Quantitative Three-Dimensional Color Flow Echocardiography of Chronic Mitral Regurgitation: New Methods, New Perspectives, New Challenges

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> Progress is impossible without change, and those who cannot change their minds cannot change anything.
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> —George Bernard Shaw

Echocardiography is the imaging modality of choice to quantify chronic mitral regurgitation (MR), and the current American College of Cardiology/American Heart Association and European Society of Cardiology guidelines on valve disease emphasize the central role of quantitative parameters obtained from color flow Doppler (CFD) imaging in grading the severity of chronic MR.[1,2] However, given the well-described limitations of quantitative CFD imaging, an integrated approach (which includes data from spectral Doppler), and measurements of left ventricular (LV) size and function, are also included in the recommendations for quantitating MR.[3,4] In the real world, trivial, mild, and severe MR are obvious, and quantitative measures often confirm eyeball assessments of severity. But the classification of "moderate" MR poses uncertainty with respect to visual assessment, and there is considerable variability among interpreters. In fact, the use of descriptors in everyday practice such as "moderate to severe MR" and "solid moderate MR" reflect this uncertainty. It is in this situation in which quantitative methods have the most impact, either confirming moderate MR or upgrading or downgrading the degree of MR, similar to the nature of the benefit seen with stress imaging testing for chest pain in patients with intermediate pretest risk for coronary artery disease. Another more contemporary indication for routine quantification of MR is in the assessment of residual MR after transcatheter or surgical valve repair, when eyeball assessment is often extremely difficult if not impossible. Even if qualitative assessment was possible, accurate quantification is necessary in these circumstances for appropriate clinical decision making.

WHY THREE-DIMENSIONAL CFD IMAGING?

The current approach to the calculation of effective regurgitant orifice area (EROA) using the two-dimensional (2D) proximal isovelocity surface area (PISA) method has many limitations. From a practical standpoint, the assumption of a hemispheric flow convergence region (FCR) and the use of single-frame (largest) PISA are chief among them. The advantages of three-dimensional (3D) echocardiography, specifically 3D CFD, are widely recognized, and this technique is recommended to overcome these limitations of 2D CFD. However, there are technical and practical challenges with 3D CFD, which have hindered its routine use. In this issue of *JASE*, Pierce *et al.*[5] and Tan *et al.*[6] describe an approach using an algorithm called the 3D field optimization method (FOM), which generates a 3D flow vector velocity field in the FCR by comparing the modeled flow field with the observed spatial distribution of flow velocity vectors in the FCR proximal to the orifice. The FOM then computes regurgitant volume (RVol) using the instantaneous flow velocities integrated over the duration of MR. In their in vitro study, Pierce *et al.* examined the differences in RVol computed using the conventional 2D CFD PISA method and the 3D FOM when applied to circular and slit-shaped regurgitant orifices, using measures from a flow probe as a reference. Compared with 2D PISA results, they found that the 3D FOM was more accurate for slitlike orifices and for severe MR. For round orifices and mild MR, 3D FOM was no more accurate than 2D PISA, but for moderate MR with circular and slitlike orifice, 3D FOM was only modestly accurate and 2D PISA fared even worse. The accompanying in vivo animal study by Tan *et al.*, and the results of their application of 3D FOM to 3D transesophageal echocardiographic CFD data sets in patients with MR, largely confirm the results of the in vitro study by Pierce *et al.* There are many limitations in both studies, which the investigators have clearly elucidated. Chief among them is the lack of an independent reference standard in the work by Tan *et al.*, meaning that they could not verify the accuracy of 3D FOM. Even the accuracy data from the in vitro work is not compelling in the moderate MR category, which is where we need the most help for decision making. Taken together, the data from the two studies suggest that 3D FOM adds to the more established 3D CFD methods to quantify MR but that this approach will need further refinement and validation before routine clinical use.

Despite these limitations, 3D FOM is a novel approach in that it does not require data from continuous-wave spectral Doppler, which is often not optimal, especially in eccentric MR jets. Another notable feature is that velocities over the duration of the MR are used in computing EROA and RVol, thus avoiding the potential for overestimation of the degree of MR in dynamic and nonholosystolics MR. An alternative 3D CFD approach uses voxel segmentation to identify isovelocity in the FCR and automatically quantify the 3D surface area.[7] Then, using the peak velocity and the velocity-time integral from continuous-wave spectral Doppler of the MR jet, 3D EROA and RVol are computed. When the 3D surface area of the frame with the largest FCR is used along with the peak velocity of the MR jet, we can determine "peak PISA" EROA, and when this is combined with the VTI of the MR jet, "peak instantaneous" RVol is obtained. Both of these variables overestimate the degree of MR compared with cardiac magnetic resonance (CMR)–based classification of MR

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Dr. Vannan has received research grants and speaking honoraria from Siemens Healthiers.

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2016.08.004

severity, especially with dynamic MR, as is often seen with secondary MR, and when MR is not holosystolic in timing. However, the 3D surface area of the FCR at each time point over the duration of MR can be measured, and "peak instantaneous" RVol at each of these time points can be derived using the peak MR velocity from continuous-wave Doppler. By integrating these individual peak instantaneous RVol values over the duration of MR, "integrated PISA"–derived RVol is determined; this measure shows significantly better agreement with RVol measured by CMR.[7,8] Thus, both automated 3D FOM and the 3D voxel segmentation approach to identify the FCR overcome the potential for overestimating MR severity using the single-frame approach. Integration of data from 2D CFD of the FCR over the duration of MR can be done, but it requires manual computation and still suffers from limitations of using 2D images to describe what is essentially a 3D shape.

THE BENEFITS OF AUTOMATED QUANTITATIVE 3D CFD

Perhaps the most important finding in the studies by Pierce *et al.*[5] and Tan *et al.*[6] is the value of automation. Three-dimensional data sets are inherently rich in data, and the need for manual extraction of quantitative data has been and continues to be one of the most important challenges to its routine use in everyday practice, even when the acoustic window is optimal. Specifically, with regard to quantification of MR, the cumulative science and common wisdom that 3D CFD is superior to 2D CFD is compelling enough for guidelines and standards to recommend its use, at least in challenging situations.[9] But two key factors, among others, have discouraged the routine use of 3D CFD: the need for electrocardiographically gated imaging and manual (often tedious) interaction with the data to obtain parameters. Both of these are counterintuitive to work flow (all work for flow, or all work and no flow!) and reproducibility. It is now possible to perform real-time (nongated, nonstitched) CFD imaging at temporal resolution not significantly different from that of gated imaging,[7] although there is clearly room for improvement. Furthermore, gated 3D CFD is virtually impossible in atrial fibrillation, which is not uncommon in chronic MR. Even if cardiac rhythm is not an issue, flow is instantaneous, and it makes sense to measure it beat by beat, which also makes averaging data feasible. One of the criticisms leveled at CMR is that it is a gated technique and hence "not real time"; if this is a true limitation, then it behooves us to embrace real-time (nongated) CFD imaging and to push for all platforms to provide this. In addition, we should welcome automation and not use the argument that an expert, extracting data manually, is irreplaceable. The problem in 3D echocardiography is not abuse of automation but rather underuse and often misplaced skepticism. The fact is that both accuracy and reproducibility are improved by automation, and reproducibility is considerably worse when experts perform tasks manually, whether in a fully manual manner or by making subtle "adjustments" to the automation.[10-12] This is not to argue that automation is infallible and that it should be implemented without the ability to override what is obviously incorrect. However, we would note that if automation works in excess of 90% of the time, it will improve work flow significantly and encourage wider use. Furthermore, it is not unreasonable to anticipate that continuous refinement of technology and intelligence will improve automation to the levels that are seen in new airplanes and space technology, which have similar degrees of complexity. Work flow is one of the strengths of echocardiography, and given that it is the most commonly performed and recommended test for the quantification of MR, automated extraction of parameters from a complex 3D data will only enhance its value.

WHAT IF 3D PISA IS NOT APPLICABLE?

Both the 3D FOM and the 3D PISA method, however, do not overcome the limitations of resolving velocities in the FCR, which are not aligned with the ultrasound beam. This is a technical limitation for which there may be no practical solutions with current transducer technology. Another more relevant challenge is the presence of multiple MR jets, constrained PISA, and postintervention residual MR for which even 3D imaging of the FCR may not be accurate or helpful. In those circumstances, obtaining RVol by approaches other than those described by 3D FOM and PISA methods is necessary. Thavendiranathan *et al.*[13] described such an approach using transthoracic real-time volume color Doppler imaging and automated computation of mitral and aortic stroke volumes. In patients without valvular disease, mitral and aortic stroke volumes are not different,[13] whereas when MR is present, the difference between mitral and aortic stroke volume yields RVol.[7] Initial studies in relatively small numbers of patients have shown good accuracy in normal control subjects and in patients with chronic MR compared with CMR.[7,14] Recently, the automated 3D CFD-based stroke volume measurement also has been extended to transesophageal echocardiography, providing an alternative when conventional transthoracic echocardiography is suboptimal. The advantages of this method are that it does not depend on analysis of the FCR and that RVol is computed over the duration of MR. The measurement of mitral stroke volume using this approach is akin to phase-contrast CMR for direct measurement of mitral stroke volume. But the latter is technically very demanding and hence not used in routine clinical CMR practice. Instead, total stroke volume is measured as the difference in LV end-diastolic and end-systolic volumes, from which the aortic stroke volume (measured by phase-contrast CMR) is subtracted to yield RVol. Of course, the presence of greater than mild aortic regurgitation voids this 3D CFD stroke volume method for absolute quantification of MR, although it may be still applicable to assess changes in the degree of MR after intervention. Another limitation is the need to dealias CFD of high-velocity flow across the mitral annulus even when the Nyquist limit is maximized. But this dealiasing process is automated, with the ability to manually refine this step. Three-dimensional vena contracta area (VCA), which is related to anatomic regurgitant orifice area, is also a useful CFD parameter, which has shown promise in small studies of chronic MR in native valves.[8] It is currently a manual process, although it takes less time than FCR-based methods. Also, 3D VCA is superior to 2D vena contracta width across a range of severity of MR, especially in noncircular orifices. Integrating the velocity-time integral of the MR jet with 3D VCA yields RVol, which has shown good correlation with CMR-measured RVol. Automation of 3D VCA measurement will significantly enhance the clinical utility and together with 3D FCR and stroke volume methods will add to the concept of multiparametric assessment of MR from a single data set. However, 3D VCA has similar limitations as the FCR-based approaches and has been largely untested in patients with postintervention residual MR.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Arguably, from a single real-time volumetric CFD acquisition from an apical transducer position using transthoracic echocardiography or midesophageal transducer position using transesophageal

echocardiography, both CFD-based and LV volume–based RVol can be computed to provide confirmation of the degree of MR by independent methods.[15] Additionally, the FCR of the MR jet from the same data can be used to measure 3D EROA by the 3D PISA or the 3D FOM to further increase the reliability of grading the severity of MR. Finally, 3D VCA can be measured for a comprehensive quantitation of MR. Real-time (nongated) volume imaging will mean that these 3D CFD techniques can also be used in patients with chronic MR and atrial fibrillation, in whom CMR cannot be used. CMR does have the advantage of more reproducible and perhaps more accurate measurement of LV volumes. But when acoustic images are of sufficient technical quality, automated 3D echocardiographic LV volumes are as good as CMR-measured LV volumes and can be done even in patients with atrial fibrillation. One of the remaining issues to be resolved is the cutoffs for grading the severity of MR on the basis of these 3D CFD methods. There are reports suggesting that cutoffs are larger than current 2D CFD cutoffs, but various 3D EROA and VCA numbers have been reported for classification of severe MR.[8] The resolution of this dilemma is clearly important, but this will require large studies with clinical events as end points, in addition to comparisons with CMR.

Accurate and reproducible quantitation of chronic MR is not optional anymore, especially in the evolving paradigm of earlier intervention, combined with burgeoning options for transcatheter treatment to add to conventional surgical mitral valve repair. In the contemporary heart team approach to the management of valvular heart disease, we imagers have a pivotal role in shaping future paradigms. Accurate determination of the severity of MR is central to the timing and selection of interventional strategies and is also required to assess procedural success. It was nearly 40 years ago that 2D CFD imaging was introduced as a technique to image blood flow.[16,17] As we reflect on this, the following passage from Nora Ephron's *I Feel Bad about My Neck* is apt:

> According to my dermatologist, the neck starts to go at forty-three, and that is that…short of surgery, there's not a damn thing you, can do about a neck. Our faces are lies and our necks are the truth.

Perhaps qualitative or eyeball methods (our face) and quantitative 2D CFD techniques (our neck—the truth standard) have aged gracefully. In any event, integrated 2D and 3D echocardiography should be the new standard to quantify MR, which will also spur technological developments to match the clinical needs and to incentivize the wider adoption of 3D echocardiographic techniques. Ultimately, the predictive value of this integrated approach will have to be tested in prospective multicenter studies with clinical events as end points, such as the Progression and Outcome of Secondary Mitral Regurgitation study (POMAR).[15] This study will test the accuracy of automated 3D PISA and stroke volume methods and will examine the incremental value of 3D quantitation in predicting clinical outcomes compared with CMR. An additional question to be answered is when and how CMR incrementally complements the integrated assessment of MR severity using these newer 3D echocardiographic approaches.

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