

eSie Flow: **Making Echo** **More Quantitative**

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Executive Summary

Blood flow through the heart can now be visualized and measured with volume color Doppler echocardiography. Cardiology guidelines on valve disease emphasize the importance of quantification in the assessment of regurgitant severity. Clinical decision making today is based on a combination of qualitative and quantitative parameters. Siemens Healthineers eSie Flow quantification package enables measurement of flow throughout the cardiac cycle captured by 3D volume color Doppler data. This method complements the existing integrative methods and offers a more quantitative approach in the assessment of cardiac stroke volume as well as assessment of regurgitation.

Current methods to assess cardiac output are mostly invasive or indirect. Quantification methods for regurgitation are applied during one point in time and come with geometric assumptions. The eSie Flow analysis provides a new direct, non-invasive quantitative approach that measures 3D volume color Doppler throughout the entire cardiac cycle for up to three heart beats.

The ACUSON SC2000 PRIME and the ACUSON Bonsai¹ ultrasound systems are the dedicated premium cardiovascular ultrasound offerings in Siemens Healthineers, cardiology segment. The ACUSON SC2000 PRIME is the only system that offers eSie Flow.

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¹ Please note, the ACUSON Bonsai ultrasound system is only available in the USA.

Please note eSie Flow is to be demoed and sold ONLY to qualifying KOLs/Luminaries and key strategic customers.

Mitral regurgitation (MR) is one of the most prevalent valve diseases worldwide, even in developed countries. In the United States, nearly one in ten people age 75 or older has moderate or severe MR.¹

In the Framingham study, MR was seen in 88% of men and 92% of women but most of this was trivial.² Mild or more severe regurgitation was seen in 19% of participants.²

MR is a relevant and progressive disease. It initiates a cascade of events which if left untreated progresses to heart failure (HF) then death.

There is a general consensus among clinicians that the timely and accurate diagnosis of regurgitation severity is important for appropriate clinical decision making and optimal patient outcomes.³

While guidelines profess the need for utilizing quantitative measures for the assessment of MR, challenges remain in the wider adoption of quantitative approaches, as the available 2- and 3-dimensional quantitative methods are time-consuming, require mathematical assumptions, and are subject to significant inter-observer variability.^{3,4} Advances in 3D echocardiography, cardiac magnetic resonance imaging and cardiac computed tomography have all provided new tools for the quantification of MR. Echocardiography remains the most commonly used, inexpensive and safe modality for this purpose.

Using 3D Doppler ultrasound imaging, echo quantification of MR volume and MR fraction can be performed using 3D proximal isovelocity surface area (PISA). An even more comprehensive approach is to use 3D volume color Doppler to directly measure mitral inflow and left ventricular stroke volume. As described and validated by Thavendiranathan, et al., there are several merits to this 3D color Doppler technique over traditional 2D-based pulsed Doppler methods for the quantification of flow through any heart valve. In the pulsed-wave Doppler method, flow is computed based on a single velocity sample from the entire cross section and relies on an assumed cross section of the anatomy. In contrast, the 3D volume color Doppler-based method samples flow velocities across the entire cross section and aggregates them to compute flow through a valve. No assumptions are made about the left ventricular outflow tract (LVOT) or mitral annular geometry that often are associated with errors in any 2D-based methods. Furthermore, an automated angle-correction technique is applied by utilizing a hemispheric disc for 3D volume color Doppler data. Additionally a de-aliasing algorithm is applied to overcome errors associated with color Doppler aliasing.

Introduction

¹ Lloyd-Jones D, Adams RJ, Brown TM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee.

² Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999;83:897–902. [http://dx.doi.org/10.1016/S0002-9149\(98\)01064-9](http://dx.doi.org/10.1016/S0002-9149(98)01064-9) doi:10.1016/S0002-9149(98)01064-9

³ Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16:777–802.

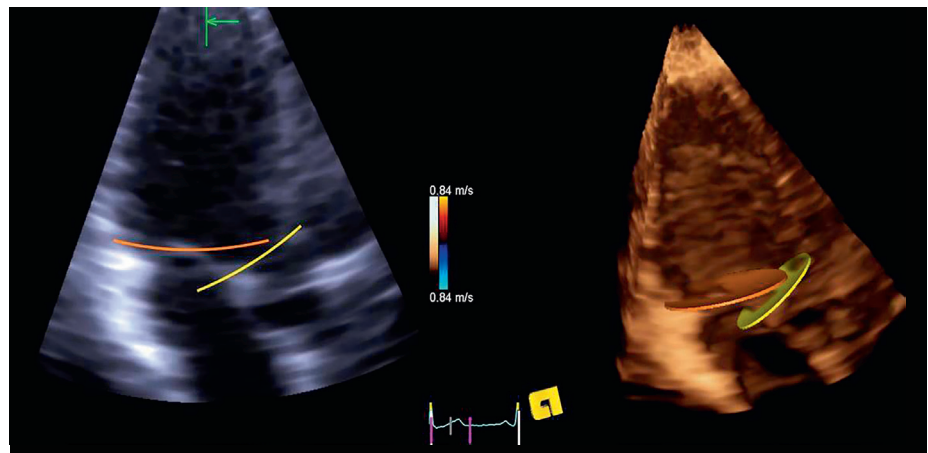
⁴ Thavendiranathan P, Phelan D, Thomas JD, et al. Quantitative assessment of mitral regurgitation. *J Am Col. Card*. 2012;60:1470–1483.

Methods

Step 1:

Placement of an inflow and outflow disc: With the placement of an inflow and outflow disc, a user can define the location through which the measurement of flow is performed. The inflow disc is designed to measure flow toward the transducer, which in this case (Figure1) is flow entering the heart, and the outflow disc is designed to measure flow away from the transducer, which in this acquisition is flow exiting the heart. An example of the placement of such discs in trans-thoracic echo would be placement of the inflow disc at the location of the mitral valve (MV) annulus and placement of the outflow disc at the LVOT location.

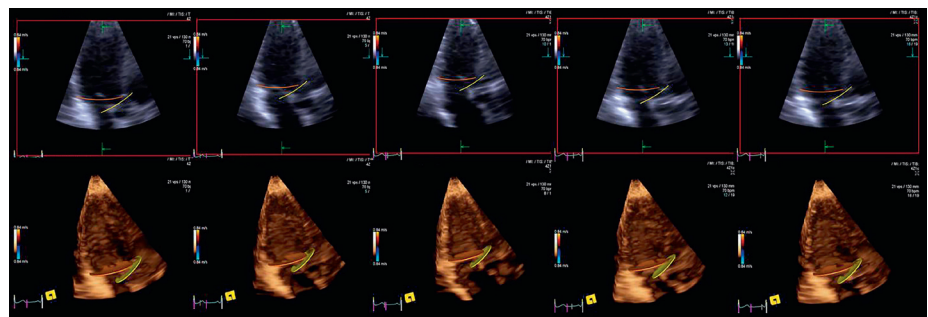
Figure 1: Example of appropriate inflow and outflow disc position



Step 2:

Cardiac motion tracking: The discs are tracked with the 3D motion of the heart such that the manually placed disc follows the movement of the heart and remain spatially consistent with flow passing through them. The tracking is accomplished using multiple cues including optical flow, boundary detection and motion prior.

Figure 2: Example of a tracked inflow disc and outflow disc throughout one cardiac cycle



Step 3:

3D flow sampling: The tracked locations of the inflow and outflow discs are used to construct the color flow data. Consequently, the flow volume is computed by aggregating the sampled color voxel flow values in the 3D space.

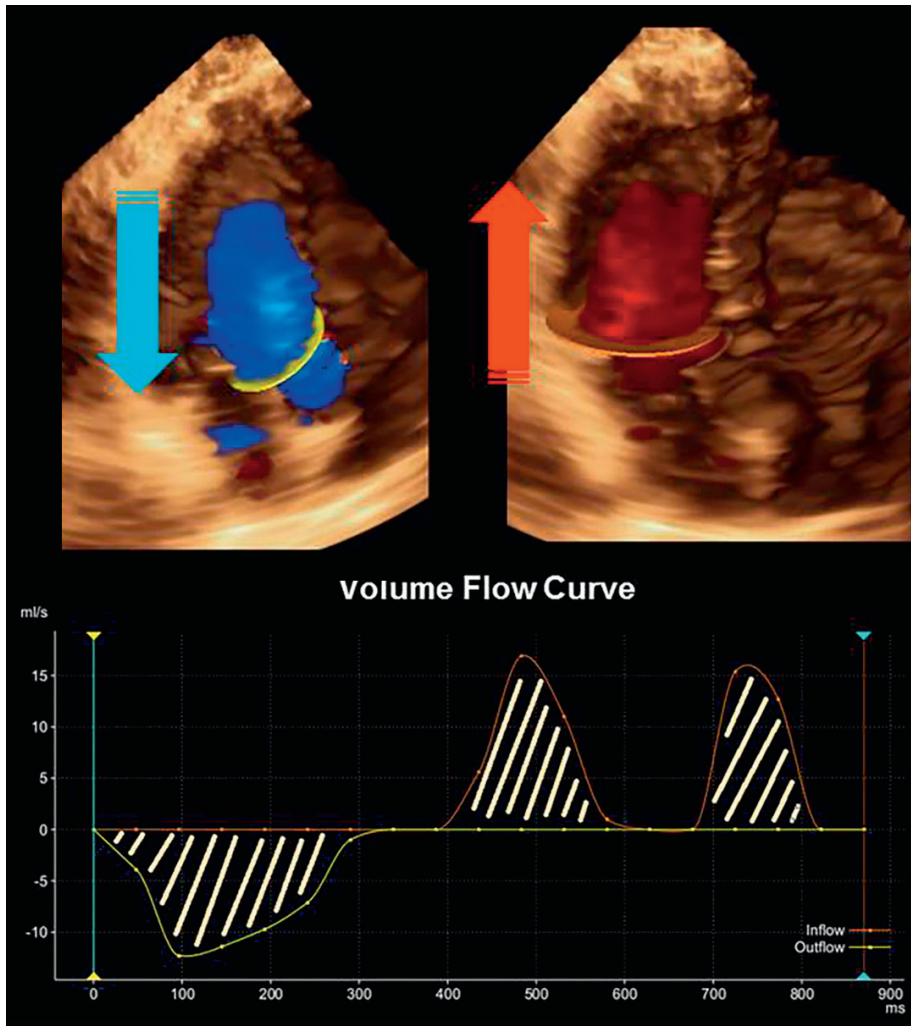
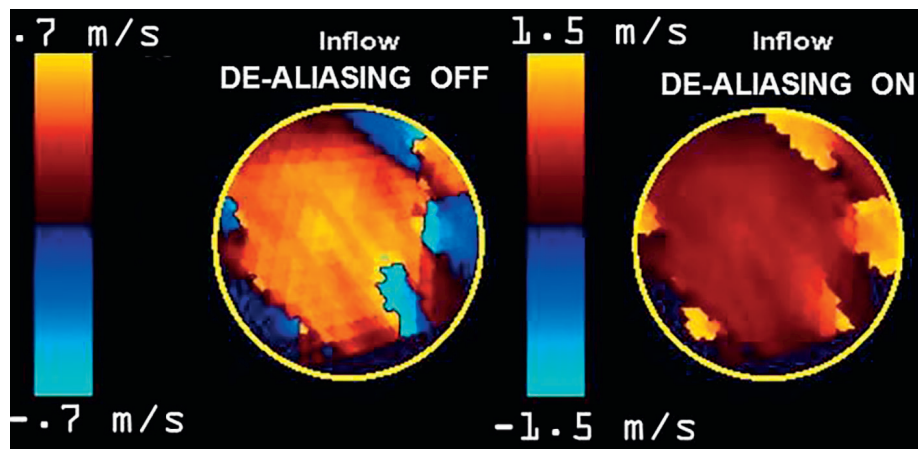


Figure 3: Example of volume color Doppler with tracked disc. The results are used to construct the cross-sectional color flow data. The area under the curve is used to calculate the inflow and outflow stroke volume.

Step 4:

Flow de-aliasing: De-aliasing is applied automatically to all the frames of the analyzed sequence to correct for aliased velocities and thus shifting the Nyquist limit for color Doppler. The acquisition velocity is doubled for flows moving toward and away from the transducer. This is akin to shifting the baseline up or down with pulse-wave Doppler.

Figure 4: Example of de-aliasing of color Doppler voxels in a disc. Automated de-aliasing is applied when entering the review step. At this time, the color velocity scale is extended and aliased velocities are converted. In the example to the right, the aliased (blue) flow is re-coded to red when velocity scale is extended from .7 m/s to 1.5 m/s.



The accuracy and feasibility of the quantification of MR using 3D volume color Doppler was validated and published by Thavendiranathan, et al.⁵ both in vitro and in vivo. The authors quantified regurgitation using both the 3D PISA method and volume flow quantification approach and compared the results with the measurements obtained on the same patients using Cardiac magnetic resonance imaging (CMRI) as a reference method. The results indicate that both 2D- and 3D-based effective regurgitant orifice area (EROA) measurements were lower than the ground truth. However, the regurgitation volume (RVol) measurements were statistically comparable to the ground truth as measured by the flow meter in vitro. In a sample size of 30 patients, the RVol measured by the volume flow quantification method was shown not to be statistically significantly different from the RVol measured by the CMRI reference method. In the analysis of reproducibility, the authors did an inter- and intra-observer variability analysis and reported a concordance correlation coefficient (CCC) of 0.96 for RVol, and for a test-retest analysis of RVol, they observed CCC of 0.97. Based on this data, the authors concluded that regurgitation volume measured with integrated 3D PISA and the volume flow quantification method can be used as an adjunctive method to quantify MR severity.

In another publication, Thavendiranathan, et al.⁶ studied the volume flow quantification method on patients without valvular heart disease to quantify mitral inflow and aortic outflow stroke volume and compared the results with pulsed Doppler-based methods and CMRI. In a sample size of 44 patients, they observed an excellent correlation between CMRI and the volume flow quantification method for both aortic outflow and mitral inflow. Additionally, they reported the method to be feasible for 86% of the patients in their clinical setting.

Heo, et al. compared MR quantification with 2D echo conventional methods, cardiac magnetic resonance imaging and volume color Doppler-based prototype software in a study with 186 patients. They reported underestimation of MR with conventional 2D echo methods especially in multijet and dilated ventricles. They reported better agreement in MR assessment between cMR and 3D volume color Doppler ($r = 0.94$) compared to the 2D PISA method ($r = 0.87$). They also observed a higher risk of misclassification in identifying surgical candidates in the multijet group. They concluded that advanced volume color Doppler-based methods may be of use in guiding treatments for patients with multijet MR.

Most recently Kato et al. published validation work comparing right and left heart stroke volumes measured with SC2000 volume color Doppler imaging and eSie Flow application to Qp/Qs determined by the Fick method in 34 children, 31 of these with atrial shunts. They reported a mean temporal resolution > than 22 volumes per second. In conditions with no shunts they report excellent correlation of ($r = .98$) for AV with MV flows and ($r = .96$) for TV with PV flows, RV SV with PV flows $r = .95$ and TV flows ($r = .93$), LV stroke volume with AV flow ($r = 0.87$) and with MV flow ($r = 0.89$). Fick Qp/Qs correlations were: PV/AV ratio ($r = 0.84$), TV/MV ratio ($r = 0.87$) and RV/ LV ratio ($r = 0.70$). They concluded that Flow measurement using automated real-time three-dimensional volume color Doppler flow analysis is feasible in children including in the right side of the heart and that the technology potentially provides a non-invasive bedside alternative to historically invasively acquired hemodynamic data.

Validation

⁵ Thavendiranathan P, Liu S, Datta S, et al. Quantification of Chronic Functional Mitral Regurgitation by Automated 3-Dimensional Peak and Integrated Proximal Iso-velocity Surface Area and Stroke Volume Techniques Using Real-Time 3-Dimensional Volume Color Doppler Echocardiography. In Vitro and Clinical Validation. *Circ Cardiovasc Imaging*. 2013;6:125–133

⁶ Thavendiranathan P, Liu S, Datta S, et al. Automated Quantification of Mitral Inflow and Aortic Outflow Stroke Volumes by Three-Dimensional Real-Time Volume Color-Flow Doppler Transthoracic Echocardiography: Comparison with Pulsed-Wave Doppler and Cardiac Magnetic Resonance Imaging *J Am Soc Echocardiogr* 2012;25:56–65

⁷ Kato A, Sandoval JP, Mroczek D, Chaturvedi R, Houle H, Georgescu B, Yoo SH, Benson L, Lee KJ. Automated 3-dimensional single beat real-time volume color-flow Doppler echocardiography in children: a validation study of right and left heart flows. *CJC*. 2018 in Press.

Discussion

We should be excited about the new capabilities provided by Siemens Healthineers eSie Flow package, but at the same time, keep in mind that innovation comes with a price in breaking our own barriers, which requires us to think outside the box.

It is well understood that stroke volume is the amount of blood that leaves the heart with every beat. The heart beats roughly 60 times per minute. If we take that amount of blood and multiply it by 60 that is the cardiac output (CO) per minute. This is a fundamental understanding. The use of new quantitative techniques does not change these fundamental facts.

The next important principle in flow is preservation of flow in a closed circuit. What comes into the chamber should leave the chamber. If 60 ml comes into the heart, 60 ml should leave. That is normal physiology. If only 30 ml leaves, we need to account for the missing 30 ml.

eSie Flow has potential for being a new, valuable clinical tool that can change the way we evaluate Mitral Regurgitation (MR), one of the more difficult cardiac disorders to accurately quantify. The ACUSON SC2000 PRIME is the platform that provides a completely integrated solution for 2D and 3D quantification of MR.

How is MR quantified today, and where does eSie Flow fit into our daily workflow?

The expert recommendations can be found in the recent guidelines. The following is a simple summary. In today's practice, clinical experts usually start the assessment of MR severity with a visual assessment of 2D B-mode with color in A4C, A3C and A2C views of the MR jet. The size of the jet can also be evaluated from the parasternal long axis (PLAX) and parasternal short axis (PSAX) for the origin localization. This is a semi-quantitative direct observation.

The second step is to quantify the regurgitation (the amount of blood not leaving the left or right heart chamber with each beat). The methods recommended in the latest valve assessment guidelines include the PISA-based effective regurgitation orifice area (EROA) and vena contracta width (VCW). Regardless of etiology, if there is a small central jet, a normal leaflet morphology, a VC < 0.3 cm, no proximal flow convergence, and an A-wave dominant mitral inflow pattern, then MR is considered mild and further quantitation is not necessary. Conversely, if there is a large jet with a prominent flow convergence, a large VC > 0.7 cm, and flow reversal in the pulmonary veins, then MR is considered severe – quantitation would substantiate the severity of the regurgitation. Everything in the middle is classified as moderate. Concerns exist with accurate quantification of mild to moderate where patients need regular follow-up, and moderate to severe MR when intervention decisions are made. Reliable assessment and quantification of regurgitation remains a clinical challenge.

To improve the accuracy of the measurement if done from 2D imaging, the measurement should be performed from two views and then averaged. The size of the lesion can also be measured directly by planimetry of the valvular orifice from 2D and 3D transesophageal imaging and is called the anatomical orifice. The measurement should be made over several frames and integrated to get a more accurate measure. To calculate the EROA of each frame, we need to know the peak velocity. The average velocity across the orifice is not measured and therefore only measures peak regurgitation. In a larger-size orifice, this can be a variable. All secondary MR lasts for several frames, and single-frame peak measurement is often not accurate as it changes dynamically throughout the systolic cycle. If only a single frame is used with secondary MR, it may overestimate the amount of regurgitation. In primary regurgitation, PISA sometimes is impossible – multiple jets or wall-hugging jets make it complicated to perform measurements, other methods must be used to assess primary MR.

In patients where inflow stroke volume measurement is not possible, as is the case in mitral stenosis, the total stroke volume measured by 2D or 3D volume analysis can be substituted. This method is also utilized by CMRI.

Quantification of the total amount of blood leaking through the lesion is called regurgitant volume (RVol). This can be measured with the continuity equation method. The mitral valve annulus and the LVOT diameter are measured to estimate the cross sectional area. Small errors can have a big impact on the final stroke volume. The velocity time integral (VTI) is acquired through pulsed Doppler with the cursor positioned at the LVOT and the mitral annulus. The flow envelopes are traced and then measured. Subtraction of the mitral inflow stroke volume (SV) minus the aortic outflow SV equal (RVol). This method is rarely used today because small errors in the mitral annulus diameter can make huge differences in the final analysis, and it is difficult to measure accurately.

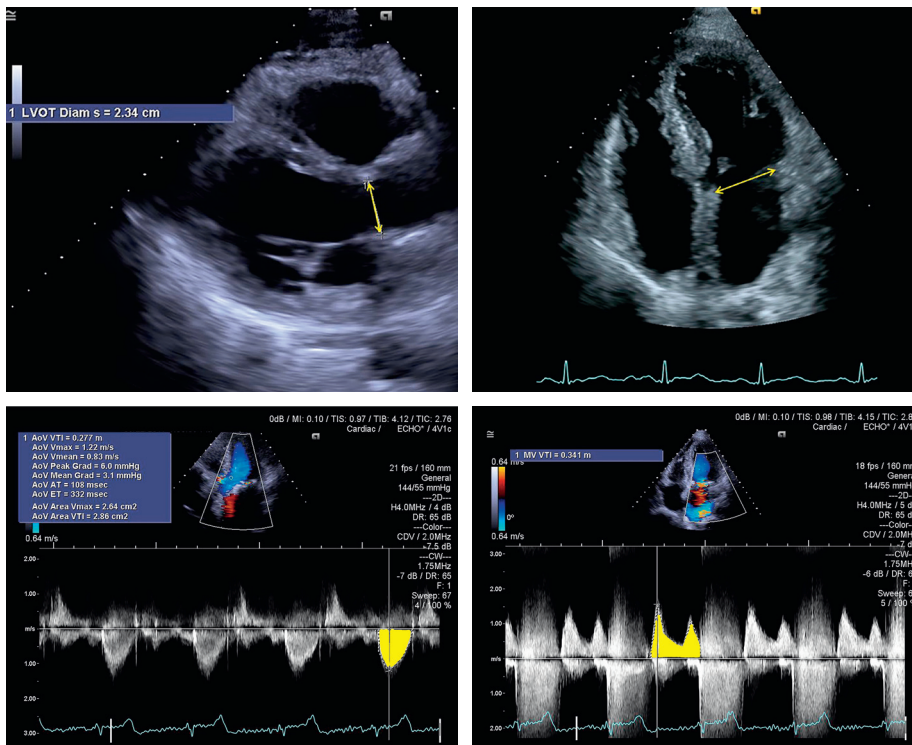
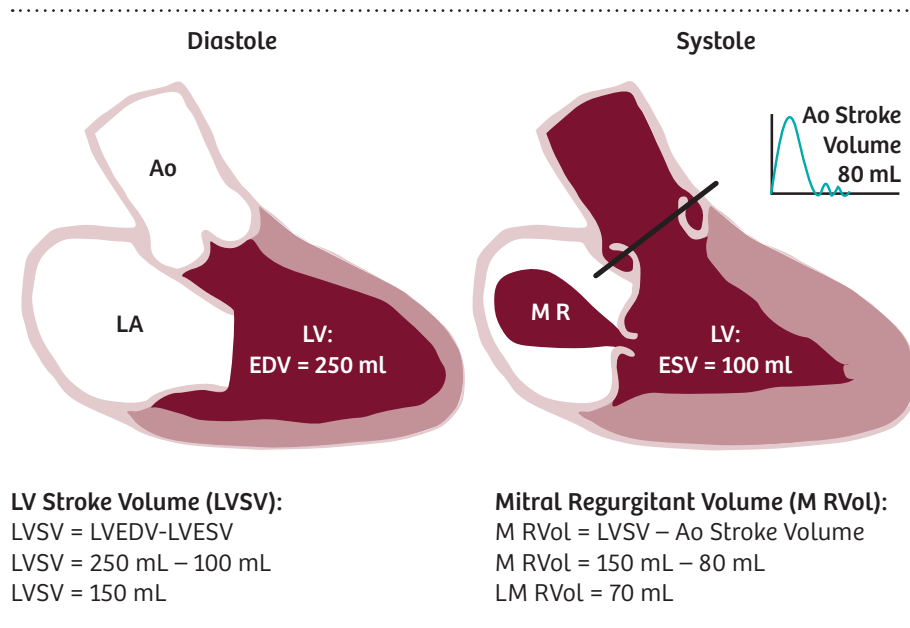


Figure 5: Example of Echo and Doppler measurements utilizing the continuity equation to measure stroke volume. The LVOT and mitral valve annular diameter are measured. Pulse-wave Doppler of the systolic outflow and mitral inflow are used to measure the VTI of both flows. In this example of severe MR, the MV SV was 183 ml and LVOT SV 58 ml. This results in a regurgitant volume of 125 ml and an RF of 68% (125/183).

Phase contrast cardiac MR now offers a new quantitative approach to measuring MR. The LV SV is measured by the disc method, and the amount of blood leaving the heart is measured, thus deriving the net regurgitant volume.

Figure 6: Example of a CMRI method for quantification of MR. The volume of the LV is calculated at end-diastole (LVEDV) and end-systole (LVESV) by manual trace of multiple sax slices of the LV from apex to base. The total volume of blood ejected from the LV. LV SV is computed as the difference between LV end-diastolic volume and LV end-systolic volume. In this example, LV SV is 150 mL. The volume of blood crossing the aortic valve (AV) is measured by performance of a phase-contrast acquisition in the aorta, in this example 80 mL. The mitral RVol is computed as the difference between the LV SV and aortic forward SV, in this example 70 mL.



eSie Flow is proving to be a valuable clinical tool for assessing mitral regurgitant severity. Coupled with the ACUSON SC2000 PRIME ultrasound system, you have a complete integrated solution for 2D and 3D quantification of MR. For the first time, we are able to directly measure stroke volume in a way that is practical. Diastolic inflow stroke volume minus systolic outflow stroke volume provides a simple measure of regurgitation.

The proportion of blood that goes backward compared to what comes in is called regurgitation fraction (RF). If 50 mL went out (RVol), and 100 mL came in, divide the RVol by the inflow SV to derive RF. This measure is not necessary when out-flow stroke volume is normal. It is useful when outflow SV is below 35 mL. When the outflow SV is normal, there is still a good amount of blood leaving the ventricle. If the RF is > 50%, then the MR is severe.

If at this stage there is still uncertainty, the pulmonary vein flow should be evaluated with Doppler. The normal pattern is two peaks above the baseline. The first peak is the systolic wave, and the second is the diastolic peak. In severe MR, the first peak will be below the baseline or absent. A clinician should always sample more than one vein to make an integrative assessment.

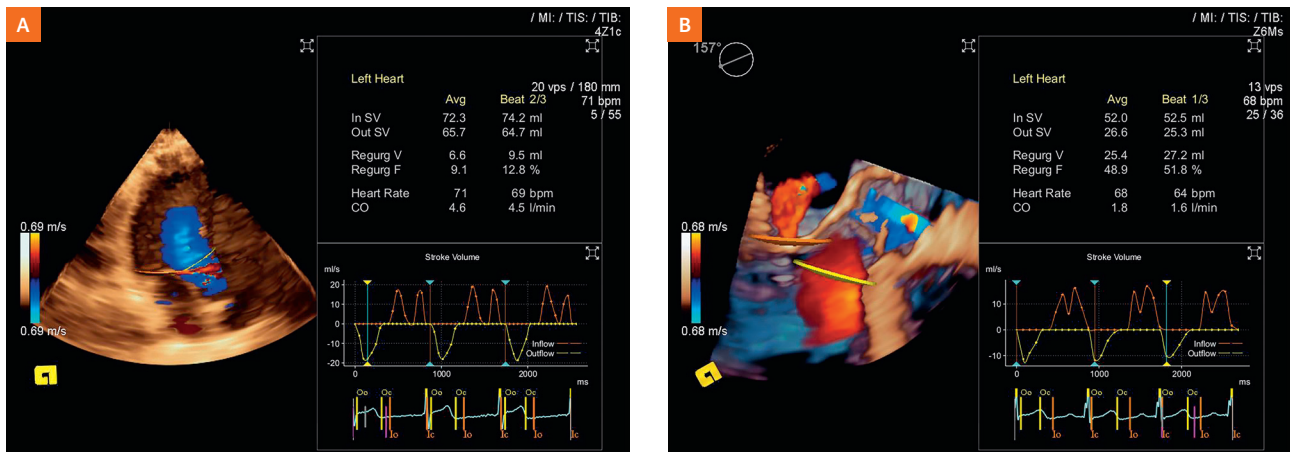


Figure 7:

A. Example of inflow and outflow stroke volume from normal volunteer where both inflow and outflow stroke volume are within normal values and less than 10 ml difference.

B. Patient with known MR. The inflow and outflow stroke volume are different with an outflow volume > than 10 ml difference of the inflow volume. In a closed system with no aortic regurgitation the difference provides a good estimation of regurgitation volume.

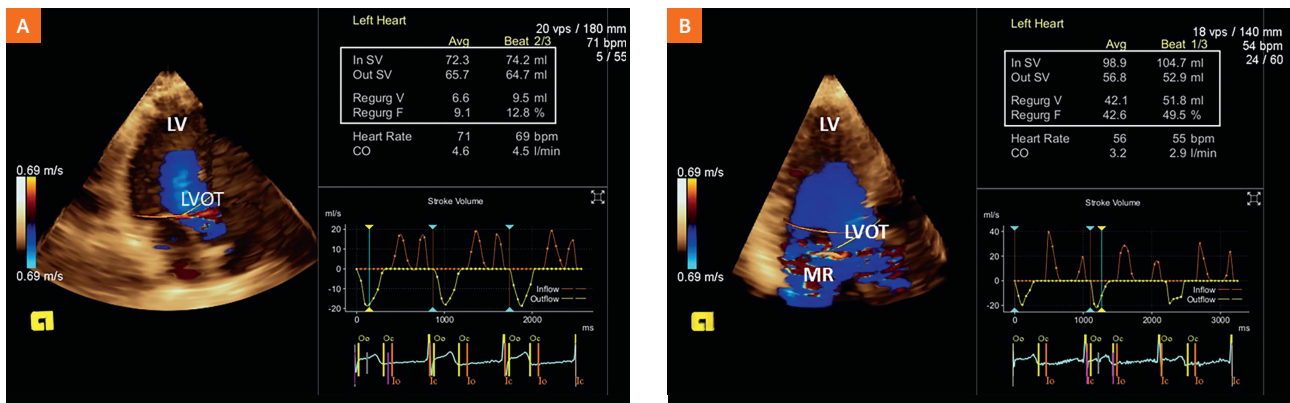


Figure 8:

A. Visualization of volume color Doppler across the LVOT during Systole. The summarized report displays inflow and outflow stroke volume with the derived regurgitant volume and fraction. Cardiac Output is also displayed. The orange, curve on the graph above the baseline, represents the integrated velocities of the orange disc (mitral inflow) tracked over 3 cardiac cycles. The yellow curve, on the graph below the baseline, represents the integrated velocities of the yellow (outflow) disc tracked over 3 cardiac cycles. The Inflow – Outflow difference is less than 10ml and is representative of normal flow without mitral regurgitation.

B. Visualization of volume color Doppler across the LVOT during systole with reverse flow into the left atrium. The summarized report displays inflow and outflow stroke volume with the derived regurgitant volume and fraction. Cardiac Output is also displayed. The orange, curve on the graph above the baseline, represents the integrated velocities of the orange disc (mitral inflow) tracked over 3 cardiac cycles. The yellow curve, on the graph below the baseline, represents the integrated velocities of the yellow (outflow) disc tracked over 3 cardiac cycles. The Inflow – Outflow difference is above 40 ml considered severe mitral regurgitations.

Like all quantitative methods, the technique has limitations. When the discs are placed in flows that exceed the Nyquist limit the level of the measured SV accuracy diminishes and the de-aliased velocities will not be reliable. If a patient has acute, severe MR with a hyper-dynamic ventricle, the method cannot be used to quantify MR. The same goes for heart rates above 100 bpm and low frame rates as there will not be sufficient frames in a heart cycle to make an accurate measurement. The minimal recommended frame rate for eSie Flow analysis is 15 and the minimum number of frames in a heart cycle is 12 frames; 4 frames for outflow and 5 frames for inflow. With any ultrasound technique, reliable results require quality acquisitions to produce accurate quantification.

In patients where inflow stroke volume is not possible, as is the case in mitral stenosis, the inflow SV measured by 2D or 3D volume analysis can be substituted. This method is equivalent to the CMRI technique.

Figure 9: Echo methods utilized to measure stroke volume. Total stroke volume can be substituted for inflow stroke volume measurement.

SV	LVA SV	RVA SV	2D LV SV	Continuity Equation	eSie Flow Package
Total SV	✓	✓	✓		
Inflow SV				✓	✓
Outflow SV				✓	✓

The eSie Flow package will need maturity and clinical experience before it is widely accepted as a routine clinical tool. For this reason, we focus on MR to gain knowledge but also to address one of the most relevant clinical challenges today.

Conclusion

eSie Flow is a new volume color Doppler application providing the first direct analysis of cardiac stroke volumes. Regurgitation volume and regurgitation fraction are derived from the net flows of the inflow and outflow stroke volumes.

- Volume color Doppler can now be analyzed across an entire heart cycle
- Accurate and reproducible analysis is possible
- The simple method is time efficient
- Direct analysis of cardiac stroke volume is feasible
- eSie Flow package can be performed at the bedside
- MR can now be comprehensively quantified

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