CARDIOVASCULAR AND METABOLIC SCIENCE www.ancam.org.mx

REVIEW

Vol. 32 No. 4
October-December 2021

doi: 10.35366/102770

The emerging added value of cardiac magnetic resonance over echocardiography in the assessment of functional mitral regurgitation

El valor añadido emergente de la resonancia magnética cardiaca sobre la ecocardiografía en la evaluación de la insuficiencia mitral funcional

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Keywords:
Functional mitral regurgitation, multimodality cardiac imaging, cardiac magnetic resonance, regurgitant fraction.

Palabras clave:
Insuficiencia mitral funcional, imagen multimodal cardiaca, resonancia magnética cardiaca, fracción regurgitante.

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Received: 08/02/2021
Accepted: 08/10/2021

ABSTRACT

According to a new conceptual viewpoint, functional mitral regurgitation (FMR) is consistent with a variety of structural and dynamic characteristics in several clinical scenarios regarding the involvement of the left ventricle (LV) and the mitral valve (MV) integrity. Echocardiography is, for sure, the first-line cardiac modality to the classification of the etiology and the severity of FMR. However, it does not provide complete and accurate information on the LV compromise and tends to have some methodological errors in calculations. Cardiac magnetic resonance (CMR) is the gold standard technique for LV volumes, left ventricular ejection fraction (LVEF) and could fully integrate LV tissue characterization in several cardiomyopathies and allow the quantitative estimation of the severity valve insufficiency and could help to guide better clinical decision-making.

RESUMEN

De acuerdo con un nuevo punto de vista conceptual, la insuficiencia mitral funcional es consistente con una variedad de características estructurales y dinámicas en varios escenarios clínicos con respecto a la afectación del ventrículo izquierdo (VI) y la integridad de la válvula mitral. La ecocardiografía es sin duda, la modalidad cardíaca de primera línea para la clasificación de la etiología y la gravedad de la insuficiencia mitral funcional. Sin embargo, no proporciona información completa y precisa del compromiso del VI y tiende a tener algunos errores metodológicos en los cálculos en su estimación. La resonancia magnética cardíaca es la técnica de referencia para la estimación de los volúmenes y la fracción de eyección del VI y podría integrar el estudio de la caracterización tisular del VI en varias miocardiopatías; permite la estimación cuantitativa de la gravedad de la insuficiencia valvular y podría mejorar la toma de decisiones clínicas.

INTRODUCTION

The comprehensive assessment of FMR requires integrating MV anatomy features, regurgitant severity by quantitative parameters, LV volumes, and LVEF that are primarily best evaluated by the transthoracic echocardiography (TTE). MV morphology should be carefully assessed in multiple views using B-mode imaging to evaluate structure and motion; color flow Doppler is utilized to localize MR jet origin. However, if the image quality is poor with TTE, transesophageal echocardiography (TEE) may be needed to define anatomy and valvular function more precisely.[1] Therefore, TEE may identify lesions such as vegetations or flail segments not detected by TTE for determining the etiology of mitral regurgitation (MR).[2,3] The measurements of LV dimensions, volumes, and LVEF are performed according to the American Society of Echocardiography (ASE) guidelines for chamber quantification.[4]

How to cite: Chango-Azanza DX, Rosales-Uvera S, Vásquez Z, Munín MA, Obregón R. The emerging added value of cardiac magnetic resonance over echocardiography in the assessment of functional mitral regurgitation. Cardiovasc Metab Sci. 2021; 32 (4): 188-196. https://dx.doi.org/10.35366/102770

MR can have a primary (organic) or secondary (functional) etiology.[5] The primary MR is generally due to degenerative disease, also is characterized by direct damage to the structure of the leaflets (prolapse or rupture), which leads in the progression to an increase in volumes and a decrease in LVEF directly related to the primary MV involvement, and these patients will benefit from the direct intervention of this etiological cause (repair or replacement of the mitral valve).[1] In the setting of FMR, it reflects the severity of an underlying LV disease, which is the primary determinant of disability and death, and MR is a simple biomarker of advanced ventricular myopathy. For that reason, we traditionally interpret it as secondary or functional MR.[5,6]

The estimation of MR by quantitative measures is strongly recommended for assessing MR severity.[7] The calculation of effective regurgitant orifice area (EROA) is a quantitative marker of severity, as well as regurgitant volume (RV) and regurgitant fraction (RF). The echocardiographic assessment by several parameters, including the proximal iso-velocity surface area (PISA) method, volumetric methods, and 3-dimensional imaging, commonly define MR severity.[1]

It is crucial to recognize some technical limitations and imprecision of each method and the overlap of values obtained. PISA or vena contracta width are parameters that allow the estimation of EROA, RV, RF and are obtained by a single-frame measurement for

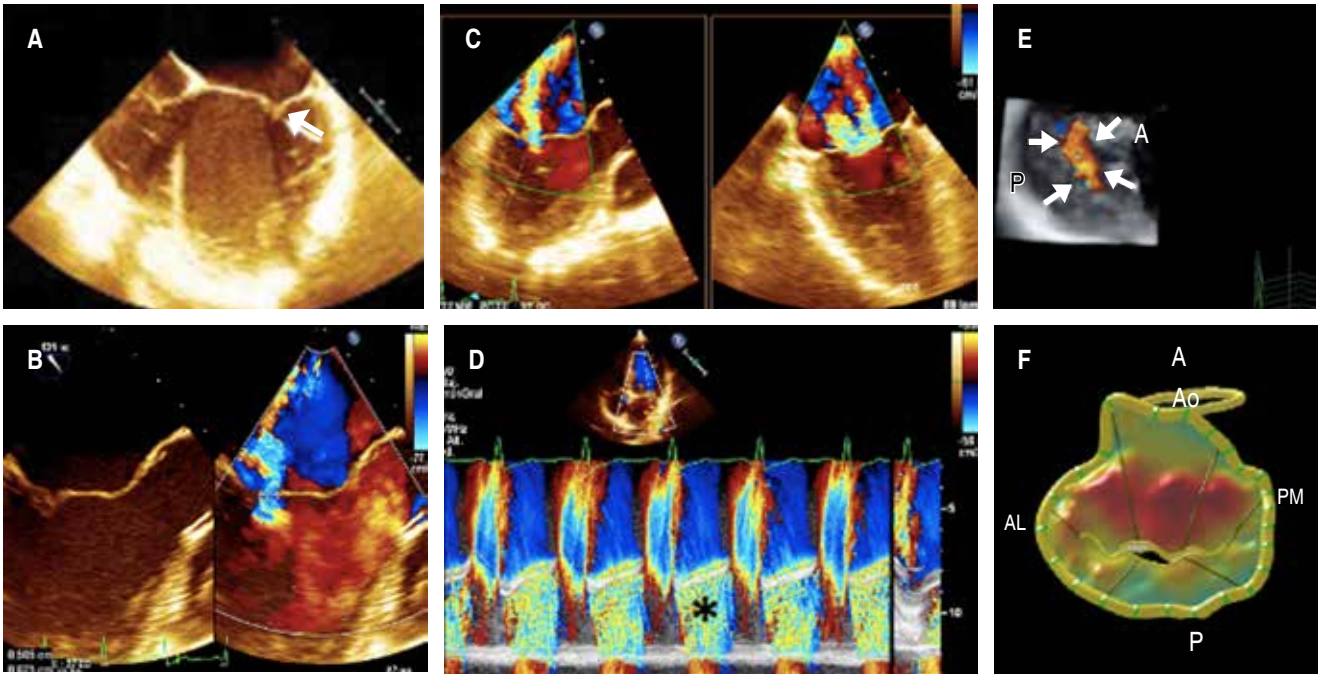
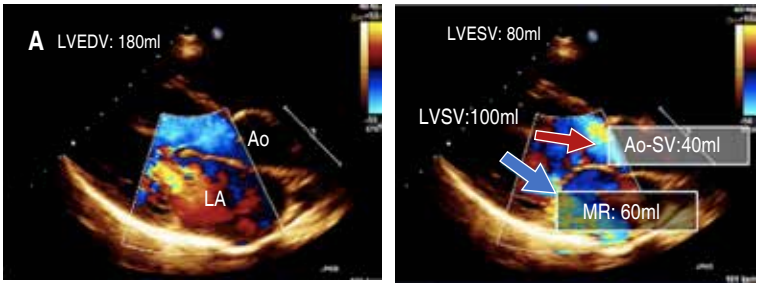


Figure 1: Echocardiographic assessment of the etiology of functional mitral regurgitation by 2-dimensional and 3-dimensional transesophageal echocardiography. All measures were obtained in a single frame during systole for estimation of mitral regurgitation severity. **A)** Mid-esophageal (0 degrees) four-chamber view showing a restricted posterior leaflet motion compatible with a Carpentier IIIb mitral regurgitation. (white arrow). **B)** Mid-esophageal three-chamber view (120 degrees) with an anteroposterior orientation of the mitral valve (A2-P2) showing underestimation of severity with a PISA of 6.7 mm a vena contracta width of 5 mm compatible with moderate mitral regurgitation. **C)** Simultaneous (X-plane) views of mitral valve with 3D assessment in an anteroposterior (three-chamber view) and bi-commissural (two-chamber view) orientation denoting an extensive MR in the bi-commissural two-chamber view. **D)** Color Doppler M-mode in mitral regurgitation with a holosystolic duration of the jet (black asterisk). **E)** Transesophageal echocardiography 3-dimensional in-face view of mitral valve with color Doppler evaluation confirming a large effective regurgitant orifice area that occupied the almost complete coaptation line in a commissural orientation. **F)** Schematic mitral valve model obtained by 3-dimensional transesophageal echocardiography.
P = posterior; A = anterior; AL = anterolateral; PM = posterior medial.



B

Left ventricle and mitral regurgitation, parameters	MITRA-FR	COAPT
Left ventricular ejection fraction (%)	Reported	31	31
Effective regurgitant orifice area (cm^2)	Reported	0.3	0.4
Left ventricular end-diastolic volume (mL)	Reported	245	193
Left ventricular end-systolic volume (mL)	Calculated: (LVEDV-LVESV) in MITRA-FR (calculated from LVEDV and LVEF	76	51
Regurgitant volume (mL)	Reported	45	60
Aortic stroke volume (mL)	Calculated: LVSV-RV	31	-9
Regurgitant fraction (%)	Calculated: (RV/LVSV)	59	118

LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction, LVSV = left ventricular stroke volume, RV = regurgitant volume.

Figure 2: Illustrative findings of functional mitral regurgitation in MITRA-FR and COAPT trials. **A)** In quantitative mitral regurgitation severity assessment, the left ventricular end-diastolic volume (upper left) and left ventricular end-systolic volume (upper right) allow the estimation of left ventricular stroke volume. This left ventricular stroke volume is ejected in systole throughout the aorta, and other parts of blood flow return to the LA representing the RV. **B)** Left ventricle and regurgitant volume parameters of quantitative evaluation in both trials.
LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVSV = left ventricular stroke volume, LA = left atrium, Ao = aorta, RV = right ventricle, LV = left ventricle.

TTE or TEE that can markedly overestimate MR severity when the jet is limited to early or late systole.[8] Nevertheless, when MR is holosystolic, properly measured values of EROA > 0.4 cm^2, RV > 60 mL, or RF > 50% are precise for severe MR. In the setting of FMR, a lower value of EROA and RV may underestimate lesion severity associated with markedly crescentic orifice geometry, where PISA yields a falsely low value for EROA due to its inherent assumption of a round orifice.[9-13] 3-dimensional TEE can directly visualize of these characteristics and precise quantification of EROA *(Figure 1)*.

The results of two recent transcatheter mitral valve repair trials in FMR with MitraClip® compared with medical therapy alone concerning all-cause mortality and the rate of hospitalization for heart failure showed different and contradictory results. In the MITRA-FR, investigators did not observe any effect on death and hospitalization within 12-month follow-up,[14] and in the COAPT trial, it was documented a 29% reduction of death and a 46% reduction of hospitalization within a 24-month follow-up.[15]

The disparity results of these two trials arrived in discussions in this setting addressed in different recent published data.[16,17] A part of these discussions made special attention to the inconsistencies in the assessment of MR severity when assessed by echocardiography in both trials. It is known that echocardiographic parameters are highly predisposed to methodological errors when defining MR severity by EROA and RV determined by the PISA method.[18-20] According to this technique, MR severity is estimated by a single snapshot during the cardiac cycle when it is better and larger visualized. Nevertheless, the PISA method was the parameter used in the two trials when defining MR severity.

When comparing and analyzing parameters of LV and MR in both trials, we found several inconsistencies. The reported LVEF was similar in both trials, about 31% compatible with severe LV dysfunction. The MR severity estimated by EROA in the MITRA-FR trial was lower than COAPT (0.3 vs 0.4 cm^2). In the MITRA-FR, the mean value of LV end-diastolic volume was about 245 mL (reported indexed value of 135 mL/m^2), and in the COAPT trial, a lower value of 195 mL. The total LV stroke volume in MITRA-FR

was about 76 mL (calculated from LVEDV and LVEF) and was reported in 51 mL in the COAPT trial. The RV in MITRA-FR was informed to be 45 mL and in COAPT of 60 mL.[21] Therefore, based on these MITRA-FR parameters, if the LV stroke volume was 76ml, and the RV was 45 mL, the estimated aortic stroke volume was 31 mL (LV stroke volume-RV). Whereby, the calculated RF (RV to LV stroke volume) was about 59%, while in the COAPT trial, if the LV stroke volume was 51 mL and the RV was 60 mL, the estimated aortic stroke volume (LV stroke volume - RV) had an inconsistent value of -9 mL during systole, and the calculated FR was about 118% (RV to LV stroke volume). Because of these considerations and errors, the MR severity assessment by semiquantitative parameters has to be reconsidered.[18,19] Also, this indicates the difficulties in the estimation of LV volumes, the stroke volume, and the severity of MR by quantifying with a value that represents only a single shot of MR with a lack of data for dynamics quantitative evaluation echocardiography in FMR *(Figure 2)*.

Determination of different phenotypes in functional MR

Defining several phenotypes of FMR may help determine the efficacy of different interventions. Severe MR in the setting of new-onset cardiomyopathy often resolves with aggressive medical optimization. However, a subgroup of patients persists despite optimal medical treatment, in whom the eventual benefit of MR correction arises. In the COAPT trial, 40% of the candidates screened were categorized to have severe MR that was truly medically refractory.[15] Another essential part of the discussion regarding the discordant results of MITRA-FR and COAPT trials is the relation of EROA and RV to LV end-diastolic volume and to distinguish between new conceptual discrimination in FMR proportionate and disproportionate according to the LV size[16] with less LV remodeling after treatment secondary to higher LV dimensions. When quantifying LV volumes using 2D TTE, we have a standard error of 20% using Simpson's method generally due

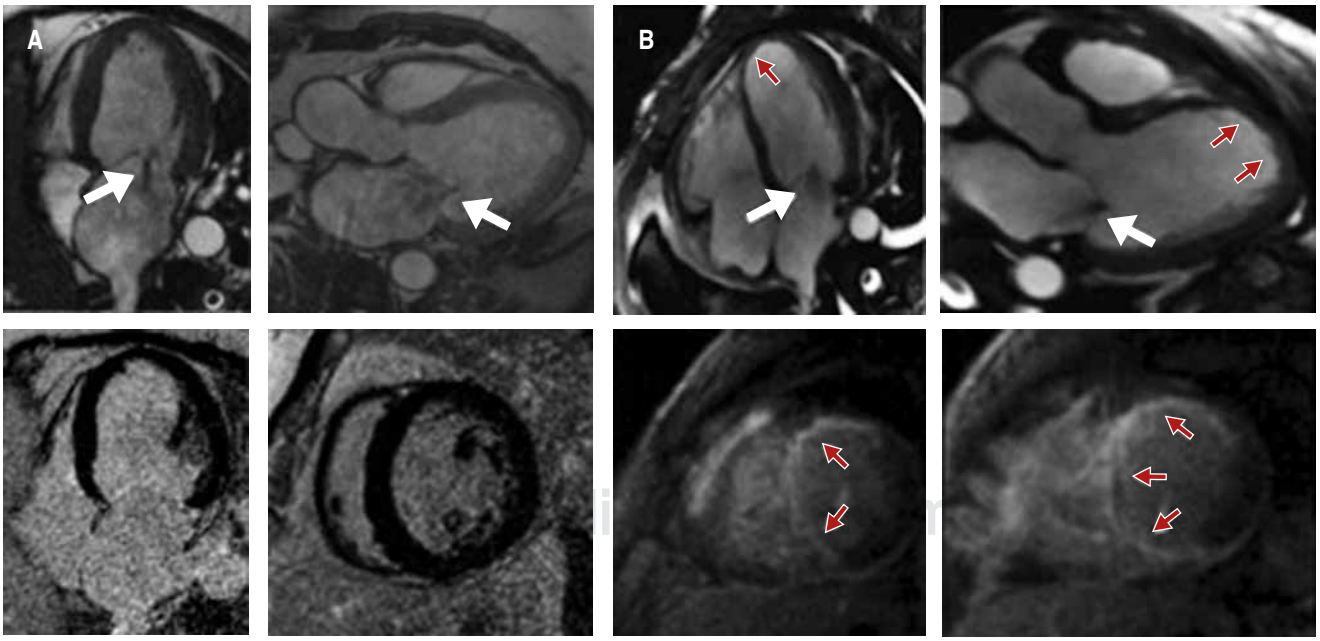


Figure 3: «Ventricular functional mitral regurgitation» (white arrows) in the setting of: **A)** non-ischemic cardiomyopathy with the absence of late gadolinium enhancement, **B)** ischemic cardiomyopathy with the presence of transmural late-gadolinium enhancement in left descending coronary artery left ventricle territory (red arrows).

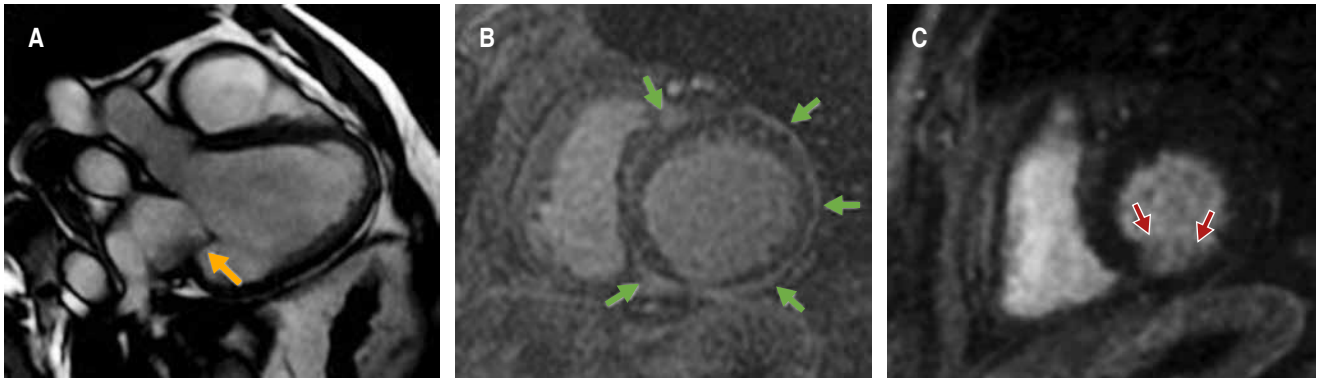


Figure 4: A) «Ischemic» functional mitral regurgitation presenting with restricted posterior leaflet motion leads to a homolateral excentric jet (yellow arrow). **B)** Non-ischemic cardiomyopathy showing subepicardial late-gadolinium enhancement distribution (green arrows). **C)** Showing ischemic cardiomyopathy with subendocardial inferior late-gadolinium enhancement by prior myocardial infarction (red arrows).

to foreshortening views. The mean difference of LV end-diastolic volume in both trials was «only» 45 mL, making this distinction difficult to determine precisely by 2D TTE. Thus, conclusions should be drawn with care based on LV end-diastolic volume and LVEF in FMR patients in MITRA-FR and COAPT.[21] Other parameters to analyze reverse LV remodeling after treatment were not reported in both trials and limits the interpretation of results, such as parameters of LV systolic function as peak power index, global longitudinal peak systolic strain, and papillary muscle involvement as the lateral and posterior dislocation, interpapillary muscle distance, tenting mitral valve area, and tethering mitral valve angles.

The more prevalent FMR arises due to symmetric retraction of the leaflets due to ventricular dilation with a centrally directed regurgitant jet, often aggravated by ventricular dyssynchrony. This type of MR has been called by some authors «ventricular functional MR». It could respond to medical therapy directed by guidelines or cardiac resynchronization,[22] these patients may have an ischemic-type etiology with altered contractility of the most apical segments or a non-ischemic type etiology with different degrees of ventricular dilation, to be considered as a true alteration of the LV and not of the MV itself *(Figure 3)*.

Another subgroup of patients presents abnormal contractility of the most basal segments of the inferior wall, predominantly due to coronary disease in an ischemic etiology, causing a restrictive movement and retraction of the posterior leaflet that results in a generally eccentric MR with posterior and lateral direction known as «ischemic MR».[22] Forming part of a structural anomaly of the valvular apparatus itself less susceptible to respond to medical treatment alone, in these cases surgical valve resolution has been associated with a better quality of life and a reduced amount heart failure events,[23] which supports its independent pathophysiological importance *(Figure 4)*. More recently, a functional MR of an atrial origin has been recognized, frequently associated with atrial fibrillation resulting from atrial remodeling and associated mitral annular dilation, leading to a central jet's appearance due to central coaptation deficit, without significant ventricular dilation.[24,25] So, likely, this atrial functional MR responds less to LV-directed medical therapy.

CMR imaging is not only the gold standard non-invasive imaging modality for assessing LV volumes, LVEF, and determining the etiology of several cardiomyopathies by late-gadolinium enhancement distribution, but also is a valuable technique allowing to quantifying flow to determine an accurate assessment of valvular regurgitation in discordant cases.[26,27] Assessment of valvular regurgitation is calculated on CRM by qualitative, semiquantitative, or quantitative methods. Qualitative determination of valvular regurgitation can be visually estimated as the extension of signal loss due to spin dephasing

in the left atrium on cine CRM images. However, this parameter can underestimate regurgitant severity.[28] Quantitative estimation of EROA can be calculated from the cine images after correct alignment and angulation of MV in an end-systolic frame.[29] Nevertheless, this method depends on appropriate MV plane alignment and angulation during imaging acquisition. Therefore, quantitative determination of RV and RF is the most utilized and accurate technique to define severity, mostly calculated using an indirect approach by comparing ventricular stroke volume to forward aortic flow or comparing LV and RV stroke volume in the absence of other valvular lesions.[30] This type of regurgitant valve regurgitation assessment had the advantage of being highly reproducible, and robust being not affected by some jet regurgitant features such as the direction or eccentricity, the presence of concomitant aortic regurgitation, and did not make LV geometry assumptions when estimating LV volumes and systolic stroke volume as present in echocardiography. The area under the curve of this volumetric method to define regurgitant severity was higher compared by 3D-echo, 2D-echo, and direct phase-contrast CMR (AUC: 0.98, 0.96, 0.90, and 0.83 respectively).[30]

These echocardiographic MR severity inconsistencies in valvular regurgitation assessment by semiquantitative non-accurate methods, highly

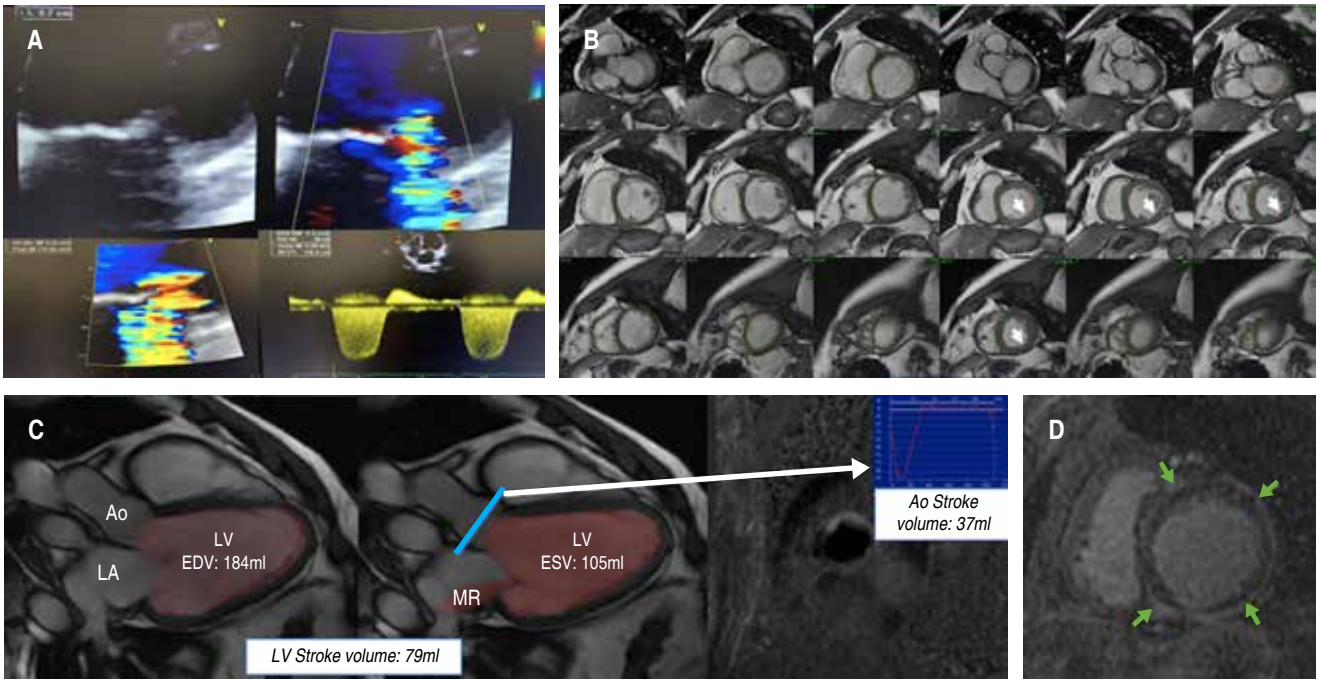


Figure 5: Representative case of the usefulness of regurgitant fraction assessing mitral regurgitation severity in functional mitral regurgitation. **A)** TTE of excentric mitral regurgitation with restricted posterior leaflet motion consistent with a moderate mitral regurgitation with an estimated effective regurgitant orifice area of 0.3 cm^2. **B)** CMR short-axis cine images in diastole [upper middle] and systole [upper right], showing thinned and akinetic contractility of inferior and inferolateral basal and middle left ventricle segments suggesting an ischemic mitral regurgitation with prior myocardial infarction. **C)** Volumetric cardiac magnetic resonance assessment of mitral regurgitation severity denoting a slightly dilated LV (LVEDV 184 mL, LVESV 105 mL), with an LVEF of 43% and left ventricle stroke volume of 79 mL. Aortic stroke volume by the phase-contrast image in ascending aorta (bottom middle) was 37 mL. The regurgitant volume was measured in 42 mL, and according to guidelines, it is consistent with moderate mitral regurgitation. Nevertheless, when assessing regurgitant fraction value is 53% confirming a severe mitral regurgitation in the specific context of left ventricle volumes, LVEF, and stroke volume in our patient. **D)** The late-gadolinium enhancement images showed non-ischemic cardiomyopathy with the global subepicardial distribution.

CMR = cardiac magnetic resonance, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction.

support a volumetric quantification to define MR severity, supporting the RF as the most reliable parameter to define severity, especially in the setting of LV dilation and dysfunction when RV may have several effects with different related volumes that can be precisely estimated by CMR imaging, such as end-diastolic volume, LVEF, stroke volume, and cardiac output in an individualized patient approach. Therefore, the LV total systolic stroke volume and RV are relevant in patients and can be related to different cardiac outputs. In this context, the RF becomes the most relevant parameter of estimation in FMR, where most have LV dilatation and systolic dysfunction and different cardiac stroke volumes where a lower RV than 60 mL could represent a RF higher than 50% *(Figure 5)*.

In functional MR, CMR can assess for ischemia, regional wall motion abnormalities, and myocardial viability. The amount of scar by late-gadolinium enhancement could be relevant in this context in patients' prognoses beyond the MR severity. The relationship between FMR severity and LV scar has been examined in a study of patients with ischemic cardiomyopathy. They used RF to assess MR severity instead of effective regurgitant orifice area alone, and both parameters were well correlated in the study. Additionally, the investigators found that although one might suppose that increasing scar burden would also worsen MR, both were not well correlated. However, the prognosis did worsen with both increasing MR and increasing scar. Most importantly, the combination of scar and MR severity worked in tandem to dramatically affect prognosis, with a 4-year survival of only 50% in patients with significant scar burden and the most severe MR (regurgitant fraction > 35%).[31]

Most patients treated with MitraClip® had an ischemic MR in MITRA-FR or COAPT, and scar burden was not measured, but it is certainly reasonable to guess that it might have had an impact. It could be that patients with the most considerable scar burden have such sick hearts that they cannot benefit from interventions. It may be that only muscle rather than scar can participate in the beneficial effects of correcting MR. This hypothesis is supported by examining the subgroup of patients who underwent mitral surgery; the patients with the highest scar burden had the worst outcomes. Perhaps the ischemic patients in MITRA-FR had a more considerable scar burden, accounting for larger ventricles and the lack of benefit after MitraClip®. Nonetheless, those data suggest that scar burden alone cannot explain the different outcomes of the two studies but might be an essential factor, and scar burden is itself a risk factor in secondary MR and might modulate the interaction between MR severity and recovery post-MitraClip®.[32]

CMR imaging is currently well recognized and recommended in international valve disease guidelines. However, it is a cardiac imaging technique with several limitations. It has a relatively long scan time compared with echocardiography. Generally, it is more expensive and has less availability. Correct electrocardiographic gatting is always necessary, and arrhythmias can deteriorate the image quality and interpretation. A breath-hold apnea period is also necessary and cannot be done in unstable conditions.[33] Another relevant limitation of CMR against echocardiography is its lower temporal resolution (typically 25-45 ms, 10-fold lower than Doppler echocardiography). Thus, it may underestimate peak values in high-velocity jets and lead to the worst detail imaging of mitral valve involvement in specific cases.[34] Transesophageal echocardiography, especially by three-dimensional technique, has an essential role in intraprocedural MitraClip® intervention, allowing the assessment for correct device position and residual MR. Compared with CMR allows the determination of immediate post-procedure ventricular systolic function and pulmonary artery systolic pressure and helps determine complications.[35]

CONCLUSIONS

Functional MR is a complex condition with the involvement of the LV and the MV in different degrees, and characterization of each scenario would be useful to determine the best individualized therapy. Echocardiography is always the first-line modality for determining the etiology of MR and severity, but CMR allows integrated and precise information about LV volumes, LVEF, and accurate volumetric assessment to clearly define a severe MR quantitatively. The RF is

the most reliable volumetric method to define severe MR in FMR. Moreover, scar burden by late-gadolinium enhancement helps to determine the etiology of the underlying cardiomyopathy but also defines patients with the worst outcomes in the follow-up even after the intervention of the MV. Randomized clinical trials with the integration of CMR data in this context are necessary to study a generalized indication in the assessment of functional mitral regurgitation in a multimodality approach.

ACKNOWLEDGEMENT

The authors thank the following individuals for their expertise and assistance throughout all aspects of our study and their help in writing the manuscript. MD. Mónica Chapa (Department of Cardiovascular Imaging. National Institute of Medical Sciences and Nutrition «Salvador Zubirán». Mexico City-Mexico). MD. Ignacio Raggio (Center for Medical Education and Clinical Research «Norberto Quirno», Buenos Aires, Argentina).

REFERENCES

1. Bonow RO, O'Gara PT, Adams DH, Badhwar V, Bavaria JE, Elmariah S et al. 2020 Focused update of the 2017 ACC expert consensus decision pathway on the management of mitral regurgitation: a report of the American College of Cardiology Solution Set Oversight Committee. Vol. 75, Journal of the American College of Cardiology. United States; 2020. 2236-2270.
2. Wang A, Grayburn P, Foster JA, McCulloch ML, Badhwar V, Gammie JS et al. Practice gaps in the care of mitral valve regurgitation: Insights from the American College of Cardiology mitral regurgitation gap analysis and advisory panel. Am Heart J. 2016; 172: 70-79.
3. Silbiger JJ. Novel pathogenetic mechanisms and structural adaptations in ischemic mitral regurgitation. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr. 2013; 26 (10): 1107-1117.
4. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. European Heart Journal - Cardiovascular Imaging. 12015; 6 (3): 233-271.
5. Gaasch WH, Meyer TE. Secondary mitral regurgitation (part 1): volumetric quantification and analysis. Heart. 2018; 104 (8): 634-638.
6. Gaasch WH, Meyer TE. Secondary mitral regurgitation (part 2): deliberations on mitral surgery and transcatheter repair. Heart. 2018; 104 (8): 639-643.
7. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA 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 (4): 303-371.
8. Topilsky Y, Michelena H, Bichara V, Maalouf J, Mahoney DW, Enriquez-Sarano M. Mitral valve prolapse with mid-late systolic mitral regurgitation: pitfalls of evaluation and clinical outcome compared with holosystolic regurgitation. Circulation. 2012; 125 (13): 1643-1651.
9. Altiok E, Hamada S, van Hall S, Hanenberg M, Dohmen G, Almalla M et al. Comparison of direct planimetry of mitral valve regurgitation orifice area by three-dimensional transesophageal echocardiography to effective regurgitant orifice area obtained by proximal flow convergence method and vena contracta area determined by color Doppler echocardiography. Am J Cardiol. 2011; 107 (3): 452-458.
10. Iwakura K, Ito H, Kawano S, Okamura A, Kurotobi T, Date M et al. Comparison of orifice area by transthoracic three-dimensional Doppler echocardiography versus proximal isovelocity surface area (PISA) method for assessment of mitral regurgitation. Am J Cardiol. 2006; 97 (11): 1630-1637.
11. Little SH, Pirat B, Kumar R, Igo SR, McCulloch M, Hartley CJ et al. Three-dimensional color Doppler echocardiography for direct measurement of vena contracta area in mitral regurgitation: *in vitro* validation and clinical experience. JACC Cardiovasc Imaging. 2008; 1 (6): 695-704.
12. Shanks M, Siebelink H-MJ, Delgado V, van de Veire NRL, Ng ACT, Sieders A et al. Quantitative assessment of mitral regurgitation: comparison between three-dimensional transesophageal echocardiography and magnetic resonance imaging. Circ Cardiovasc Imaging. 2010; 3 (6): 694-700.
13. De Agustín JA, Marcos-Alberca P, Fernandez-Golfin C, Goncalves A, Feltes G, Nuñez-Gil IJ et al. Direct measurement of proximal isovelocity surface area by single-beat three-dimensional color Doppler echocardiography in mitral regurgitation: a validation study. J Am Soc Echocardiogr [Internet]. 2012; 25 (8): 815-823. Available from: https://doi.org/10.1016/j.echo.2012.05.021
14. Obadia J-F, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med. 2018; 379 (24): 2297-2306.
15. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med. 2018; 379 (24): 2307-2318.
16. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT Trials. JACC Cardiovasc Imaging. 2019; 12 (2): 353-362.
17. Doenst T, Bargenda S, Kirov H, Moschovas A, Tkebuchava S, Safarov R et al. Cardiac surgery 2018 reviewed. Clin Res Cardiol. 2019; 108 (9): 974-989.

18. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013; 14 (7): 611-644.
19. Zoghbi WA, Asch FM, Bruce C, Gillam LD, Grayburn PA, Hahn RT et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American Society of Echocardiography developed in collaboration with the society for cardiovascular angiography and interventions, Japanese Society of Echocardiography, and Society for Cardiovascular magnetic resonance. J Am Soc Echocardiogr. 2019; 32 (4): 431-475.
20. Dujardin KS, Enriquez-Sarano M, Bailey KR, Nishimura RA, Seward JB, Tajik AJ. Grading of mitral regurgitation by quantitative Doppler echocardiography: calibration by left ventricular angiography in routine clinical practice. Circulation. 1997; 96 (10): 3409-3415.
21. Hagendorff A, Doenst T, Falk V. Echocardiographic assessment of functional mitral regurgitation: opening Pandora's box? ESC Hear Fail. 2019; 6 (4): 678-685.
22. Reddy YN V, Nishimura RA. Not all secondary mitral regurgitation is the same-potential phenotypes and implications for mitral repair. JAMA Cardiol. 2020; 5 (10): 1087-1088.
23. Goldstein D, Moskowitz AJ, Gelijns AC, Ailawadi G, Parides MK, Perrault LP et al. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. N Engl J Med. 2016; 374 (4): 344-353.
24. Aguero J, Galan-Arriola C, Fernandez-Jimenez R, Sanchez-Gonzalez J, Ajmone N, Delgado V et al. Atrial infarction and ischemic mitral regurgitation contribute to post-mi remodeling of the left atrium. J Am Coll Cardiol. 2017; 70 (23): 2878-2889.
25. Nishino S, Watanabe N, Ashikaga K, Morihisa K, Kuriyama N, Asada Y et al. Reverse remodeling of the mitral valve complex after radiofrequency catheter ablation for atrial fibrillation: a serial 3-dimensional echocardiographic study. Circ Cardiovasc Imaging. 2019; 12 (10): e009317.
26. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG 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 (16): 1387-1396.
27. Myerson SG. Heart valve disease: investigation by cardiovascular magnetic resonance. J Cardiovasc Magn Reson [Internet]. 2012; 14 (1): 7. Available from: https://doi.org/10.1186/1532-429X-14-7
28. Buchner S, Debl K, Poschenrieder F, Feuerbach S, Riegger GAJ, Luchner A et al. Cardiovascular magnetic resonance for direct assessment of anatomic regurgitant orifice in mitral regurgitation. Circ Cardiovasc Imaging. 2008; 1 (2): 148-155.
29. Chatzimavroudis GP, Oshinski JN, Franch RH, Walker PG, Yoganathan AP, Pettigrew RI. Evaluation of the precision of magnetic resonance phase velocity mapping for blood flow measurements. J Cardiovasc Magn Reson. 2001; 3 (1): 11-19.
30. Chew PG, Bounford K, Plein S, Schlosshan D, Greenwood JP. Multimodality imaging for the quantitative assessment of mitral regurgitation. Quant Imaging Med Surg [Internet]. 2018; 8 (3): 342-359. Available from: https://pubmed.ncbi.nlm.nih.gov/29774187
31. Cavalcante JL, Kusunose K, Obuchowski NA, Jellis C, Griffin BP, Flamm SD et al. Prognostic impact of ischemic mitral regurgitation severity and myocardial infarct quantification by cardiovascular magnetic resonance. JACC Cardiovasc Imaging. 2020; 13 (7): 1489-1501.
32. Carabello BA, Boyd WD. Scar in Secondary MR, Another piece to the puzzle: dead meat don't beat. Vol. 13, JACC. Cardiovascular imaging. United States; 2020. 1502-1504.
33. Lanzer P, Barta C, Botvinick EH, Wiesendanger HU, Modin G, Higgins CB. ECG-synchronized cardiac MR imaging: method and evaluation. Radiology. 1985; 155 (3): 681-686.
34. Ripley DP, Musa TA, Dobson LE, Plein S, Greenwood JP. Cardiovascular magnetic resonance imaging: what the general cardiologist should know. Heart [Internet]. 2016; 102 (19): 1589 LP-1603. Available from: http://heart.bmj.com/content/102/19/1589.abstract
35. Katz WE, Conrad Smith AJ, Crock FW, Cavalcante JL. Echocardiographic evaluation and guidance for MitraClip procedure. Cardiovasc Diagn Ther. 2017; 7 (6): 616-632.

Funding/support: No financial support was received for this study.

Conflict of interest: The authors declare no conflict of interest.

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