Original Article

Impact of Etiology on the Left Atrial Function in Patients with Severe Mitral Regurgitation

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Abstract

Introduction: Adaptation to chronic volume overload in patients with mitral insufficiency (MI) tends to increase left atrium (LA), leading to LA dysfunction and arrhythmias. Though LA dimension is a well-known cardiovascular risk predictor, LA contractile function has not been thoroughly assessed in patients with MI of distinct etiologies.

Objective: We aimed to assess LA structure and function in patients with MI due to rheumatic heart disease (RHD) and mitral valve prolapse (MVP).

Methods: We assessed 54 patients with severe MI, defined by an effective regurgitant orifice (ERO) $\geq$ 0.40 cm^2, 23 with RHD and 31 with MVP, all in sinus rhythm and with left ventricular (LV) ejection fraction > 60%. We measured LV diameters and mass, and also volumes (Simpson) to assess function, including maximal, minimal and pre-atrial contraction volumes, and total (TLAEF), passive (PLAEF) and active (ALAEF) LA emptying fraction. Transmitral and tissue Doppler measurements were obtained.

Results: Compared to MVP, patients with RHD were younger (35 ± 11 versus 55 ± 13 years) and mainly female (17 versus 7 female; $p < 0.05$); LV mass index was higher for MVP patients. Although LA maximal volume was similar for both groups, patients with RHD had higher minimal LA volumes (56.9 ± 30 versus 41.6 ± 17 ml; $p = 0.02$), resulting in lower TLAEF (0.41 ± 0.11 versus 0.47 ± 0.07; $p = 0.03$) and ALAEF (0.20 ± 0.08 versus 0.27 ± 0.07; $p < 0.001$).

Conclusion: Although younger, patients with MI due to RHD present with more severe LA dysfunction compared to MVP, possibly reflecting direct atrial impairment from RHD. (Arq Bras Cardiol: Imagem cardiovasc. 2016;29(1):3-10)

Keywords: Atrial Function Left; Mitral Valve Insufficiency; Rheumatic Heart Disease; Mitral Valve Prolapse; Echocardiography.

Introduction

Chronic volume overload in patients with mitral regurgitation (MR) brings important cardiac adaptations, including an increase in the left chambers and increase in left ventricular (LV) mass. Volume overload tends to decrease relaxation and increase the complacency of LV with a "supernormal" diastolic function in hearts with preserved ventricular function.[1,2] Increased atrioventricular gradient at the initial stage of diastole leads to an increased initial LV diastolic filling and decrease of active atrial contribution to filling. It has been demonstrated that left atrial size,[3] in particular, its volume measurement, brings important cardiovascular prognostic information;[4] in patients with severe MR of degenerative etiology it was observed that the LA volume is a predictor of atrial fibrillation.[5] However, for patients with MR, atrial mechanical function has not been consistently studied.

The purpose of this study was to assess left atrial function and its interaction with the LV diastolic function in patients with chronic MR of distinct etiologies.

Methods

Patients

We prospectively studied, by transthoracic echocardiography with color mapping and tissue Doppler, patients older than 18, of both sexes, with severe chronic MR, with etiology defined by clinical tests and echocardiography as of rheumatic etiology or mitral valve prolapse (MVP). The diagnosis of rheumatic cardiomyopathy was given by clinical history of previous episodes of rheumatic heart disease (RHD) using crystalline penicillin to prevent new episodes[6] and echocardiography compatible with rheumatic abnormalities: valvar thickening with reduced mobility of the leaflets and commissural fusion without significant stenosis (mean gradient < 5 mmHg, mitral valve area (MVA) > 2 cm^2). Diagnosis of prolapse was given by the presence of mitral valve thickening (> 5 mm) with myxomatous

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degeneration and systolic bulging > 2 mm of one or both leaflets into the LA during ventricular systole > 2 mm.[7] Exclusion criteria: Inadequate apical echocardiographic window was an exclusion criterion in this study. Besides this, patients with irregular rhythm were excluded from the analysis, particularly those with atrial fibrillation. LV ejection fraction <60% and other associated valvular heart diseases with significant lesiosn (> mild), including mitral stenosis, were also excluded from the study. All patients signed an informed consent form to participate in the study, which was approved by the Ethics Committee of Instituto do Coração, São Paulo.

Echocardiography

Transthoracic echocardiography with tissue Doppler was performed in all patients with a commercially available machine with harmonic properties (Philips HDI 5000, Andover, CA, USA). Parasternal longitudinal plane was used to obtain measurements of LV diastolic and systolic diameters and septal and posterior wall diastolic thickness for mass measurements, with subsequent indexation to body surface area. Measurement of LA systolic diameter was also obtained with two-dimensional echocardiography. LV systolic function was assessed by ejection fraction according to Simpson's biplane method.

Left atrial function measures

Measurements of left atrial volume and function were obtained by two and four-chamber apical views according to the Simpson's method. The parameters studied were the following (Figure 1):

1. **Maximum LA volume** measured at the end of ventricular systole before the mitral valve opening **(VolmaxLA)**;
2. **Atrial precontraction volume (VolPreLA)** measured immediately before atrial contraction at the beginning of the P wave in the echocardiography;
3. **Minimum LA volume** measured at the end of ventricular diastole upon mitral valve closing **(VolminLA)**.

These volumes were subsequently indexed to body surface.

LA emptying volumes were calculated as follows:

- **Total LA emptying volume (VolTELA) = Volmax - Volmin LA;**
- **LA passive emptying volume (VolPELA) = Volmax - VolPreLA;**
- **LA ejection Volume (VolEjLA) = VolPreLA - Volmin LA.**

The following parameters were then derived:

a. **LA total emptying fraction (TLAEF) = Vol TE LA/ VolmaxLA,** used as an estimate of LA global function;

b. **LA passive emptying fraction (PLAEF) = VolE P LA / VolmaxLA** used as an estimate of LA conduit function;

c. **LA active emptying fraction (ALAEF) = VolEj. LA / Vol PreLA** used as an estimate of LA contractile function.

Atrial contraction force (ACF) was measured and defined as the force exerted by the LA to accelerate blood in the LV during atrial systole. This index is based on Newton's second law of motion using the following formula: atrial contraction force (Kdyn) = 0.5 x 1.06 x MVA x (A wave velocity)^2 where 0.5 is an acceleration constant of A wave and 1.06 is the blood density (g/cm^3).[8-10] The MVA was calculated by the PHT formula in all patients according to the formula AVM = 220/PHT.

Diastolic function was assessed using E and A waves and deceleration time (DT) from transmitral flow measurements obtained from apical 4 chamber-view, with the Doppler sample volume positioned at mitral valve tips, guided by color Doppler.

Tissue Doppler

Diastolic function was assessed using E and A waves and DT from transmitral flow measurements obtained from apical 4 chamber-view, with the Doppler sample volume positioned at mitral valve tips, guided by color Doppler.[10,11]

Evaluation of mitral regurgitation

After two-dimensional evaluation of the valves, color mapping and pulsed Doppler was used to assess MR. Parameters such as E wave velocity, width of color flow regurgitant jet and flow reversal in the pulmonary veins were observed, however, degree of MR was given quantitatively by the PISA method (proximal isovelocity surface area),[12] obtained as follows: the MR convergence area radius was measured from color mapping in the apical 4-chamber view after zooming and decreasing the color mapping baseline to optimize the image. Continuous Doppler was used to measure MR peak velocity. The effective regurgitant orifice area (EROA) was given using the formula $2\pi R^2$x aliasing velocity/MR jet peak velocity; EROA ≥ 0.4 cm was considered for defining severe MR.[13]

Statistical analysis

Data were expressed as mean and standard deviation or percentages; the groups were tested using the Student's unpaired t test (two-tailed) for continuous variables and chi-square test for categorical variables, as appropriate. The Pearson correlation test was used to evaluate the linear relationship between continuous variables. Variables with non-normal distribution were tested using the Wilcoxon test. A p value < 0.05 was considered statistically significant. We used the software JMP version 1.9, SAS Institute for statistical analysis.

Results

From 61 patients, 7 were excluded, 2 with atrial fibrillation, 2 with inadequate window, 2 with LVEF < 60%, 1 with mitral stenosis associated. Therefore, 54 patients were studied, of which 30 were males with mean age 45 ± 12 years. Of the 54 patients studied, 23 had RHD and 31 had MVP. The patients were divided into two groups according to etiology. Patients with RHD were younger (35 ± 11 versus 55 ± 13, p < 0.001 respectively for RHD and MVP) and, as expected, this group had a higher proportion of female patients, with 17 women

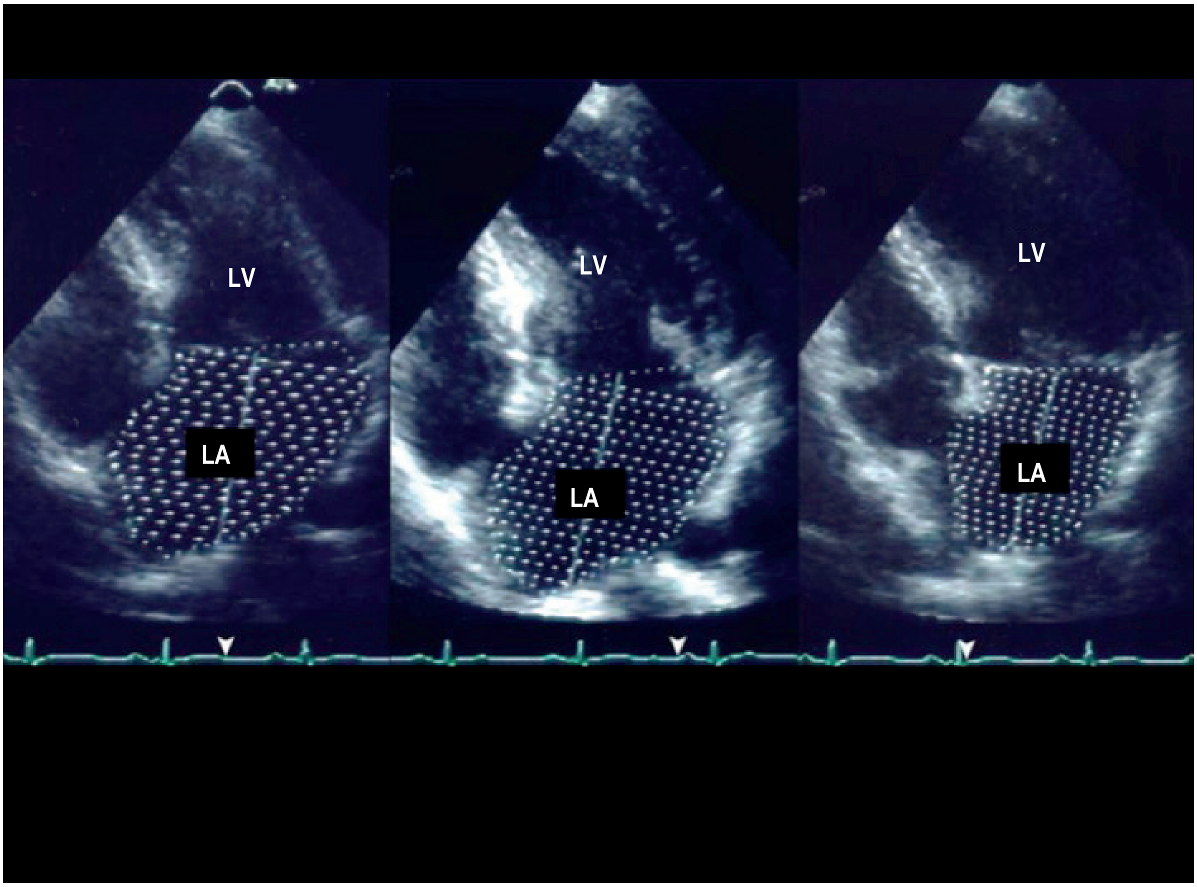

Figure 1 – *Apical 4-chamber view showing the measurements of left atrial maximum, pre A and minimum volume. LA: left atrium; LV: left ventricle.*

(74%) compared to 7 women (23%, $p < 0.001$) for the MVP group. Regarding echocardiographic data (Table 1), there was no difference in relation to systolic or diastolic LV diameters or left atrial diameter for both groups, however, patients with MVP had higher body mass index than those with RHD. Ejection fraction, according to a previously established exclusion criterion, was within the normal range and was similar for both groups. Conventional Doppler parameters were similar for both groups except for the E wave DT, which was longer for the rheumatic group. In addition, tissue Doppler findings were also similar in both groups except for the medial mitral annulus a' wave velocity, which was lower for the rheumatic group (6.8 ± 1.6 versus 9.1 ± 3.2; $p < 0.001$). In addition, a moderate correlation between the medial mitral annulus a' wave velocity with the left atrial active emptying fraction was observed ($p = 0.001$, $r^2 = 0.44$). Regarding the magnitude of MR, the EROA was similar for both groups (0.57 ± 0.1 versus 0.67 ± 0.3 cm^2; $p = 0.07$) and the MVA was not different either (3.8 ± 0.7 versus 3.4 ± 0.7 cm^2; $p = 0.06$) for the MVP and RHD groups, respectively.

Left atrial structure and function

Left atrial volumes were similar for both groups (Table 2), except for the LA indexed Volmin., which was lower for the group of patients with prolapse (56.9 ± 30 vs. 41.6 ± 17 mL; $p = 0.02$). There was a better atrial contractile function for patients with MVP compared to those with RHD (Figures 2 and 4), with reduced total emptying fraction (0.47 ± 0.07 versus 0.41 ± 0.11, respectively, for patients with MVP and RHD, $p = 0.03$) and reduced active emptying fraction (ALAEF = 0.27 ± 0.07 versus 0.20 ± 0.08; $p < 0.001$) for rheumatic patients compared to those with MVP. In addition, similar passive emptying fraction was observed in both groups (Figure 3). Regarding the atrial contraction force, there was no significant difference between the groups (Table 2), and there was no correlation between this index and the left atrial passive emptying fractions ($p = 0.07$, $r^2 = 0.06$) and active emptying fractions ($p = 0.5$, $r^2 = 0.004$).

Table 1 – Echocardiographic variables related to the two groups

Variables	RHD (n = 23)	MVP (n = 31)	p
LV mass index (g/m²)	126.2 ± 25.7	126.2 ± 25.7	< 0.001
LV EDD (cm)	6.5 ± 0.6	6.6 ± 0.4	NS
LV ESD (cm)	4.0 ± 0.4	4.0 ± 0.4	NS
LVEF (%)	64 ± 4	66 ± 6	NS
E wave (cm/s)	142 ± 35	135 ± 28	NS
A wave (cm/s)	68 ± 29	60 ± 18	NS
DT (ms)	230 ± 44	206 ± 35	0.03
septal e' wave (cm/s)	12.6 ± 4.1	11.6 ± 2.9	NS
lateral e' wave (cm/s)	14.9 ± 5.4	15.4 ± 4.4	NS
septal a' wave (cm/s)	6.8 ± 1.6	9.1 ± 3.2	< 0.001
ERO area (cm²)	0.57 ± 0.1	0.67 ± 0.3	0.07
MVA (PHT) (cm²)	3.4 ± 0.7	3.8 ± 0.7	0.06

RHD: rheumatic heart disease; MVP: mitral valve prolapse; LV: left ventricle; NS: not significant; EDD: end-diastolic diameter; ESF: end-systolic diameter; EF: ejection fraction; DT: E wave deceleration time; ERO: effective regurgitant orifice; MVA: mitral valve area; PHT: pressure half-time.

Table 2 – Echocardiographic variables related to the left atrium

Variables	RHD (n = 23)	MVP (n = 31)	p
LA (cm)	5.3 ± 0.8	5.0 ± 0.6	NS
Indexed LA Volmax (mL/m²)	92.83 ± 38	77.3 ± 26	NS
Indexed VolPre LA (mL/m²)	69.6 ± 34	57.2 ± 22	NS
Indexed LA Volmin (mL/m²)	56.9 ± 30	41.6 ± 17	0.02
VolTE Indexed LA (mL/m²)	35.9 ± 12.9	35.6 ± 12	NS
VolPE LA (mL)	39.4 ± 18	33.8 ± 18	NS
VolEj. LA (mL)	21.7 ± 11	26.9 ± 13	NS
ACF (kdyn)	9.42 ± 7.13	7.672 ± 4.38	NS

RHD: rheumatic heart disease; MVP: mitral valve prolapse; LA: left atrium; Vol: volume; max: maximum; min: minimum; P: passive; PreLA: atrial precontraction; T: total; Ej: ejection; ACF: atrial contraction force; NS: nort significant.

Discussion

This study is unique in the literature comparing the atrial function of patients with MR due to MVP and patients with rheumatic fever. Atrial volumes and function are important prognostic predictors in many cardiovascular diseases and in patients with MR; it has been observed that the maximum atrial volume is related to a higher number of late adverse events after surgery.[14] In our study, we demonstrated significant increase in maximum LA volume for the population of patients with MI, but this increase was similar for patients with MVP and RHD. Increased LA in MI directly correlates with the degree of regurgitation and, in that case, both groups had similar degrees of MI, as demonstrated by the similar EROA values. On the other hand, atrial mechanical function was different for the two groups, with patients with RHD showing worse atrial function. Atrial function can be basically defined as having three stages during the cardiac cycle: the reservoir stage, when the atrium receives blood from the pulmonary veins, during ventricular systole; the conduit stage during early diastole, when blood passively flows through the pulmonary veins to the LV according to the pressure gradients between the chambers; the active stage, when there is atrial contraction.[15] The contribution of the contractile function to this active phase is very important. In our study, we observed that the atrial contractile function of patients with RHD was decreased (higher minimum volume) compared to that of patients with MVP demonstrated by a smaller active and total LA emptying fraction. This finding provides some explanations that are relevant. Firstly, it is likely that rheumatic damage occurs not only to mitral valve but also to the atrial muscle of rheumatic patients due to the inflammatory component of rheumatic fever, leading to atrial dysfunction. The presence of LV fibrosis has been demonstrated in the magnetic resonance imaging of patients with heart valve disease;[16] histological studies have shown variable degrees of fibrosis in the atrial muscle of patients with rheumatic fever undergoing surgery, with severe loss of muscle and distortion of the atrial architecture.[17] These atrial fibrosis areas could be related to a significant atrial contractile dysfunction. Additionally, Aschoff nodules, pathognomonic for chronic RHD, were found in 21% of patients with rheumatic fever that had their left atrial appendage excised during surgery to treat mitral valve disease. This finding is more common in patients with mitral stenosis,[18] but is also found in patients with MI. Another possible explanation for more severe impairment of atrial function in rheumatic patients is the presence of some degree of associated stenosis with pressure overload added to atrial volume overload. Even without significant mitral stenosis, we observed a significantly longer DT in patients with RHD, which could be explained by the valve lesion related to the disease. It is established that patients with mitral stenosis are affected by severe dilation and atrial failure, hence the propensity to present atrial fibrillation. The coexistence of mitral stenosis is an independent risk predictor for AF in rheumatic patients with severe MI, along with LA size and female sex.[19] Chronic rheumatic disease, which for these patients begins in the early stages of life (10 - 12 years old in most cases), resulting in prolonged exposure to the disease, could also explain the higher impairment of this chamber.

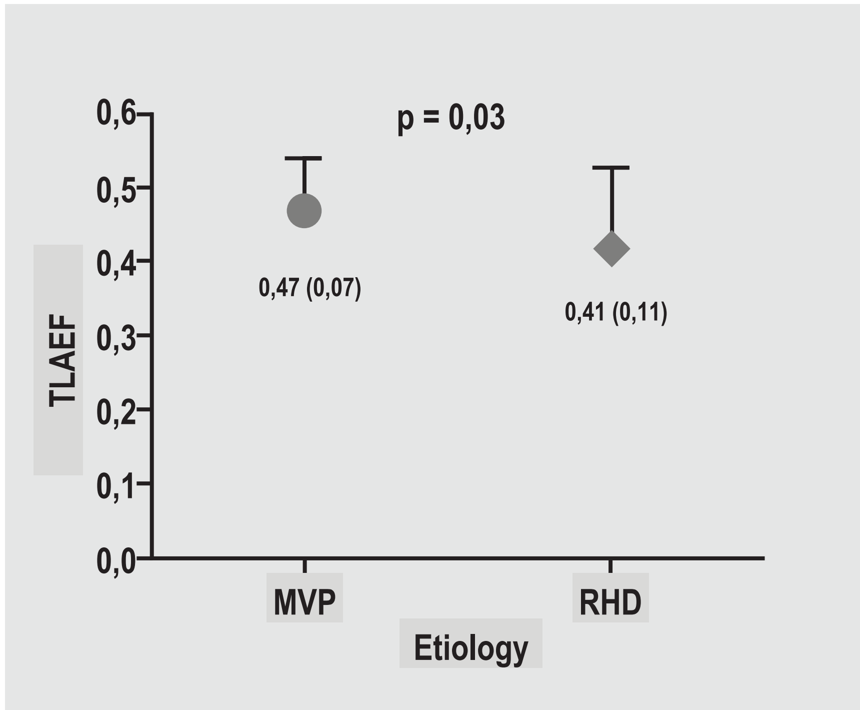

Figure 2 – *Chart showing total left atrial emptying fraction (TLAEF) for both groups, with higher values for patients with mitral valve prolapse (MVP) compared to those with rheumatic heart disease (RHD).*

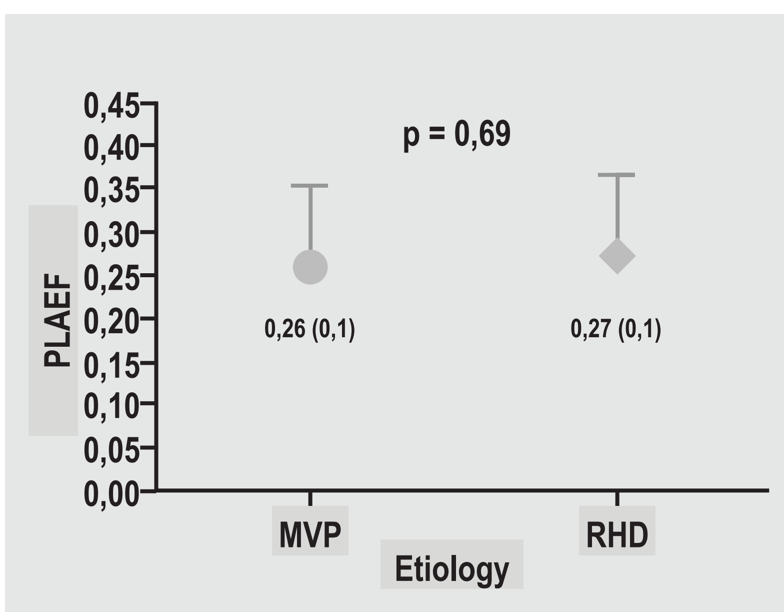

Figure 3 – *Chart showing the left atrial passive emptying fraction (PLAEF) for the mitral valve prolapse (MVP) and rheumatic heart disease (RHD) groups. There is no significant difference in the passive emptying fraction.*

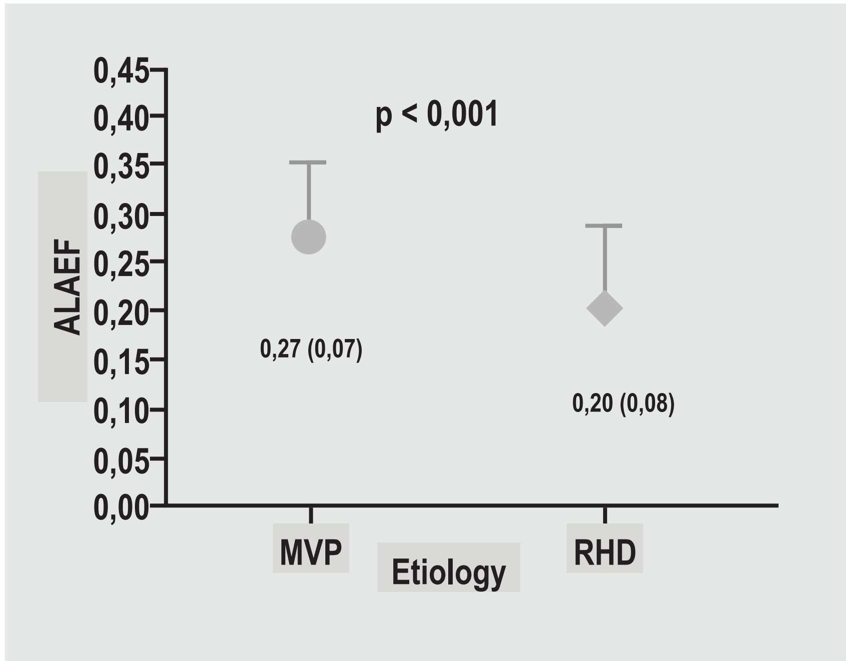

Figure 4 – *Chart showing active left atrial emptying fraction (ALAEF) for both groups, with higher values for patients with mitral valve prolapse (MVP) compared to patients with rheumatic heart disease (RHD).*

On the other hand, a reason for the difference in the atrial function between the groups could be a possible increase in the atrial contractile function in the group with MVP, consisting of older individuals, hence justifying the presence of early diastolic dysfunction (abnormal LV relaxation). With an abnormal ventricular relaxation, the relative contribution of atrial reservoir and contractile function increases as the conduit function would be adversely affected.[20] However, this group of patients did not have other echocardiographic parameters compatible with impaired LV relaxation, since DT was normal, with normal or increased E/A ratio and tissue Doppler e' wave showing normal values. In MR, a higher atrioventricular gradient at the initial stage of diastole leads to a higher initial diastolic filling flow and, consequently, a decreased active atrial contribution; in this situation, we observe an increased E wave (early diastolic filling) and decreased mitral flow A wave.

While some degree of stenosis in the rheumatic group may have influenced the values of atrial emptying fractions, we would expect its impact on the passive emptying protodiastolic phase, influencing both the atrial precontraction volume and the passive emptying fraction, which were not different in both groups. However, only the active emptying fraction, significantly smaller in the rheumatic group, and the minimum left atrial volume, significantly higher in the same group, would suggest a reduction of left atrial contractility in this etiology. Moreover, the valve area was not different in the two groups. Another fact that corroborates the little influence of the MVA in our results was the lower a' wave velocity of the medial mitral annulus on tissue Doppler in the rheumatic group. Note that this parameter has been widely used in other studies to accurately assess the atrial systolic function, since it is less dependent on load.[10,11] There was no difference between the groups in the other tissue Doppler parameters. We believe that if there was some degree of influence of stenosis, all parameters would possibly suffer modifications.

Clinical Implications

More severe earlier atrial contractile dysfunction (considering the patient's age) for the same degree of MI occurring in patients with RHD could possibly explain the higher prevalence of arrhythmias or thrombus formation in this group occurring even after valve lesion repair.

Limitations

One reason for the reduced atrial function would be the presence of paroxysmal atrial fibrillation due to severe atrial dilation; none of the patients reports this arrhythmia, but it can be asymptomatic; however, this data would have been possibly present for the two groups, since they had similar maximum left atrial volume.

Unfortunately, we do not have any data on the drug therapy prescribed to the patients, so it was not possible to assess the impact on our findings.

In addition, it is known that three-dimensional echocardiography compared to magnetic resonance imaging provides a more accurate estimate of LA volumes compared to two dimenional echocardiography; however, the measurements of atrial volumes were carried out similarly by the two-dimensional echocardiography for the two groups, showing the difference between them.

Conclusion

Though younger, patients with rheumatic MR have more severe impaired atrial function compared to patients with MVP, possibly reflecting the involvement of the atrial myocardium from the disease.

Authors' contributions

Research creation and design: Costa JM, Sampaio RO, Spina GS, Rodrigues ACT; Data acquisition: Costa JM, Sampaio RO, Mathias W; Data analysis and interpretation: Costa JM, Spina GS, Rodrigues ACT; Statistical analysis: Costa JM, Rodrigues ACT; Manuscript drafting: Costa JM, Sampaio RO, Spina GS; Critical revision of the manuscript for important intellectual content: Costa JM, Mathias W, Rodrigues ACT.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

Sources of Funding

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Academic Association

This study is not associated with any graduate program.

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