Aortic valve disease : novel imaging insights from diagnosis to therapy

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PART I

Novel imaging to assess aortic valve regurgitation – incremental role in diagnosis

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Accuracy of three-dimensional versus two-dimensional echocardiography for quantification of aortic regurgitation and validation by three-dimensional three-directional velocity-encoded magnetic resonance imaging

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Accuracy of Three-Dimensional Versus Two-Dimensional Echocardiography for Quantification of Aortic Regurgitation and Validation by Three-Dimensional Three-Directional Velocity-Encoded Magnetic Resonance Imaging

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Quantitative assessment of aortic regurgitation (AR) remains challenging. The present study evaluated the accuracy of 2-dimensional (2D) and 3-dimensional (3D) transthoracic echocardiography (TTE) for AR quantification, using 3D 3-directional velocity-encoded magnetic resonance imaging (VE-MRI) as the reference method. Thirty-two AR patients were included. With color Doppler TTE, 2D effective regurgitant orifice area (EROA) was calculated using the proximal isovelocity surface area method. From the 3D TTE multiplanar reformation data, 3D-EROA was calculated by planimetry of the vena contracta. Regurgitant volumes (RVol) were obtained by multiplying the 2D-EROA and 3D-EROA by the velocity-time integral of AR jet and compared with that obtained using VE-MRI. For the entire population, 3D TTE RVol demonstrated a strong correlation and good agreement with VE-MRI RVol (r = 0.94 and −13.6 to 15.6 ml/beat, respectively), whereas 2D TTE RVol showed a modest correlation and large limits of agreement with VE-MRI (r = 0.70 and −22.2 to 32.8 ml/beat, respectively). Eccentric jets were noted in 16 patients (50%). In these patients, 3D TTE demonstrated an excellent correlation (r = 0.95) with VE-MRI, a small bias (0.1 ml/beat) and narrow limits of agreement (−18.7 to 18.8 ml/beat). Finally, the kappa agreement between 3D TTE and VE-MRI for grading of AR severity was good (k = 0.96), whereas the kappa agreement between 2D TTE and VE-MRI was suboptimal (k = 0.53). In conclusion, AR RVol quantification using 3D TTE is accurate, and its advantage over 2D TTE is particularly evident in patients with eccentric jets. **(Am J Cardiol 2013;112:560−566)**

Quantification of aortic regurgitation (AR) remains challenging in clinical practice. Currently, the proximal isovelocity surface area (PISA) method, using 2-dimensional (2D) Doppler echocardiography, is the recommended approach to estimate the regurgitation volume (RVol) and effective regurgitation orifice area (EROA).[1,2] However, several assumptions inherent in its derivation may hamper the accuracy of 2D PISA method to quantify AR, such as noncircular orifices[3] and eccentric jets.[4] Real-time 3-dimensional (3D) echocardiography permits direct visualization of the vena contracta and measurement of the EROA, without the need for additional computation or geometric assumptions.[5−8] In addition, 3D echocardiography is not restricted by any imaging plane, unlike 2D echocardiography, which is limited to quantify flow aligned along the ultrasound beam.[4,8] Therefore, quantification of AR would be more accurate using 3D than 2D echocardiography, and this would probably become more evident in patients with eccentric AR. Recently, 3D 3-directional velocity-encoded magnetic resonance imaging (VE-MRI) has been proposed as a more accurate method to assess transvalvular flow.[7,9,10] The current evaluation assessed the accuracy of 2D and 3D transthoracic echocardiography (TTE) for quantification of AR, using 3D 3-directional VE-MRI as the reference method.

Methods

Thirty-two patients with AR who were clinically referred for TTE and MRI to quantify AR, aortic root, and aortic dimensions were retrospectively evaluated. Patients with acute AR or concomitant valvular disease of more than mild severity, atrial fibrillation, or contraindications for MRI (i.e., implanted devices, claustrophobia) were not included. Clinical data including demographics and symptoms were collected in the departmental electronic patient file (EPD vision version 8.3.3.6; Leiden, The Netherlands) and retrospectively analyzed. All patients underwent standard 2D and

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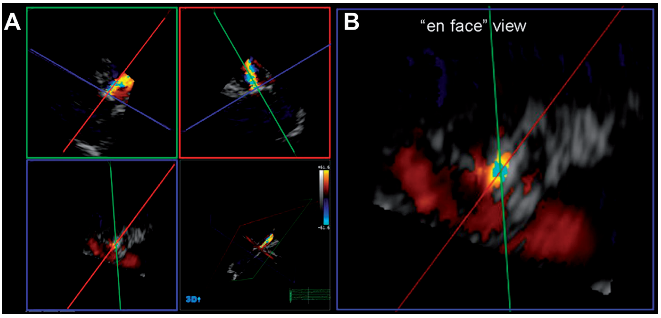

Figure 1. Three-dimensional transthoracic echocardiography for assessment of aortic EROA. First, the 3D color Doppler data set was manually cropped to provide a cross-sectional plane through the vena contracta of the regurgitant jet, perpendicular to the direction of the aortic regurgitant jet *(A)*. Next, from the en face view of the vena contracta, selecting the plane with the narrowest cross-sectional area of the regurgitant jet, the 3D-EROA was measured by manual planimetry of the color Doppler signal *(B)*. The figure provides an example of a patient with central and circular jet.

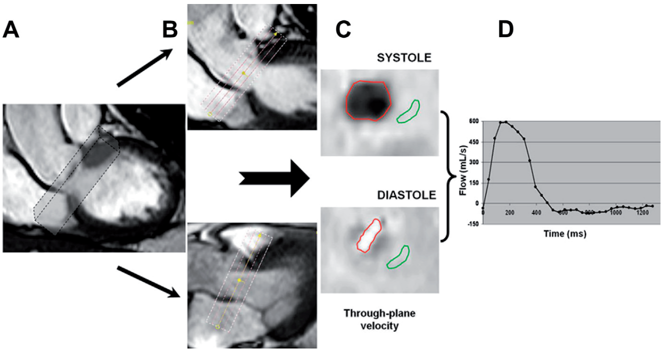

Figure 2. Postprocessing of aortic valve flow from 3D 3-directional VE-MRI data sets. The 3D acquisition volume was positioned at the level of the aortic valve, covering its full excursion during the entire cardiac cycle *(A)*. From the 2 orthogonal views of the aortic valve *(B)*, retrospective valve tracking and reformatting plane (with 5 parallel planes spaced at 5 mm) were reconstructed at the level of the aortic annulus, perpendicular to the aortic flow. The through-plane velocity-encoded images were thus obtained by reformatting in the center of the valvular plane in each cardiac phase *(C)*. During systole, the aortic forward flow was acquired (inner border of the aortic annulus was traced in *red* for flow analysis). During diastole, the regurgitant flow could be identified (*red line*). Region within the left ventricular wall was traced (*in green*) for correction of the myocardial motion, at the caudal-most reformatted plane where myocardial tissue was best visualized. *(D)* Finally, integration of the velocities over the aortic annulus, subtracted by the through-plane velocity of the myocardium, yielded the flow graph. The regurgitant volume was calculated by the Riemann sum of backward flow during diastole in the flow graph.

3D color Doppler TTE to quantify AR RVol and EROA. In addition, cardiac MRI was performed in all patients to assess left ventricular (LV) size and function, aortic valve morphology, AR severity, and aortic root and ascending aorta dimensions.[2] Severity of AR was assessed using 3D 3-directional VE-MRI data to quantify the AR Rvol.

Patients were imaged at rest in the left lateral decubitus position using a commercially available ultrasound system (iE33, Philips Medical Systems, Andover, Massachusetts) equipped with a S5-1 transducer. A complete 2D, color, pulsed, and continuous wave Doppler examination was performed according to the standard guidelines.[1,2,11] For AR quantification, color Doppler images of the aortic valve were acquired with optimized gain and Nyquist scale (50 to 60 cm/s).[1,2] From the zoomed color Doppler view of the AR jet, the vena contracta was identified as the narrowest portion of the regurgitant jet that occurred at or just downstream from the regurgitant orifice.[1,2] For a more quantitative assessment of AR, the PISA method was used. In brief, by shifting the baseline of the aliasing velocity toward the direction of the regurgitant jet (between 20 and 40 cm/s), a well-defined hemisphere of the convergence zone could be identified. From this, the maximal 2D-EROA could be estimated. Subsequently, the RVol was calculated as 2D-EROA multiplied by the velocity-time integral of the AR jet, from the continuous wave Doppler obtained either at the apical 5- or 3-chamber views.[1,2] AR severity was graded based on RVol: grade 1 (mild), <30 ml; grade 2 (mild-to-moderate), 30 to 44 ml; grade 3 (moderate-to-severe), 45 to 59 ml; and grade 4 (severe), ≥60 ml.[1,2]

The 3D TTE was performed using the same ultrasound system (the iE33 system) with a fully sampled matrix-array X3 transducer. Apical and parasternal full-volume color Doppler data sets of the AR jets were obtained using electrocardiographic gating over 7 consecutive heart beats to obtain 7 small real-time subvolumes in a larger pyramidal volume. To minimize stitch artifact, the acquisition was performed during 5 to 7 seconds of breath-holding. The color gain and scale were set as previously mentioned. All images were digitally stored and analyzed offline (Q-Lab 3DQ, Philips Medical Systems). To measure 3D-EROA, multiplanar reconstruction of the 3D data sets and manual cropping were performed. First, a cross-sectional plane through the vena contracta of the regurgitant jet, perpendicular to the direction of the AR jet, was obtained. Next, from the en face view of the vena contracta, the 3D-EROA of the narrowest cross-sectional area of the regurgitant jet was measured by manual planimetry from the diastolic frame with the most relevant lesion size (Figure 1). The 3D-RVol was derived by multiplying the 3D-EROA by the velocity-time integral of the AR jet.

MRI was performed using a 1.5-T scanner (Philips Medical Systems, Best, The Netherlands) equipped with a 5-element cardiac synergy coil. First, from a series of short-axis images, encompassing the LV from apex to base and throughout the entire cardiac cycle, quantification of LV volumes and ejection fraction were obtained by using the MASS research software (Division of Image Processing, Department of Radiology, LUMC, Leiden, The Netherlands) with contour segmentation of the epicardial and endocardial borders.[12] For AR quantification, 3D 3-directional VE-MRI was used. A detailed description of the 3D VE-MRI acquisition protocol has been described.[9,10] In brief, a free-breathing 3D phase-contrast acquisition was used with velocity encoding in 3 orthogonal directions. Imaging parameters were as follows: repetition time 7.5 milliseconds, echo time 4.3 milliseconds; field of view 370 mm, 3D volume imaging with 48-mm slab thickness reconstructed into 12 slices of 4 mm, flip angle of 10°, acquisition voxel size $2.9 \times 3.8 \times 4.0$ mm voxel reconstructed into $1.4 \times 1.4 \times 4.0$ mm voxel, 1 acquired signal, and with 30 phases reconstructed during 1 average cardiac cycle from the retrospective gated acquisition (temporal resolution between 25 and 40 milliseconds, depending on the heart rate). Echo-planar imaging was performed with a factor of 5 resulting in scan duration of approximately 5 minutes. The velocity encoding was initially set at 150 cm/s in all 3 directions. However, additional 2D VE-MRI of the aortic valve was used to determine if a higher maximal velocity was required and the optimized velocity was then applied for 3D VE-MRI in all 3 directions.

The 3D VE-MRI acquisitions were postprocessed with the in-house developed MASS research software package.[10] Two orthogonal views of the aortic valve were used for retrospective valve tracking and a reformatting plane (with 5 parallel planes equally spaced at 5 mm apart) was marked at the level of the valve annulus in every cardiac phase, perpendicular to the aortic regurgitant flow (Figure 2). Next, the 3D velocity data were reformatted in the center of the valvular plane to generate 1-directional through-plane velocity-encoded images. If aliasing occurred in any of the velocity directions as a result of high-velocity regurgitant jets, the phase unwrapping option of the software was used to correct the velocity data and to avoid underestimation of regurgitation. Background correction was performed to correct for through-plane motion of the myocardium in basal-to-apical direction and local phase offset.[10] The background region of interest was placed at the most caudal plane (i.e., 10 mm distance from the central plane in the LV anterior wall). Finally, the transvalvular volume flow was obtained by integrating the resulting velocities taken over the annular area. The MRI RVol was obtained by calculating the Riemann sum of backward flow during diastole in the flow graph (Figure 2).[13] The reformatting process required 5 minutes, and subsequent image analysis took another 5 to 10 minutes.

Continuous data are presented as mean ± SD, and categorical variables as absolute numbers (percentages). Chi-square or Fisher's exact tests were used for comparison of categorical variables as appropriate. Linear regression analysis (Pearson correlation) for continuous variables was performed to evaluate the relation between RVol measurements derived from 2D TTE, 3D TTE, and MRI. Bland-Altman plots were used for agreement analysis between 2D TTE, 3D TTE, and MRI derived RVol measurements. In

Table 1
Patient characteristics

Variable	Patients (n = 32)
Age (yrs)	53 ± 18
Male	22 (69%)
Body surface area (m^2)	1.97 ± 0.23
Heart rate (beats/min)	67 ± 13
Systolic blood pressure (mm Hg)	142 ± 20
Diastolic blood pressure (mm Hg)	73 ± 9
New York Heart Association functional class	
I	23 (72%)
II	7 (22%)
III	2 (6%)
Co-morbidities	
Hypertension*	16 (50%)
Hypercholesterolaemia*	9 (28%)
Diabetes mellitus	4 (13%)
Coronary artery disease	4 (13%)
Aortic regurgitation etiology	
Calcific degeneration	14 (44%)
Bicuspid	14 (44%)
Previous infective endocarditis	1 (3%)
Rheumatic	2 (6%)
Idiopathic dilatation of the aorta	1 (3%)
LV end-diastolic volume (ml)	210 ± 77
LV end-systolic volume (ml)	93 ± 46
LV ejection fraction (%)	58 ± 9
Aortic annulus (mm)	26 ± 4
Aortic sinus (mm)	37 ± 6
Sinotubular junction (mm)	31 ± 6
Ascending aorta (mm)	34 ± 7

Data are expressed as mean ± SD or as number (%).

* Hypertension was defined as blood pressure ≥140/90 mm Hg or on antihypertensive medication for hypertension. Hypercholesterolemia was defined as a serum low-density lipoprotein cholesterol >160 mg/dl or on lipid-lowering medication for hypercholesterolemia.

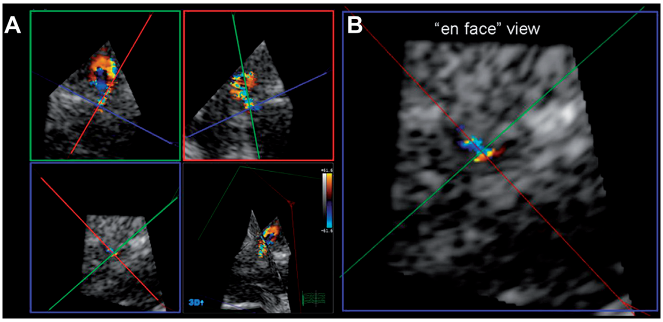

Figure 3. An example of a patient with eccentric aortic regurgitation. Multiplanar reformation of the 3D transthoracic Doppler echocardiography data sets *(A)* revealed an irregularly shaped effective regurgitant orifice area, as shown in the en face view *(B)*.

Table 2
Relationship between aortic regurgitant volume measured by echocardiography and magnetic resonance imaging

Regurgitant Volume	Total Population (n = 32)	Central AR Jet (n = 16)	Eccentric AR Jet (n = 16)
2D TTE vs VE-MRI			
Pearson correlation coefficient (r)	0.70	0.80	0.66
r—95% confidence interval	0.46–0.84	0.51–0.93	0.24–0.87
p value	<0.001	<0.001	0.005
3D TTE vs VE-MRI			
Pearson correlation coefficient (r)	0.94	0.93	0.95
r—95% confidence interval	0.89–0.97	0.82–0.98	0.86–0.98
p value	<0.001	<0.001	<0.001

addition, the kappa statistics were used to assess the agreement among different imaging methods with regard to AR severity grading. In 20 randomly selected patients, interobserver reproducibility for 3D TTE–derived measurements were performed by 2 independent, blinded observers and evaluated by intraclass correlation coefficient (ICC). To evaluate intraobserver reproducibility, the same observer repeated the measurements at 2 time points. Good agreement was defined as ICC >0.8. All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, Illinois) and MedCalc 10.0 (Mariakerke, Belgium).

Results

Table 1 summarizes the clinical characteristics and parameters of the patients, with bicuspid aortic valve anatomy in 14 patients (44%). AR was equally divided into central (50%) and eccentric (50%) jets. In patients with eccentric jets, a higher proportion of bicuspid compared with tricuspid valve anatomy was observed (75% vs 25%, p = 0.001). Figures 1 and 3 show examples of a central and an eccentric AR jet, respectively.

For the entire population, the mean aortic RVol obtained by 2D, 3D TTE, and VE-MRI were 29.6 ± 14.3, 25.3 ± 14.8, and 24.3 ± 19.6 ml/beat, respectively. There was a significant but modest correlation between the RVol as assessed by 2D TTE and VE-MRI (r = 0.70, p <0.001), and the RVol quantification by 3D TTE showed a strong correlation with VE-MRI (r = 0.94, p <0.001; Table 2). When Bland-Altman plots were performed for entire population, 3D TTE derived RVol showed a small bias (1.0 ml/beat) and narrow limits of agreement (−13.6 to 15.6 ml/beat) versus VE-MRI. In contrast, the bias and limits of agreement between 2D TTE and VE-MRI derived RVol were large (5.3 ml/beat and −22.2 to 32.8 ml/beat, respectively; Figure 4).

In patients with central jets, 2D TTE demonstrated a relatively good correlation with VE-MRI in the assessment of RVol (r = 0.80, p <0.001), but this correlation with VE-MRI could be improved by using 3D TTE (r = 0.93, p <0.001). On the other hand, in patients with eccentric jets, the correlation between RVol as assessed by 2D TTE and VE-MRI was weak (r = 0.66, p = 0.005), whereas the correlation between 3D TTE and VE-MRI derived RVol was strong (r = 0.95, p <0.001; Table 2). On Bland-Altman analysis, 3D TTE derived RVol had the best agreement with VE-MRI regardless of the direction of AR jet (central or eccentric), with the least bias and narrowest limits of agreement (Figure 4). Particularly for eccentric AR, 3D TTE demonstrated a good agreement with VE-MRI, with a small bias (0.1 ml/beat) and narrow limits of agreement (−18.7 to 18.8 ml/beat).

Based on the RVol measurements derived from 2D, 3D TTE, and VE-MRI, the severity of AR was graded accordingly.[1,2] There was a moderate agreement, in terms of AR severity grading, between 2D TTE and VE-MRI (kappa index = 0.53). In 62.5% of patients, including central (n = 13) and eccentric (n = 7) jets, 2D TTE, and VE-MRI provided concordant grading (Figure 5). Of the 12 patients who were differently graded by 2D TTE, the majority of patients had eccentric (n = 9) instead of central jets (n = 3; 75% vs 25%, p = 0.07). In patients with central AR who were misclassified by 2D TTE, the AR severity was marginally overestimated (from mild to moderate).

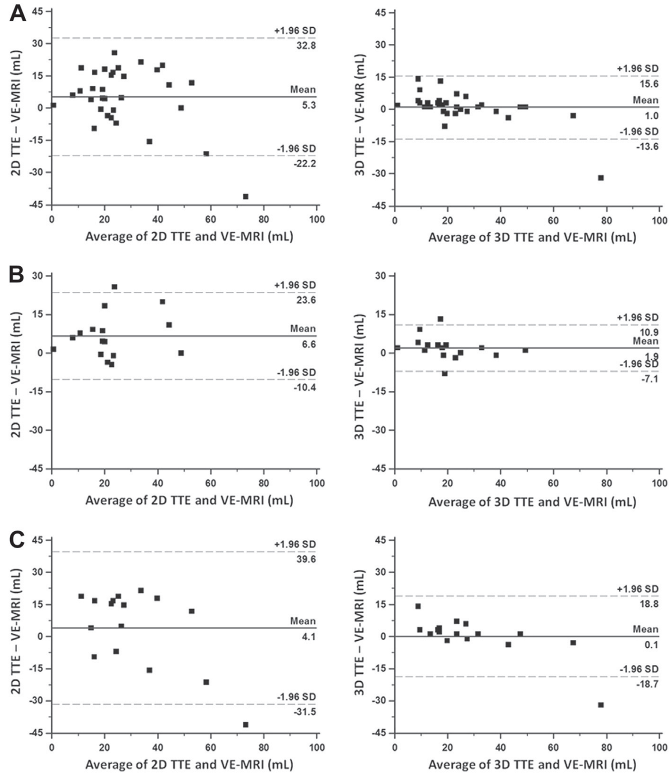

Figure 4. Scatter plots of Bland-Altman analysis for 2D and 3D TTE measurements of aortic regurgitant volume versus the 3D VE-MRI reference values for overall population *(A)*, central *(B)*, and eccentric *(C)* jets.

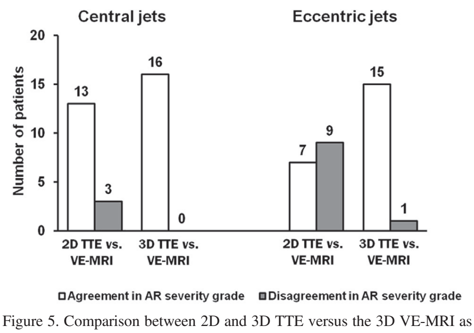

Figure 5. Comparison between 2D and 3D TTE versus the 3D VE-MRI as the reference method.

Among the eccentric AR with incorrect grading, 2D TTE underestimated AR severity in 3 patients compared with VE-MRI, misclassifying grade 3 instead of 4 (n = 2) and grade 1 instead of 2 (n = 1). In the remaining 6 patients, 2D TTE overestimated AR severity compared with VE-MRI (grade 2 instead of 1 in 5 patients, and grade 3 instead of 2 in 1 patient). Importantly, the agreement between 3D TTE and VE-MRI was markedly improved (kappa index = 0.96). All patients were correctly graded with 3D TTE (Figure 5), except 1 patient with eccentric AR (misclassifying as grade 2 instead of 1). Finally, the interobserver and intraobserver reproducibility for 3D echocardiography derived EROA were good as expressed by intraclass correlation (ICC = 0.95 and 95% confidence interval: 0.88 to 0.98 and ICC = 0.97, 95% confidence interval: 0.92 to 0.99, respectively).

Discussion

The present evaluation showed that quantification of AR with 2D TTE is challenging, particularly in eccentric regurgitant jets. In contrast, quantification of AR with direct measurement of the vena contracta area using 3D TTE is feasible and the measurement of AR RVol shows good correlation and agreement with 3D 3-directional VE-MRI, the reference standard. In addition, the measurement of 3D

TTE derived AR RVol showed high inter- and intraobserver reproducibility.

Accurate assessment of valvular regurgitation severity is paramount for prognosis and clinical management of patients with AR.[14,15] This is primarily performed using echocardiography, with the integration of multiple parameters, including the hemodynamic consequences of AR on the LV.[1,2] The assessment of AR severity is usually performed using both quantitative and semiquantitative echocardiographic criteria.[1,2] However, Messika-Zeitoun et al have shown that the commonly used semiquantitative methods in AR assessment, such as pressure half-time, diastolic flow reversal, and LV cardiac output, lack sensitivity.[16] In contrast, the quantitative assessment of AR, using RVol and EROA, not only supersedes the semiquantitative markers of AR severity but also has prognostic clinical implications in patients with AR.[17] Thus, quantitative assessment of AR should always be used, as recommended.[1,2]

The present evaluation shows the superior accuracy of 3D TTE to quantify AR compared with 2D TTE, particularly in eccentric regurgitant jets. 3D TTE-derived AR RVol had the best agreement with that obtained by 3D 3-directional VE-MRI. It is not surprising that 3D TTE provides a more accurate quantification for AR than 2D PISA method because direct planimetry of the AR vena contracta can be performed without any geometric or flow assumptions or multiple computation steps.[1,5−8] By using multiplanar reconstruction of the 3D full-volume data set, 3D TTE has the advantage of unlimited plane orientation, allowing the exact shape and size of the true cross-sectional view of the regurgitant orifice to be measured accurately. In addition, the use of 3D 3-directional VE-MRI sequences as the method of reference, with retrospective valve tracking,[7,9,10] further strengthens the results of the present evaluation because the 3D VE-MRI sequence permits direct measurement of the through-plane transaortic blood flow, taking into consideration the valve and heart motion throughout the cardiac cycle. Moreover, MRI is the reference standard to evaluate LV size and function (a measure of the hemodynamic consequence of AR) and dimensions of the thoracic aorta,[18] all of which are important parameters to consider in clinical decision making for managing patients with AR.[14,15]

Most important, the present evaluation demonstrated a high accuracy of using 3D TTE to quantify AR especially in patients with eccentric jets, whereas 2D TTE was less precise in AR quantification in these patients. Indeed, this translated into less accurate grading of eccentric AR with 2D TTE based on the PISA-derived method, causing significant misclassification in 56.3% of patients (9 of 16). With 3D TTE, misclassification only occurred in 3.1% (1 of 16 patients). These results are in line with the series reported by Pouleur et al., including 21 patients with central jets and 29 patients with eccentric jets.[4] The PISA derived RVol obtained by 2D echocardiography had only fair correlation ($r = 0.69$) with that measured by MRI in patients with eccentric jets, whereas the correlation between 2D echocardiography and MRI in central AR jets was good ($r = 0.92$). In addition, that study also demonstrated that in eccentric jets, the differences between 2D TTE−derived PISA and MRI-derived RVol could be nullified by imaging from the left parasternal window, yielding a better view of the AR jet and flow convergence compared with the conventional apical window, thus underscoring the limitation of 2D TTE in aligning the eccentric jets with ultrasound beam.[4] Of interest, the present evaluation demonstrated that 3D TTE permitted accurate quantification of AR, even in the presence of an eccentric jet. Moreover, nonplanar flow convergence angle, commonly seen in AR patients with concomitant aneurismal dilatation of the ascending aorta, could represent another source of error in the calculation of AR quantification using the PISA derived method.[19] However, this would not be a consideration if the 3D TTE approach was used.

The retrospective design of the present evaluation precluded investigation of the clinical and prognostic implications of these findings, which should be further evaluated in prospective studies.

Disclosures

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