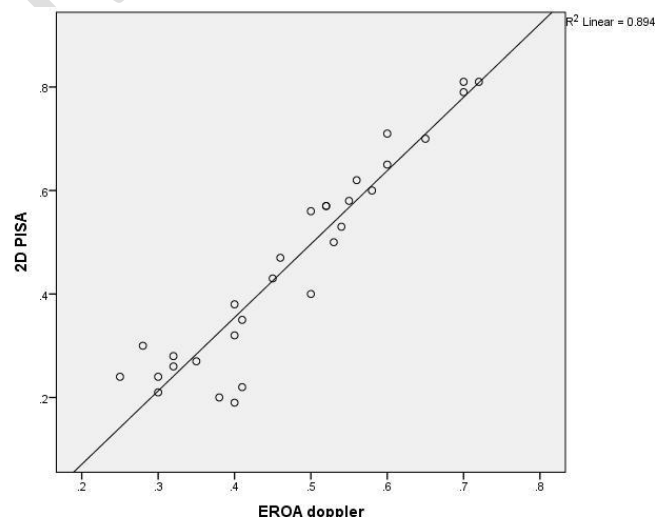
There was significant positive correlation between 2D PISA and 3D EROA using PISA method and EROA, p value was 0.0001.

Correlation between EROA by 2D PISA and 3D PISA in different MR jet directions:

There was significant positive correlation between 2D PISA and 3D EROA using PISA method in central jet of MR , p value was 0.001 .

Also there were positive correlation between 2D PISA and 3D EROA using PISA method in eccentric jet of MR , p value was 0.02.

Figure (2): Correlation between 2D PISA and EROA



3) Comparison in different direction of the jet of MR :

The mean value of EROA by 2D PISA in central MR was 0.41 ± 0.19 cm² ,while it was 0.41 ± 0.87 cm² by 3D PISA .

While the mean value of EROA by 2D PISA in eccentric MR was 0.53 ± 0.21 cm² ,and it was 0.44 ± 0.096 cm² by 3D PISA .

Fig 3:

Correlation between 2D PISA and 3D EROA using PISA method :

Figure (3) Figure (2): Correlation between 3D EROA using PISA method and EROA

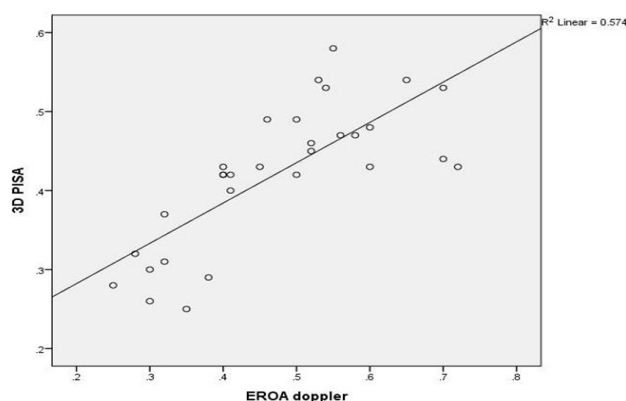
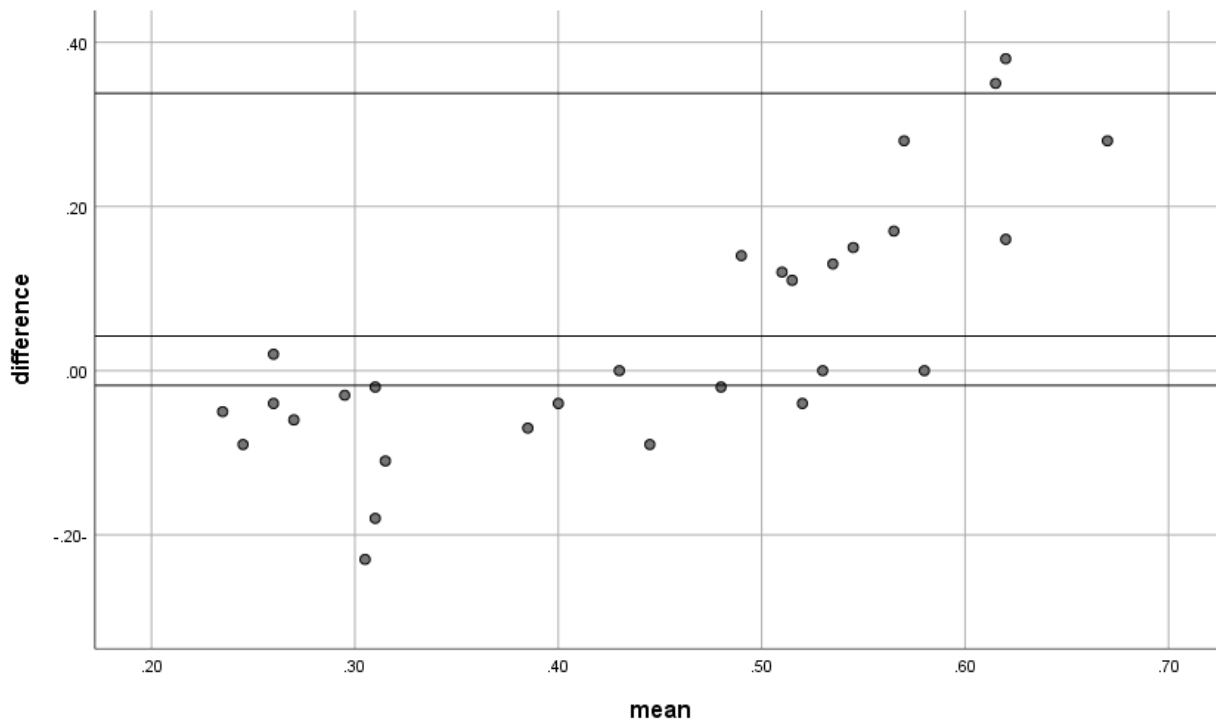


Figure (4) bland altman curve of *3D EROA using PISA method*



DISCUSSION

Integrating different parameters would be more reliable for MR grading by minimizing the limitations of each method (Zoghbi et al., 2003).

So the present study demonstrates that direct measurement of MR *3D EROA using PISA method* with single-beat, real-time 3D color Doppler echocardiography in clinical setting is feasible without relying on hemispheric assumptions by the transthoracic approach. In our study, both EROA and mitral Rvol calculated by the 3D PISA method showed better correlation and agreement with the previously validated reference methods than those calculated by the 2D PISA method.

Our results suggest that the *3D EROA using PISA method* should be used in daily routine echocardiographic practice and may avoid the need for TEE imaging to assess the MR severity. As reliable quantification of MR is required to indicate the correct timing for surgery and evaluate the efficacy of treatment.

Our results shows significant correlation between *3D EROA using PISA method* and 2D PISA and this consistent with de Agustín JA. etal., which showed that agreement when comparing 3D PISA–determined EROA with the reference methods than when comparing the former with 2D PISA–determined EROA. Also concluded that direct measurement of PISA without geometric assumptions using single-beat, real-time 3D color Doppler echocardiography is feasible in the clinical setting. MR quantification using this methodology is more accurate than the conventional 2D PISA method.

Our results showed higher values for *3D EROA using PISA method* when compared with 2 D PISA in different degrees of MR as summarized in ((The mean value of EROA by 2D PISA in moderate MR was 0.25 ± 0.042 cm² ,while it was 0.32 ± 0.059 cm² by 3D method . While the mean value of EROA by 2D PISA in severe MR was 0.58 ± 0.14 cm², and it was 0.47 ± 0.049 cm² by 3D method) and this results supported by results of *Ashikhmina E.etal., 2015* which showed that three-dimensional *EROA using PISA method* was

significantly larger than both HS-PISA and HE-PISA (mean \pm SD: $4.65 \pm 2.03 \text{ cm}^2$ vs $2.10 \pm 1.58 \text{ cm}^2$ and $2.75 \pm 1.42 \text{ cm}^2$; both $P < 0.0001$).

Several techniques have been proposed for quantification of MR. EROA is the central parameter to define MR severity, because it is independent of hemodynamic considerations, and its impact on prognosis has been widely demonstrated. (Rossi A. et al., 2011).

The PISA method has been established for determining EROA and is well correlated with the severity of MR assessed with quantitative Doppler echocardiography or angiography.

This method has been included in guidelines for quantification of MR as a corner stone technique. However, important problems and pitfalls have been defined in the application of the proximal flow convergence method for the quantitative assessment of valvular regurgitation severity. This method is based on the assumption of hemispheric symmetry of the velocity distribution proximal to the regurgitant lesion, which may not hold for eccentric regurgitant jets, multiple jets, or complex or elliptical regurgitant orifices. (Zoghbi WA. et al., 2003).

Another limitation is related to the need to accurate definition of the regurgitant orifice level on the 2D color Doppler image. This limitation is important, because this radial measure is squared to derive isovelocity surface area, and minor inaccuracies result in imprecise determination of EROA.

Previous studies have reported that EROA obtained using the PISA method underestimates MR degree in patients with non-hemispheric geometry of PISA. (Iwakura K. et al., 2006).

Moreover, it has been demonstrated that EROA calculated using a hemielliptic assumption of PISA is more accurate than that using the hemispheric assumption in the PISA method. However, even the hemielliptic assumption may not be accurate enough for determining EROA when the shape of PISA is complex (Enriquez-Sarano M. et al., 2005).

Three-dimensional color Doppler echocardiography is expected to overcome the limitations of the 2D PISA method. Three-dimensional imaging has the advantage of avoiding any geometric assumptions and determining the actual PISA. Therefore, complete 3D visualization of the convergent flow zone is the ideal solution for the accurate calculation of EROA.

LIMITATIONS

Although the 3D EROA using EPISA method as used in this study appears to be superior to its 2D counterpart, we must be aware of the limitations of color Doppler in detecting the true iso-velocity surface. Detected velocities depend on the angle of flow relative to the transducer which represents a theoretical limitation to the method. Furthermore calculation of EROA assumes the PISA and peak velocity to occur simultaneously, which is never true due to limitations in temporal resolution of color Doppler and the technical inability to acquire both Doppler modalities simultaneously. Nevertheless, we were able to demonstrate that EROA determined with 3D color Doppler is useful in clinical practice and averaging over the cardiac cycle further improves results.

CONCLUSION

The use of 3D EROA using EPISA method and simple calculation of a mean systolic regurgitation orifice area proved to be superior to 2D measures (VC, 2D-PISA) for distinguishing moderate from severe MR. Use of Real-time non-stitched 3D-Color-Doppler echocardiography with semi-automated PISA analysis is helpful in the evaluation, classification and grading of MR in a routine clinical cardiology setting. 3D EROA using EPISA method reduces assumptions and seemingly improves diagnostic value as compared with 2D-PISA.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country.

There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES

- 1) **Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, et al.** Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 2005;352:875-83.
- 2) **Rosenhek R, Rader F, Klaar U, Gabriel H, Krejc M, Kalbeck D, et al.** Outcome of watchful waiting in asymptomatic severe mitral regurgitation. *Circulation* 2006;113:2238-44.
- 3) **Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al.** Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777-802.
- 4) **Recusani F, Bargiggia GS, Yoganathan AP, Raisaro A, Valdez-Cruz L, Sung HW, et al.** A new method for quantification of regurgitant flow rate using color flow imaging of the flow convergence region proximal to a discrete orifice: an vitro study. *Circulation* 1991;83:594-604.
- 5) **Yosefy C, Levine RA, Solis J, Vaturi M, Handschumacher MD, Hung J.** Proximal flow convergence region as assessed by real-time 3-dimensional echocardiography: challenging the hemispheric assumption. *J Am Soc Echocardiogr* 2007;20:389-96.
- 6) **Iwakura K, Ito H, Kawano S, Okamura A, Kurotobi T, Date M, et al.** Comparison of orifice area by transthoracic three-dimensional Doppler echocardiography versus proximal isovelocity surface area (PISA) method for assessment of mitral regurgitation. *Am J Cardiol* 2006;97:1630-7.
- 7) **Ashikhmina E, Shook D, Cobey F, Bollen B, Fox J, Liu X, et al.** Three-dimensional versus two-dimensional echocardiographic assessment of functional mitral regurgitation proximal isovelocity surface area. *Anesth Analg.* 2015;120:534-42.
- 8) **Buck T, Plicht B, Erbel R.** Current recommendations on echocardiographic evaluation of the severity of mitral regurgitation: standardization and practical application using a scoring system. *Herz.* 2015;31:30-7.
- 9) **Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al.** Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J.* 2012;33:2451-96.

- 10) **Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al.** 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.
- 11) **Kahlert P, Plicht B, Schenk IM, Janosi RA, Erbel R, Buck T.** Direct assessment of size and shape of noncircular vena contracta area in functional versus organic mitral regurgitation using real-time three dimensional echocardiography. *J Am Soc Echocardiogr.* 2008;21:912–21.
- 12) **Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M.** Burden of valvular heart diseases: a population-based study. *Lancet.* 2006;368:1005–11. 2.
- 13) **Matsumura Y, Fukuda S, Tran H, Greenberg NL, Agler DA, Wada N, et al.** Geometry of the proximal isovelocity surface area in mitral regurgitation by 3-dimensional color Doppler echocardiography: difference between functional mitral regurgitation and prolapse regurgitation. *Am Heart J.* 2008;155:231–8.
- 14) **Matsumura Y, Saracino G, Sugioka K, Tran H, Greenberg NL, Wada N, et al.** Determination of regurgitant orifice area with the use of a new three-dimensional flow convergence geometric assumption in functional mitral regurgitation. *J Am Soc Echocardiogr.* 2008;21:1251–6.
- 15) **Cobey FC, McInnis JA, Gelfand BJ, Rapo MA, D'Ambra MN.** A method for automating 3-dimensional proximal isovelocity surface area measurement. *J Cardiothorac Vasc Anesth.* 2012;26:507–11. 42.
- 16) **Little SH, Igo SR, Pirat B, McCulloch M, Hartley CJ, Nose Y, et al.** In vitro validation of real-time three-dimensional color Doppler echocardiography for direct measurement of proximal isovelocity surface area in mitral regurgitation. *Am J Cardiol.* 2007;99:1440–7. 43.
- 17) **Ashikhmina E, Shook D, Cobey F, Bollen B, Fox J, Liu X, et al.** Three-dimensional versus two-dimensional echocardiographic assessment of functional mitral regurgitation proximal isovelocity surface area. *Anesth Analg.* 2015;120:534–42.
- 18) **Plicht B, Kahlert P, Goldwasser R, Janosi RA, Hunold P, Erbel R, et al.** Direct quantification of mitral regurgitant flow volume by real-time three-dimensional echocardiography using aliasing of color Doppler flow at the vena contracta. *J Am Soc Echocardiogr.* 2008;21:1337–46.
- 19) **Grayburn PA, Weissman NJ, Zamorano JL.** Quantitation of mitral regurgitation. *Circulation.* 2012;126:2005–17.
- 20) **Baumgartner H, Schima H, Kuhn P.** Value and limitations of proximal jet dimensions for the quantitation of valvular regurgitation: an invitro study using

Doppler flow imaging.
JAmSocEchocardiogr. 1991;4:57–66.

assessment of functional mitral regurgitation proximal isovelocity surface area. Anesth Analg. 2015 Mar;120(3):534-542.doi: 10.1213/ANE.00000000000000409. PMID: 25166465.

21) **Perk G, Lang RM, Garcia-Fernandez MA, Lodato J, Sugeng L, Lopez J, Knight BP, Messika-Zeitoun D, Shah S, Slater J, Brochet E, Varkey M, Hijazi Z, Marino N, Ruiz C, Kronzon I.** Use of real time three-dimensional trans esophageal echocardiography in intra cardiac catheter based interventions. J Am SocEchocardiogr 2009;22:865–82.

22) **Ashikhmina E, Shook D, Cobey F, Bollen B, Fox J, Liu X, Worthington A, Song P, Shernan S.** Three-dimensional versus two-dimensional echocardiographic

23) **de Agustín JA, Marcos-Alberca P, Fernandez-Golfin C, Gonçalves A, Feltes G, Nuñez-Gil IJ, Almeria C, Rodrigo JL, Perez de Isla L, Macaya C, Zamorano J.** Direct measurement of proximal isovelocity surface area by single-beat three-dimensional color Doppler echocardiography in mitral regurgitation: a validation study. J Am Soc Echocardiogr. 2012 Aug;25(8):815-23. doi: 10.1016/j.echo.2012.05.021. Epub 2012 Jun 26. PMID: 22739217.

UNDER PEER REVIEW