

Left Atrial Function Analysis in Patients with Functional Mitral Regurgitation Associated with Dilated Cardiomyopathy

Análise da Função Atrial Esquerda em Pacientes com Insuficiência Mitral Funcional Associada à Miocardiopatia Dilatada

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Abstract

Background: Functional mitral regurgitation (FMR) is associated with dilated cardiomyopathy (DC), heart failure (HF) and worsening left atrial function (LAF). Patients with DC and FMR may present left atrial dysfunction resulting from both ventricular dysfunction and valve disease, but it is unknown whether the presence of valve disease will lead to greater LAF impairment.

Objective: This study aimed to evaluate the relationship between LAF parameters and FMR degree in patients with DC.

Methods: This cross-sectional observational study included 214 patients with DC, 46 without FMR (control group) and 168 with mild, moderate or severe FMR. An LAF analysis was performed by speckle tracking echocardiography (STE) and atrial volumetric variation.

Results: LAF analyzed by STE by means of reservoir strain, conduit strain and active contraction strain was reduced in the sample, with values of 14.3%, 8.49% and 5.92%, respectively. FMR degree was significantly associated with reservoir strain (0.27 ± 0.16 versus 0.15 ± 0.09 ; $p < 0.001$) and contraction strain (19.2 ± 7.3 versus 11.2 ± 2.7 ; $p < 0.001$). FMR was also associated with a reduced LAF assessed by volumetric analysis: total atrial emptying fraction of 0.51 ± 0.13 versus 0.34 ± 0.11 and active atrial emptying fraction of 0.27 ± 0.16 versus 0.15 ± 0.09 ($p < 0.001$).

Conclusion: In a population with DC, FMR was associated with reduced LAF assessed by STE and atrial volume variation.

Keywords: Atrial Function, Left; Mitral Valve Insufficiency; Cardiomyopathy, Dilated; Echocardiography.

Resumo

Fundamento: A insuficiência mitral funcional (IMF) está associada à miocardiopatia dilatada (MD), à insuficiência cardíaca (IC) e à piora da função atrial esquerda (FAE). A FAE pode decair tanto pela disfunção ventricular quanto pela valvopatia, mas não se sabe se esta leva a um prejuízo maior da FAE.

Objetivo: Avaliar a relação entre a piora de parâmetros de FAE com o grau de IMF, em pacientes com MD.

Métodos: Trata-se de estudo observacional transversal, que incluiu 214 pacientes com MD, sendo 46 sem IMF (controle) e 168 com IMF discreta, moderada ou grave. A análise da FAE foi realizada por ecocardiografia por speckle tracking (STE) e por variação volumétrica atrial.

Resultados: A FAE, analisada por STE – por meio do strain de reservatório, conduto e contração ativa – encontrou-se reduzida na amostra, com valores respectivos de 14,3%, 8,49% e 5,92%. O grau de IMF associou-se significativamente com os valores do strain de reservatório ($0,27 \pm 0,16$ versus $0,15 \pm 0,09$; $p < 0,001$) e de contração ($19,2 \pm 7,3$ versus $11,2 \pm 2,7$; $p < 0,001$). A IMF também apresentou correlação com a redução da FAE avaliada por análise volumétrica, observada pela medida da fração de esvaziamento atrial total (FEAT): $0,51 \pm 0,13$ versus $0,34 \pm 0,11$ e da fração de esvaziamento atrial ativa (FEAA): $0,27 \pm 0,16$ versus $0,15 \pm 0,09$ com $p < 0,001$.

Conclusão: Em uma população com MD, a presença de IMF associa-se à redução da FAE de reservatório e de contração, avaliada por STE e pela variação volumétrica atrial.

Palavras-chave: Função do átrio esquerdo; Insuficiência da valva mitral; Cardiomiopatia dilatada; Ecocardiografia.

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Introduction

Mitral regurgitation (MR) is characterized by blood regurgitation into the left atrium (LA) during ventricular systole. Functional MR (FMR) results from valve geometry changes induced by left ventricular (LV) dilation that separates the papillary muscles, or from annulus dilation due to atrial enlargement that creates a central area of poor valve leaflet coaptation and, subsequently, reflux into the LA. The most common causes of FMR are myocardial ischemia and dilated cardiomyopathy (DCM).¹⁻³

It is difficult to estimate the epidemiology of FMR due to differences in definitions in the literature, but some studies suggest that about 40% of patients with DCM will develop FMR.⁴⁻⁶ Data on the Brazilian population show that the main etiologies of DCM are ischemic, hypertensive, and dilated idiopathic heart failure (HF), which affect 30.1%, 20.3% and 14.6% of patients, respectively.⁷

The LA is a functional cavity that works as a volume reservoir and contractile myocardium and plays a crucial role in cardiac performance.⁸ LA function (LAF) is classically divided into three phases (reservoir, conduit, and active contraction), which can be obtained through two-dimensional echocardiography by speckle tracking (STE) or atrial volume variation.⁹⁻¹¹ Good LA functioning is even more important in patients with HF since atrial output can correspond to up to 30% of cardiac output, something relevant in patients with LV dysfunction.¹⁰

Patients with DCM and FMR may have atrial dysfunction resulting from ventricular dysfunction and valvular heart disease, but whether the presence of valvular heart disease leads to greater LAF impairment it is unknown. This study aimed to evaluate the correlation between LAF worsening assessed by STE and phasic volumetric variation and the degree of FMR in patients with DCM.

Method

Population

This cross-sectional observational study enrolled patients who underwent HF treatment in a specialized tertiary hospital in 2007–2011. The inclusion criteria were sinus rhythm; left ventricular ejection fraction (LVEF) < 40%; and mild, moderate, or severe MR with functional characteristics on two-dimensional echocardiography. The exclusion criteria were history of acute myocardial infarction or unstable angina less than 90 days before the examination; acute myocarditis; history of organic (primary) valve disease or previous valve surgery; or echocardiographic image of inadequate quality. All participants signed an informed consent form, and the institution's research ethics committee approved the study. Of the 280 patients who met the inclusion criteria, 25 were excluded due to inadequate image quality or echocardiographic monitoring, leaving 255 participants for the analysis. Of them, data were available for FMR assessment for only 214: 46 had no FMR (control group), 124 had mild FMR, 29 had moderate FMR, and 15 had severe FMR.

Echocardiography

Echocardiographic images were acquired using Vivid 7 and Vivid E9 devices (GE Healthcare), and images were

analyzed by advanced techniques (STE) on an appropriate workstation using EchoPAC PC® software version 6.0.1 (GE Healthcare).

Echocardiography was performed with electrocardiographic monitoring following American Society of Echocardiography guidelines.^{12,13} FMR degree was assessed following the same guidelines, favoring quantitative measures such as effective regurgitant orifice (ERO; cm²) and regurgitant volume (RV; mL).^{14,15}

Images were obtained in different phases of the cardiac cycle for LA volume measurements as recommended by Abhayaratna et al.¹⁶ Three volumes were obtained in apical four- and two-chamber windows: maximum volume (at the end of ventricular systole), pre-P-wave volume (immediately before the P-wave on electrocardiography), and minimum volume (at the end of ventricular diastole). The reservoir function is represented by the total atrial emptying fraction (TAEF) and active contraction function by the active atrial emptying fraction (AAEF). TAEF is calculated as (maximum volume - minimum volume)/maximum volume. AAEF is calculated as (pre-P volume - minimum volume)/pre-P volume.

LA strain was analyzed by STE using the software originally developed for LV assessment. This evaluation was performed in apical four- and two-chamber views with six different segments analyzed in each. Each segment generated a regional atrial strain curve. The mean between these curves in both acquisitions was used to measure the reservoir function, which corresponds to the greatest positive longitudinal strain measured after the T wave by electrocardiography and the contraction function, which corresponds to the ascending P-wave strain. The conduit function corresponds to the difference between these values (Figure 1).¹⁷

Statistical analysis

Quantitative variables were subjected to the Kolmogorov-Smirnov test for a normality assessment. Normally distributed variables are presented as mean and standard deviation. Non-normally distributed variables are described as median and interquartile range (Q1–Q3). Categorical variables are presented as percentages.

The Pearson's and Spearman's methods were used to assess the correlation between the variables representing LA function, the quantitative variables for FMR grading, and LVEF.

Analysis of variance was used to assess the association between atrial emptying volumes and fractions and reservoir, conduit, and contraction atrial strain values by FMR (mild, moderate, and severe).

Values of $p < 0.05$ were defined as significant in all analyses performed using SPSS software for Windows (version 20.0; IBM) and tabulated using Microsoft Excel 2003 software.

Results

Clinical characteristics

Most patients were men (62%), with a mean age of 59 ± 13 years and New York Heart Association functional classes II

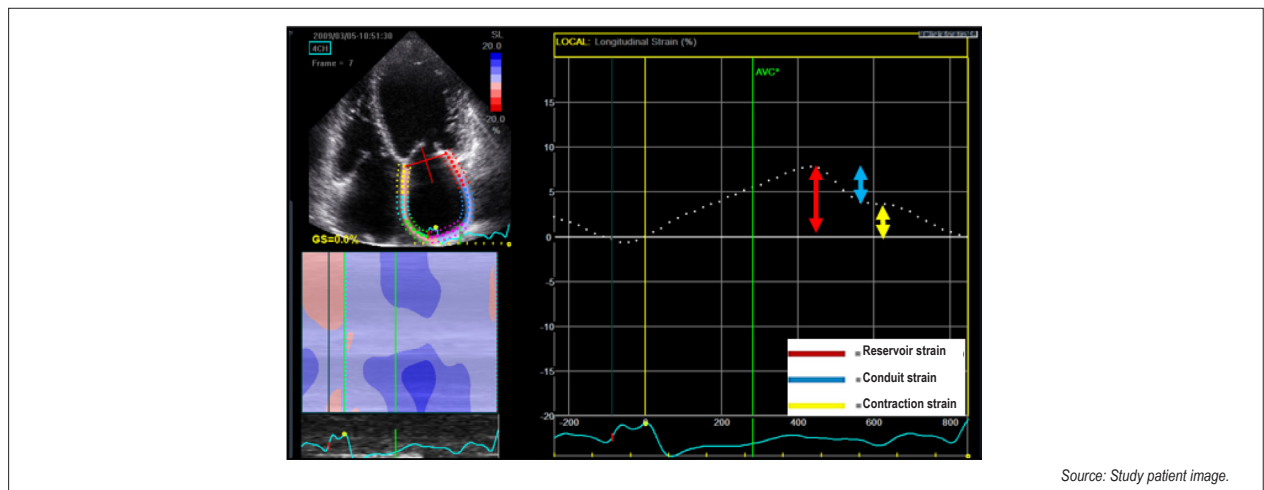


Figure 1 – Atrial strain phases by two-dimensional speckle tracking echocardiography in apical four-chamber view synchronized by QRS. The dotted curve in the center represents the mean between the regional strain curves with their reservoir and contraction strain peaks. The difference between them represents the conduit strain.

and III. The most frequent comorbidities were arterial hypertension (62.7%), coronary artery disease (32.9%), and previous infarction (38.4%).

Most patients were on optimized treatment for HF, with angiotensin-converting enzyme inhibitors being used by 65.7%, angiotensin 2 receptor blockers by 25.7%, beta-blockers by 89.8%, and spironolactone by 72%.

Table 1 demonstrates the clinical characteristics of the study population.

Echocardiographic characteristics

Most patients in the study had significant LV dysfunction, with a mean LVEF of $29.7 \pm 6.4\%$. The main echocardiographic variables are described in Table 2.

LA function

All atrial function components – reservoir, conduit and active contraction – measured by STE were significantly reduced in the sample by 14.3%, 8.49%, and 5.92%, respectively. LA volumes increased, with a mean of 45.3 ± 17.2 mL/m² at maximum volume. The atrial function variables are described in Table 3.

The analysis of ischemic versus non-ischemic etiology showed no difference except for the maximum LA volume, which was greater in non-ischemic patients (Table 4).

Mitral regurgitation

FMR degree was significantly correlated with LAF assessed by a volume analysis using the total and active emptying fractions. The STE analysis showed that FMR degree was associated with reservoir and contraction strain. FMR degree was directly associated with increased LA volume and inversely related to LVEF. Table 5 shows the analysis of these data.

As for FMR quantitative variables, ERO and RV were directly correlated with atrial volume and inversely correlated with atrial

function. LVEF showed the same correlation pattern but with a less strong association (Table 6).

Discussion

Two findings were especially relevant in this study: variables related to LAF reservoir and contraction were reduced in this sample of patients with DCM; and FMR degree was significantly associated with most echocardiographic parameters related to volume and LAF.

Ischemic MR severity was associated with all variables related to left atrial volume, atrial emptying fractions, and reservoir and active contraction strain, possibly due to MR pathophysiology in which the blood returns to the LA, increasing its pressure and dimensions and, consequently, reducing its function. The literature reports the same finding, mostly related to organic MR as no studies on FMR are currently available. A study of 144 patients with FMR subdivided into groups 1 (absent or mild MR) and 2 (moderate or severe MR) reported a correlation between degree of regurgitation and left atrial volume, but parameters related to atrial function were not analyzed.¹⁸

As for prognosis, FMR is classically one factor associated with lower survival, worse functional class, and greater morbidity in DCM.¹⁹⁻²³ However, it is unclear whether atrial dysfunction associated with this condition represents an additional adverse prognostic factor.

LA volume has been extensively studied and is currently a more reliable LA dimension measurement than anteroposterior diameter.²⁴⁻²⁷ In fact, it has prognostic value in several cardiovascular diseases.²⁸⁻³⁷

A European multicenter study of 371 healthy participants reported indexed LA volume, TAEF, and AAEF values of 26.3 mL/m², 68.5%, and 43.1%, respectively.³⁸ In our study, the atrial volumes were increased and the phasic function variables were decreased. Indexed LA volume, TAEF, and AAEF values were 45.3 ± 17 mL/m², $42 \pm 15\%$, and $22 \pm 14\%$, respectively.

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Table 1 - Clinical characteristics of the population.

Variable	Value (N = 255)
Sex	
Male	158 (62)
Female	97 (38)
Age, years	59 ± 13
NYHA functional class	
I	24 (9.4)
II	112 (43.9)
III	82 (32.2)
IV	37 (14.5)
Heart rate, bpm	68.9 ± 12.3
DM	
No	189 (74.1)
Yes	66 (25.9)
SAH	
No	95 (37.3)
Yes	160 (62.7)
CAD	
No	150 (58.8)
Yes	105 (41.2)
Previous AMI	
No	157 (61.6)
Yes	98 (38.4)
Chagas	
No	225 (88.2)
Yes	30 (11.8)
Myocarditis	
No	241 (94.5)
Yes	14 (5.5)
Previous rheumatic disease	
No	254 (99.6)
Yes	1 (0.4)
Alcoholism	
No	235 (92.2)
Yes	20 (7.8)
Other comorbidities	
No	200 (78.4)
Yes	55 (21.6)
Drugs	
Digoxin	68 (26.8)
Loop diuretic	200 (78.7)
Thiazide diuretic	22 (8.7)
Spironolactone	183 (72)
Angiotensin-converting enzyme inhibitors	167 (65.7)
Angiotensin 2 receptor blockers	65 (25.7)
Beta-blocker	228 (89.8)
Calcium channel blocker	15 (5.9)
Nitrate	39 (15.4)
Hydralazine	10 (3.9)
ASA	148 (58.3)
Statin	128 (50.4)
Other drug	122 (48.6)

AMI, acute myocardial infarction; ASA, acetylsalicylic acid; BMI, body mass index; BPM, beats per minute; CAD, coronary artery disease; DM, diabetes mellitus; NYHA, New York Heart Association; SAH, systemic arterial hypertension; SD, standard deviation. Values are shown as n (%) or mean ± standard deviation.

Table 2 - Echocardiographic characteristics of the population.

Variable	Value
LA diameter, cm	(n = 214)
Mean ± SD	4.65 ± 0.67
Median (min, max)	4.6 (2.8; 6.9)
VE end-diastolic volume, mL	(n = 214)
Mean ± SD	196.9 ± 73.3
LV end systolic volume, mL	(n = 214)
Mean ± SD	140.5 ± 59.3
LVEF (Simpson's method), %	(n = 214)
Mean ± SD	29.7 ± 6.4
Median (min, max)	0.3 (0.15; 0.4)
LV global longitudinal strain, %	(n = 203)
Mean ± SD	-8.14 ± 2.56
Diastolic dysfunction	(n = 213)
I	59 (27.7)
II	43 (20.2)
III/IV	97 (45.5)
Inconclusive	14 (6.6)
Mitral regurgitant volume, mL	(n = 214)
Mean ± SD	22.7 ± 17.3
Mitral regurgitation ERO, cm ²	(n = 214)
Mean ± SD	0.15 ± 0.12
Mitral regurgitation	(n = 214)
Absent	46 (21.5)
Mild	124 (57.9)
Moderate	29 (13.6)
Severe	(7)

ERO, effective regurgitant orifice; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; SD, standard deviation.

Table 3 - Atrial function variables and synchrony.

Variable	Description
Maximum LA volume, mL/m ²	(n = 214)
Mean ± SD	45.3 ± 17.2
Minimum LA volume, mL/m ²	(n = 214)
Mean ± SD	27.6 ± 15.3
Pre-P LA volume, mL/m ²	(n = 214)
Mean ± SD	36.7 ± 15.8
Total atrial emptying fraction, %	(n = 214)
Mean ± SD	42 ± 15
Active atrial emptying fraction, %	(n = 214)
Mean ± SD	22 ± 14
LA reservoir strain, %	(n = 182)
Mean ± SD	14.3 ± 6.6
LA contraction strain, %	(n = 181)
Mean ± SD	8.49 ± 5.01
LA conduit strain, %	(n = 181)
Mean ± SD	5.92 ± 3.32

LA, left atrium; SD, standard deviation.

Table 4 - Atrial function and synchrony variables according to myocardial disease etiology.

Variable	Etiology		p
	Non-ischemic	Ischemic	
Maximum LA volume, mL/m ²			0.029
Mean ± SD	47.4 ± 18	42.1 ± 15.6	
Minimum LA volume, mL/m ²			0.238
Mean ± SD	28.6 ± 16.1	26.2 ± 13.9	
Pre-P LA volume, mL/m ²			0.083
Mean ± SD	38.2 ± 16.3	34.4 ± 14.7	
Total atrial emptying fraction, %			0.193
Mean ± SD	0.43 ± 0.15	0.4 ± 0.14	
Active atrial emptying fraction, %			0.358
Mean ± SD	0.23 ± 0.15	0.21 ± 0.12	
LA reservoir strain, %			0.259
Mean ± SD	14.8 ± 7.1	13.7 ± 5.8	
LA contraction strain, %			0.407
Mean ± SD	8.8 ± 5.5	8.2 ± 4.4	
LA conduit strain, %			0.207
Mean ± SD	6.2 ± 3.5	5.6 ± 3.1	

Student's t-test. LA, left atrium; SD, standard deviation.

These values tend to be lower in populations with DCM and LV systolic dysfunction. Triposkiadis *et al.* reported a correlation between AAEF reduction in idiopathic DCM and between a ischemic and control group ($18 \pm 10\%$ vs. $32 \pm 10\%$ vs. $36 \pm 10\%$, respectively; $p = 0.05$).³⁹ D'Andrea *et al.* reproduced this finding with an AAEF of $22.5 \pm 10\%$ for idiopathic DCM and $33.1 \pm 9.3\%$ for ischemic DCM.⁴⁰ In our study, atrial function was reduced in the entire group and no differences were observed between the ischemic and non-ischemic etiologies.

STE LAF values in patients with HF with reduced EF tend to be reduced as evaluated by Cameli *et al.*, who found values of $13 \pm 11.3\%$ for reservoir strain and of $5.26 \pm 5.54\%$ for contraction strain in a group of patients with an LVEF < 30%.⁴¹ Another study with a population with DCM and LVEF < 40% reported reservoir and contraction strain values of $12.3 \pm 3.6\%$ and $6.2 \pm 1.6\%$ in patients with increased LV filling pressures, respectively.⁴² In our sample, reservoir, contraction, and conduit functions assessed by two-dimensional strain were also decreased at 14.3%, 8.49%, and 5.92%, respectively.

Table 5 - Echocardiographic parameters by degree of mitral regurgitation.

Variable	Mitral regurgitation				r	p
	Absent	Discrete	Moderate	Severe		
Maximum LA volume, mL/m ²					0.495	< 0.001
Mean ± SD	33.7 ± 11.6	44.5 ± 14	54.7 ± 19.9	68.8 ± 18.6		
Minimum LA volume, mL/m ²					0.515	< 0.001
Mean ± SD	17.2 ± 8.9	27 ± 13.1	37.7 ± 17.6	45.7 ± 15.5		
Pre-P LA volume, mL/m ²					0.512	< 0.001
Mean ± SD	25.6 ± 9.5	36.4 ± 13.4	46 ± 18.9	55.4 ± 15.4		
Total atrial emptying fraction, %					-0.396	< 0.001
Mean ± SD	0.51 ± 0.13	0.41 ± 0.15	0.33 ± 0.11	0.34 ± 0.11		
Active atrial emptying fraction, %					-0.271	< 0.001
Mean ± SD	0.27 ± 0.16	0.23 ± 0.13	0.16 ± 0.09	0.15 ± 0.09		
LA reservoir strain, %					-0.324	< 0.001
Mean ± SD	19.2 ± 7.3	13.5 ± 6.3	12.2 ± 5.1	11.2 ± 2.7		
LA contraction strain, %					-0.408	< 0.001
Mean ± SD	12.25 ± 5.19	8.11 ± 4.58	6 ± 3.87	5.65 ± 2.42		
LA conduit strain, %					-0.007	0.932
Mean ± SD	6.98 ± 4.23	5.58 ± 3.42	6.21 ± 2.74	5.51 ± 1.96		
LVEF (Simpson's method), %					-0.299	< 0.001
Mean ± SD	32.4 ± 5.4	29.3 ± 5.7	26.6 ± 4.9	28.1 ± 5.7		

Spearman correlation. LA, left atrium; LVEF, left ventricular ejection fraction; SD, standard deviation.

Table 6 - Atrial function variables, left ventricular ejection fraction, and quantitative parameters of mitral regurgitation.

Variable	MR ERO		MR RV		LVEF (Simpson's)	
	Correlation	p	Correlation	p	Correlation	p
Maximum LA volume, mL/m ²	0.516	<0.001	0.521	<0.001	-0.254	<0.001
Minimum LA volume, mL/m ²	0.502	<0.001	0.506	<0.001	-0.265	<0.001
Pre-P LA volume, mL/m ²	0.480	<0.001	0.497	<0.001	-0.285	<0.001
Total atrial emptying fraction, %	-0.373	<0.001	-0.381	<0.001	0.234	0.001
Active atrial emptying fraction, %	-0.311	<0.001	-0.289	<0.001	0.088	0.202
LA reservoir strain, %	-0.390	<0.001	-0.334	<0.001	0.344	<0.001
LA contraction strain, %	-0.451	<0.001	-0.379	<0.001	0.275	0.001
LA conduit strain, %	-0.109	0.189	-0.112	0.176	0.274	0.001

Pearson's correlation. ERO, effective regurgitant orifice; LA, left atrium; LVEF, left ventricular ejection fraction; MR, mitral regurgitation, RV, regurgitant volume.

No studies correlating these variables with the presence of FMR have been published.

The fact that we observed an association between LAF variables expressing reservoir and contraction functions and not between FMR and the conduit function may be because the latter is physiologically related to LV compliance and relaxation, which were likely to be homogeneously reduced in this DCM population regardless of FMR degree.

Further studies are needed to understand the prognostic impact of atrial dysfunction in the population with DCM and FMR, especially in terms of the genesis of atrial fibrillation, which has high morbidity and mortality rates among DCM patients.

Conclusions

Patients with myocardial ischemia and dilated cardiomyopathy (DCM) and Functional mitral regurgitation

(FMR) present global left atrium function (LAF) impairment.

FMR is associated with increased atrial volumes and reduced phasic reservoir function and atrial contraction parameters.

Authors' contribution

Research conception and design: Le Bihan DCS; Data collection: Andrade SM, Barretto RBM, Sousa FTT; Data analysis and interpretation: Andrade SM, Barretto RBM, Le Bihan DCS; Statistical analysis: Le Bihan DCS, Andrade SM; Manuscript writing: Andrade SM; Critical review of the manuscript for important intellectual content: Le Bihan DCS.

Conflict of interest

The authors have declared that they have no conflict of interest.

Referências

- Schmitto JD, Lee LS, Mokashi SA, Bolman RM 3rd, Cohn LH, Chen FY. Functional mitral regurgitation. *Cardiol Rev*. 2010;18(6):285-91. doi: <https://doi.org/10.1097/CRD.0b013e3181e8e648>
- Tarasoutchi F, Montera MW, Ramos AI, Sampaio RO, Rosa VE, Accorsi TA, et al. Atualização das Diretrizes Brasileiras de Valvopatias: Abordagem das Lesões Anatomicamente Importantes. *Arq Bras Cardiol*. 2017;109(6 suppl 2):1-34. doi: <https://doi.org/10.5935/abc.20180007>. Erratum in: *Arq Bras Cardiol*. 2018;110(5):497.
- Tarasoutchi F, Montera MW, Ramos AI, Sampaio RO, Rosa VE, Accorsi TA, et al. Update of the Brazilian Guidelines for Valvular Heart Disease - 2020. *Arq Bras Cardiol*. 2020;115(4):720-75. doi: <https://doi.org/10.36660/abc.20201047>
- lung B. Management of ischaemic mitral regurgitation. *Heart*. 2003;89(4):459-64. doi: <https://doi.org/10.1136/heart.89.4.459>
- Miller DC. Ischemic mitral regurgitation redux--to repair or to replace? *J Thorac Cardiovasc Surg*. 2001;122(6):1059-62. doi: <https://doi.org/10.1067/mtc.2001.120341>
- Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al.; ESC Committee for Practice Guidelines (CPG); Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg*. 2012;42(4):S1-44. doi: <https://doi.org/10.1093/ejcts/ezs455>
- Albuquerque DC, Neto JD, Bacal F, Rohde LE, Bernardes-Pereira S, Berwanger O, et al.; Investigadores Estudo BREATHE. I Brazilian Registry of Heart Failure - Clinical Aspects, Care Quality and Hospitalization Outcomes. *Arq Bras Cardiol*. 2015;104(6):433-42. doi: <https://doi.org/10.5935/abc.20150031>. Erratum in: *Arq Bras Cardiol*. 2015;105(2):208.
- Sousa FT. Avaliação ecocardiográfica da função do átrio esquerdo como marcadora de eventos em pacientes com insuficiência cardíaca [Doutorado]. São Paulo: Universidade de São Paulo; 2017 [citado 2022 Mai 25]. Disponível em: <https://www.teses.usp.br/teses/disponiveis/98/98131/tde-02012018-133920/pt-br.php>
- Cameli M, Caputo M, Mondillo S, Ballo P, Palmerini E, Lisi M, et al. Feasibility and reference values of left atrial longitudinal strain imaging by two-dimensional speckle tracking. *Cardiovasc Ultrasound*. 2009;7:6. doi: <https://doi.org/10.1186/1476-7120-7-6>
- Mehrzad R, Rajab M, Spodick DH. The three integrated phases of left atrial macrophysiology and their interactions. *Int J Mol Sci*. 2014;15(9):15146-60. doi: <https://doi.org/10.3390/ijms150915146>
- Sirbu C, Herbots L, D'hooge J, Claus P, Marciniak A, Langeland T, Bijnens B, et al. Feasibility of strain and strain rate imaging for the assessment of regional left atrial deformation: a study in normal subjects. *Eur J Echocardiogr*. 2006;7(3):199-208. doi: <https://doi.org/10.1016/j.euje.2005.06.001>
- Lang RM, Badano LP, Mor-Avi V, Filalo 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. *J Am Soc Echocardiogr*. 2015;28(1):1-39.e14. doi: <https://doi.org/10.1016/j.echo.2014.10.003>
- Picard MH, Adams D, Bierig SM, Dent JM, Douglas PS, Gillam LD, et al; American Society of Echocardiography. American Society of Echocardiography recommendations for the assessment of valvular laboratory operations. *J Am Soc Echocardiogr*. 2011;24(1):1-10. doi: <https://doi.org/10.1016/j.echo.2010.11.006>
- Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al.; European Association of Echocardiography. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr*. 2010;11(4):307-32. doi: <https://doi.org/10.1093/ejechocard/jeq031>
- 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. doi: [https://doi.org/10.1016/S0894-7317\(03\)00335-3](https://doi.org/10.1016/S0894-7317(03)00335-3)
- Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol*. 2006;47(12):2357-63. doi: <https://doi.org/10.1016/j.jacc.2006.02.048>
- Vieira MJ, Teixeira R, Gonçalves L, Gersh BJ. Left atrial mechanics: echocardiographic assessment and clinical implications. *J Am Soc Echocardiogr*. 2014;27(5):463-78. doi: <https://doi.org/10.1016/j.echo.2014.01.021>
- Park SM, Park SW, Casaclang-Verzosa G, Ommen SR, Pellikka PA, Miller FA Jr, et al. Diastolic dysfunction and left atrial enlargement as contributing factors to functional mitral regurgitation in dilated cardiomyopathy: data from the Acorn trial. *Am Heart J*. 2009;157(4):762.e3-10. doi: <https://doi.org/10.1016/j.ahj.2008.12.018>
- Cioffi G, Tarantini L, De Feo S, Pulignano G, Del Sindaco D, Stefanelli C, et al. Functional mitral regurgitation predicts 1-year mortality in elderly

- patients with systolic chronic heart failure. *Eur J Heart Fail.* 2005;7(7):1112-7. doi: <https://doi.org/10.1016/j.ejheart.2005.01.016>
20. Crawford MH, Soucek J, Oprian CA, Miller DC, Rahimtoola S, Giacomini JC, et al. Determinants of survival and left ventricular performance after mitral valve replacement. Department of Veterans Affairs Cooperative Study on Valvular Heart Disease. *Circulation.* 1990;81(4):1173-81. doi: <https://doi.org/10.1161/01.cir.81.4.1173>
 21. Hickey MS, Smith LR, Muhlbaier LH, Harrell FE Jr, Reves JG, Hinohara T, et al. Current prognosis of ischemic mitral regurgitation. Implications for future management. *Circulation.* 1988;78(3 Pt 2):I51-9.
 22. Lee R, Haluska B, Leung DY, Case C, Mundy J, Marwick TH. Functional and prognostic implications of left ventricular contractile reserve in patients with asymptomatic severe mitral regurgitation. *Heart.* 2005;91(11):1407-12. doi: <https://doi.org/10.1136/hrt.2004.047613>
 23. 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. doi: [https://doi.org/10.1016/s0002-9149\(02\)03301-5](https://doi.org/10.1016/s0002-9149(02)03301-5)
 24. Jenkins C, Bricknell K, Marwick TH. Use of real-time three-dimensional echocardiography to measure left atrial volume: comparison with other echocardiographic techniques. *J Am Soc Echocardiogr.* 2005;18(9):991-7. doi: <https://doi.org/10.1016/j.echo.2005.03.027>
 25. Le Bihan DC, Della Togna DJ, Barretto RB, Assef JE, Machado LR, Ramos AI, et al. Early improvement in left atrial remodeling and function after mitral valve repair or replacement in organic symptomatic mitral regurgitation assessed by three-dimensional echocardiography. *Echocardiography.* 2015;32(7):1122-30. doi: <https://doi.org/10.1111/echo.12817>
 26. Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. *Am J Cardiol.* 1999;84(7):829-32. doi: [https://doi.org/10.1016/s0002-9149\(99\)00446-4](https://doi.org/10.1016/s0002-9149(99)00446-4)
 27. Messika-Zeitoun D, Bellamy M, Avierinos JF, Breen J, Eusemann C, Rossi A, et al. Left atrial remodeling in mitral regurgitation—methodologic approach, physiological determinants, and outcome implications: a prospective quantitative Doppler-echocardiographic and electron beam-computed tomographic study. *Eur Heart J.* 2007;28(14):1773-81. doi: <https://doi.org/10.1093/eurheartj/ehm199>
 28. Aurigemma GP, Gottdiener JS, Arnold AM, Chinali M, Hill JC, Kitzman D. Left atrial volume and geometry in healthy aging: the Cardiovascular Health Study. *Circ Cardiovasc Imaging.* 2009;2(4):282-9. doi: <https://doi.org/10.1161/CIRCIMAGING.108.826602>
 29. Moller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, et al. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. *Circulation.* 2003;107(17):2207-12. doi: <https://doi.org/10.1161/01.CIR.0000066318.21784.43>
 30. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Risks for atrial fibrillation and congestive heart failure in patients ≥ 65 years of age with abnormal left ventricular diastolic relaxation. *Am J Cardiol.* 2004;93(1):54-8. doi: <https://doi.org/10.1016/j.amjcard.2003.09.012>
 31. Kottkamp H. Fibrotic atrial cardiomyopathy: a specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications. *J Cardiovasc Electrophysiol.* 2012;23(7):797-9. doi: <https://doi.org/10.1111/j.1540-8167.2012.02341.x>
 32. Flaker GC, Fletcher KA, Rothbart RM, Halperin JL, Hart RG. Clinical and echocardiographic features of intermittent atrial fibrillation that predict recurrent atrial fibrillation. Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Am J Cardiol.* 1995;76(5):355-8. doi: [https://doi.org/10.1016/s0002-9149\(99\)80100-3](https://doi.org/10.1016/s0002-9149(99)80100-3)
 33. Bolca O, Akdemir O, Eren M, Dagdeviren B, Yildirim A, Tezel T. Left atrial maximum volume is a recurrence predictor in lone atrial fibrillation: an acoustic quantification study. *Jpn Heart J.* 2002;43(3):241-8. doi: <https://doi.org/10.1536/jhj.43.241>
 34. Barnes ME, Miyasaka Y, Seward JB, Gersh BJ, Rosales AG, Bailey KR, et al. Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. *Mayo Clin Proc.* 2004;79(8):1008-14. doi: <https://doi.org/10.4065/79.8.1008>
 35. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. *Circulation.* 1995;92(4):835-41. doi: <https://doi.org/10.1161/01.cir.92.4.835>
 36. Lønborg JT, Engstrøm T, Møller JE, Ahtarovski KA, Kelbæk H, Holmvang L, et al. Left atrial volume and function in patients following ST elevation myocardial infarction and the association with clinical outcome: a cardiovascular magnetic resonance study. *Eur Heart J Cardiovasc Imaging.* 2013;14(2):118-27. doi: <https://doi.org/10.1093/ehjci/jes118>
 37. Tsang TS, Barnes ME, Gersh BJ, Takemoto Y, Rosales AG, Bailey KR, et al. Prediction of risk for first age-related cardiovascular events in an elderly population: the incremental value of echocardiography. *J Am Coll Cardiol.* 2003;42(7):1199-205. doi: [https://doi.org/10.1016/s0735-1097\(03\)00943-4](https://doi.org/10.1016/s0735-1097(03)00943-4)
 38. Sugimoto T, Robinet S, Dulgheru R, Bernard A, Ilardi F, Contu L, et al.; NORRE Study. Echocardiographic reference ranges for normal left atrial function parameters: results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging.* 2018;19(6):630-8. doi: <https://doi.org/10.1093/ehjci/jeu018>
 39. Triposkiadis F, Moyssakis I, Hadjilicolaou L, Makris T, Zioris H, Hatzizaharias A, et al. Left atrial systolic function is depressed in idiopathic and preserved in ischemic dilated cardiomyopathy. *Eur J Clin Invest.* 1999;29(11):905-12. doi: <https://doi.org/10.1046/j.1365-2362.1999.00563.x>
 40. D'Andrea A, Caso P, Romano S, Scarafilo R, Cuomo S, Salerno G, et al. Association between left atrial myocardial function and exercise capacity in patients with either idiopathic or ischemic dilated cardiomyopathy: a two-dimensional speckle strain study. *Int J Cardiol.* 2009;132(3):354-63. doi: <https://doi.org/10.1016/j.ijcard.2007.11.102>
 41. Cameli M, Sparla S, Losito M, Righini FM, Menci D, Lisi M, et al. Correlation of Left Atrial Strain and Doppler Measurements with Invasive Measurement of Left Ventricular End-Diastolic Pressure in Patients Stratified for Different Values of Ejection Fraction. *Echocardiography.* 2016;33(3):398-405. doi: <https://doi.org/10.1111/echo.13094>
 42. Guler A, Tigen KM, Dundar C, Karaahmet T, Karabay CY, Aung SM, et al. Left atrial deformation and nonischemic dilated cardiomyopathy. A 2D speckle-tracking imaging study. *Herz.* 2014;39(2):251-7. doi: <https://doi.org/10.1007/s00059-013-3817-z>