

## THE PRESENT AND FUTURE

### STATE-OF-THE-ART REVIEW

# Use of Cardiac Magnetic Resonance Imaging in Assessing Mitral Regurgitation

## Current Evidence



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#### ABSTRACT

Accurate quantification of regurgitant volume is a central component to the management of mitral regurgitation. Cardiac magnetic resonance imaging (CMR) accurately quantifies mitral regurgitation as the difference between left ventricular stroke volume and forward stroke volume using steady state free precession and phase contrast imaging. The CMR measurement of mitral regurgitant volume is reproducible and can quantify mitral regurgitation in patients without regard to regurgitant jet morphology, such as patients with multiple and eccentric jets. It can be used to quantify regurgitant volume in patients with multiple valve lesions and concomitant intracardiac shunts without the use of intravenous contrast. Studies have highlighted the accuracy and reproducibility of CMR in quantifying mitral regurgitation and have begun to link CMR to clinical outcomes. (J Am Coll Cardiol 2018;71:547–63) © 2018 by the American College of Cardiology Foundation.

**M**itral regurgitation is a common valvular heart disease lesion affecting approximately 2 million people in the United States (1,2). While transcatheter interventions are evolving, the current method of treatment is mitral valve surgery, with medical therapies playing a limited role in the management of this disease. In 2015, there were 16,006 lone mitral valve repairs and replacements performed in the ~1,000 medical centers that report their data to the Society of Thoracic Surgeons national database (3). According to the Society of Thoracic Surgeons national database, the number of mitral valve surgeries has been growing on average 4%/year between 2010 and 2015. When deciding which patients are appropriate for mitral valve surgery, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of valvular heart disease place significant emphasis on the severity of mitral regurgitation (4). Thus, accurately quantifying the severity of mitral regurgitation

and being able to differentiate nonsevere from severe mitral regurgitation is the most important question in the clinical evaluation of patients with mitral regurgitation. Complicating the clinical assessment of patients with mitral regurgitation is the difficulty in assessing whether a patient is symptomatic due to effects of the valvular leak or other common disease states. The most common symptoms associated with mitral regurgitation include dyspnea, fatigue, palpitations, and decreased exercise tolerance, which are often associated with other common diseases that may be undiagnosed or concurrent. Additionally, patients with severe mitral insufficiency may be asymptomatic, and the absence of symptoms should not rule out the presence of severe disease. Supportive signs of severe mitral insufficiency, such as a dilated left atrium, dilated left ventricle, and pulmonary hypertension, can be associated with other common disease states and may not reflect the presence of severe mitral regurgitation. More recently, some now



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## ABBREVIATIONS AND ACRONYMS

**2D** = 2-dimensional

**3D** = 3-dimensional

**ACC** = American College of  
Cardiology

**AHA** = American Heart  
Association

**ASE** = American Society of  
Echocardiography

**CMR** = cardiac magnetic  
resonance imaging

**EROA** = effective regurgitant  
orifice area

**FSPGR** = fast spoiled gradient  
echo

**LVSV** = left ventricular stroke  
volume

**PISA** = proximal isovelocity  
surface area

**RVSV** = right ventricular stroke  
volume

**SSFP** = steady state free  
precession

**TEE** = transesophageal  
echocardiography

**TTE** = transthoracic  
echocardiography

advocate performing early mitral valve surgery on asymptomatic patients with the hope that the patient is more likely to get a mitral valve repair (5). This emphasizes the central importance for accurate and reproducible quantification of mitral insufficiency using a technique that can accurately differentiate severe from nonsevere mitral regurgitation.

The most commonly employed method to assess the severity of mitral regurgitation is echocardiography. The current ACC/AHA guidelines for the management of valvular heart disease emphasize echocardiography as the principal technique in determining the severity of mitral regurgitation (4). The advantages of echocardiography are its availability, its portability, the long experience using this modality, its ability to assess the mechanism of mitral valve disease, the supportive signs of severe mitral regurgitation (such as left atrial and ventricular dilatation, as well as pulmonary hypertension), and its unique ability to evaluate exercise or immediate post-exercise hemodynamics. Excellent spatial resolution, especially of transesophageal echocardiography (TEE), allows reliable assessment of the valve morphology

and leaflet motion. However, the quantitative methods for assessment of mitral regurgitation severity, such as flow convergence-based effective regurgitant orifice area (EROA) and regurgitant volume, pulse Doppler-based regurgitant volume, and the vena contracta, have some important limitations (6-14). These limitations stem from the mitral regurgitation characteristics (such as orifice morphology, temporal change in orifice geometry, and multiple jets), ultrasound examination settings, and inherent limitations due to assumptions underlying these estimations. Despite limited temporal resolution, use of 3-dimensional (3D) echocardiographic techniques and software-based automation may overcome some of these limitations, but more evidence is needed. In addition, significant interobserver and intraobserver variability for the most commonly used parameters of mitral regurgitation severity is a known limitation of echocardiographic assessment (6-8). Finally, the lack of a single reproducible echocardiographic parameter for severity of mitral regurgitation and the need to integrate multiple parameters, which can often be discordant, lead to difficulty in quantifying mitral regurgitation with accuracy and precision (15). In addition to the issues cited in the previous text, there is no gold standard against which imaging parameters of mitral regurgitation could be tested. Due to the

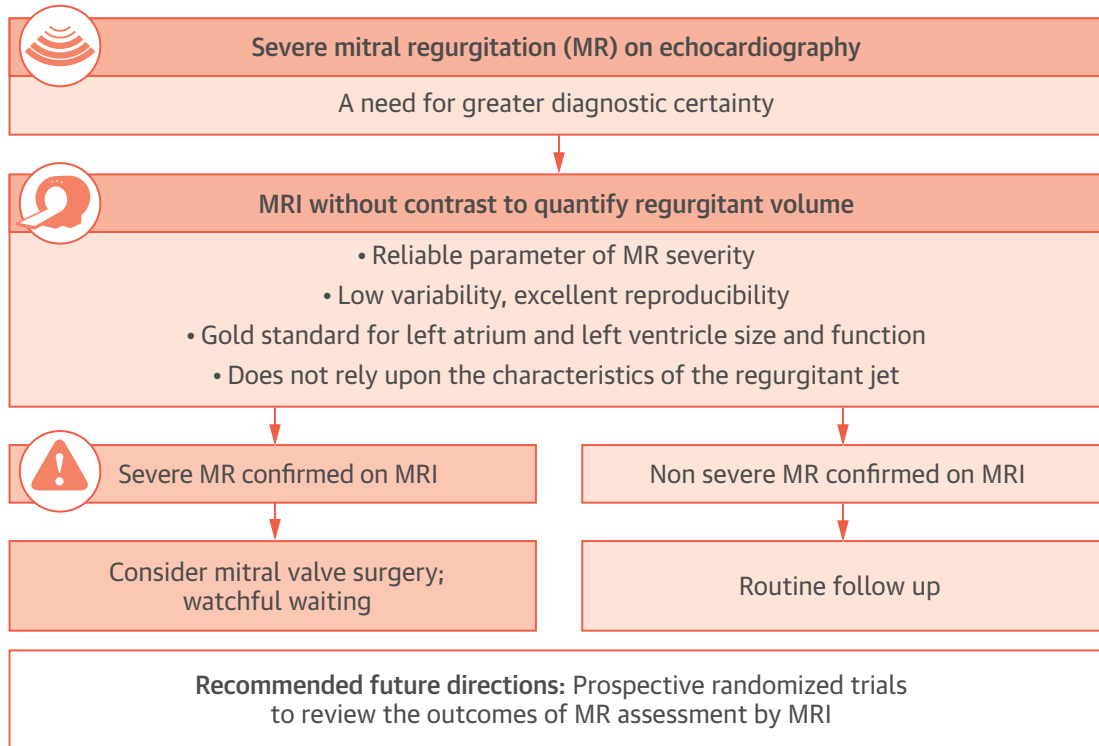
limitations of echocardiography and the difficulty in assessing symptoms of mitral regurgitation in patients with other diagnosed or undiagnosed comorbidities that may mimic symptoms of mitral regurgitation, there has been an interest in the use and development of cardiac magnetic resonance imaging (CMR) as a noninvasive imaging modality to assess mitral regurgitant severity (Central Illustration).

## CMR TECHNIQUES AND SEQUENCES USED IN THE EVALUATION OF MITRAL REGURGITATION SEVERITY

CMR is a versatile technique that can measure both the severity of mitral regurgitation and the hemodynamic consequences of the volume overload (16,17). Advantages of CMR include the naturally occurring contrast between the blood pool and the myocardium using steady state free precession (SSFP) imaging without the use of intravenous contrast; the ability to image the whole chest, in which the plane of imaging can be chosen without limitations of body habitus; and the fact that CMR evaluation of mitral regurgitation does not rely on the characteristics of the mitral regurgitant jet. CMR has become the gold standard for left and right atrial and ventricular volumes and function, allowing evaluation of the hemodynamic effects of mitral regurgitation on the left ventricle (18-20). The quantification of mitral regurgitation relies primarily on 2 imaging techniques: SSFP imaging to quantify left ventricular stroke volume, and phase contrast imaging to quantify left ventricular forward stroke volume. Figure 1 illustrates an example of an SSFP short-axis stack (top panel) of the heart that was planned from a long-axis localizer (right lower panel). Note the high contrast between the blood and the myocardium, making delineation of the blood pool easy. In Figure 2 (Online Video 1), we illustrate segmentation of the myocardial blood pool at end-diastole and end-systole, which generates ventricular volumes, ejection fractions, left ventricular stroke volume (LVSV), and right ventricular stroke volume (RVSV). The SSFP cine images and fast spoiled gradient echo (FSPGR) cine images allow detection of anatomic abnormalities of the mitral valve and localization of the regurgitant jet. Figure 3 and Online Video 2 show an example of posterior leaflet prolapse with an anteriorly directed mitral regurgitant jet using SSFP and FSPGR imaging. This illustrates the different appearance of the regurgitant jet depending upon the sequence used.

Phase contrast imaging uses velocity-encoded images to assess flow in blood vessels. In cardiovascular applications, this is most commonly acquired in the

**CENTRAL ILLUSTRATION Proposed Clinical Pathway and Rationale for the Use of Cardiac MRI in the Assessment of Patients With Severe Mitral Regurgitation**



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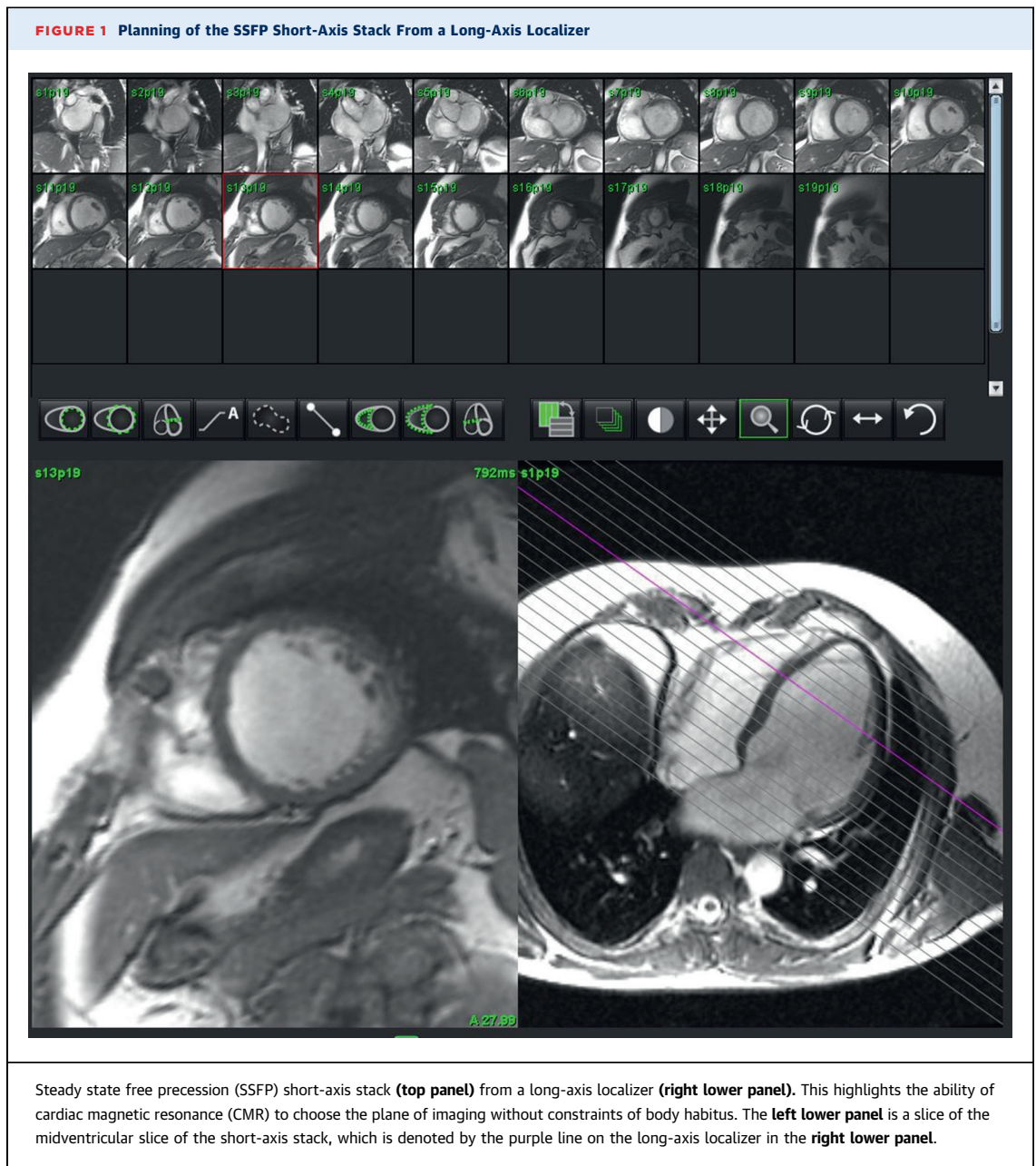
MRI = magnetic resonance imaging.

proximal aorta and/or main pulmonary artery, but can also, in principle, be acquired to measure forward flow at the level of the mitral or tricuspid valve. In phase contrast imaging, applications of gradient pulses induce phase shifts in moving protons that are directly proportional to their velocity along the direction of the gradient. Phase contrast is capable of measuring velocities, and thus flow, in the “through plane” orientation. The imaging plane is acquired perpendicular to the desired vessel. This technique allows measurement of blood flow in vessels and is particularly suited to quantifying flow in the ascending aorta (Figure 4A, Online Video 3A) and the main pulmonary artery (Figure 4B, Online Video 3B). Studies have validated the flow measured by phase contrast images using ventricular stroke volume as the standard of reference (21).

**ASSESSMENT OF MITRAL REGURGITATION USING CMR**

The ACC/AHA guidelines for the assessment of mitral regurgitation and the American Society of

Echocardiography (ASE) guidelines for the assessment of native valve regurgitation highlight the importance of evaluating both the severity of the regurgitant lesion as well as the hemodynamic effects the valvular lesion has on the left ventricle and the left atrium. As discussed in the previous text, CMR provides highly accurate and reproducible assessment of left and right atrial and ventricular size and function and has become the gold standard for evaluating cardiac chamber size (18-20). Left ventricular assessment is performed with SSFP imaging, which allows for the measurement of left ventricular end-diastolic and -systolic volumes, stroke volume, and ejection fraction. Left ventricular volumes can be indexed to body surface area and compared with published normal ranges (22-24). Left ventricular end-systolic dimension can also be measured using SSFP images in either a short-axis slice or a 3-chamber view. The current ACC/AHA guidelines highlight left ventricular ejection fraction and end-systolic dimension as important parameters in determining which



patients are appropriate for mitral valve surgery, and the American Society of Echocardiography recommends quantifying the left atrial and ventricular size when assessing mitral regurgitant severity (4,15). Furthermore, the reproducibility of left ventricular size and function make CMR a useful tool in longitudinal patient follow-up (19,20).

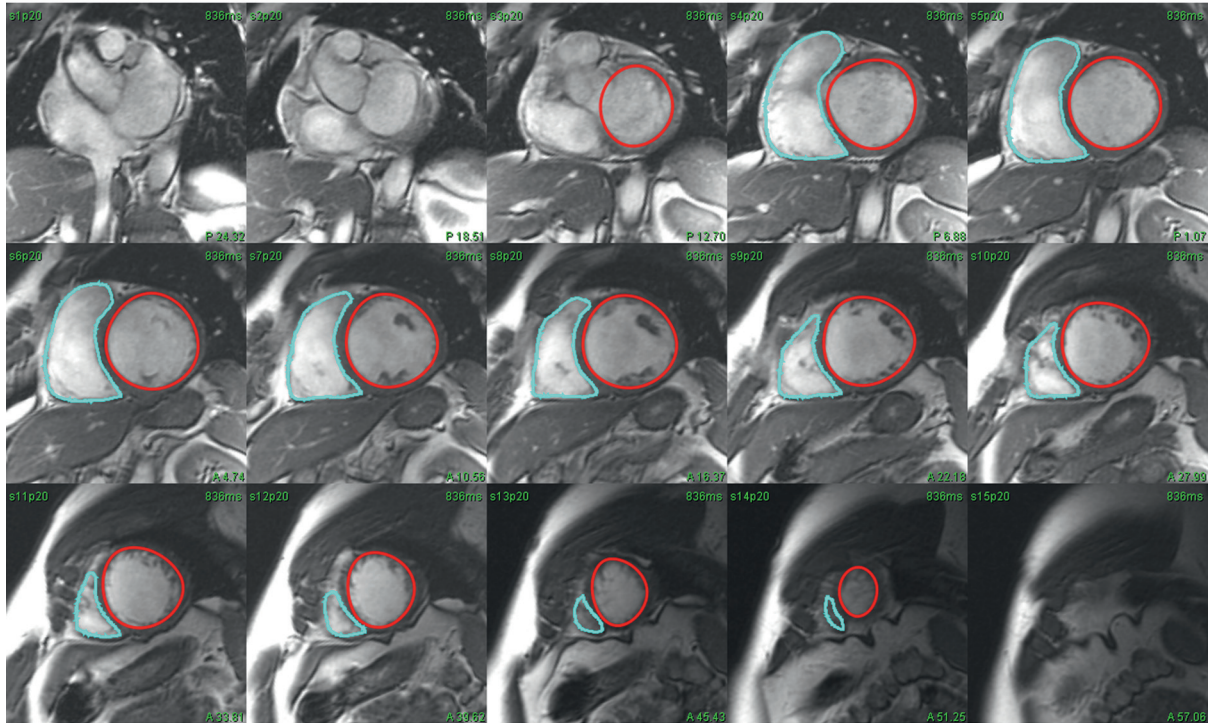
Several methods have been described to assess the severity of mitral regurgitation. The most commonly studied methods have relied upon indirect methods to quantify mitral regurgitant volume utilizing ventricular stroke volumes and/or phase-contrast

imaging (Table 1). However, other, less-studied semiquantitative methods have been described including the use of signal void, the size of the regurgitant jet (25,26) as well as the regurgitant orifice area measures using phase contrast imaging (27).

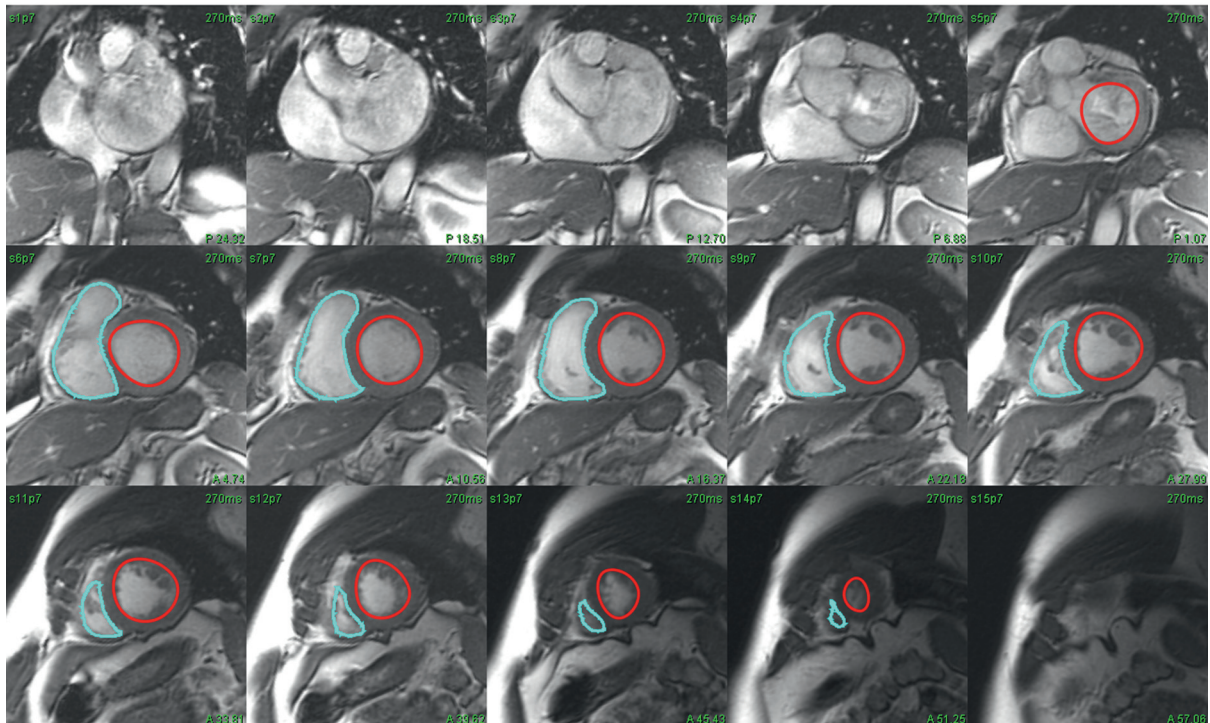
The currently recommended method for assessing mitral regurgitant severity by CMR focuses on quantifying regurgitant volume and fraction (15). The methods used to quantify mitral regurgitation using CMR are listed in Table 1. The most studied technique is LVSF—forward stroke volume. LVSF is quantified using SSFP short-axis images and represents the total

**FIGURE 2** End-Diastolic and -Systolic Segmentation of an SSFP Short-Axis Stack

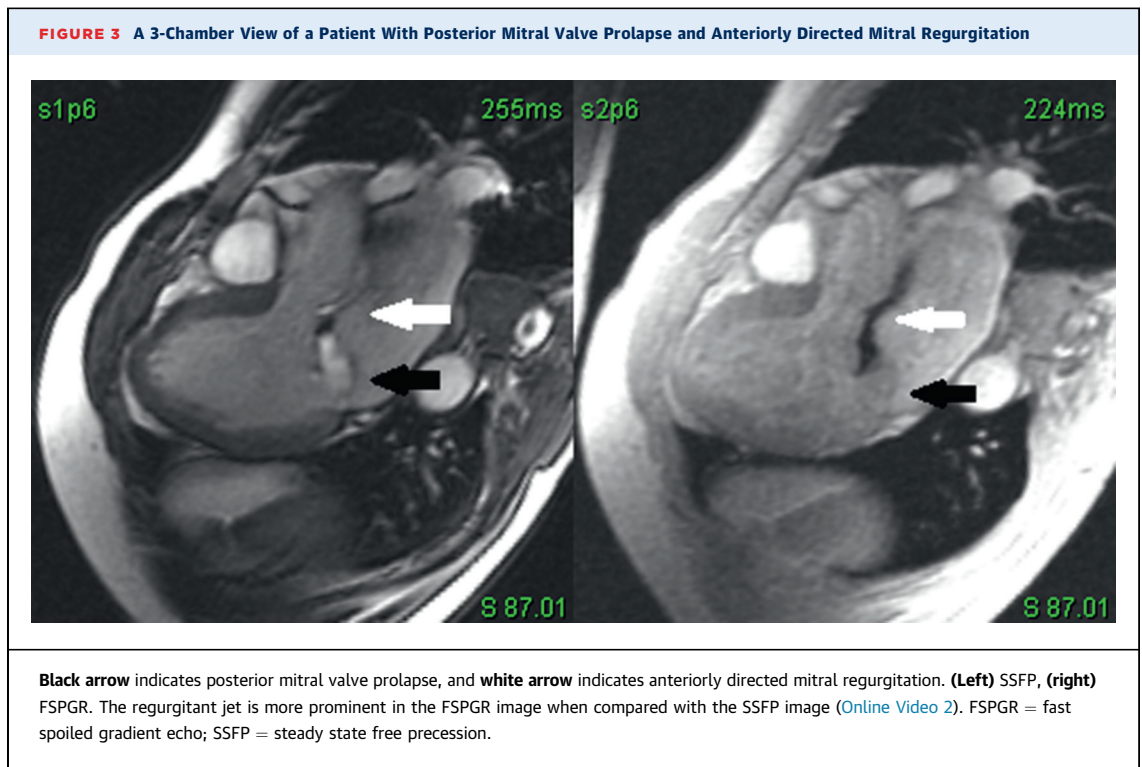
**A**



**B**



End-diastolic (**A**) and end-systolic (**B**) segmentation showing the left ventricular traces in red and the right ventricular trace in blue. The contrast between the blood pool and the myocardium makes delineation of the endocardial border easy (Online Video 1). SSFP = steady state free precession.



stroke volume consisting of the regurgitant volume and the forward stroke volume. The forward stroke volume is quantified using phase-contrast images of the proximal aorta or main pulmonary artery. This calculation is valid in patients without aortic regurgitation or a cardiac shunt. **Figure 5** illustrates how CMR can be used to quantify mitral regurgitation in patients with lone valve disease, multiple valve disease, and intracardiac shunts. In the patient without valve disease or an intracardiac shunt, the LVSV, RVSV, aortic flow, and pulmonary artery flow are equal (**Figure 5A**). In patients with lone mitral regurgitation, the LVSV is larger because it contains both the forward stroke volume and the mitral regurgitant volume, and the mitral regurgitant volume is the difference between the LVSV and the aortic or pulmonary artery flow (**Figure 5B**). In patients with mitral and aortic regurgitation (**Figure 5C**), the LVSV contains the forward stroke volume, the mitral regurgitant volume, and the aortic regurgitant volume. The amount of aortic regurgitation is quantified directly from the diastolic flow of the aortic phase-contrast images. The mitral regurgitation is then calculated as LVSV - (aortic regurgitation + forward stroke volume). In patients with mitral regurgitation and an atrial septal defect, the mitral regurgitation is calculated as the difference between the LVSV and the aortic flow, while the Qp/Qs is calculated as the ratio of the pulmonary artery flow to aortic flow

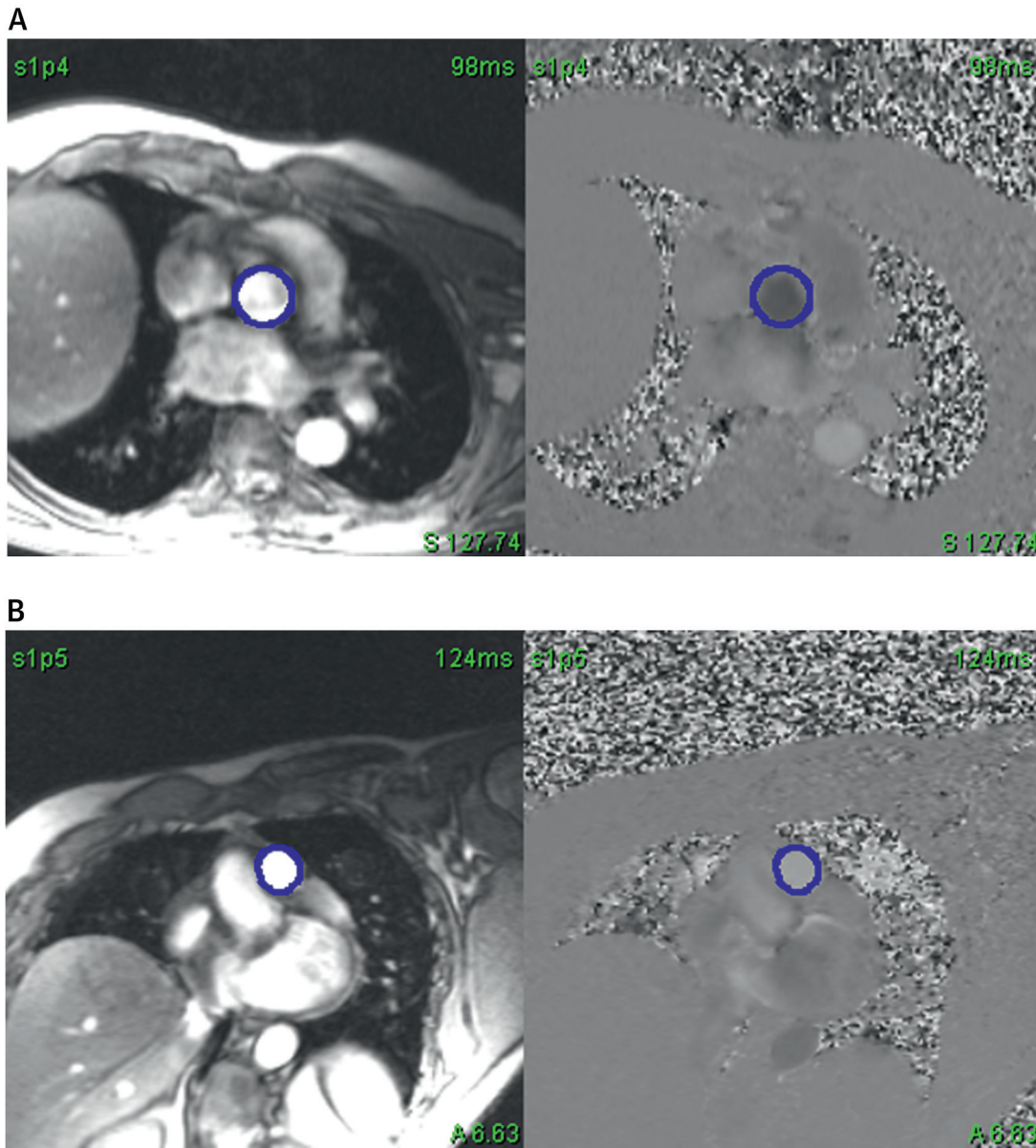
(**Figure 5D**). In patients with mitral regurgitation and tricuspid regurgitation, the mitral regurgitation is the difference between LVSV and forward stroke volume, while the tricuspid regurgitation is quantified by the difference between the RVSV and the forward stroke volume (**Figure 5E**).

Other techniques used to assess mitral regurgitation include calculating the difference between the LVSV and the RVSV or the mitral inflow and the aortic flow. Both of these methods rely on the same concept as LVSV-forward stroke volume, in that LVSV and mitral inflow will contain both the mitral regurgitant volume and the forward stroke volume, and the RVSV and the aortic flow represent forward stroke volume. These calculations are valid in patients without aortic regurgitation or a cardiac shunt. In addition, regurgitant fraction can be calculated using the regurgitant volume and the LVSV.

#### TECHNICAL CONSIDERATIONS IN QUANTIFICATION OF MITRAL REGURGITATION

As stated in the previous text, quantification of mitral regurgitation by CMR is based on SSFP cine images of the short axis and phase-contrast imaging of the proximal pulmonary artery and aorta. Thus, it is important that high-quality SSFP images and phase-contrast images be acquired to ensure accurate

**FIGURE 4** Phase Contrast Images of the Proximal Ascending Aorta and Proximal Ascending Aorta



(A, [Online Video 3A](#)) Proximal ascending aorta and (B, [Online Video 3B](#)) proximal pulmonary artery. (Left) Magnitude image, and (right) phase image. The blue circles highlight the vessel in which flow is being measured.

quantification of mitral regurgitation by CMR ([Table 2](#)). It is important for centers that perform CMR to consistently perform quality assurance. This entails using the “checks and balances” system that is inherent when performing cardiovascular CMR. Routine studies should include analysis of both the right and left ventricles in addition to phase contrast images of the proximal aorta and pulmonary artery. This allows comparison of RVSV, LVSV, aortic

flow, and pulmonary artery flow, alerting the physician to possible errors in acquisition or analysis. If these analyses are performed routinely in patients without valve disease or cardiac shunts, internally consistent results will increase the diagnostic confidence of the interpreting physician when confronted with quantifying valve disease in a patient. This is particularly important for phase-contrast images, which may be more susceptible to error if technicians

are not careful to ensure perpendicular slices to the aorta and pulmonary artery and the correct maximum velocity encoding value is chosen. Caution should be taken in using the aortic phase contrast flow in patients with aortic stenosis and aortic sclerosis in whom the blood flow in the ascending aorta is nonlaminar and ejected at a high velocity. In these patients, it is often better to use the pulmonary artery flow when quantifying mitral regurgitation. Another potential error in measuring flows using phase contrast images is baseline phase offset errors, which can introduce inaccuracies in flow quantification. However, the use of phantom correction or automated baseline correction based on surrounding static tissue, which is now available in commercial software packages, has largely eliminated this potential error (28). An advantage of repeating the aortic and pulmonary artery phase-contrast sequences during a study is that it allows assessment for consistent results, particularly in patients with cardiac arrhythmias. Caution should be taken with the use of phase contrast in patients with cardiac arrhythmias, and acquiring the aortic and pulmonary artery phase-contrast sequences 2 or 3 times each decreases the likelihood of using erroneous data and can alert the technologist and the physician to spurious measurements.

Potential errors during segmentation of the ventricles can be introduced by not choosing the correct basal slice of the ventricles. Incorporating an extra basal slice or leaving one out can have a substantial effect on the stroke volume, thereby falsely increasing or decreasing the regurgitant volume. To minimize this potential error, some commercial software packages now give the option to use a long-axis slice to identify the bases of the left and right ventricle (Figure 6).

### STUDIES OF CMR ASSESSMENT OF MITRAL REGURGITATION

The majority of studies that have assessed CMR quantification of mitral regurgitation have compared CMR and echocardiography using quantitative techniques, and are listed in Table 3. Other studies have either used invasive angiography as a comparator (29), hemodynamic response of the left ventricle as a comparator (17,30,31), or no comparator at all (32). Historically, the initial technique used to assess mitral insufficiency was left ventriculography. Left ventriculography, an invasive technique, most commonly used a semiquantitative method dependent upon the amount and briskness of the appearance of contrast in the left atrium. Left

**TABLE 1** Methods for Quantifying Mitral Regurgitant Volume Using CMR

LVSV – PA flow
LVSV – aortic flow
LVSV – RVSV
Mitral inflow – aortic flow
CMR = cardiac magnetic resonance; LVSV = left ventricular stroke volume; PA = pulmonary artery; RVSV = right ventricular stroke volume.

ventriculography was eventually replaced by echocardiography as the first-line assessment of the severity of mitral regurgitation (33,34). Echocardiography developed several semiquantitative and quantitative parameters to assess mitral regurgitation. Standard cutoffs for mild, moderate, and severe mitral regurgitation were based primarily on comparison to left ventriculography and outcomes from retrospective studies (33). As mentioned in the previous text, the difficulty with echocardiography is the need to integrate numerous parameters of mitral regurgitation severity and the high intraobserver and interobserver variability of these techniques (15). In addition, the lack of a gold standard for which to compare, makes developing accurate parameters difficult.

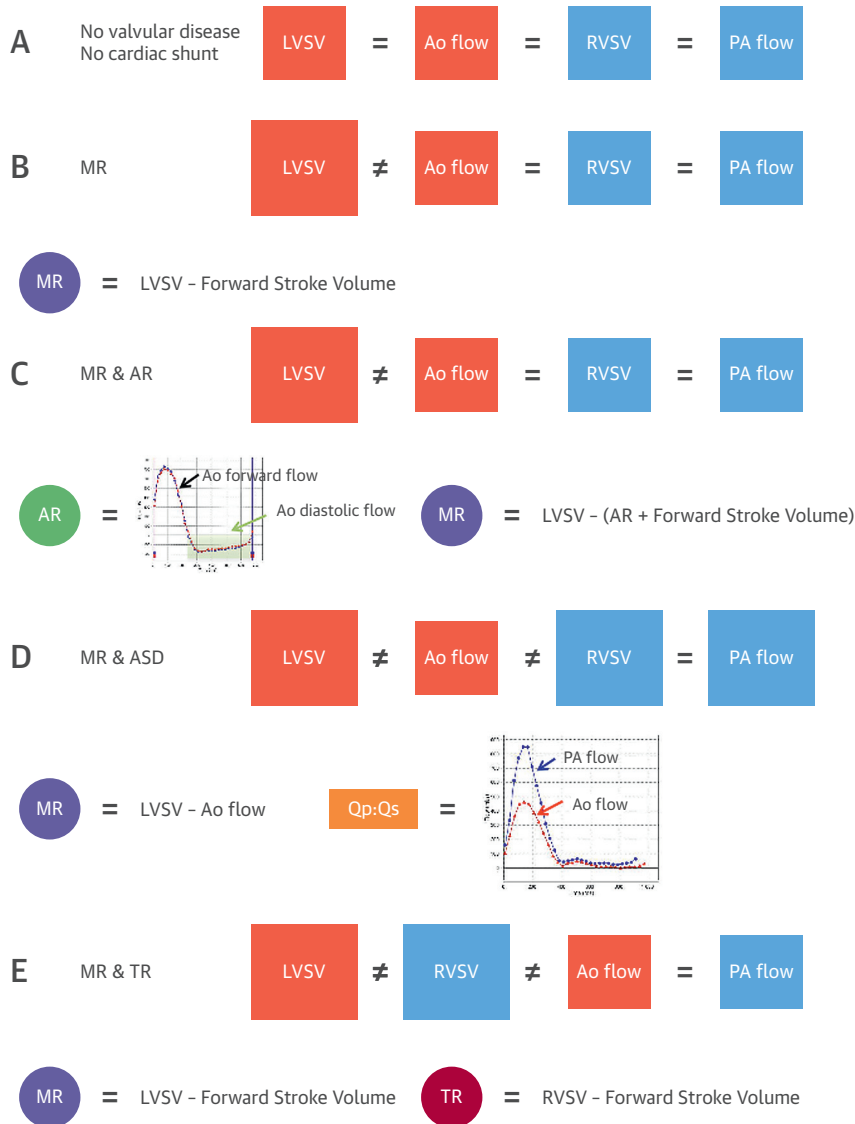
Most studies that have evaluated CMR have been small, single-center studies. The large majority of studies have used a similar technique to calculate mitral regurgitant volume as the difference between the LVSV and forward stroke volume, most commonly determined by aortic phase-contrast velocity-encoding images. This reflects the fact that CMR has a single reproducible method to quantify mitral insufficiency. The first study to assess CMR quantification of mitral regurgitation was Hundley et al. (29), who compared CMR with invasive angiography in 23 subjects and found a good correlation ( $r = 0.97$ ) for calculated mitral regurgitant volume (29). However, the large majority of comparative studies have been between CMR and echocardiography as discussed in the following text.

### CMR COMPARISON WITH 2-DIMENSIONAL ECHOCARDIOGRAPHY

Table 3 lists studies that have compared CMR and echocardiography using quantitative methods. It details the agreement between echocardiography and CMR as well as the agreement between echocardiography and CMR among studies that were considered to have severe mitral regurgitation. In general, there is a significant degree of discordance between CMR and echocardiography when quantifying mitral regurgitation. Five studies compared CMR-calculated



**FIGURE 5 Multiple Scenarios for Calculating Mitral Regurgitant Volume Using Quantification of Ventricular Stroke Volume and Phase Contrast Images on CMR**



**(A)** A patient with no valve disease or cardiac shunt; the ventricular stroke volumes and PA and Ao flows are similar. **(B)** A patient with mitral regurgitation. The LVSV is larger than the RVSV and PA/Ao flows, and the mitral regurgitant volume is the difference between the LVSV and the forward stroke volume. **(C)** A patient with mitral and aortic regurgitation. The LVSV is larger than the RVSV and PA/Ao flows. The aortic regurgitant volume is quantified directly from the diastolic flow of the Ao phase contrast. The mitral regurgitant volume is the difference between the LVSV and the aortic regurgitant volume and forward stroke volume. **(D)** A patient with mitral regurgitation and an atrial septal defect. The mitral regurgitant volume is the difference between the LVSV and Ao flow. The Qp:Qs is the PA flow:Ao flow. **(E)** A patient with mitral and tricuspid regurgitation. The mitral regurgitant volume is the difference between the LVSV and forward stroke volume, and the tricuspid regurgitant volume is the difference between the RVSV and the forward stroke volume. Ao = aorta; AR = aortic regurgitation; LVSV = left ventricular stroke volume; MR = mitral regurgitation; MRI = magnetic resonance imaging; PA = pulmonary artery; RVSV = right ventricular stroke volume; TR = tricuspid regurgitation.

mitral regurgitant volume to the recommended ASE-integrated method for assessing mitral regurgitation (16,35-38). Overall, there was poor to moderate agreement between the modalities (range of  $r = 0.40$

to 0.84), with an absolute agreement ranging from 36% to 70%. When considering agreement among patients diagnosed with severe mitral regurgitation by either modality, the agreement ranged between

**TABLE 2 Technical Considerations in Quantification of Mitral Regurgitation Using CMR**

General considerations	Routine comparison of LVSV, RVSV, aortic flow, and pulmonary artery flow in patients without valvular heart disease or cardiac shunts.
Stroke volumes	Routine segmentation of the left and right ventricles Check traces using cine of the short axis Careful selection of the basal left and right ventricular slice Use of analysis software that allows demarcation of the base of the ventricles on a long-axis image
Phase contrast	Perform at least 2 acquisitions of aortic flow and pulmonary artery flow to ensure consistent data; consider more acquisitions in patients with arrhythmia Ensure perpendicular slice selection Caution using flow measurements in patients with nonlaminar flow, such as aortic stenosis. Choose appropriate VENC

LVSV = left ventricular stroke volume; RVSV = right ventricular stroke volume; VENC = velocity encoding.

20% and 66%, with echocardiography generally diagnosing severe mitral regurgitation more frequently than CMR. Five studies compared 2-dimensional (2D) transthoracic echocardiography (TTE) flow convergence-derived and Doppler-derived regurgitant volumes with CMR regurgitant volume (16,38-41). In these studies, there was a moderate to good agreement (range of  $r = 0.60$  to  $0.92$ ) between CMR and echocardiography, with an absolute agreement ranging from 47% to 87%. When considering agreement among patients diagnosed with severe mitral regurgitation by either modality, the agreement worsened, with a range of 26% to 66%. Two studies reported 2D TEE-derived regurgitant volumes compared with CMR, and found a moderate absolute agreement between TEE and CMR (66% and 70%) with poor agreement among patients diagnosed with severe mitral regurgitation in the 1 study that reported this data (37,42). It must be noted that unlike TTE and CMR, TEE is a semi-invasive study often requiring sedation, while CMR and TTE are noninvasive techniques that does not require sedation.

In addition to accuracy, studies have reported the variability of measurement (reproducibility) for these techniques. Low variability, or excellent reproducibility, is important if a technique is to be accurate. Uretsky et al. (17) found excellent reproducibility of mitral regurgitation quantification using CMR in a retrospective study (intraclass Correlation: 0.99; 95% confidence interval: 0.95 to 0.99;  $p < 0.0001$ ; limits of agreement  $-9$  to  $17$  ml). In a prospective multicenter study, Uretsky et al. (16) reported excellent reproducibility of CMR that was superior to that of echocardiography (CMR: ICC: 0.9; echocardiography: 0.65) (16). Similarly, Lopez-Mattei et al. (37) found CMR to have a lower interobserver variability compared with TEE for regurgitant volume (CMR:  $0.3 \pm 8.5$  ml,

TTE:  $-4.7 \pm 18.0$  ml) and regurgitant fraction (CMR:  $0.1 \pm 7.3\%$ ; TEE:  $-5.5 \pm 15.0\%$ ) (37). Cawley et al. (39) reported low intraobserver variability with CMR ( $r = 0.96$ ; Bland-Altman limits of agreement  $-18$  to  $17$ ) with variable reproducibility for differing echocardiographic techniques (range of  $r = 0.85$  to  $0.97$ ).

Based on the available data, there appears to be significant discordance between 2D echocardiography and CMR. This discordance is highlighted among patients who are considered to have severe mitral regurgitation and who are likely to be referred for mitral valve surgery. In addition, the excellent reproducibility of CMR shows this technique to be reliable.

### CMR COMPARISON WITH 3D ECHOCARDIOGRAPHY

Investigators, noting the limitations of 2D echocardiography, have begun assessing 3D echocardiography using CMR as a reference standard. The majority of these studies exclusively studied patients with functional mitral regurgitation. The advantages of 3D echocardiography are less of a reliance on geometric assumptions when assessing left ventricular volumes and 3D visualization of the flow convergence, EROA, and Doppler color jet. However, investigators have noted that reliance on the characteristics of the Doppler jet using 3D still remains challenging and prone to subjective acquisition and interpretation error. Thus, some investigators using 3D TTE have employed automation software to alleviate some of this user subjectivity with mixed results (43,44). At this time, there has been no agreed upon method to assess mitral regurgitation using 3D echocardiography. Choi et al. (43) reported improvement in agreement and correlation between CMR and echocardiography when using 3D TTE PISA-derived regurgitant volume compared with 2D TTE PISA-derived regurgitant volume (67% to 88%). There was also an improved agreement among patients diagnosed with severe mitral regurgitation by either modality (49% to 79%). In this study, patients were more likely to be diagnosed with severe mitral regurgitation by CMR, although the use of 3D TTE did increase the number of patients called severe mitral regurgitation by echocardiography. Interestingly, the use of 3D TTE in this study did not improve the wide limits of agreement between echocardiography and CMR (2D TTE vs. CMR:  $-8.9$  to  $29.8$  ml; 3D TTE vs. CMR:  $-14.7$  to  $12.8$  ml). In contrast to the previously mentioned study, Thavendiranathan et al. (44) reported poor agreement between 3D TTE and CMR using the traditional PISA-derived regurgitant

volume based on a measurement of the peak PISA and an automated integrated PISA-based regurgitant volume, which integrates the PISA over all of systole. The investigators reported an improvement in correlation with CMR using the integrated PISA (peak PISA-regurgitant volume vs. CMR  $r = 0.84$ ; integrated PISA regurgitant volume vs. CMR  $r = 0.92$ ). However, on Bland-Altman analysis, there were wide limits of agreement between 3D techniques and CMR (peak PISA vs. CMR: 10 to  $-41$  ml, integrated PISA vs. CMR: 17.0 to 19.8 ml), which is reflected in the poor agreement among patients considered to be severe using either the peak PISA or the integrated PISA (22% vs. 40%). Of note, the author found that echocardiography was more likely to categorize patients as having severe mitral regurgitation than CMR.

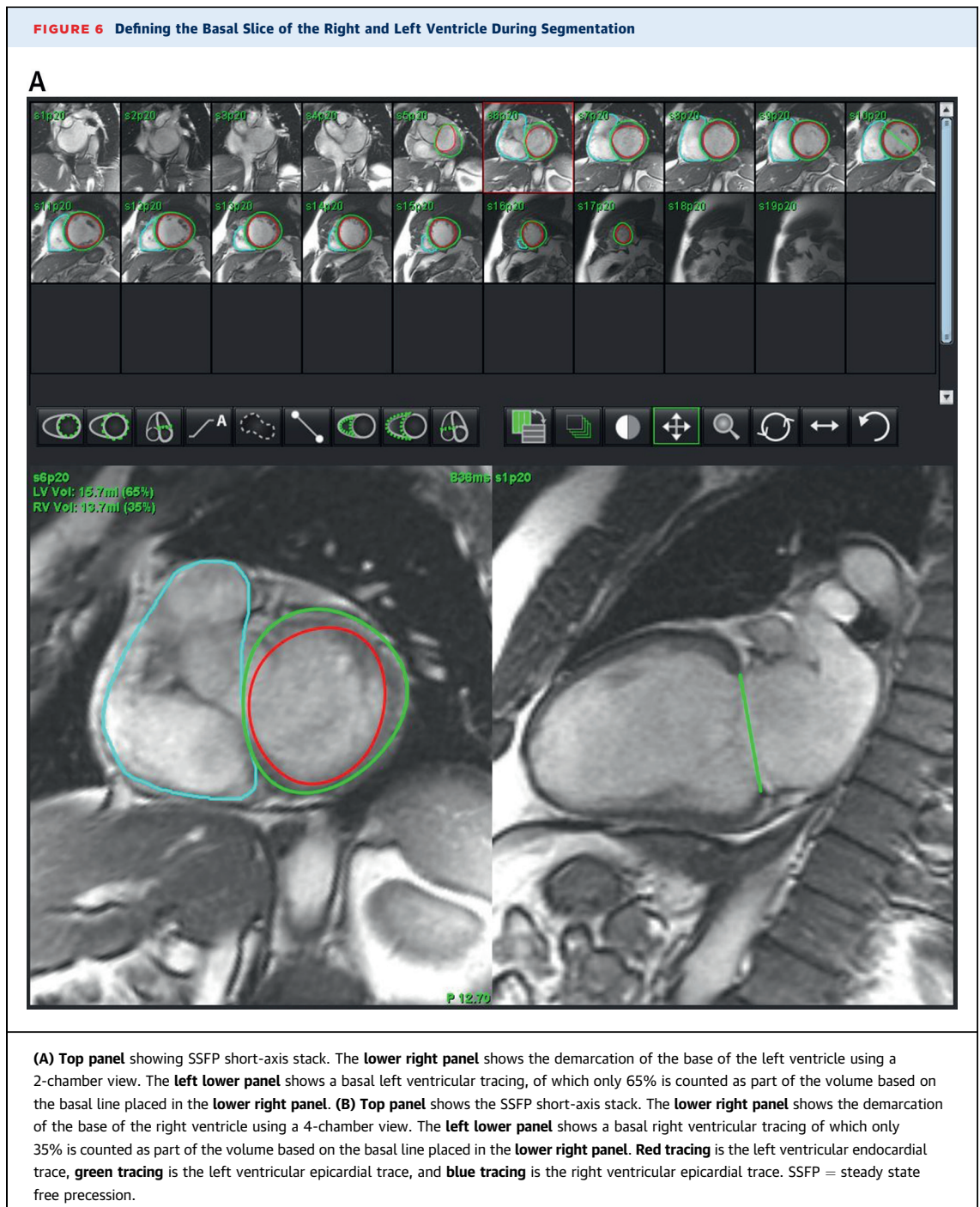
Shanks et al. (42) studied 30 patients and compared 2D and 3D TEE-derived regurgitant volumes using CMR as the reference standard. The authors reported an absolute agreement of 66% between 2D TEE and CMR, which improved to 97% when comparing 3D TEE with CMR. Bland-Altman analysis of comparison of 3D TEE and CMR regurgitant volume found a small mean difference of 2 ml, but with wide limits of agreement (95% limits of  $-18.6$  to 13.9 ml/beat). Heo et al. (45) compared 2D and 3D TTE with CMR and found an improved agreement among those with more severe mitral regurgitation when using 3D TTE with agreement in 80% of patients. Like prior reports, although the linear correlation between 3D TTE and CMR was good ( $r = 0.94$ ), there remained wide limits of agreement between the modalities ( $-14$  to 31 ml). Marsan et al. (46) reported an 82% absolute agreement between 3D TTE and CMR. A major limitation of this study was that it included only 1 patient with severe mitral regurgitation. In summary, overall 3D TTE had improved absolute agreement with CMR compared with 2D TTE. There still remains significant discordance between 3D echocardiography and CMR, particularly among patients diagnosed with severe mitral regurgitation. One constant among these studies is the wide limits of agreement between CMR and 2D TTE or 3D TTE, suggesting that the central and critical clinical question of severe or not severe mitral regurgitation remains problematic.

## STUDIES OF CMR USING A REFERENCE STANDARD

As noted in the previous text, a difficulty in studying the accuracy of an imaging modality to quantify mitral regurgitation is the lack of a gold standard. Thus, it is important to have a reference standard to

assess the accuracy of imaging techniques. Two approaches have been used to address this problem. The first approach is the use of a physiological reference standard of left ventricular volumes and its response to the volume overload of mitral regurgitation and removal of the volume overload with surgery (47). The second approach is the use of clinical outcomes to determine the value of quantitative parameters used by echocardiography and CMR. Two studies have taken the first approach (16,17). Uretsky et al. (17) studied 23 patients with lone mitral regurgitation and found a tight relationship between the mitral regurgitant volume and the size of the left ventricle, with greater amounts of regurgitant volume associated with greater degrees of left ventricular dilatation. This is based on the physiological response of the left ventricle to volume overload and the fact that more volume begets increased remodeling. In a prospective multicenter study, Uretsky et al. (16) compared CMR and echocardiography in the assessment of mitral regurgitation. Similar to prior studies, the authors reported significant discordance between CMR and echocardiography using both the ASE-integrated method and PISA-based regurgitant volume. This discordance was also seen in patients with severe mitral regurgitation by either modality, with an agreement between CMR and echocardiography of 22% and 26% using the ASE-integrated method and PISA-based regurgitant volume, respectively. This is of concern because these are the patients considered for mitral valve surgery. In this study, 38 patients underwent guideline-directed mitral valve surgery (Class I or IIa). The authors report that only 32% of these patients had severe mitral regurgitation by CMR. Of the 38 patients who underwent surgery, 26 were evaluated post-surgery to assess the degree of left ventricular remodeling. The authors found a tight correlation between the mitral regurgitant volume calculated using CMR and the degree of post-surgical reverse remodeling ( $r = 0.85$ ;  $p < 0.0001$ ). In patients in whom CMR indicated mild mitral regurgitation, there was little post-surgical reverse remodeling, and in patients with severe mitral regurgitation, there was a greater degree of remodeling. The authors found no correlation between PISA-derived regurgitant volume and post-surgical remodeling ( $r = 0.32$ ;  $p = 0.1$ ). This study suggests that mitral regurgitant volume by CMR is more accurate than echocardiography, and particularly highlights this in patients who underwent mitral valve surgery.

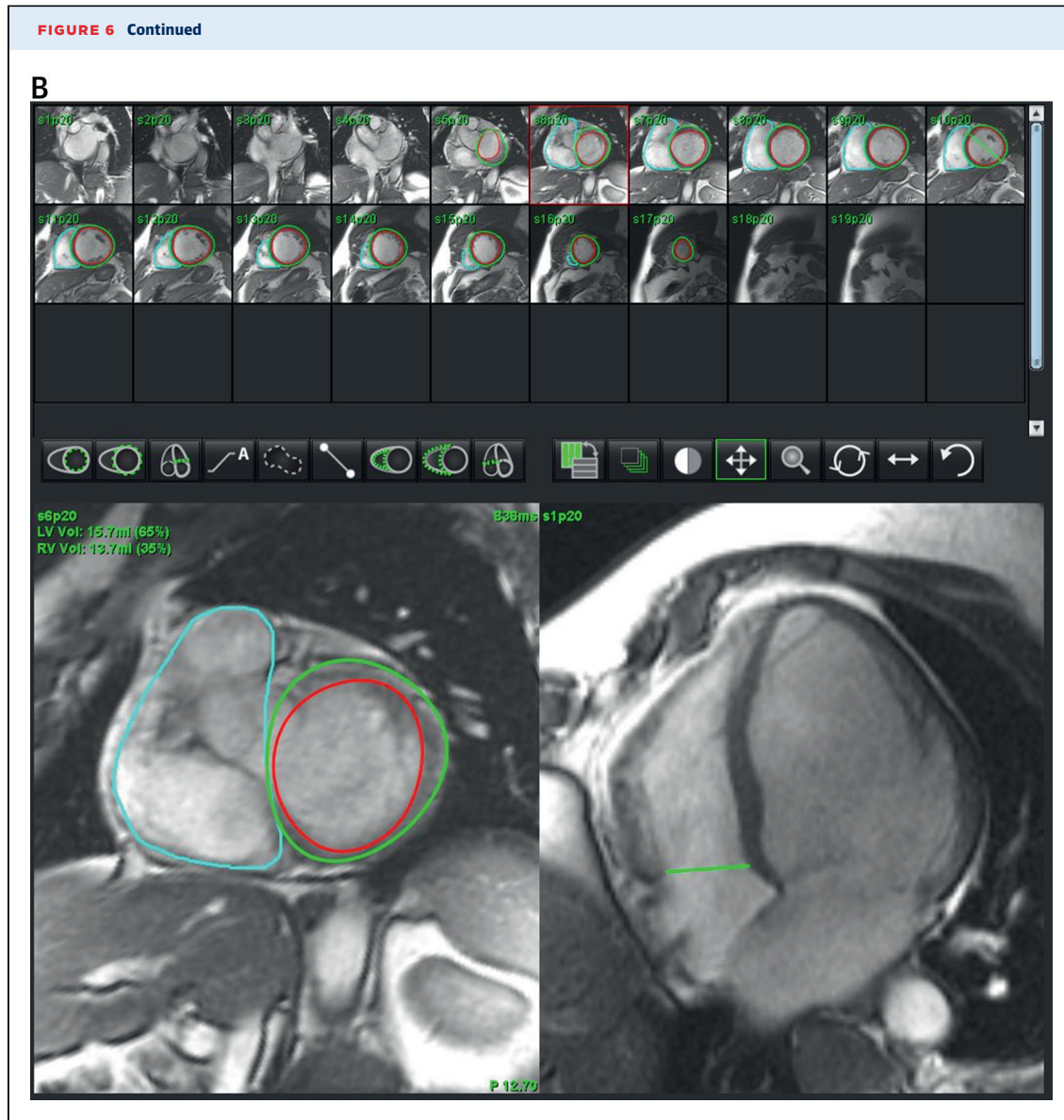
In a recent multicenter prospective study, Myerson et al. (48) studied 109 asymptomatic patients with moderate or severe mitral regurgitation on echocardiography who also had CMR scans. These patients



*Continued on the next page*

were followed up for up to 8 years with a mean follow-up duration of  $2.5 \pm 1.9$  years with the endpoint of developing symptoms or other indicators for surgery (excessive left ventricular dilatation, end-systolic dimension  $>40$  mm, or pulmonary hypertension with a repairable valve). A total of 32 patients in the study group underwent surgery: 7 with no clear indication for surgery, and 25 who developed a clear

indication for surgery. The authors report that regurgitant volume by CMR was the best predictor of which patients would develop an indication for surgery, with an area under the curve of 0.81 for a regurgitant volume of  $>55$  ml. Although regurgitant volume by CMR was able to differentiate those who would go on to surgery, echocardiographic parameters could not. An echocardiographic EROA of



0.40 cm<sup>2</sup> could not differentiate those patients who would develop an indication for surgery. Similar to the study by Uretsky et al. (16), the authors found that echocardiography was more likely to diagnose severe mitral regurgitation. The authors report that 28 patients who were diagnosed with severe mitral regurgitation by echocardiography had nonsevere mitral regurgitation by CMR, and none of those developed an indication for surgery. Among the 84 patients who did not have an indication for surgery, the mean echocardiographic regurgitant volume and EROA was in the severe range ( $74 \pm 74$  ml and  $0.58 \pm 0.75$  cm<sup>2</sup>, respectively), whereas the mean regurgitant volume by CMR was in the moderate range ( $39 \pm 20$  ml).

Among the patients who had an indication for surgery, both the echocardiographic indexes and the CMR regurgitant volume were in the severe range, again underscoring the ability of CMR to determine clinical outcomes, whereas echocardiography could not. In a third smaller, single-center study that included 22 asymptomatic patients with chronic mitral regurgitation and used the clinical outcomes of heart failure hospitalizations and an indication for surgery (40). In agreement with prior studies, the authors report significant discordance between echocardiography and CMR with an absolute agreement of 62% between the modalities and an even worse agreement of 29% among patients considered

**TABLE 3 Studies That Have Assessed the Use of CMR in Mitral Regurgitation With or Without a Comparator**

First Author (Ref. #)	Year	MR Type		Method	Comparator	CMR	Echo Integrated vs. CMR				Doppler or PISA RVol. vs. CMR RVol								
		N	Deg				Fn	r	Absolute Agreement	Agreement if Severe	CMR Severe	Echo Severe	r	Absolute Agreement	Agreement if Severe	CMR Severe	Echo Severe		
Fujita et al. (35)	1994	19	+	+	2D TTE Jet/LA area, CW pattern, E-wave vel.	MiPC-AoPC		12/28 (43%)	2/4 (50%)	2	4								
Hundley et al. (29)	1995	17			Invasive angiography	LVSV-AoPC													
Kizilbash et al. (41)	1998	22	+	+	2D TTE Doppler RVol	LVSV-AoPC						0.92	19/22 (86%)	3/5 (60%)	4	4			
Gelfand et al. (36)	2006	83			2D TTE Jet/LA area, PV flow	LVSV-AoPC	0.84	53/83 (70%)	8/19 (42%)	12	15								
Buck et al. (59)	2008	73	+	+	2D TTE PISA	MiPC-AoPC						0.63	40/73 (55%)*	0/1 (0%)*	1	0			
Ozdogan et al. (60)	2009	21			2D TTE	Signal void													
Marsan et al. (46)	2009	64	-	+	2D TTE PISA RVol	MiPC													
					3D TTE PISA RVol	MiPC				0.94	23/28 (82%)	1/1 (100%)*	1	1					
Uretsky et al. (17)	2010	23	+	+	N/A	LVSV-PAPC													
Myerson et al. (32)	2010	55			N/A	LVSV-AoPC													
Shanks et al. (42)	2010	30	+	+	2D TEE PISA RVol	LVSV-AoPC							20/30 (66%)						
					3D TEE PISA RVol								29/30 (97%)						
Hamada et al. (61)	2012	43	+	+	3D TEE	LVSV-AoPC													
Cawley et al. (39)	2013	26			2D TTE Doppler RVol and PISA RVol	LVSV-AoPC						0.64		5/12 (42%)*†	10	7			
Van De Heyning et al. (62)	2013	38			2D TTE Doppler RVol,	LVSV-AoPC							-0.1						
					2D TTE PISA RVol	LVSV-AoPC						0.45							
Thavendirathan et al. (44)	2013	30	-	+	3D TTE Peak PISA RVol	LVSV-AoPC						0.84	16/30 (53%)*	2/9 (22%)*	2	9			
					3D TTE Doppler integrated PISA	LVSV-AoPC				0.91	20/27 (74%)*	2/5 (40%)*	2	9					
Choi et al. (43)	2014	52	-	+	2D PISA R Vol.	LVSV-AoPC						0.84	35/52 (67%)*	12/28 (49%)*	28	12			
					3D TTE PISA RVol.	LVSV-AoPC				0.97	46/52 (88%)*	22/28 (79%)*	28	22					
Uretsky et al. (16)	2015	103	+	+	2D TTE Doppler RVol and PISA RVol	LVSV-FSVPC	0.4	37/103 (36%)	13/60 (22%)	15	58	0.6	48/103 (47%)	11/43 (26%)	11	38			
Sachdev et al. (38)	2016	58	+	-	2D TTE Doppler RVol and PISA RVol	LVSV-AoPC	0.81	23/50 (46%)	10/15 (66%)	11	14	0.79	30/47 (64%)	8/12 (66%)	10	10			
Lopez-Mattei et al. (37)	2016	70	+	+	2D TTE ASE and TEE Doppler RVol	LVSV-AoPC	0.44	34/70 (49%)	2/10 (20%)	2	8	0.59	40/60 (67%)*‡	2/7 (29%)*‡	4	4			
Aplin et al. (30)	2016	72	+	-	2D TTE PISA RVol.	LVSV-AoPC						0.8		18/29* (62%)	20	27			
Myerson et al. (48)	2016	109			N/A	LVSV-AoPC													
Harris et al. (40)	2017	22			2D TTE Doppler RVol and PISA RVol	LVSV-AoPC							11/22 (50%)	2/7 (29%)	4	5			
Polte et al. (31)	2017	40	+	-	N/A	LVSV-AoPC MiPC-AoPC													
Heo et al. (45)	2017	38	+	+	2D PISA RVol,	LVSV-AoPC						0.81		10/21 (48%)*†	18	10			
					2D Doppler RVol,	LVSV-AoPC					0.56		18/32 (56%)*†	19	32				
					3D TTE RVol	LVSV-AoPC				0.94		20/25 (80%)*†	20	25					

\*Estimated from figure. †Using regurgitant volume of 50 ml as severe. ‡Personal communication from the authors.

AoPC = aortic phase contrast; CW = continuous wave; Deg = degenerative; Fn = functional; FSVPC = forward stroke volume phase contrast; LA = left atrium; LVSV = left ventricular stroke volume; MiPC = mitral phase contrast; MR = mitral regurgitation; N/A = not applicable; PISA = proximal isovelocity surface area; RVol = regurgitant volume; TEE = transesophageal echocardiogram; TTE = transthoracic echocardiogram.

to be severe by either modality. In contrast to prior studies, the authors find that the only predictor of outcomes was regurgitant volume by echocardiography. One limitation to this study is the fact that only 2 of the 7 patients who underwent mitral valve surgery had severe mitral regurgitation by echocardiography, and 1 had mild mitral regurgitation. Thus, it is clear that imaging by echocardiography did not drive decision making in these patients with regard to referral for surgery.

Based on the studies discussed in the previous text, it appears that mitral regurgitant volume quantified by CMR is accurate based on the physiological response of the left ventricle and clinical outcomes. Although these data are encouraging, larger prospective and randomized studies are needed to assess the clinical value of CMR-based regurgitant volume in both symptomatic and asymptomatic patients. There are no randomized controlled trials assessing the prognostic value of any echocardiographic or CMR parameter for mitral regurgitant severity in patients undergoing mitral valve surgery. Despite this, echocardiography is the imaging modality of choice in the ACC/AHA guidelines based on primarily retrospective outcomes studies. In a prospective study by Enriquez-Sarano et al. (49), 495 patients were followed, of which 224 patients were treated medically. The authors found that incremental increases in EROA were associated with an increase in mortality and cardiac events in patients not undergoing surgery. Although this study was prospective, it was not randomized, and the reasons patients did not undergo surgery was not reported. Possibilities for patients not undergoing surgery might include nonsevere mitral regurgitation, high risk for surgery, and refusal of surgery, and may have introduced significant bias into this study. Thus, there remains a need for large prospective and randomized studies to assess the clinical value of imaging in predicting outcomes in those undergoing mitral valve surgery.

## FUTURE DIRECTIONS

Despite emerging evidence that CMR can quantify mitral regurgitation accurately, the benefit of mitral valve surgery based on the severity of mitral regurgitation by any modality has never been studied in a randomized controlled trial. Thus, there remains a significant lack of medical evidence for basing decisions on who would benefit from mitral valve surgery based on the severity of mitral regurgitation in both asymptomatic and symptomatic patients. This type of trial is especially

important given the increasing number of mitral valve surgeries performed in the United States, the significant costs associated with this surgery, the development of percutaneous mitral valves, and the emerging evidence of discordance between imaging modalities among patients considered for mitral valve surgery.

The timing of mitral valve surgery is still complicated by the lack of good markers of left ventricular deterioration in patients with mitral valve surgery. Many investigators advocate for watchful waiting, especially in patients who are asymptomatic or in patients in whom it is in doubt whether the symptoms are due to valve disease (50). Thus, the inability to predict the point in time when the left ventricular function will decline is troubling. Left ventricular ejection fraction and end-systolic dimension have been used as surrogates for determining left ventricular decline but have notable shortcomings (51). Some investigators have suggested that myocardial fibrosis may prove to be a helpful guide (52). CMR has 2 methods to determine left ventricular fibrosis, late gadolinium enhancement, and T<sub>1</sub> mapping. Late gadolinium enhancement can detect myocardial scar and/or fibrosis, its clinical significance has been well documented in the diagnosis and management in ischemic and nonischemic cardiomyopathy disease, and it has emerging application in hypertrophic cardiomyopathy (53,54). However, late gadolinium enhancement is not adept at detecting diffuse fibrosis. T<sub>1</sub> mapping is an emerging CMR technique that can detect diffuse fibrosis. When T<sub>1</sub> is acquired pre- and post-contrast, the extra cellular volume can be calculated, which is an indicator of the percentage of myocardium not made up of myocardial cells (55). There have been a few small studies that have reported on late gadolinium enhancement or T<sub>1</sub> mapping in patients with mitral regurgitation, but they have been limited by small sample size and lack of longitudinal follow-up (56-58).

## CONCLUSIONS

CMR has become an established noninvasive imaging modality to assess mitral regurgitation severity. Quantification of mitral regurgitant volume by CMR does not rely upon the characteristics of the regurgitant jet. Instead, the assessment of mitral regurgitation by CMR relies upon the difference between the left ventricular stroke volume and forward stroke volume, both of which are quantified using already established accurate and reproducible techniques. While studies have shown significant discordance

between CMR and echocardiography, data has accumulated showing that mitral regurgitant volume by CMR is more accurate. Despite this, much work remains to be done with regard to clinical decision making in referring patients for surgery based on regurgitant volume.

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**KEY WORDS** CMR, imaging, mitral regurgitation, mitral regurgitant volume

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 **APPENDIX** For supplemental videos, please see the online version of this paper.