Original Article

Criteria for Mitral Regurgitation Classification were inadequate for Dilated Cardiomyopathy

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Abstract

Background: Mitral regurgitation (MR) is common in patients with dilated cardiomyopathy (DCM). It is unknown whether the criteria for MR classification are inadequate for patients with DCM.

Objective: We aimed to evaluate the agreement among the four most common echocardiographic methods for MR classification.

Methods: Ninety patients with DCM were included. Functional MR was classified using four echocardiographic methods: color flow jet area (JA), vena contracta (VC), effective regurgitant orifice area (ERO) and regurgitant volume (RV). MR was classified as mild, moderate or important according to the American Society of Echocardiography criteria and by dividing the values into terciles. The Kappa test was used to evaluate whether the methods agreed, and the Pearson correlation coefficient was used to evaluate the correlation between the absolute values of each method.

Results: MR classification according to each method was as follows: JA: 26 mild, 44 moderate, 20 important; VC: 12 mild, 72 moderate, 6 important; ERO: 70 mild, 15 moderate, 5 important; RV: 70 mild, 16 moderate, 4 important. The agreement was poor among methods (kappa = 0.11; $p < 0.001$). It was observed a strong correlation between the absolute values of each method, ranging from 0.70 to 0.95 ($p < 0.01$) and the agreement was higher when values were divided into terciles (kappa = 0.44; $p < 0.01$)

Conclusion: The use of conventional echocardiographic criteria for MR classification seems inadequate in patients with DCM. It is necessary to establish new cutoff values for MR classification in these patients. (Arq Bras Cardiol. 2013;101(5):457-465)

Key Words: Mitral Valve Insufficiency / classification; Cardiomyopathy, Dilated; Echocardiography / utilization.

Introduction

Functional mitral regurgitation (MR) is the secondary MR to left ventricle (LV) dilation[1] and it is often shown in patients with dilated cardiomyopathy (DCM), where the significant MR occurs in 35-50% of patients with chronic heart failure[2]. It has already been shown that presence and severity of a functional MR are independently associated with the prognosis in patients with non-ischemic DCM[3-5].

The functional MR pathophysiology is different from that of the MR by primary valvular disease. Functional MR is the result of a complex phenomenon, with displacement of the papillary muscles caused by LV dilation, valve ring dilatation and tethering of the mitral valve[1,6-8]. Furthermore, in patients with DCM, the left atrium works as a low resistence chamber to which the LV can eject blood[9].

Although some authors support mitral valve surgery for patients with significant functional MR and heart failure, it is still controversial the suggestion for surgery in these patients[10-12]. Currently, mitral valve surgery is considered as Class IIb for patients with refractory heart failure and significant functional MR[13].

Doppler echocardiography is the test of choice for the noninvasive assessment of MR mechanism and severity[14]. It is unknown whether the recommendations of the American Society of Echocardiography (ASE), together with the European Society of Cardiology Working Group for evaluation and classification of primary valvular insufficiency by Doppler echocardiography[14] are suitable for patients with functional MR and DCM. Additionally, the different methods using Doppler echocardiography and color flow mapping were validated in clinical studies

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for patients showing different causes of primary MR[15], but not specifically for patients with DCM.

This study aimed to evaluate the agreement for patients with DCM, among the four most commonly used echocardiographic methods for MR classification.

Methods

Patients

This study included 90 consecutive outpatients with non-ischemic DCM and functional MR of a tertiary center for treatment of heart failure and cardiomyopathies, of the Escola Paulista de Medicina / Universidade Federal de São Paulo, from September 2007 to September 2009. Inclusion criteria were: age ≥ 18 years old, functional class ≤ III (New York Heart Association), medical treatment optimized for heart failure, sinus rhythm, LV ejection fraction ≤ 0.40 (Simpson method modified) and good quality image. Patients with primary valvular disease, hypertension, coronary artery disease (for epidemiology and/or coronary angiography), end stage renal disease or chronic obstructive pulmonary disease were excluded. All participants signed an informed consent and the institution of ethics committee approved the project.

Echocardiography

All subjects performed a full two-dimensional echocardiography by using the IE 33 machine (Philips, Andover, Massachusetts), equipped with a 2-5 MHz transducer and under continuous electrocardiographic monitoring. Patients were assessed in left lateral decubitus by an echocardiograph qualified-physician, only. LV ejection fraction was calculated using the Simpson method modified.

Mitral Regurgitation Echocardiographic Assessment

MR was assessed by four echocardiographic methods that are part of the recommendations of the American Society of Echocardiography[14]: area of the regurgitant jet (RJ), vena contracta (VC), effective regurgitant orifice area (ERO) and regurgitant volume (RV) by the converging flow method (PISA). All methods were assessed at the apical window using image zoom.

RJ was measured in the apical 4-chamber view using Nyquist limit of 50-60 cm/s, the color gain adjusted to exclude artifacts from non-mobile structures (Figure 1). VC was measured in the apical 4-chamber view as the narrowest MR jet, after the orifice (Figure 1).

The converging flow method (proximal isovelocity surface area; PISA) was used to calculate the ERO and RV. PISA radius was measured using the Nyquist limit at which the flow convergence assumed a hemispherical shape (Figure 1). ERO was calculated using the formula: $2 \times \pi \times R^2 \times$ V aliasing / V peak (R: radius, in cm; V aliasing: proximal flow convergence velocity in cm/s, V peak: MR maximum velocity in cm/s). RV was calculated using the formula: ERO x VTI (VTI: MR jet velocity time integral).

The IM was classified as mild, moderate or important using each of the methods described according to the criteria and cutoff values of the recommendations of the American Society of Echocardiography[14]. MR was also divided into terciles (lower, intermediate and higher values) according to the absolute values obtained by each method.

Statistical Analysis

Statistical analysis was performed using the *SPSS* 13.0 software (SPSS Inc., Chicago, Illinois). Continuous data are shown as mean ± PD and categorical data are described in percentages. Pearson correlation coefficient was used to assess the correlation between the absolute values of the four methods used for MR quantification. Kappa agreement test was used to assess the agreement between methods used to classify the MR. Significance values of $p < 0.05$ were considered.

Results

Clinical Data

Patient clinical basal characteristics are detailed in Table 1. From the total 90 patients, 60 (67%) showed idiopathic dilated cardiomyopathy and 30 (33%) patients showed Chagas cardiomyopathy. Functional class mean was 2.2 ± 0.6. All patients were on beta-blockers (carvedilol 76%, 48 ± 6 mg/day, and metoprolol 24%, 178 ± 43 mg/day), ACE inhibitors (captopril 62%, 133 ± 24 mg/day, and enalapril 38%, 31 ± 10 mg/day), and furosemide (97 ± 62 mg/day). Eighty-one (90%) patients were on spironolactone and 20 (22%) were taking digoxin.

Doppler echocardiography

Doppler echocardiography data are described in Table 2. LV ejection fraction average was 0.30 ± 0.07 and 24 (27%) patients showed restrictive filling pattern. The E/e' ratio was 18.0 ± 7.9 and the mean systolic pulmonary pressure was 44 ± 13 mmHg.

Mitral Regurgitation - Echocardiographic Data

The mean values for each method were: RJ: 6.8 ± 4.1 cm^2, VC: 0.44 ± 0.15 cm; ERO: 0.14 ± 0.10 cm^2, and RV: 22.1 ± 15.3 ml (Table 3). The MR jets were central in all patients, as expected. Pearson calculated correlation coefficient (r) indicated a strong correlation between the absolute values of each method, ranging from 0.70 to 0.95 ($p < 0.01$) (Figure 2).

According to the cutoff values of the recommendations of the American Society of Echocardiography, MR was classified by the RJ method as mild in 26 patients, moderate in 44 patients and important in 20 patients. Through the VC, MR was considered mild in 12 patients, moderate in 72 patients and important in 6 patients. Through the ERO, 70 patients showed mild MR, 15 patients moderate MR and 5 patients important MR. Through the RV, MR was mild in 70 patients, moderate in 16 patients and important in 4 patients (Figure 3). The agreement among the four methods evaluated was poor (kappa = 0.11, $p < 0.01$).

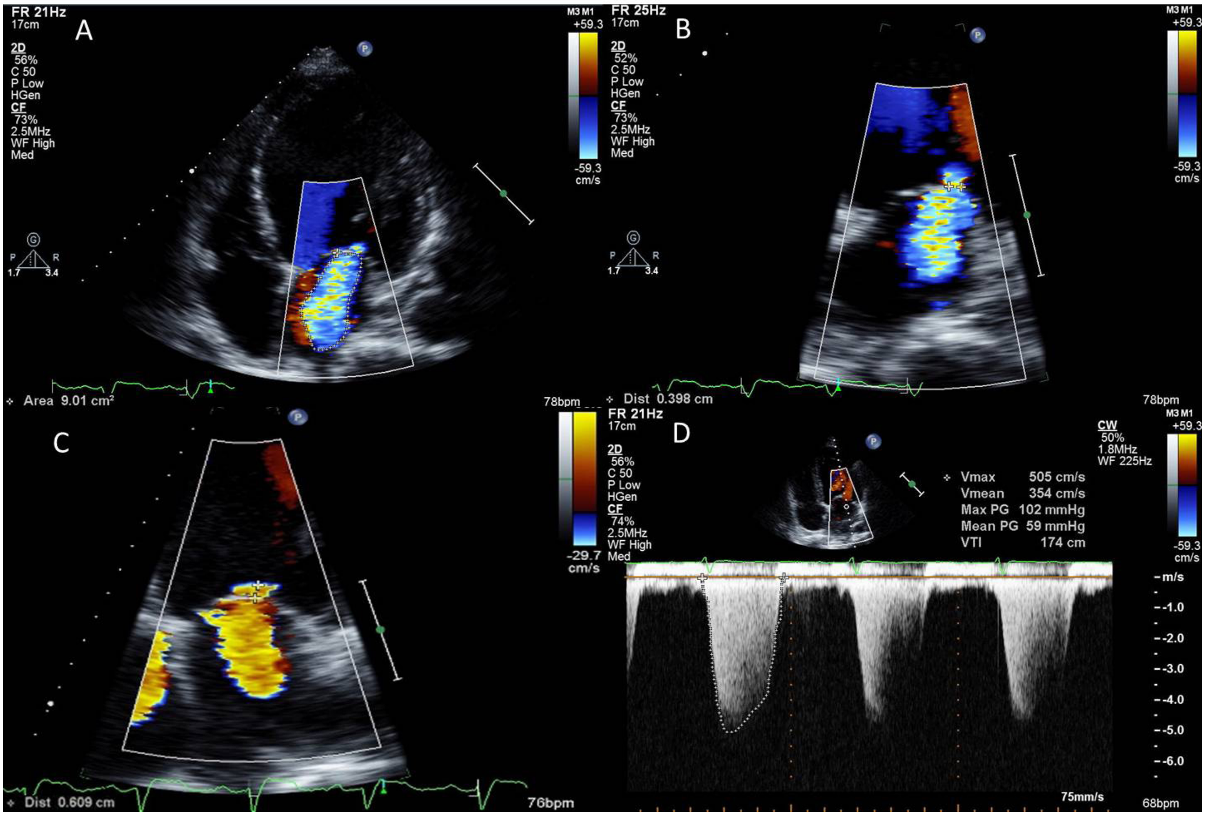

Figure 1 - *Mitral regurgitation assessment using four echocardiographic methods in a patient with idiopathic dilated cardiomyopathy. A) Mitral regurgitation jet area measurement showing an area of 9.01 cm^2; B) Vena contracta measurement (0.40 cm), in; C/D) Magnified image of the measure of hemisphere radius, maximum velocity and VTI for calculation of effective regurgitant orifice area and regurgitant volume. In this patient, the effective regurgitant orifice area was 0.14 cm^2 and the regurgitant volume was 23.8 ml.*

Table 1 – Patient Basal Clinical Features

	N = 90 patients
Age (years)	53 ± 11
Male (%)	70
BSA (kg/m²)	1.73 ± 0.17
HR (bpm)	69 ± 12
SBP (mmHg)	109 ± 20
DBP (mmHg)	69 ± 14
Cardiomyopathy	60 (67%)
Idiopathic Dilated	
Cardiomyopathy (%)	30 (33%)
Chagas (%)	
Functional Class (NYHA)	2.2 ± 0.6
FC I	7 (8%)
FC II	55 (61%)
FC III	28 (31%)

Values expressed as mean ± standard deviation or frequency (%).
BSA: body surface area; FC: functional class; HR: heart rate; NYHA: New York Heart Association; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Twenty patients with important MR by the RJ showed the same LV ejection fraction as the other patients (28.04 ± 5.21 *vs*. 31.01 ± 7.79, p = 0.11).

The absolute values of each method were divided into terciles: 30 lower values, 30 intermediate values and 30 higher values (Figure 4). The cutoff values that divided the terciles were different from the cutoff values of the American Society of Echocardiography. With the cutoff values used to divide into terciles for the MR classification in each method, we observed a better agreement among the methods (kappa = 0.44, p <0.01). Figure 5 shows the MR classification box-plots according to the cutoff values of the American Society of Echocardiography and the terciles.

Discussion

The main finding of this study is the poor ruim agreement among the quantitative echocardiographic methods for MR classification in patients with DCM, using the criteria and cutoff values of the *American Society of Echocardiography*. The MR evaluation and classification remains a challenge, even in patients with primary valvular disease, which has been the reason for recent publications[15-18]. This is the first study to address the MR classification by different echocardiographic methods in patients with DCM. A previous study, which

Table 2 – Doppler echocardiography data

	N = 90 patients
LA Diameter	46 ± 6 mm
LAVi	54 ± 19 ml/m^2
LVEDV	273 ± 100 ml
LVESV	194 ± 84 ml
LVEF	30.4 ± 7.4 %
E Wave Velocity	79.5 ± 29.7 cm/s
A Wave Velocity	65.6 ± 31.9 cm/s
E/A ratio	1.4 ± 1.5
Restrictive filling standard	27 %
e' septal Wave Velocity	4.8 ± 1.8 cm/s
E/e' ratio	18.0 ± 7.9
PASP	44 ± 13 mmHg

Values expressed as mean ± standard deviation or frequency (%).
LA: left atrium; LVEF: left ventricle ejection fraction; PASP: pulmonary artery systolic pressure; LAVi: left atrial volume indexed by surface area; LVEDV: left ventricle end-diastolic volume; LVESV: left ventricle end-systolic volume.

included patients with myxomatous or rheumatic etiology MR, unlike our study, showed a good agreement between the quantitative echocardiographic methods[15].

Although we have observed a good correlation between the absolute values of each method, there was a poor agreement in the MR classification. The highest correlation was between the ERO and RV, as expected, since both measures derives from PISA method. These findings suggest that the main reason for the poor agreement between the methods is that, although the cutoff values of the American Society of Echocardiography are appropriate for patients with primary valvular disease[15], they are inadequate for patients with functional MR and DCM. The best agreement observed when using different cutoff values, based on the division into terciles, reinforces this hypothesis. Further studies are required to establish specific cutoff values for the classification of functional MR in patients with DCM.

Functional Mitral Regurgitation: Echocardiographic Assessment Mechanisms

Differences between the pathophysiological mechanisms of primary and functional MR[6,7], as well as particularities of

Table 3 – Mitral regurgitation data (n = 90 patients)

	Values	Range
Jet Area	6.8 ± 4.1 cm^2	1.3 – 19 cm^2
Vena contracta	0.44 ± 0.15 cm	0.13 – 0.94 cm
ERO	0.14 ± 0.10 cm^2	0.02 – 0.61 cm^2
RV	22.1 ± 15.3 ml	4.5 – 83.4 ml

Values expressed as mean ± standard deviation
ERO: effective regurgitant orifice area; RV: regurgitant volume.

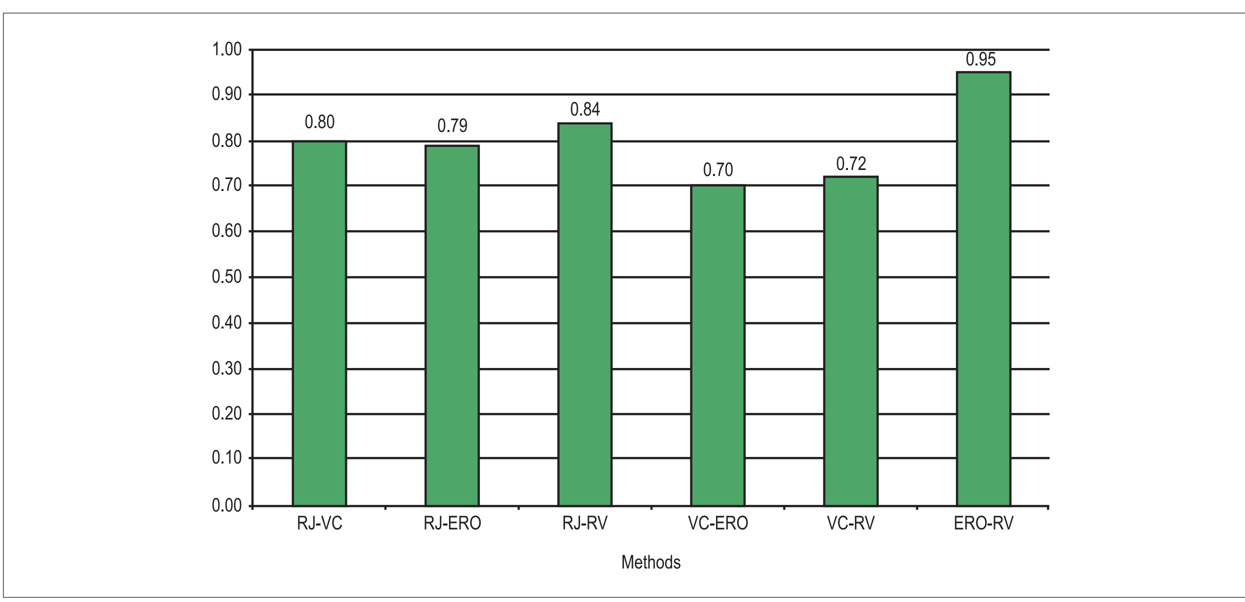

Figure 2 - *Scatter charts for the correlation between absolute values for each of the four methods used for Mitral Regurgitation classification (p < 0.01). RJ: regurgitant jet area; ERO: effective regurgitant orifice area; VC: vena contracta; RV: regurgitant volume.*

Figure 3 – *Mitral Regurgitation classification using the four methods described in the study, according to the cutoff values of the American Society of Echocardiography. There was a poor agreement between the methods; kappa: 0.11, p < 0.01. RJ: regurgitant jet area; ERO: effective regurgitant orifice area; VC: vena contracta; RV: regurgitant volume.*

echocardiographic techniques may also have contributed to the discrepancies in the MR classification observed in this study.

The structural changes that occur in the mitral valve apparatus are different among patients with MR and those with primary MR and those with functional MR by DMC. In functional MR, there is a posterolateral and apical displacement of the papillary muscle, apical tethering of the valve cusps, and reduced mobility[19]. Recently, with the use of three-dimensional transesophageal echocardiography, Matsumara et al. demonstrated that PISA geometry is different for patients with DCM, where the converging flow zone radius is longer in functional MR, when compared to the MR per mitral valve prolapse. The authors also observed that PISA method underestimates the ERO in functional MR[16]. Previously, an *in vitro* study demonstrated that ERO underestimates PISA when this is not hemispherical[20]. These findings, in part, explain the poor agreement between the MR classification methods observed in our study, especially for the exceeding MR classified as mild by ERO and RV.

Particular technical aspects of Doppler echocardiography for each of the methods used for MR quantification should also be considered. The frequency of the transducer and color gain adjustment may influence the RJ, where the method is considered less accurate[14,21]. In patients with DCM, lower LV ejection fraction may also affect the RJ. VC may modify with changes in hemodynamic conditions and it is different at several times in the cardiac cycle[21]. Furthermore, VC intermediate values do not necessarily correspond to moderate MR, since there is a significant overlap of values with this method[14]. In our study, VC classified MR classified as moderate in most patients, which may also have contributed to the observed poor agreement between the methods. ERO and RV by the PISA method may be less accurate in patients with DMC due to non-circular ERO that occurs in functional MR, besides the irregular shape of the convergence flow zone in these patients[16]. It was recently shown that ERO and RV calculated by echocardiography are underestimated when compared to these parameters obtained by three-dimensional echocardiography and nuclear magnetic resonance[22]. Therefore, the PISA method may underestimate ERO and RV in patients with DCM and functional MR, which explains the fact that few patients in our study have important MR presented according to the ERO and RV methods.

The evaluation of left atrial and LV dimensions provide important data for the classification of primary MR[14]. However, in patients with DCM, the dimensions of these heart chambers do not provide indirect information about MR severity, since the expansion of these cavities is primarily by their own cardiomyopathy.

The criteria for the MR classification have not been validated for patients with functional MR and DCM. Although some previous studies have considered different cutoff values for MR classification by the ERO method in patients with heart failure, these values were chosen arbitrarily[23,24]. Furthermore, only patients with functional MR by ischemic cardiomyopathy were included in these, condition with MR different mechanisms from those of the nonischemic DCM. Also, MR was classified only as important and not important by these authors[23,24], unlike our study in which MR was classified as mild, moderate or important, according to the recommendations of the American Society of Echocardiography[14].

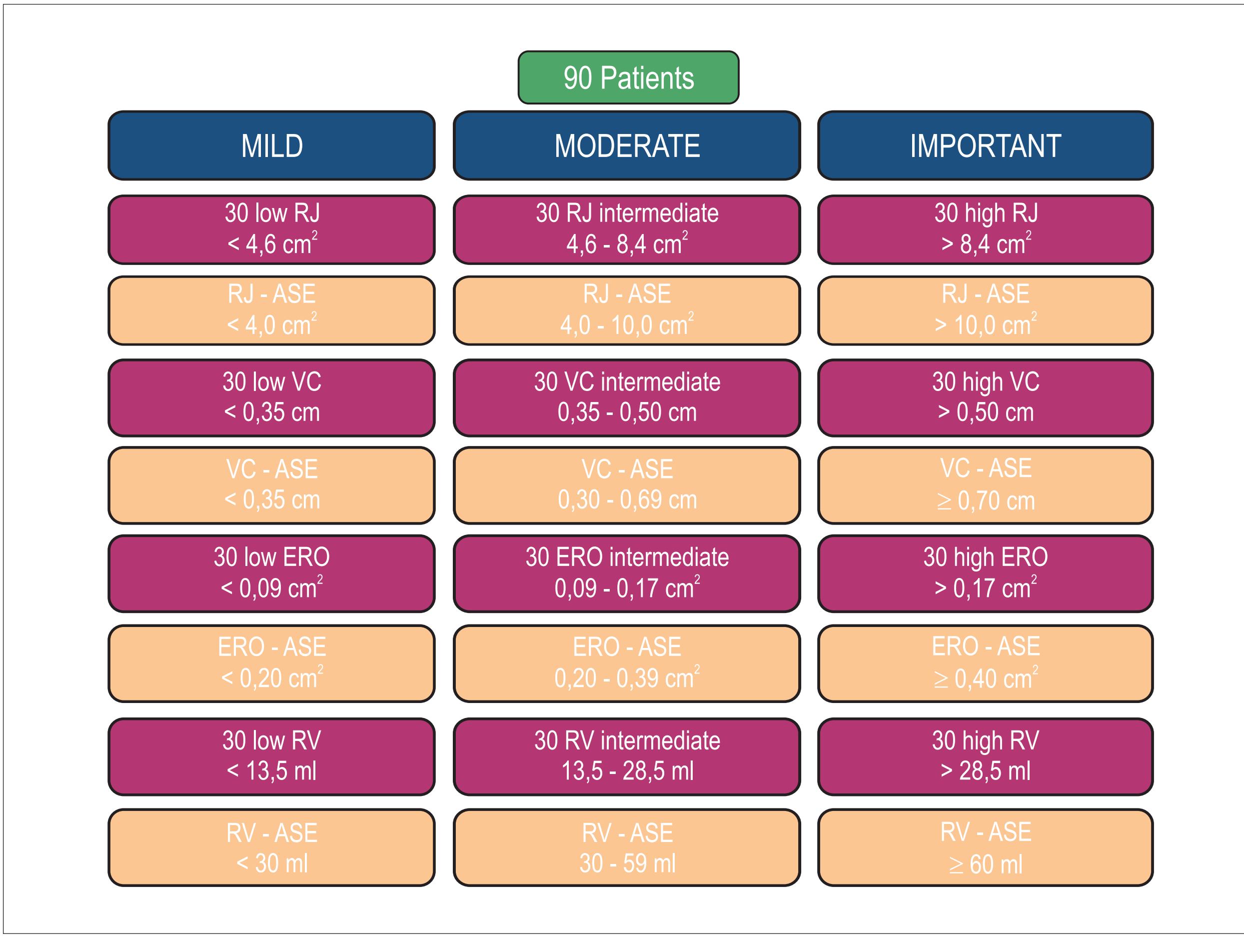

Figure 4 - *Redistribution of absolute values into terciles (30 low values, 30 intermediate values and 30 high values). They are also showing the cutoff values of the American Society of Echocardiography. A better agreement was observed when the values that divided terciles were used for mitral regurgitation classification by each method (kappa: 0.44, p <0.01). RJ: regurgitant jet area; ERO: effective regurgitant orifice area; ASE: American Society of Echocardiography; VC: vena contracta; RV: regurgitant volume.*

Finally, the strong correlation finding between absolute values of each method, associated with the poor agreement in the MR classification when cutoff values of the American Society of Echocardiography are used together with the previous study, which showed a good agreement in the primary MR classification, reinforces the hypothesis that the cutoff values for MR classification, although appropriate in primary mitral valve diseases, are inadequate to classify the MR in DCM patients.

Clinical Implications

The MR classification in patients with heart failure and DCM is important, since the MR degree has prognostic and therapeutic value[25,26]. The functional MR is associated with LV volume overload and remodeling[26]. Additionally, the MR contributes to the increase in LV filling pressures and in pulmonary pressure[27]. The MR classification has a role for therapeutic decisions in the clinical practice. MR decreases with the clinical treatment of heart failure and is associated with the improvement in LV hemodynamic conditions, and has been used as one of the criteria for response to cardiac resynchronization therapy[28].

Patients with refractory symptoms of heart failure and important MR may be eligible for MR surgical treatment. However, clinical studies evaluating mitral valve surgery in these patients showed controversial results[10-12]. These findings may reflect the difficulty in classifying the MR, which consequently makes the selection of appropriate patients for surgery difficult.

Findings of this study reinforce the need to integrate the results of multiple echocardiographic methods used in the MR classification. Moreover, it is necessary to establish new cutoff values for MR classification, specific to patients with functional MR and DCM, since the correct MR classification is important for their clinical management. In cases where the two-dimensional transthoracic echocardiography provides conflicting data for MR assessment, the transesophageal echocardiography is recommended for a better assessment of the MR degree[29]. Another possibility in cases of disagreement between methods is the use of three-dimensional echocardiography, which seems to be a promising method for assessment of mitral regurgitation

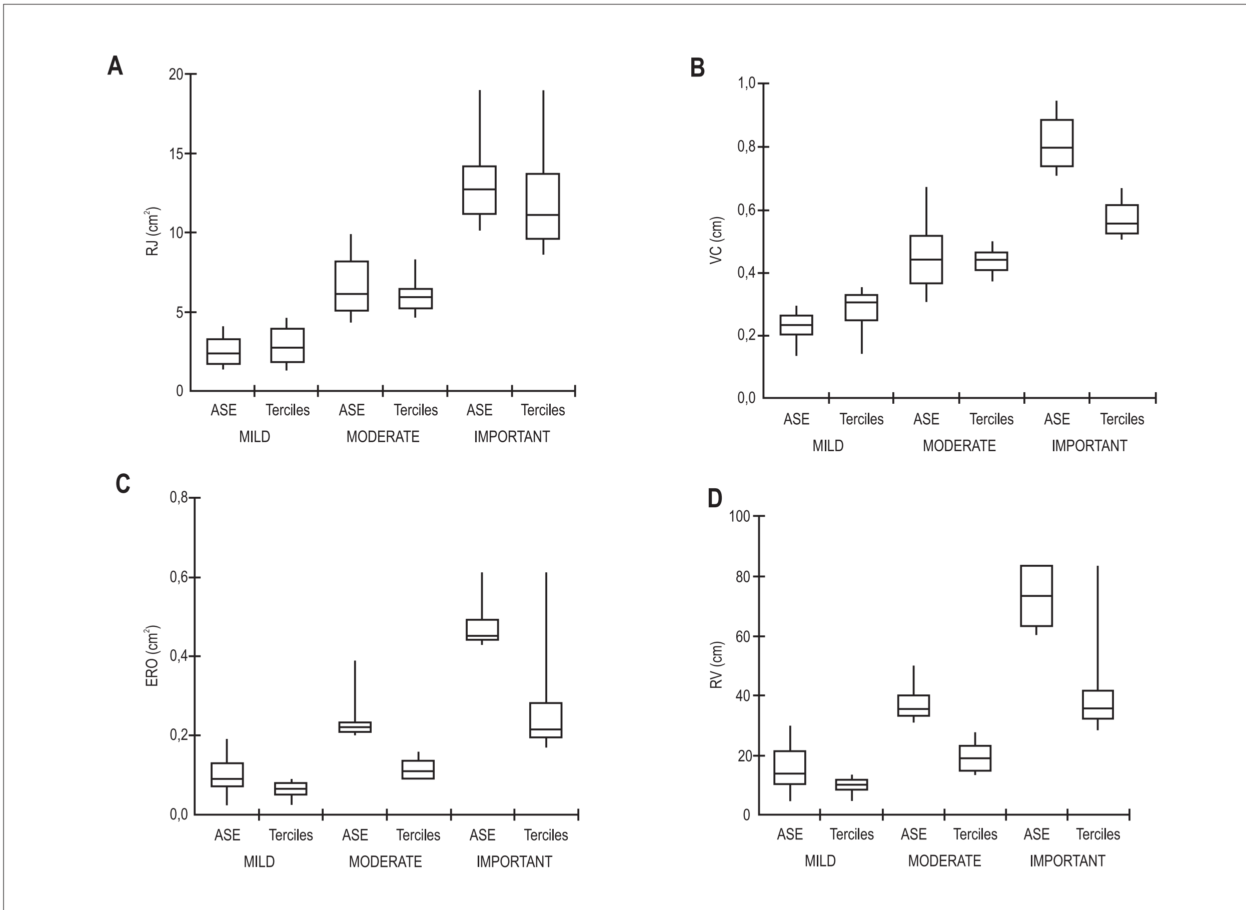

Figure 5 - *Box plot graphs of the MR classification showing absolute values variation according to the cutoff values of the American Society of Echocardiography and the terciles. A) regurgitant jet area (RJ), B) vena contracta (VC) C) effective regurgitant orifice area (ERO) and D) regurgitant volume (RV).*

by measuring the vena contracta three-dimensionally and the regurgitant volume directly, but such measures still need validation[29]. A better MR classification can improve the selection of patients to surgical treatment of functional MR. In the near future, with the MR percutaneous techniques advances, treatment indication for invasive functional MR must increase, where it is essential that a reliable MR degree classification is available for patient selection.

Limitations

A gold standard test for comparison of the MR classification such as cardiac angiography or MRI was not used, but actually, there is no true gold standard test for the MR assessment[18], which makes the MR classification by echocardiography even harder, especially when several methods are available and different MR mechanisms are involved. Furthermore, it is important to observe that variations may occur in the regurgitation intensity with range of hemodynamic or load conditions in the same patient, as well as the use of medications that modify these loading/hemodynamics conditions[14].

The study could not establish a new cutoff value for MR classification in this specific population. The division of values into terciles was only used to test whether the discrepancy was due to the inadequacy of the methods or whether it was due to the cutoff values recommended for MR classification. A long-term prospective study is required, designed specifically for this purpose, comparing the MR assessment by other imaging methods (angiography or magnetic resonance imaging), in order to establish new cutoff values for MR classification in DCM patients.

Conclusion

The echocardiographic criteria for MR classification are in disagreement with patients with DCM. It is essential to integrate multiple methods in the MR assessment and establish new cutoff values for MR classification for this specific population, since the correct MR assessment has therapeutic and prognostic implications to these patients.

Author contributions

Conception and design of the research: Mancuso FJN, Moisés VA, Poyares D, Campos O; Acquisition of data: Mancuso FJN, Almeida DR, Oliveira WA, Brito FS; Analysis and interpretation of the data: Mancuso FJN, Moisés VA, Oliveira WA, Campos O; Statistical analysis: Mancuso FJN; Writing of the manuscript: Campos O; Critical revision of the manuscript for intellectual content: Moisés VA, Almeida DR, Paola AAV, Carvalho ACC, Campos O.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

1. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. Circulation. 2000;102(12):1400-6.
2. Allen LA, Felker GM. Advances in the surgical treatment of heart failure. Curr Opin Cardiol. 2008;23(3):249-53.
3. Koelling TM, Aaronson KD, Cody RJ, Bach DS, Armstrong WF. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. Am Heart J. 2002;144(3):524-9.
4. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol. 2003;91(5):538-43.
5. Patel JB, Borgeson DD, Barnes ME, Rihal CS, Daly RC, Redfield MM. Mitral regurgitation in patients with advanced systolic heart failure. J Card Fail. 2004;10(4):285-91.
6. Otsuji Y, Handschumacher MD, Schwammenthal E, Jiang L, Song JK, Guerrero JL, et al. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. Circulation. 1997;96(6):1999-2008.
7. Kwan J, Shiota T, Agler DA, Popovic ZB, Qin JX, Gillinov MA, et al. Geometric differences of the mitral apparatus between ischemic and dilated cardiomyopathy with significant mitral regurgitation: real-time three-dimensional echocardiography study. Circulation. 2003;107(8):1135-40.
8. Kirkpatrick JN, Vannan MA, Narula J, Lang RM. Echocardiography in heart failure: applications, utility, and new horizons. J Am Coll Cardiol. 2007;50(5):381-96.
9. Bach DS. Nonischemic mitral regurgitation and left ventricular dysfunction. In: Lang RM. (editor). Dynamic echocardiography. St Louis, MO: Saunders Elsevier; 2010. p. 81-3.
10. Bolling SF, Deeb GM, Brunsting LA, Bach DS. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. J Thorac Cardiovasc Surg. 1995;109(4):676-82.
11. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol. 2005;45(3):381-7.
12. DiSalvo TG, Acker MA, Dec GW, Byrne JG. Mitral valve surgery in advanced heart failure. J Am Coll Cardiol. 2010;55(4):271-82.
13. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, et al; American College of Cardiology Foundation; American Heart Association. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol. 2009;53(15):e1-e90. Erratum in: J Am Coll Cardiol. 2009;54(25):2464.
14. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al; American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003;16(7):777-802.
15. Pinheiro AC, Mancuso FJ, Hemerly DF, Kiyose AT, Campos O, de Andrade JL, et al. Diagnostic value of color flow mapping and Doppler echocardiography in the quantification of mitral regurgitation in patients with mitral valve prolapse or rheumatic heart disease. J Am Soc Echocardiogr. 2007;20(10):1141-8.
16. Matsumara Y, Fukuda S, Tran H, Greenberg NL, Agler DA, Wada N, et al. Geometry of the proximal isovelocity surface area in mitral regurgitation by 3-dimensional color Doppler echocardiography: difference between functional mitral regurgitation and prolapse regurgitation. Am Heart J. 2008;155(2):231-8.
17. Marsan NA, Westenberg JJ, Ypenburg C, Delgado V, van Bommel RJ, Roes SD, et al. Quantification of functional mitral regurgitation by real-time 3D echocardiography: comparison with 3D velocity-encoded cardiac magnetic resonance. JACC Cardiovasc Imaging. 2009;2 (11):1245-52.
18. Biner S, Rafique A, Rafii F, Tolstrup K, Noorani O, Shiota T, 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(3):235-43.
19. He S, Fontaine AA, Schwammenthal E, Yoganathan AP, Levine RA. Integrated mechanism for functional mitral regurgitation: leaflet restriction versus coapting force: in vitro studies. Circulation. 1997;96(6):1826-34.
20. Utsunomiya T, Ogawa T, Doshi R, Patel D, Quan M, Henry WL, et al. Doppler color flow "proximal isovelocity surface area" method for estimating volume flow rate: effects of orifice shape and machine factors. J Am Coll Cardiol. 1991;17(5):1103-11. Erratum in: J Am Coll Cardiol. 1993;21(6):1537.
21. Kizilbash AM, Willett DL, Brickner ME, Heinle SK, Grayburn PA. Effects of afterload reduction on vena contracta width in mitral regurgitation. J Am Coll Cardiol. 1998;32(2):427-31.
22. Hamada S, Altiok E, Frick M, Almalla M, Becker M, Marx N, et al. Comparison of accuracy of mitral valve regurgitation volume determined by three-dimensional transesophageal echocardiography versus cardiac magnetic resonance imaging. Am J Cardiol. 2012;110(7):1015-20.
23. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation. 2001;103(13):1759-64.
24. Grigioni F, Detaint D, Avierinos JF, Scott C, Tajik J, Enriquez-Sarano M. Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. J Am Coll Cardiol. 2005;45(2):260-7.
25. Blondheim DS, Jacobs LE, Kotler MN, Costacurta GA, Parry WR. Dilated cardiomyopathy with mitral regurgitation: decreased survival despite a low frequency of left ventricular thrombus. Am Heart J. 1991;122(3 Pt 1):763-71.
26. Junker A, Thayssen P, Nielsen B, Andersen PE. The hemodynamic and prognostic significance of echo-Doppler-proven mitral regurgitation in patients with dilated cardiomyopathy. Cardiology. 1993;83(1-2):14-20.

27. Enriquez-Sarano M, Rossi A, Seward JB, Bailey KR, Tajik AJ. Determinants of pulmonary hypertension in left ventricular dysfunction. J Am Coll Cardiol 1997;29(1):153-9.

28. Breithardt OA, Sinha AM, Schwammenthal E, Bidaoui N, Markus KU, Franke A, et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol. 2003;41(5):765-70. Erratum in J Am Coll Cardiol. 2003;41(10):1852.

29. Tarasoutchi F, Montera MW, Grinberg M, Barbosa MR, Piñeiro DJ, Sánchez CR, et al; Sociedade Brasileira de Cardiologia. Diretriz brasileira de valvopatias - SBC 2011. / I Diretriz Interamericana de Valvopatias - SIAC 2011. Arq Bras Cardiol. 2011;97(5 supl. 3):1-67.