Pivotal role of cardiac MRI in mitral valve regurgitation

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Abstract

Cardiac imaging is the cornerstone of defining the etiology, quantification and management of mitral regurgitation (MR). This continues to be even more so the case with emerging trans-catheter techniques to manage MR. Transthoracic echocardiography remains the first line imaging modality to assess MR but has limitations. Cardiac MRI(CMR) provides the advantages of quantitative non-visual estimation, 3D volumetric data, late gadolinium, T1 and extracellular volume measurements to comprehensively assess mitral valvular pathology, cardiac remodeling and the prognostic impact of therapies. This review describes the superiority, technical aspects and growing evidence behind CMR, and lays the roadmap for the future of CMR in MR.

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Pivotal role of cardiac MRI in mitral valve regurgitation Kushani Gajjar, Kartikeya Kashyap, Jayshiv Badlani, Ronald Williams, Robert W. W. Biederman

Abstract Cardiac imaging is the cornerstone of defining the etiology, quantification and management of mitral regurgitation (MR). This continues to be even more so the case with emerging trans-catheter techniques to manage MR. Transthoracic echocardiography remains the first line imaging modality to assess MR but has limitations. Cardiac MRI(CMR) provides the advantages of quantitative non-visual estimation, 3D volumetric data, late gadolinium, T1 and extracellular volume measurements to comprehensively assess mitral valvular pathology, cardiac remodeling and the prognostic impact of therapies. This review describes the superiority, technical aspects and growing evidence behind CMR, and lays the roadmap for the future of CMR in MR.

Key Words: Cardiac MRI, Mitral valve, Mitral regurgitation, CMR, MR

Introduction: Is CMR ready for Primetime?

Mitral regurgitation (MR) is the most common valvular heart disorder. (1) About 9% of the general population aged more than 75 years in the USA have MR. As the incidence of MR increases with age, the number of patients with MR who require intervention and inpatient care will only increase in the coming decades. (2) MR is generally divided into two categories: primary organic MR, which occurs as a result of an intrinsically abnormal mitral valve, and secondary or functional MR, which develops secondary to left ventricular (LV) dysfunction or annular dilatation prohibiting normal valve closure.(3,4) Differentiating between these phenotypes of severe MR by imaging modalities is critical to allow accurate diagnosis as well as guidance in choosing timing and type of intervention.(5)

Untreated severe MR is associated with poor outcomes due to the adverse consequences of long-standing volume overload on the left ventricle. It can cause LV volume overload, which may lead to progressive dilatation of the left ventricle and left atrium, heart failure, and pulmonary hypertension.(5) Echocardiography and CMR play a complementary role in the diagnosis and understanding the mechanism of MR. They also help define prognosis along with the optimal treatment strategies for MR. (6,7)

Decisions regarding surgical interventions, being mitral valve repair or replacement, rely on symptomatology as well as the regurgitation severity, LV ejection fraction (LVEF), and LV end-systolic diameter (LVESD).(8,9) The role of imaging is as follows: to identify the etiology of the MR; to quantify the severity of the regurgitation; to assess the response of the left ventricle to the volume overload; and to determine the feasibility of durable repair.(4-7)

Transthoracic echocardiography (TTE) remains the first line modality per ASE/ACC/AHA guidelines. The quantitative methods for assessment of MR severity via TTE involves the assessment of several independent data points as indicated in the ASE guidelines which includes, but is not limited to, flow convergence-based effective regurgitant orifice area (EROA) and regurgitant volume, pulse Doppler-based regurgitant volume, and the vena contracta.(4,10-13) Many assumptions underlie the assessment of MR by echocardiography and hence this assessment has several important limitations which arise from mitral regurgitation characteristics such as temporal change in orifice geometry, the possibility of multiple jets, the direction of the jet itself, and the ultrasound settings including angle dependence. (4, 10) In addition, significant inter-observer and intra-observer variability in the echocardiographic parameters of MR severity is a well-known limitation of this modality. (10-14) What may be the most important limitation of the echocardiographic assessment of MR is that there is no single reproducible parameter for severity of regurgitation, and in fact the assessment is reached by integrating multiple parameters which may be discordant from each other. It is as a result of these limitations that echocardiography often lacks accuracy as well as reproducibility in the assessment of MR. (4)

What can CMR provide?

Until the last decade, the majority of textbooks mostly decried the use of CMR for valvular pathology. Early adopters in this field however recognized the substantial attributes attendant to CMR based on its spatial resolution, inherent physics and mathematical capabilities and, chiefly, on its non-reliance on a pure visual assessment to formally quantify mitral regurgitation. CMR innately provides highly accurate and reproducible assessment of left and right atrial and ventricular size and function with superior endocardial definition and has become the 'gold standard' for evaluating cardiac chamber size. (10,15-17). It is then a natural extension to apply all of the considerations of an ideal chamber volumetric capability towards a valvular volumetric challenge. (Table I)

A comprehensive CMR study is able to quantitate both atrial and ventricular remodeling, which plays a crucial role in understanding both the severity as well as the mechanism of regurgitation. Quantitative parameters include regurgitant volume, regurgitant fraction, and regurgitant orifice area. CMR offers several important advantages in the assessment of MR. (4,7,10) This includes identifying the mechanism of MR, quantifying MR severity, and determining its consequences on cardiac remodeling. CMR can provide information about the mechanism of MR by identifying morphologic abnormalities of the MV apparatus (Figure 1, Figure 2). (18) Dedicated cine imaging on a CMR study can offer insights into pathology of mitral valve leaflets including the presence of prolapse or flail leaflets. (Figure 2, Figure 3a, Figure 3b). (19,20)

Two multicenter observational studies have clearly defined the role of CMR quantification of primary MR and its use to be a better predictor for mortality than echocardiography.(21,22) In one study, there was high disagreement between echocardiography and MRI derived regurgitation volumes, especially in patients with multiple or late systolic jets of MR.(22) These studies point to a multi-modality approach in predicting mortality, follow up and interventions in MR.

In secondary MR, CMR offers accurate assessment of LV dilation and function in addition to identification of myocardial and papillary muscle scar. (23,24) Additionally, late gadolinium enhancement in CMR in patients with MR can provide additional consolidating information about features such as myocardial infarct size as well as the significance of scarring of papillary muscles and mitral valve fibrosis. (25-27)

Imaging protocols and methodology for assessment of MR via CMR

The ASE/ACC/AHA guidelines for the assessment of native valvular regurgitation highlight the importance of evaluating not only the severity of the regurgitant but also the hemodynamic effects the valvular lesion has on the LV as well as the left atrium.(4,9,28) Evaluating LV function and structure via cine images and flow imaging via phase contrast imaging is the cornerstone of the CMR evaluation of MR.

Initial imaging protocols for evaluating MR should follow the Society of Cardiac Magnetic Resonance (SCMR) recommendations and start with standard cine images. Steady state free-precession (SSFP) images should be taken in standard views: in the four-chamber, two-chamber and three-chamber views.

To optimize visualization of the mitral valve apparatus, a contiguous stack of cines should be taken perpendicular to the mitral valve and transect the principal line of cooptation. These should be contiguous with zero gap, and a slice thickness of 5-8 mm should be used to maximize special resolution with a goal temporal resolution of under 50 milliseconds.

Using this protocol, CMR can view the entire mitral valve interface and cooptation of the anterior and posterior leaflets along all three scallop-interfaces- from the lateral interface near the appendage, to the medial interface.

Additionally, standard cine short-axis LV imaging should be performed to evaluate LV function, but should be extended to cover the mitral valve.

In addition to cine imaging of the LV, the CMR protocol in patients with MR should include flow imaging through the aortic valve using the standard phase-contrast, velocity encoded methods. The SCMR recommendations include standard parameters for flow imaging. (4,7,10,29)

Quantitative assessment and imaging protocols:

Standard volumetric assessment of LV function is done using SSFP imaging, which gives accurate measurements LV systolic and diastolic dimensions and volumes, stroke volume, and ejection fraction; these can be interpreted both as absolute and indexed and standardized based on body surface area (4,10,30,31). Having accurate, gold-standard measurements for these values is crucial; ACC/AHA guidelines ejection fraction and LV systolic dimension into the decision-making process for determining appropriateness and timing of mitral valve surgery. Left atrial and ventricular volumes are included in ASE recommendations in assessing MR. (4,28) The intra and inter-reader variability for calculating LV size and function is low for CMR, thus making it an excellent tool for long term patient follow-up(16,17).

There are many methods to assess the severity of mitral regurgitation via CMR. Most commonly, indirect methods are used to quantify mitral regurgitant volume utilizing 3D ventricular stroke volumes or phase-contrast velocity encoded mapping. (10) Other less semi-quantitative assessment include the use of signal void, regurgitant jet size and regurgitant orifice area measures using phase velocity encoded mapping. (7,10,32,33) Here we will discuss the most common method utilizing LVSV and forward flow to determine regurgitant volume. (Table II)

Left ventricular stroke volume (LVSV) can be quantified using volumetric data obtained from SSFP imaging. This "volumetric" stroke volume includes both forward stroke volume as well as regurgitant volume; in short, any volume of blood leaving the left ventricle during systole via any route.

The forward stroke volume can be obtained using flow data using phase velocity mapping the proximal aorta (or main pulmonary artery, assuming no shunt is present).

By subtracting out the forward stroke volume (from flow data), from the volumetric stroke volume, one can accurately derive the regurgitant volume. This calculation assumes no aortic regurgitation (AR) or cardiac shunt.

If there is significant AR, the equation can be modified to incorporate the AR volume: MR volume=LVSV by volumetric data- (AR by phase velocity mapping + Net Stroke volume through aorta by phase velocity mapping).

For reference, when no valve disease or shunts are present, the LVSV by volumetric data, right ventricular stroke volume (RVSV) by volumetric data, aortic flow, and pulmonary artery flow should all measure approximately the same.

In patients with mitral regurgitation, the LVSV includes not only forward flow but also mitral regurgitant volume, making it larger. The regurgitant volume can thus be obtained by taking the difference between that volumetric stroke volume and any of the other measures of forward stroke volume: RVSV (assuming no tricuspid or pulmonic regurgitation), aortic flow or pulmonary artery flow. (4,7,10,21) (Figure 4)

Garg et al suggest a comprehensive MR protocol should assess the mitral valve anatomy and function to define the cause of the MR, LV and right ventricular (RV) volumes and function, in addition to quantifying the MR. They observe that in those patients for whom high quality TTE images are able to be obtained which are adequate for the assessment of LV and RV function, an abbreviated quantification-based protocol can be used as opposed to the comprehensive protocol. Figure 5 demonstrates the protocol they suggest for imaging of MR via CMR.

The following values of regurgitant fraction and regurgitant volume to categorize MR have been proposed based on data from prognostic studies (Table III).(14,21,22)

CMR can also assess the impact of systolic variation on mitral regurgitation estimation. Uretsky et al determined a method to assess this systolic variation by dividing systole into 3 parts: early, mid, and late. The MR jets were categorized as holosystolic, early, or late based on the portions of systole the jet was visible. The aortic flow and left ventricular stroke volume (LVSV) acquired by CMR are then plotted against time. The instantaneous regurgitant rate is calculated for each third of systole as the difference between the LVSV and the aortic flow. They concluded that there is significant variation of the mitral

regurgitant rate even among patients with holosystolic MR jets and concluded that quantitative ways of assessing MR as suggested above via CMR effectively take into consideration this important confounding factor. A subsequent multicenter study determined that systolic variation is one of the factors that accounts for the discordance between echocardiographic and CMR assessment of MR, as the use of the color Doppler jet at a single point in time is the basis of many echocardiographic methods, and hence cannot factor in systolic variation.(34,35) *Qualitative assessment of mitral valve anatomy and MR:* When assessing mitral valve anatomy, the anterior and posterior leaflets, the annulus, the subvalvular apparatus (papillary muscles), and LV contractility including any regional wall motion abnormalities, are carefully visually assessed and their pathophysiology is commented upon. Abnormal leaflet morphology includes thickening, calcification, redundancy, perforation, vegetations, other masses and clefts. These abnormalities should be described in detail (diffuse versus focal, the size and the leaflet location). Such observations have far reaching clinical implications in areas such as mitral regurgitation. CMR with its superior spatial resolution as compared to echocardiography has developed an in-vivo contemporary model of human anatomy and defines the cypress tree like pattern of the papillary muscle adding a new dimension to our understanding of mitral valve apparatus. This understanding can help guide therapy decisions, with restoration of local heart geometry and reconstruction of appropriate tethering length potentially helping surgeons cure MR. (36)

Abnormal subvalvular morphology can involve chordal rupture, thickening, fusion, very large vegetations and masses, which should similarly be described in detail by size and location. Abnormal annular morphology comprises dilatation and/or calcification (seen as signal loss).

The long-axis stack is best for making the visual assessment of the mitral valve leaflets. Mitral annular disjunction is defined by the displacement of atrial junction and the mitral valve leaflet at end systole in long-axis cines and is considered significant if the distance is [?]1.0mm. Leaflet motion can be described using Carpentier's classification: type I (normal leaflet motion); type II (excessive leaflet motion); and type III (restricted leaflet motion), subcategorized as type IIIa (restricted during both systole and diastole) and type IIIb (restricted only during systole). (Figure 6) The etiology should be consistent with the overarching diagnosis. (4,7) Our lab has described how tenting area, annulus and posterior leaflet length are possible determinants of MR severity. Additionally, there is single center data from our lab demonstrating that even visual assessment of cardiac regurgitant lesions is reliable, accurate and reproducible when compared to formal quantitative analysis via CMR.(37,38)

Role of 4D CMR:

With the development of 4D-flow CMR, it's implication on the assessment of MR must also be considered. 4D-flow CMR techniques offer further improvements in the assessment of MR and are entering clinical practice. (7,39) Advantages of MR quantification with 4D-flow CMR includes a multiplanar and multi-directional retrospective analysis that allows valve tracking and reliable intra and interobserver agreement of MR.(7,40) Direct quantification of the regurgitant jet is particularly useful in pathologies involving multiple valves. A systematic review of seven studies with 4D flow-derived methods for MR quantification showed accuracy and reliability in direct measurement when compared to standard CMR techniques and establishes a complementary role with echocardiography. (41) In one retrospective study, as compared to multiplanar standard techniques for CMR, 4D flow methods had excellent correlation with high inter and intra-observer reliability. (42)

Impact of late gadolinium enhancement in assessment of MR:

Late gadolinium enhancement (LGE) can detect myocardial scar and/or fibrosis, which has a significant impact in understanding the pathophysiology of mitral regurgitation.

LGE has been reported on CMR images in patients with primary MR, especially in those with mitral valve prolapse.(20,43) Left ventricular remodeling seems to be associated with the presence of delayed enhancement on CMR in primary MR.(43) In addition, in patients with primary MR, LGE of papillary muscles is associated with complex ventricular arrhythmias.(44) Persistent volume overload from MR results in impaired LV function and the presence of diffuse myocardial fibrosis.(45) Mitral annulus disjunction is an abnormal atrial

displacement of the hinge point of the mitral valve away from the ventricular myocardium as noted above; it has been associated with mitral valve prolapse and sudden cardiac death owing to ventricular arrhythmias. (46,47)

In severe secondary MR in the setting of ischemic cardiomyopathy, the presence of severe scarring in the region of the posterior papillary muscle, as detected by preoperative CMR, can render these patients unsuitable for mitral annuloplasty.(48) Moreover, the extent of myocardial scarring is also informative about the progression of ischemic MR.(27) In one large prospective trial, presence of both significant ischemic MR (mitral regurgitation fraction [?]35%) and large myocardial infarct size as determined by LGE ([?]30% of LV mass) carries a very high risk for all-cause mortality and/or heart transplant, despite surgical mitral valve intervention. On the other hand, patients with significant ischemic MR (mitral regurgitant fraction [?]35%) and low myocardial infarct size (<15% of LV mass) had survival benefit after surgical intervention. Taken together, these results show that CMR is an important noninvasive imaging modality, not only for risk stratification but also for the individualization of treatment decisions for these complex patients.(26) Mitral valve enhancement is present in a large number of post myocardial infarction (MI) patients but rarely in non-post-MI patients in one observational study. Post-MI patients with mitral valve enhancement are far more likely to have MR. (25)

CMR is the future of imaging in MR: comparison of CMR with TTE and its role in prognostication and procedural planning

A factor that significantly impacts the decision of intervening upon mitral valve in the setting of MR is its impact on left ventricular deterioration and the lack of reliable and reproducible markers to assess the same. Many clinicians opt for the strategy of watchful waiting especially in those patients who have no symptoms, or in whom other pathophysiology may be contributing to symptoms in addition to mitral regurgitation. (49) However, as noted in the ACC/AHA guidelines, there is concern that "mitral regurgitation begets mitral regurgitation". The notion is that the initial level of MR causes LV dilatation, which perpetuates a cycle of ever-increasing LV volumes and MR by causing stress on the mitral apparatus, which in turn leads to more severe MR and further LV dilation. This perpetual volume overload leads to irreversible LV dysfunction and thereby poor long term prognosis.(9) Patients with severe MR who develop an EF [?]60% or LVESD [?]40 have already developed LV systolic dysfunction.(50-53) There is data to show that for LV function and size to normalize after mitral valve repair, the left ventricular ejection fraction (LVEF) should be >64% and LVESD <37mm.(50) LVEF and LVESD have been used as surrogates for determining left ventricular decline- however there is concern that in using them alone the window of opportunity for LV recovery may have been crossed by the time the mitral valve is intervened upon.(54) Myocardial fibrosis may prove to be a helpful guide here.(55) CMR has two techniques to detect left ventricular fibrosis which include late gadolinium enhancement (LGE) and parametric T1 mapping. LGE can detect myocardial fibrosis as noted above (Figure 7a, Figure 7b, Figure 7c). T1 mapping is better at detecting diffuse fibrosis than LGE. When T1 is acquired pre- and post-contrast, the myocardial extra cellular volume can be calculated, which is a surrogate for extracellular matrix and diffuse fibrosis. (56)

Interestingly, in a subgroup of patients undergoing mitral valve surgery, MRI-based severity grading had superior prognostic value over echocardiography in predicting the degree of postsurgical LV remodeling. Also, recent large-scale studies found MRI-derived regurgitant volume to be a better predictor of referral for surgery and all-cause mortality than echocardiographic parameters. (21,22) Myerson et al, demonstrated that quantifying MR with CMR showed a strong association with the future need for surgery over the subsequent 5 years. They studied the impact of regurgitant volumes and left ventricular size on surgery free survival. The study shows high discriminative power with cut off limits of 55ml of regurgitant volume and 40% of regurgitation fraction in predicting survival. While the study was limited by small sample size, it provided important data on the impact of regurgitant volume of MR as measured by CMR as a variable that can be used to determine need for surgery. (21) (Figure 8)

Uretsky et al, in a prospective multicenter trial demonstrated that agreement between MRI and echocardiographic estimates of MR severity was modest in the overall cohort, and there was a poorer correlation in

the subset of patients sent for mitral valve surgery. There was a strong correlation between post-surgical LV remodeling and MR severity as assessed by MRI, and no correlation between post-surgical LV remodeling and MR severity as assessed by echocardiography. (14)

In the seminal paper on the role of CMR in MR, Urestky et al describe significant discordance in quantification between CMR and echocardiography using the ASE integrated method for assessment of MR. There was low to moderate concordance between the two modalities, with a r value of 36%-70%. Quantification of severe MR by either modalities had a r value of 20-66% with TTE more frequently diagnosing severe MR.(10) These limits of agreement, when placed in a fuller socio-economic context, suggest a sobering commentary on the state-of-the-art contemporary echocardiographic MR assessment.

Penicka et al in a prospective observational study demonstrated that CMR derived assessment of primary MR can better identify patients with severe MR and adverse outcomes than echo derived integrative approach. The CMR derived regurgitant volume showed the largest area under the curve to predict mortality or its combination with the development of indication for mitral valve surgery.

CMR can also play a valuable role in the assessment of cardiac reverse remodeling and the impact of that on MR post procedures such as pulmonary vein isolation for atrial fibrillation and transcatheter aortic valve replacement for aortic stenosis. For example, in those with durable maintenance of normal sinus rhythm, cardiac reverse remodeling demonstrated by 3D CMR occurs and is matched by marked improvements in MR and mitral apparatus, likely contributing to continued maintenance of sinus rhythm.(57) Meta-analysis of post TAVR patients has found that there is strong association between moderate to severe MR and 1 year mortality after TAVR.(58) A study from our lab also showed that post aortic valve replacement in 24 severe AS patients who were followed by CMR for 4 years, there was stabilization or reduction of MR in 80% of the patients which correlated to changes in LV mass and LV EDVI and LVEF post AVR which was in conjunction with improvement in clinical sequelae. (59)

Additionally, there have been recent advances in mitral percutaneous repair techniques for high surgical risk patients with use of transcatheter mitral valve systems including Mitra Clip (Abbott) and Pascal (Edwards Lifesciences) currently used mostly for primary MR. The quantification of MR post MitraClip can be challenging due to limited visualization, acoustic shadowing and multiple complex eccentric jets secondary to a double orifice mitral valve. In two small studies post-MitraClip, CMR had excellent reproducibility and lower interobserver variability in comparison with TTE. Cine-CMR is useful for the assessment of prosthetic mitral valve-associated MR, which manifests concordant quantitative and qualitative changes in size and density of inter-voxel dephasing. It provides an accurate non-invasive means of screening for TEE-evidenced severe MR (60) In one of the these studies, clinical benefit and LV remodeling had good correlation with CMR in post-procedural follow up.(61,62) This signifies an emerging role of CMR in clinical follow up of this subgroup of patients.

The use of MitraClip for functional MR is bound to expand with the recent CO-APT and MITRA-FR trials. There were key differences in outcomes of these trials related to the presence of LV remodeling and the presence of disproportionate versus proportionate MR. CMR is positioned to play a unique role for identifying the right patient at the right time for mitral valve interventions given its strengths as we described above. In a recent study by Cavalcante et al quantification of functional mitral regurgitation along with myocardial infarction size using CMR, CMR was a powerful predictor of adverse outcomes.(26) This further underscores the importance of the interplay between LV remodeling, myocardial infarct size (MIS), and volume overload in functional MR where CMR has a distinct advantage over TTE and will play an important role in determining candidacy in the growing field of transcatheter MV therapies in the future.

In summary, CMR has proven to be the more reliable imaging modality in the qualitative assessment of MR as compared to echocardiography. It also has important advantages in terms being able to better define the etiology as well as more accurately prognosticate the impact of procedural interventions on MR. With tools such as LGE enhancement as well as T1 mapping, it accurately detects scar and the impact of it not only on MR but also on underlying cardiomyopathy. As noted extensively in our review, it has

repeatedly proven to accurate predict the appropriate time as well as impact of surgical intervention of MR on the left ventricle and long-term outcomes. The role of CMR in MR has important implications as the cardiovascular community embarks on more sophisticated surgical and non-surgical approaches for which accurate determination of MR is naturally, critical. CMR overcomes most of the current limitations of TTE including inter-observer variability, over-estimation of MR and inability to predict the impact of intervention of post-surgical outcomes. Hence, we conclude that CMR is the future of the imaging assessment of mitral regurgitation.

References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005-11.

2. Andell P, Li X, Martinsson A et al. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. Heart 2017;103:1696-1703.

3. Levine RA, Hagege AA, Judge DP et al. Mitral valve disease–morphology and mechanisms. Nat Rev Cardiol 2015;12:689-710.

4. Zoghbi WA, Adams D, Bonow RO et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303-371.

5. El Sabbagh A, Reddy YNV, Nishimura RA. Mitral Valve Regurgitation in the Contemporary Era: Insights Into Diagnosis, Management, and Future Directions. JACC Cardiovasc Imaging 2018;11:628-643.

6. Baumgartner H, Falk V, Bax JJ et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-2791.

7. Garg P, Swift AJ, Zhong L et al. Assessment of mitral valve regurgitation by cardiovascular magnetic resonance imaging. Nat Rev Cardiol 2020;17:298-312.

8. Blanken CPS, Farag ES, Boekholdt SM et al. Advanced cardiac MRI techniques for evaluation of left-sided valvular heart disease. J Magn Reson Imaging 2018;48:318-329.

9. Nishimura RA, Otto CM, Bonow RO et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159-e1195.

10. Uretsky S, Argulian E, Narula J, Wolff SD. Use of Cardiac Magnetic Resonance Imaging in Assessing Mitral Regurgitation: Current Evidence. J Am Coll Cardiol 2018;71:547-563.

11. Thomas N, Unsworth B, Ferenczi EA, Davies JE, Mayet J, Francis DP. Intraobserver variability in grading severity of repeated identical cases of mitral regurgitation. Am Heart J 2008;156:1089-94.

12. Biner S, Rafique A, Rafii F et al. Reproducibility of proximal isovelocity surface area, vena contracta, and regurgitant jet area for assessment of mitral regurgitation severity. JACC Cardiovasc Imaging 2010;3:235-43.

13. Grayburn PA, Bhella P. Grading severity of mitral regurgitation by echocardiography: science or art? JACC Cardiovasc Imaging 2010;3:244-6.

14. Uretsky S, Gillam L, Lang R et al. Discordance between echocardiography and MRI in the assessment of mitral regurgitation severity: a prospective multicenter trial. J Am Coll Cardiol 2015;65:1078-88.

15. Grothues F, Moon JC, Bellenger NG, Smith GS, Klein HU, Pennell DJ. Interstudy reproducibility of right ventricular volumes, function, and mass with cardiovascular magnetic resonance. Am Heart J 2004;147:218-23.

16. Bellenger NG, Burgess MI, Ray SG et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J 2000;21:1387-96.

17. Grothues F, Smith GC, Moon JC et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol 2002;90:29-34.

18. Buchner S, Poschenrieder F, Hamer OW et al. Direct visualization of regurgitant orifice by CMR reveals differential asymmetry according to etiology of mitral regurgitation. JACC Cardiovasc Imaging 2011;4:1088-96.

19. Gabriel RS, Kerr AJ, Raffel OC, Stewart RA, Cowan BR, Occleshaw CJ. Mapping of mitral regurgitant defects by cardiovascular magnetic resonance in moderate or severe mitral regurgitation secondary to mitral valve prolapse. J Cardiovasc Magn Reson 2008;10:16.

20. Han Y, Peters DC, Salton CJ et al. Cardiovascular magnetic resonance characterization of mitral valve prolapse. JACC Cardiovasc Imaging 2008;1:294-303.

21. Myerson SG, d'Arcy J, Christiansen JP et al. Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantification. Circulation 2016;133:2287-96.

22. Penicka M, Vecera J, Mirica DC, Kotrc M, Kockova R, Van Camp G. Prognostic Implications of Magnetic Resonance-Derived Quantification in Asymptomatic Patients With Organic Mitral Regurgitation: Comparison With Doppler Echocardiography-Derived Integrative Approach. Circulation 2018;137:1349-1360.

23. Chinitz JS, Chen D, Goyal P et al. Mitral apparatus assessment by delayed enhancement CMR: relative impact of infarct distribution on mitral regurgitation. JACC Cardiovasc Imaging 2013;6:220-34.

24. Srichai MB, Grimm RA, Stillman AE et al. Ischemic mitral regurgitation: impact of the left ventricle and mitral valve in patients with left ventricular systolic dysfunction. Ann Thorac Surg 2005;80:170-8.

25. Bogabathina H, Doyle M, Williams R, Yamrozik J, Vido D, Biederman RW. Is there an alternative explanation to post-myocardial infarction emergence of mitral regurgitation? A CMR-LGE observational study. J Heart Valve Dis 2013;22:669-74.

26. Cavalcante JL, Kusunose K, Obuchowski NA et al. Prognostic Impact of Ischemic Mitral Regurgitation Severity and Myocardial Infarct Quantification by Cardiovascular Magnetic Resonance. JACC Cardiovasc Imaging 2019.

27. Kwon DH, Kusunose K, Obuchowski NA et al. Predictors and Prognostic Impact of Progressive Ischemic Mitral Regurgitation in Patients With Advanced Ischemic Cardiomyopathy: A Multimodality Study. Circ Cardiovasc Imaging 2016;9.

28. Nishimura RA, Otto CM, Bonow RO et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-643.

29. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. J Cardiovasc Magn Reson 2020;22:17.

30. Cain PA, Ahl R, Hedstrom E et al. Age and gender specific normal values of left ventricular mass, volume and function for gradient echo magnetic resonance imaging: a cross sectional study. BMC Med Imaging 2009;9:2.

31. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER et al. Normal values for cardiovascular magnetic resonance in adults and children. J Cardiovasc Magn Reson 2015;17:29.

32. Thavendiranathan P, Phelan D, Thomas JD, Flamm SD, Marwick TH. Quantitative assessment of mitral regurgitation: validation of new methods. J Am Coll Cardiol 2012;60:1470-83.

33. Krombach GA, Kuhl H, Bucker A et al. Cine MR imaging of heart valve dysfunction with segmented true fast imaging with steady state free precession. J Magn Reson Imaging 2004;19:59-67.

34. Uretsky S, Chaudhry FA, Gillam L et al. A novel technique to quantify the instantaneous mitral regurgitant rate. J Cardiovasc Magn Reson 2013;15:74.

35. Uretsky S, Aldaia L, Marcoff L et al. The Effect of Systolic Variation of Mitral Regurgitation on Discordance Between Noninvasive Imaging Modalities. JACC Cardiovasc Imaging 2019;12:2431-2442.

36. Khan MS, Biederman R. Dynamic cardiac anatomy: the "cypress tree" papillary muscle root. J Cardiovasc Thorac Res 2018;10:138-143.

37. Reddy ST, Shah M, Doyle M et al. Evaluation of cardiac valvular regurgitant lesions by cardiac MRI sequences: comparison of a four-valve semi-quantitative versus quantitative approach. J Heart Valve Dis 2013;22:491-9.

38. Fernandes AM, Rathi V, Biederman RW et al. Cardiovascular magnetic resonance imaging-derived mitral valve geometry in determining mitral regurgitation severity. Arq Bras Cardiol 2013;100:571-8.

39. Dyverfeldt P, Bissell M, Barker AJ et al. 4D flow cardiovascular magnetic resonance consensus statement. J Cardiovasc Magn Reson 2015;17:72.

40. Roes SD, Hammer S, van der Geest RJ et al. Flow assessment through four heart valves simultaneously using 3-dimensional 3-directional velocity-encoded magnetic resonance imaging with retrospective valve tracking in healthy volunteers and patients with valvular regurgitation. Invest Radiol 2009;44:669-75.

41. Fidock B, Barker N, Balasubramanian N et al. A Systematic Review of 4D-Flow MRI Derived Mitral Regurgitation Quantification Methods. Front Cardiovasc Med 2019;6:103.

42. Feneis JF, Kyubwa E, Atianzar K et al. 4D flow MRI quantification of mitral and tricuspid regurgitation: Reproducibility and consistency relative to conventional MRI. J Magn Reson Imaging 2018;48:1147-1158.

43. Van De Heyning CM, Magne J, Pierard LA et al. Late gadolinium enhancement CMR in primary mitral regurgitation. Eur J Clin Invest 2014;44:840-7.

44. Kitkungvan D, Nabi F, Kim RJ et al. Myocardial Fibrosis in Patients With Primary Mitral Regurgitation With and Without Prolapse. J Am Coll Cardiol 2018;72:823-834.

45. Edwards NC, Moody WE, Yuan M et al. Quantification of left ventricular interstitial fibrosis in asymptomatic chronic primary degenerative mitral regurgitation. Circ Cardiovasc Imaging 2014;7:946-53.

46. Perazzolo Marra M, Basso C, De Lazzari M et al. Morphofunctional Abnormalities of Mitral Annulus and Arrhythmic Mitral Valve Prolapse. Circ Cardiovasc Imaging 2016;9:e005030.

47. Dejgaard LA, Skjolsvik ET, Lie OH et al. The Mitral Annulus Disjunction Arrhythmic Syndrome. J Am Coll Cardiol 2018;72:1600-1609.

48. Flynn M, Curtin R, Nowicki ER et al. Regional wall motion abnormalities and scarring in severe functional ischemic mitral regurgitation: A pilot cardiovascular magnetic resonance imaging study. J Thorac Cardiovasc Surg 2009;137:1063-70 e2.

49. Gillam LD, Schwartz A. Primum non nocere: the case for watchful waiting in asymptomatic "severe" degenerative mitral regurgitation. Circulation 2010;121:813-21; discussion 821.

50. Tribouilloy C, Rusinaru D, Szymanski C et al. Predicting left ventricular dysfunction after valve repair for mitral regurgitation due to leaflet prolapse: additive value of left ventricular end-systolic dimension to ejection fraction. Eur J Echocardiogr 2011;12:702-10.

51. Quintana E, Suri RM, Thalji NM et al. Left ventricular dysfunction after mitral valve repair–the fallacy of "normal" preoperative myocardial function. J Thorac Cardiovasc Surg 2014;148:2752-60.

52. Enriquez-Sarano M, Suri RM, Clavel MA et al. Is there an outcome penalty linked to guideline-based indications for valvular surgery? Early and long-term analysis of patients with organic mitral regurgitation. J Thorac Cardiovasc Surg 2015;150:50-8.

53. Suri RM, Schaff HV, Dearani JA et al. Determinants of early decline in ejection fraction after surgical correction of mitral regurgitation. J Thorac Cardiovasc Surg 2008;136:442-7.

54. Matsumura T, Ohtaki E, Tanaka K et al. Echocardiographic prediction of left ventricular dysfunction after mitral valve repair for mitral regurgitation as an indicator to decide the optimal timing of repair. J Am Coll Cardiol 2003;42:458-63.

55. Uretsky S, Gillam LD. Myocardial fibrosis in asymptomatic degenerative mitral regurgitation: what does T1 mapping tell us? Circ Cardiovasc Imaging 2014;7:860-2.

56. Wong TC, Piehler KM, Kang IA et al. Myocardial extracellular volume fraction quantified by cardiovascular magnetic resonance is increased in diabetes and associated with mortality and incident heart failure admission. Eur Heart J 2014;35:657-64.

57. Reddy ST, Belden W, Doyle M et al. Mitral regurgitation recovery and atrial reverse remodeling following pulmonary vein isolation procedure in patients with atrial fibrillation: a clinical observation proof-of-concept cardiac MRI study. J Interv Card Electrophysiol 2013;37:307-15.

58. Chakravarty T, Van Belle E, Jilaihawi H et al. Meta-analysis of the impact of mitral regurgitation on outcomes after transcatheter aortic valve implantation. Am J Cardiol 2015;115:942-9.

59. Biederman RW, Magovern JA, Grant SB et al. LV reverse remodeling imparted by aortic valve replacement for severe aortic stenosis; is it durable? A cardiovascular MRI study sponsored by the American Heart Association. J Cardiothorac Surg 2011;6:53.

60. Simprini LA, Afroz A, Cooper MA et al. Routine cine-CMR for prosthesis-associated mitral regurgitation: a multicenter comparison to echocardiography. J Heart Valve Dis 2014;23:575-82.

61. Krumm P, Zuern CS, Wurster TH et al. Cardiac magnetic resonance imaging in patients undergoing percutaneous mitral valve repair with the MitraClip system. Clin Res Cardiol 2014;103:397-404.

62. Hamilton-Craig C, Strugnell W, Gaikwad N et al. Quantitation of mitral regurgitation after percutaneous MitraClip repair: comparison of Doppler echocardiography and cardiac magnetic resonance imaging. Ann Cardiothorac Surg 2015;4:341-51.

Figure Legends:

Figure 1: Steady state free precession sequence (SSFP) demonstrating 3 chamber view with central dephasing jet of MR between the A2-P2 scallops of the mitral valve in one of our patients. MR: mitral regurgitation, LA: left atrium, RV: right ventricle, LV: left ventricle, LVOT: left ventricle outflow tract, AO: aorta

Figure 2: Steady state free precession sequence (SSFP) from our lab demonstrating 3 chamber view with anteriorly directed dephasing jet of MR with prolapse of the posterior mitral leaflet. MR: mitral regurgitation, LA: left atrium, RV: right ventricle, LV: left ventricle, LVOT: left ventricle outflow tract, AO: aorta

Figure 3a: Steady state free precession sequence (SSFP) from our lab demonstrating 3 chamber view with flail posterior mitral valve leaflet with eccentric jet of mitral regurgitation (white arrow). MR: mitral regurgitation, LA: left atrium, RV: right ventricle, LV: left ventricle, LVOT: left ventricle outflow tract, AO: aorta

Figure 3b: Steady state free precession sequence (SSFP) from our lab demonstrating 4 chamber view with subtle flail posterior mitral valve leaflet with eccentric jet of mitral regurgitation (white arrow). MR: mitral

regurgitation, LA: left atrium, RV: right ventricle, LV: left ventricle, LVOT: left ventricle outflow tract, AO: aorta

Figure 4: Example CMR method for quantification of MR. The volume of the LV is calculated during end-diastole (LVEDV) and during end-systole (LVESV). The total volume of blood ejected from the left ventricle (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 (AO) valve is measured by performance of a phase-contrast acquisition in the aorta; in this example, 80 mL. The mitral RVol (M RVol) is computed as the difference between the LV SV and aortic forward SV; in this example, 70 mL. Reused with permission from Zoghbi, William A., et al. "Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance." Journal of the American Society of Echocardiography 30.4 (2017): 303-371.

Figure 5: Recommended cardiovascular magnetic resonance imaging protocols for the assessment of mitral regurgitation. a Comprehensive cardiovascular magnetic resonance imaging protocol for the assessment of mitral regurgitation. b Focused, quantitative protocol. LGE, late gadolinium enhancement; LV, left ventricular; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract. Reused under Creative Commons Attribution 4.0 International Licence from Fig 1 in Garg, Pankaj, et al. "Assessment of mitral valve regurgitation by cardiovascular magnetic resonance imaging." Nature Reviews Cardiology (2019): 1-15.

Figure 6: Depiction of mechanisms of MR as per the Carpentier classification

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Figure 7a: Steady state free precession sequence (SSFP) from our lab demonstrating 3 chamber view in a patient with hypertrophic cardiomyopathy with asymmetric septal hypertrophy and LVOT and SAM with dense dephasing jet of MR

RV: Right ventricle, LV: Left ventricle, LA: Left atrium, Ao: Ascending aorta, PM: Papillary muscle, LVOT: Left ventricular outflow tract turbulence, SAM: Systolic anterior motion, MR: Mitral regurgitation

Figure 7b: Steady state free precession sequence (SSFP) demonstrating of the same patient with hypertrophic cardiomyopathy showing two separate jets of MR in a coronal view. LV: Left ventricle, RV: Right Ventricle, AO: Ascending aorta, PA: Pulmonary artery, MR: Mitral Regurgitation

Figure 7c: Magnitude inversion recovery late gadolinium enhanced (LGE) sequence demonstrating diffuse patchy hyperenhancement most prominent in the inferolateral wall in the same patient with hypertrophic obstructive cardiomyopathy and mitral regurgitation. RV: Right ventricule, IVS: Interventricular septum, LV: Left Ventricle

Figure 8: Surgery-free survival stratified by both cardiovascular magnetic resonance (CMR) regurgitant volume (RVol) and left ventricular end-diastolic volume index (LVEDVi; Note that there were too few subjects [n=2] with CMR regurgitant volume [?]55 mL and LVEDVi [?]100 mL/m^2, so this group was excluded). **B** , CMR regurgitant volume and echocardiographic mitral regurgitation (MR) grade. Note that the group with CMR regurgitant volume >55 mL and moderate MR on echocardiography contains only 5 subjects. Reused with permission from Myerson, Saul G., et al. "Determination of clinical outcome in mitral regurgitation with cardiovascular magnetic resonance quantification." Circulation 133.23 (2016): 2287-2296.

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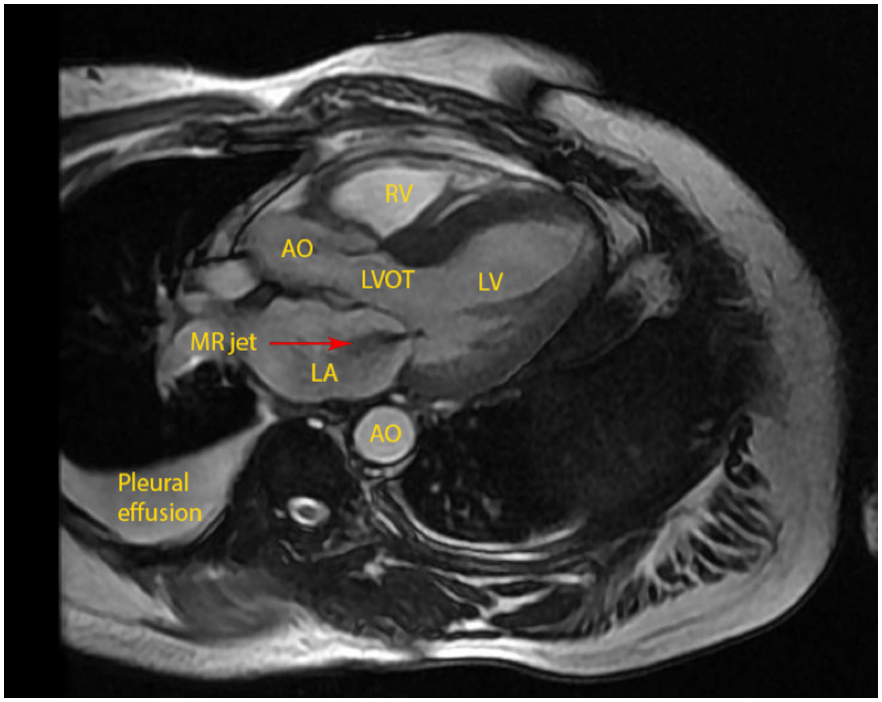

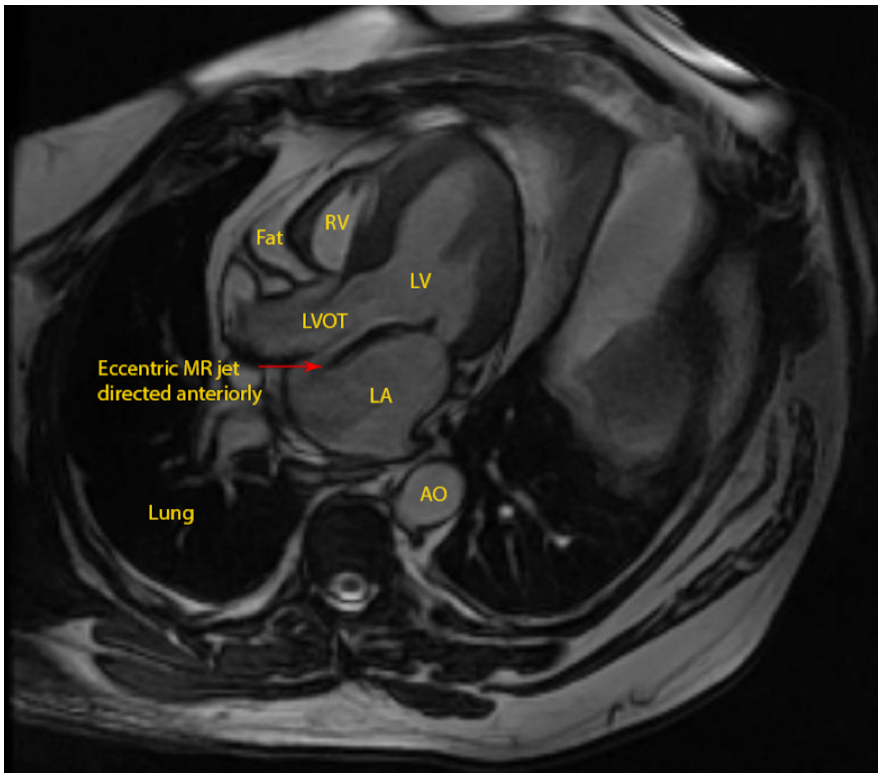

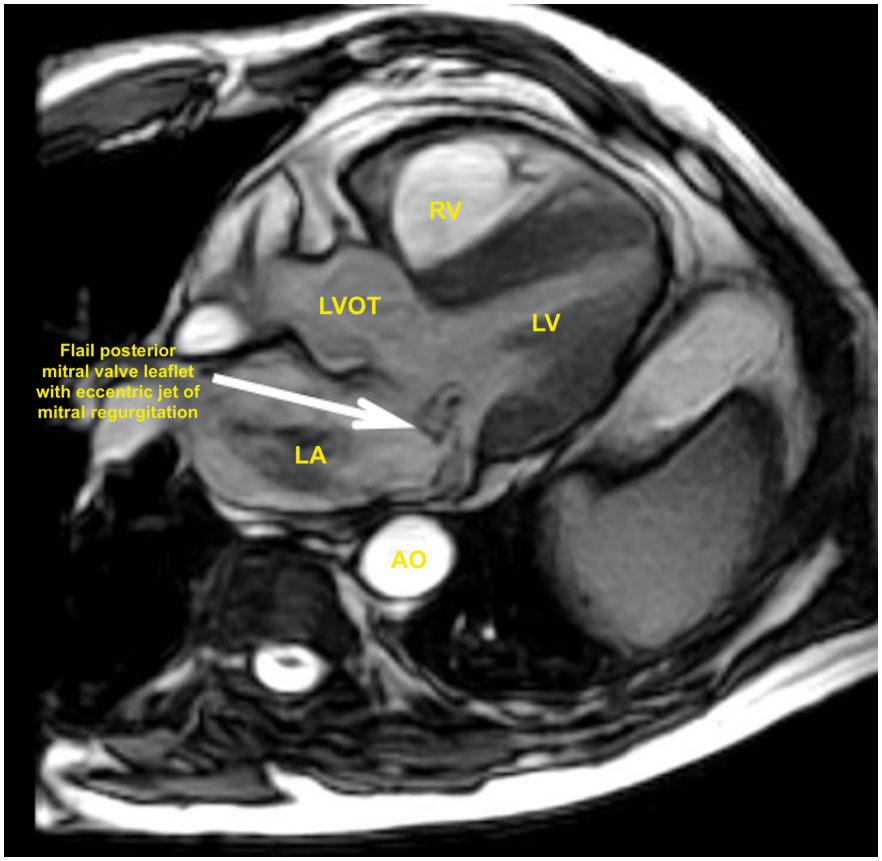

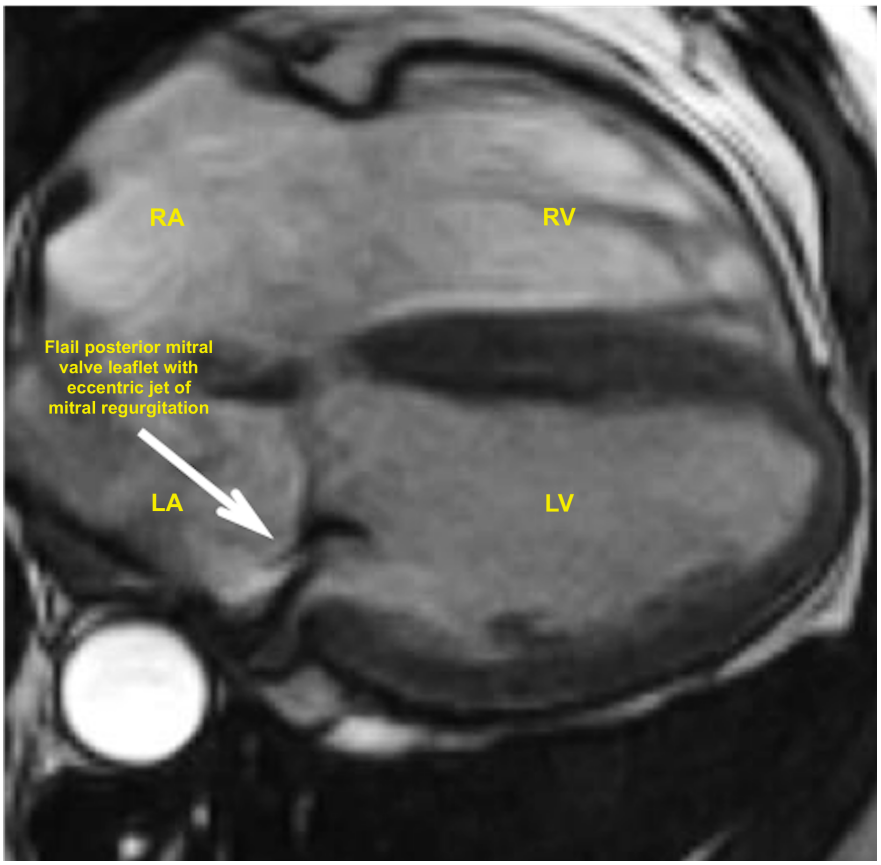

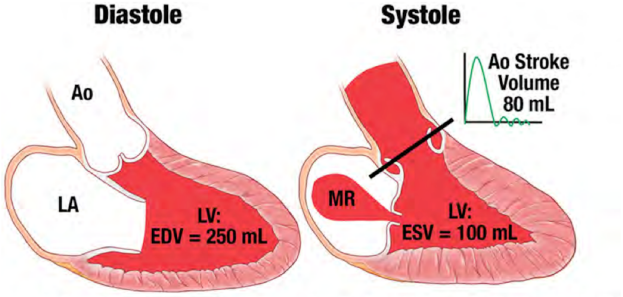

LV Stroke Volume (LVSV):
LVSV = LVEDV-LVESV
LVSV = 250 mL - 100 mL
LVSV = 150 mL

Mitral Regurgitant Volume (M RVol):
M RVol = LVSV - Ao Stroke Volume
M RVol = 150 mL - 80 mL
M RVol = 70 mL