

# Article/Artigo

# Echocardiographic parameters associated with pulmonary congestion in outpatients with Chagas' cardiomyopathy and non-chagasic cardiomyopathy

Parâmetros ecocardiográficos associados com a congestão pulmonar nas miocardiopatias chagásica e não-chagásica

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#### ABSTRACT

Introduction: Despite significant left ventricular (LV) systolic dysfunction and cardiomegaly, pulmonary congestion does not seem to be a major finding in Chagas' cardiomyopathy (CC). This study sought to identify echocardiographic parameters associated with pulmonary congestion in CC and in dilated cardiomyopathy of other etiologies, such as non-CC (NCC), and to compare pulmonary venous hypertension between the two entities. Methods: A total of 130 consecutive patients with CC and NCC, with similar echocardiographic characteristics, were assessed using Doppler echocardiography and chest radiography. Pulmonary venous vessel abnormalities were graded using a previously described pulmonary congestion score, and this score was compared with Doppler echocardiographic parameters. Results: NCC patients were older than CC patients  $(62.4 \pm 13.5 \times 47.8 \pm 11.2, p = 0.00)$ , and there were more male subjects in the CC group  $(66.2\% \times 58.5\%, p = 0.4)$ . Pulmonary venous hypertension was present in 41 patients in the CC group (63.1%) and in 63 (96.9%) in the NCC group (p = 0.0), the mean lung congestion score being 3.2 ± 2.3 and 5.9 ± 2.6 (p = 0.0), respectively. On linear regression multivariate analysis, the E/e' ratio ( $\beta = 0.13$ ; p = 0.0), LV diastolic diameter ( $\beta = 0.06$ ; p = 0.06), left atrial diameter  $(\beta = 0.51; p = 0.08)$ , and right ventricular (RV) end-diastolic diameter ( $\beta = 0.02; p = 0.48$ ) were the variables that correlated with pulmonary congestion in both groups. Conclusions: Pulmonary congestion was less significant in patients with CC. The degree of LV of systolic and diastolic dysfunction and the RV diameter correlated with pulmonary congestion in both groups. The E/e' ratio was the hallmark of pulmonary congestion in both groups.

**Keywords:** Chagas' cardiomyopathy. Pulmonary congestion. Dilated cardiomyopathy. Echocardiography.

#### RESUMO

Introdução: Na miocardiopatia chagásica, ocorre uma discrepância entre os achados de disfunção ventricular e uma menor magnitude de congestão pulmonar em relação a outras miocardiopatias. Foram associados parâmetros morfofuncionais ecocardiográficos com achados de congestão pulmonar à radiografia do tórax em pacientes portadores de miocardiopatia chagásica e não chagásica, sendo a intensidade dos achados radiológicos comparada nos dois grupos. Métodos: Foram recrutados 130 pacientes portadores de miocardiopatia chagásica e não chagásica, tendo os dois grupos parâmetros ecocardiográficos semelhantes. Todos realizaram o estudo radiológico do tórax, sendo atribuída uma pontuação aos achados sugestivos de congestão pulmonar, conforme escore já previamente estabelecido, sendo este comparado com os achados ecocardiográficos de disfunção ventricular. **Resultados**: Os pacientes não chagásicos eram mais idosos (62,4±13,5 x 47,8±11,2, p=0,0), havendo um predomínio do sexo feminino nos chagásicos (66,2% x 58,5%, p=0,4). A hipertensão venocapilar pulmonar esteve presente em 41 chagásicos (63,1%) e 63 (96,9%) não-chagásicos (p=0,0), com escore da congestão pulmonar de  $3,2\pm2,3$  e  $5,9\pm2,6$  (p=0,0) respectivamente. Na análise de regressão linear, a relação E/e' ( $\beta$ =0,13; p=0,0), o diâmetro diastólico do ventrículo esquerdo ( $\beta$ =0,06; p=0,06), o diâmetro do átrio esquerdo ( $\beta$ =0,51; p=0,08) e o diâmetro diastólico final do ventrículo direito ( $\beta$ =0,02; p=0,48) foram as variáveis que mais se associaram com a congestão pulmonar nos dois grupos. **Conclusões:** Os pacientes chagásicos apresentaram um menor grau de congestão pulmonar. Os parâmetros de disfunção sistólica e  $diastólica \ associaram \ com \ a \ intensidade \ da \ congest\~ao \ pulmonar, sendo \ a \ rela\~{\it ç$\~ao} \ E/e' \ a \ vari\'avel$ que mais determinou a congestão pulmonar nos dois grupos.

**Palavras-chaves:** Miocardiopatia chagásica. Congestão pulmonar. Miocardiopatia dilatada. Ecocardiografia.

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# INTRODUCTION

A century after its description by the Brazilian Carlos Chagas, Chagas' disease continues to be a serious health and economic problem in several Latin American countries<sup>1-3</sup>. Recent estimates from the World Health Organization indicate that 12 million persons are chronically infected with *Trypanosoma cruzi*, with 100,000 new cases occurring each year<sup>4</sup>.

Chest radiography is an important and inexpensive tool for the evaluation of patients with Chagas' dilated cardiomyopathy (CC). The finding of an enlarged heart by this method indicates a poor prognosis<sup>5</sup>. However, the intensity of pulmonary congestion is usually less than expected for the degree of cardiomegaly and of left ventricular (LV) systolic dysfunction<sup>6</sup>. The mechanism underlying this discrepancy remains unknown<sup>7</sup>.

Doppler echocardiography represents one of the most important methods for the evaluation of CC<sup>8-9</sup>. In a previous study, we compared the degree of pulmonary congestion with echocardiographic parameters in CC. In that study, the degree of pulmonary congestion correlated with Doppler echocardiographic left and right ventricular dysfunction parameters<sup>10</sup>. Thus, the objective of the present study was to verify if CC presents with less pulmonary congestion when compared with non-CC (NCC) with the same echocardiographic characteristics.

# **METHODS**

Sixty-five consecutive patients with CC and 65 patients with NCC were prospectively enrolled.

Chagas' dilated cardiomyopathy patients were included in the study if they had at least two positive serological tests for Chagas' disease (indirect immunofluorescence, indirect hemagglutination, and/or enzyme-linked immunosorbent assay) and cardiomyopathy. The NCC group was composed of patients with other forms of dilated cardiomyopathy

(ischemic, hypertensive, idiopathic, and peripartum) and who were negative for Chagas' disease. Dilated cardiomyopathy found in both Chagas and non-Chagas' disease is characterized by the echocardiographic finding of a dilated left ventricle with impaired ventricular systolic function.

Patients were selected if they had a left ventricular diastolic diameter/body surface area ≥31mm and a left ventricular ejection fraction <55%11. All patients underwent clinical examination, and their New York Heart Association (NYHA) functional class was established. Medical therapy was individually adjusted, according to a standardized treatment regimen, and all patients received optimized treatment for heart failure. Patients who had associated heart diseases or systemic arterial hypertension were not included in the Chagas' group. Patients with renal failure, low serum albumin levels, hypothyroidism, pregnancy, alcoholism, anemia, or other conditions leading to pulmonary congestion were excluded from both study groups. Chest radiographs were obtained at the same time Doppler echocardiograms were performed in all patients. Radiographs were obtained in the posteroanterior and lateral positions. All films were acquired using the conventional technique of the Radiology Department of the University Teaching Hospital<sup>12</sup>. All radiological parameters were graded, the intensity of changes in the pulmonary venous vessels on chest radiographs being established (Table 1) with the use of a previously described pulmonary congestion score (PCS)<sup>13-14</sup>. Two independent observers simultaneously evaluated all chest radiographs, any discordance being solved by consensus. The interobserver variability was analyzed.

# **Echocardiography**

Images were acquired using a Sonos 5,500 echocardiographer (Hewlett-Packard Corporation, Palo Alto, CA), with 2.5-MHz to 3.5-MHz transducers. All recordings were performed by one investigator blind to the clinical evaluation of the patients. The echocardiographic techniques and calculations of cardiac chamber dimensions and volumes were performed according to the recommendations of the American Society of Echocardiography. Left ventricular ejection fraction was calculated according to the modified Simpson's rule<sup>11</sup>.

Right ventricular (RV) morphology and function were evaluated qualitatively on multiple echocardiographic views<sup>11</sup>. Quantitative evaluation of global RV function was performed with the use of the Doppler-derived index of myocardial performance (Tei index), as previously described<sup>15</sup>.

The presence and degree of mitral and tricuspid regurgitation were evaluated using pulsed and continuous wave Doppler, guided by color flow mapping<sup>16</sup>. Maximal velocity of the tricuspid regurgitation flow was obtained, and systolic pulmonary pressure was calculated<sup>17</sup>.

Diastolic function was assessed using pulsed-wave Doppler examination of mitral, pulmonary venous inflow and Doppler tissue imaging (S, e', and A' waves)<sup>18-19</sup>. The ratio between peak early diastolic transmitral flow velocity (E) and e' was calculated. Color Doppler M-mode also was used to assess ventricular diastolic function<sup>19</sup>. According to these Doppler parameters, four patterns of diastolic function were established: normal, and grades I (abnormal relaxation pattern), II (pseudonormal pattern), and III (restriction to filling) of diastolic dysfunction.

		Estimated pulmonary		
Pulmonary venous vessels distribution	Physiopathology	venous pressure		Value
Normal	None	8-12mmHg	-	1
Equalization	Pulmonary venous hypertension	13-15mmHg	Mild	2
			Moderate	3
			Severe	4
nversion	Pulmonary venous hypertension	16-18mmHg	Mild	5
			Moderate	6
			Severe	7
Perihilar haze	Interstitial edema	>18mmHg	Mild	+1*
			Moderate	+2*
			Severe	+3*
ubpleural thickening	Interstitial edema	>18mmHg	Mild	+1*
			Moderate	+2*
			Severe	+3*
eribronchial cuffing	Interstitial edema	>18mmHg	Mild	+1*
			Moderate	+2*
			Severe	+3*
Pleural effusion	Interstitial edema	>18mmHg	Mild	+1*
			Moderate	+2*
			Severe	+3*
Cerley lines	Interstitial edema	>18mmHg	Mild	+1*
			Moderate	+2*
			Severe	+3*
Consolidation	Alveolar edema	> 25mmHg		11

# Statistical analysis

Data were expressed as the mean value ± standard deviation for continuous variables and absolute or relative frequencies for categorical variables. The interobserver variability on chest radiograph interpretation was assessed with the Kappa coefficient, a value close to 1 being considered satisfactory.

Correlations between PCS and Doppler echocardiographic variables were assessed using linear regression analysis.

Multiple linear regression analysis was performed to obtain the best regression model, with the PCS as the dependent variable and the echocardiographic parameters as independent variables. The permanence of all variables in the final model was established when the significance level was <0.05. The 13<sup>th</sup> version of the SPSS (SPSS Inc., Chicago, Illinois) was used for all analyses.

#### **Ethical considerations**

The research protocol was approved by the research ethics committee of both institutions, and a written informed consent was obtained from all patients.

# **RESULTS**

A total of 65 patients with CC and 65 patients with NCC were enrolled. Among the NCC patients, 35 (53.8%) had ischemic cardiomyopathy, 20 (30.8%) were hypertensive, 8 (12.3%) were hypertensive and had ischemic cardiomyopathy, 1 (1.5%) had peripartum cardiomyopathy, and 1 (1.5%) had idiopathic cardiomyopathy.

Their clinical data are shown on **Table 2**. Gender and functional class did not differ between the two groups (p = 0.4 and p = 0.6, respectively) (**Table 2**). Age and heart rate differed between the two groups, but the difference did not influence the degree of pulmonary congestion (p = 0.3 for age and p = 0.1 for heart rate). Age differences

 $TABLE\,2-Clinical\,characteristics\,and\,pharmacologic\,therapy\,in\,CG\,and\,NCG.$ 

Characteristics	CG	NCG	p
Age	47.8 ± 11.2	62.43 ± 13.5	0.0
Body surface (m <sup>2</sup> )	$1.7 \pm 0.1$	$1.8 \pm 0.2$	0.7
Systolic blood pressure (mmHg)	117.6 ± 12.8	127.8 ± 19.6	0.1
Diastolic blood pressure (mmHg)	74.1 ± 9.4	$77.8 \pm 13.3$	0.1
Heart rate (bpm)	62.7 ± 11.0	78.0 ± 11.7	0.0
ACE inhibitors (%)	67.7	83.1	0.0
Digital	13.8	26.2	0.1
Amiodarone	50.8	6.2	0.0
Anticoagulants	4.6	47.7	0.0
Spironolactone	41.5	18.5	0.0
Nitrate	0	56.9	0.0
Carvedilol	4.6	18.5	0.0
Furosemide	32.3	66.2	0.0
NYHA Class I	49.2	67.7	
NYHA Class II	43.1	23.1	
NYHA Class III e IV	7.7	9.2	
Gender male	66.2	58.5	
Gender female	33.8	48.5	

**CG:** Chagas' cardiomyopathy; **NCG:** non-Chagas' dilated cardiomyopathy; **ACE:** angiotensin-converting enzyme; **NYHA:** New York Heart Association.

between the two groups probably occurred because CC usually manifests at a younger age, compared with other cardiomyopathies.

There was a significant association between the NYHA functional class and the degree of pulmonary congestion in CC patients (p=0.0) and in NCC patients (p=0.0). As for treatment of heart failure, results are shown on **Table 2**. Differences between the drugs used did not influence the degree of pulmonary congestion in both groups (p=0.1 for spironolactone, p=0.1 for amiodarone, p=0.1 for furosemide, p=0.6 for nitrate, p=0.6 for anticoagulants, p=0.7 for carvedilol, and p=0.1 to ACE (angiotensin-converting enzyme) inhibitors.

The radiological findings of pulmonary congestion are shown on **Table 3**. The mean value of lung congestion score was  $3.23 \pm 2.32$  in CC patients and  $5.91 \pm 2.6$  in the control group (p = 0.0). In the CC group, the kappa coefficient was 0.58 for perihilar haze; 0.86 for the presence of subpleural thickening; 0.78 for peribronchial cuffing; and 1.0 for equalization, inversion, consolidation, and pleural effusion. In the NCC group, the kappa coefficient was 0.7 for perilar haze, 0.85 for subpleural thickening, 0.87 for peribronchial cuffing, 0.95 for pulmonary venous flow distribution, and 0.89 for pleural effusion.

TABLE 3 - Pulmonary congestion score.

	CG		NCG		
Characteristics	absolute	relative	absolute	relative	PCS
Normal	24	36.9	2	3.1	1
Mild equalization	16	24.6	17	26.2	2
Moderate equalization	10	15.4	13	20.0	3
Severe equalization	3	4.6	6	9.2	4
Mild inversion	6	9.2	18	27.7	5
Moderate inversion	6	9.2	8	12.6	6
Severe inversion	0	0.0	1	1.5	7
Perihilar haze	1	1.5	36	5.4	1
Mild subpleural thickening	7	7.7	9	13.8	1
Moderate subpleural thickening	g 5	4.0	1	1.5	2
Pleural effusion	1	1.5	16	24.6	1

**CG:** Chagas' cardiomyopathy; **NCG:** non-Chagas' dilated cardiomyopathy, **PCS:** pulmonary congestion score.

Doppler echocardiographic parameters are shown on **Table 4**. NCC patients had a larger right ventricle (18.4  $\pm$  75mm  $\times$  13.5  $\pm$  4.6mm; p = 0.0), a larger left ventricle (65.6  $\pm$  7.2mm  $\times$  62.8  $\pm$  6.3mm; p = 0.0), and a larger left atrial diastolic diameter (47.5  $\pm$  6.8mm  $\times$  42.6  $\pm$  9.1mm; p = 0.0). Left ventricular ejection, calculated by the area-length method, was 37.8  $\pm$  10.7 in CC patients and 40.8  $\pm$  9.2 in the NCC group (p = 0.1). The LV ejection fraction correlated with the degree of pulmonary congestion in CC (r = -0.5; p = 0.0) and NCC patients (r = -0.3; p = 0.0), as shown in **Figure 1**.

Various Doppler echocardiographic parameters were used to evaluate the association of diastolic function with pulmonary congestion (Table 4). Age and heart rate differences did not explain the observed differences in parameters of systolic and diastolic function between the two groups. E/e' was different between the two groups ( $7.2 \pm 3.9$  in CC patients ×  $15.5 \pm 7.9$  in NCC patients; p = 0.0). According to the established classification of diastolic dysfunction, 8 patients (12.3%) in the CC group had normal diastolic function, 41 (63.1%) had grade I diastolic dysfunction, 7 (10.8%) had grade II, and 9 (13.8%) had grade III. In the NCC group, 5 patients (7.7%) had normal diastolic function, 33 (50.8%) had grade I diastolic dysfunction, 18 (27.7%) had grade II, and 9 (13.8%)

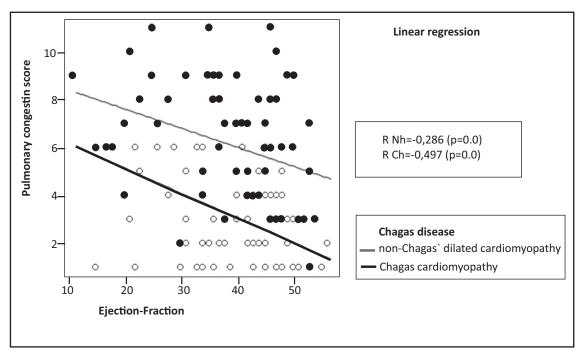


FIGURE 1 – Correlation between ejection-fraction and pulmonary congestion score in Chagas' cardiomyopathy and non-Chagas' dilated cardiomyopathy.

had grade III (p = 0.094 between the two groups). The degree of diastolic dysfunction correlated with the PCS (r = 0.6; p = 0.0 in CC patients, and r = 0.3; p = 0.0 in NCC patients).

Among the CC patients, mitral regurgitation was mild in 47 (72.3%), moderate in 13 (20%), and severe in 5 (7.7%). Among NCC patients, it was mild in 58 (89.2%), moderate in 3 (4.6%), severe in 1 (1.5%), and absent in 3 (4.6%). The degree of mitral regurgitation also was associated with PCS (in CC patients: r = 0.4, p = 0.0; and in NCC patients: r = 0.3, p = 0.0; p = 0.3 between the two groups).

On multivariate analysis, the echocardiographic variables that were found to correlate with the PCS were E/e' ( $\beta$  = 0.133), left ventricular end-diastolic diameter ( $\beta$  = 0.065), left atrium diastolic diameter ( $\beta$  = 0.051), and right ventricular diastolic diameter ( $\beta$  = 0.024, r = 0.494).

# **DISCUSSION**

The present study showed that in CC patients, pulmonary congestion is less significant than in patients with the same degree of ventricular involvement but with other etiologies for their dilated cardiomyopathy. Pulmonary congestion

score correlated with LV function and right ventricular diameter; E/e' was found to be a hallmark of PCS in both groups. PCS was used by Milne et al., 13 who analyzed 216 chest radiographic studies to establish the differences among several etiologies of pulmonary congestion (cardiac, renal, or increased capillary permeability), with an accuracy varying from 86% to 89%.

It has been previously reported that in CC, the lungs usually do not show findings of severe pulmonary congestion<sup>6</sup>. This is a peculiar

TABLE 4 - Doppler echocardiographic parameters associated with the pulmonary congestion score.

Variables	R value CG	P value CG	R value NCG	P value NCG	P value groups
RVd (mm)	0.2	0.0	0.2	0.0	0.0
LVd (mm)	0.3	0.0	0.2	0.0	0.0
LVs (mm)	0.4	0.0	0.2	0.0	0.3
LAd (mm)	0.2	0.0	0.2	0.0	0.0
FS (%)	-0.4	0.0	-0.2	0.0	0.1
EF (%)	-0.4	0.0	-0.2	0.0	0.1
LA vol	0.28	0.03	0.22	0.04	0.27
E wave (cm/s)	0.5	0.0	0.3	0.0	0.0
A wave (cm/s)	-0.3	0.0	-0.2	0.0	0.2
E/A	-0.1	0.5	-0.3	0.0	0.0
DT (ms)	0.5	0.0	0.0	0.7	0.3
IVRT (ms)	-0.4	0.0	-0.3	0.0	0.4
E'/E	0.3	0.0	0.3	0.0	0.0
E'/A'	0.5	0.0	0.5	0.0	0.1
SPAP (mmHg)	0.6	0.0	0.4	0.0	0.1

CG: Chagas' cardiomyopathy; NCG: non-Chagas' dilated cardiomyopathy; RVd: right ventricular diastolic diameter; LVd: left ventricular diastolic diameter; LVs: left ventricular systolic diameter; LAd: left atrium diastolic diameter; FS: fractional shortening; EF: ejection fraction; LA vol: left atrium volume; E wave: early diastolic transmitral flow velocity; A wave: late transmitral flow velocity; E/A: ratio of early to late transmitral flow velocity; DT: deceleration time of the E wave; IVRT: isovolumic relaxation time; E/E': ratio of the early diastolic transmitral flow velocity to early diastolic mitral annular velocity; E'/A': ratio of the early diastolic mitral annular velocity to late diastolic mitral annular velocity; SPAP: systolic pulmonary artery pressure.

aspect of this cardiomyopathy, which shows more congestion in the systemic circulation than in the pulmonary territory. In fact, in the present study, the degree of pulmonary congestion was lower in the CC than in the NCC group. In LV dysfunction, an increase in left atrial pressure and pulmonary venous congestion leads to flow across the pulmonary microvasculature<sup>20</sup>.

In our study, left ventricular and atrial diastolic diameters remained important factors associated with pulmonary congestion. Right ventricular diastolic diameter also was associated with the degree of pulmonary congestion in the two groups, and it was included in the final model. Right ventricular function is more associated with afterload, which is established by the pulmonary vascular resistance, than with RV intrinsic contractility or with preload. This may explain the fact that the intensity of pulmonary congestion, associated with elevated pulmonary vascular resistance, promotes RV enlargement<sup>21</sup>. In CC, the right ventricular diastolic diameter was larger than that in NCC, probably reflecting the fact that CC shows more involvement of the RV than other etiologies of dilated cardiomyopathy<sup>7</sup>.

Left atrial volume reflects the duration and severity of increased left atrial pressure, and it is determined by the same factors that influence diastolic filling of the left ventricle<sup>22</sup>. Accordingly, in the present study, there was a correlation between the left atrial volume and the PCS in both groups.

The current study demonstrates that, in both groups, an elevated E/e' ratio correlated with pulmonary congestion. A previous study has shown that an E/e' > 10 was the optimal cutoff point for the prediction of a pulmonary capillary wedge pressure higher than 15mmHg in patients with depressed ejection fraction, with 97% sensitivity and 78% specificity<sup>23,24</sup>. Based on the present study, the E/e' ratio reflected higher pulmonary wedge pressure in both CC and NCC patients. Pulmonary congestion was more significant, and E/e' was higher in NCC patients.

#### **Study limitations**

Our patients were NYHA functional class I or II; thus, these results cannot be extrapolated to the whole population of patients with cardiomyopathy. This is due to the fact that our subjects were selected from an outpatient referral center, most of them being clinically stable. Further studies enrolling class III or IV patients are required to assess pulmonary congestion in this group.

# Conclusion

Pulmonary congestion was less marked in CC patients than in patients with dilated cardiomyopathy of other etiologies. The degree of LV systolic and diastolic dysfunction, as well as the size of the RV and the left atrium, correlated with pulmonary congestion, both in CC and NCC patients.

The  $E/E^{\prime}$  ratio was the hallmark of pulmonary congestion in both groups.

# **CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

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