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Reverse Left Atrial Remodeling after Treatment with Carvedilol in Patients with HFREF

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Abstract

Background: Half of the patients with reduced ejection fraction have diastolic dysfunction associated and the data related to the impact of carvedilol therapy in these patients are still conflicting.
Objective: To evaluate the behavior of echocardiographic, scintigraphic and left atrial volume (LAV) indexes before and after three months of therapy with carvedilol in patients with HFREF, New York Heart Association (NYHA) functional class (FC) II and III.
Methods: Nineteen patients with HF, CF II and III, ejection fraction <45% (Simpson method) without previous therapy with carvedilol were selected. For statistical analysis, Wilcoxon and McNemar tests, Spearman coefficient and multiple linear regression were used.
Results: There was significant improvement in the left ventricular (LV) systolic function parameters: DSF, ESV, Simpson EF, EFVI. There was no significant improvement in the diastolic function parameters derived from Doppler: E', E/E', VP, E/VP. Diastolic function behavior through VAE showed significant improvement: LAV (83.2±33.4 mL vs. 73.7±29.8 mL, p=0.009), LAV index (44.8±15.8 mL/m^2 vs. 39.7±14.5 mL/m^2, p=0.014).
Conclusions: LAV regression after short-term therapy with carvedilol was not associated with improvement in other diastolic function indexes, but was associated with improved LV systolic function. These findings suggest that LAV reduction is secondary to improvement in systolic performance.

Keywords: Heart failure; Heart atria; Adrenergic beta-antagonists

Introduction

About 23 million people have heart failure (HF) and, each year, two million new cases are diagnosed in the world.[1] This disease is epidemic and its prevalence increases in parallel to population aging. Most common syndrome in cardiology clinical practice, it affects 6.5 million people in Europe[2] and 5 million in the United States of America, with 500,000 new cases per year. It is the leading cause of hospitalization of individuals > 65 years of age and is responsible for 350,000 deaths per year.[3,4]

Epidemiological information about HF in Brazil are still scarce; it is estimated, however, that 6.4 million individuals have HF.[5,6] The study EPICA-Niterói,[7] pioneer in epidemiology of HF in Brazil, evaluated patients in the public and private sector admitted with decompensated HF. It concluded that socioeconomic differences, duration of hospital stay and mortality rate adjusted for age were higher in public health services.

HF treatment, which in the past was based on an hemodynamic model, is currently focused on a

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ABBREVIATIONS AND ACRONYMS

- *EF – ejection fraction*
- *FC – functional class*
- *HF – heart failure*
- *HFREF – heart failure with reduced ejection fraction*
- *HUAP – Hospital Universitário Antônio Pedro*
- *LA – left atrium*
- *LAV – left atrial volume*
- *LV – left ventricle*
- *MIBG – metaiodobenzylguanidine*
- *NE – norepinephrine*
- *NYHA – New York Heart Association*
- *PFR – peak filling rate*
- *TPF – time to peak filling*

neuroendocrine model and remodeling process.[8] Beta-2 blockers are used as an antiadrenergic therapy that blocks the receptors beta (b)1 and b2, including alpha receptors (a)1 or specific beta-blockers b1.[9] Carvedilol is a third generation beta-blocker (bb) with blocking properties for a1, b1 and b2 and antioxidant activity, which was extensively tested in studies on HF due to systolic dysfunction.[9] Since the publication of the studies US-CARVEDILOL,[10,11] CIBIS-II,[12] MERIT-HF,[13] COPERNICUS,[14,15] CAPRICORN[16] and CARMEN,[17] there is extensive documentation showing that beta-blockers associated with standard therapy reduce morbidity and mortality of patients with HF.[10]

Noninvasively, nuclear medicine can assess the cardiac presynaptic neuronal function using ^{123}I-labeled metaiodobenzylguanidine (^{123}I-MIBG), which presents a cellular uptake mechanism similar to that of norepinephrine in the sympathetic nerve terminal. In patients with HF, reduced uptake of this radiopharmaceutical drug would be correlated with reduced uptake of norepinephrine (NE) and, consequently, worse prognosis.[18] Myocardial uptake three times higher than the mediastinum uptake can provide potential candidates with satisfactory response to the use of beta-blockers, including improvement in ejection fraction (EF).[19]

Treatment with carvedilol has been able to improve cardiac sympathetic activity, as assessed by 123I-MIBG in patients with HF undergoing the treatment.[10,11,14-17] In parallel to this improvement in adrenergic activity, we observed improved left ventricular systolic function. However, most studies evaluated patients in the long term, i.e., six months to one year of treatment.[10,11,14-17]

Left atrial volume (LAV) is a measure of chronicity and severity of diastolic dysfunction and it is less load-dependent. Then, the left atrium (LA) expands in response to the persistent increase in left ventricular (LV) and LA filling pressures over time. In contrast, the transmitral flow parameters are more load-dependent, float more, and are more representative of immediate conditions. Altogether, these echocardiographic measures provide important complementary prognostic information. Left atrial volume complements many parameters of diastolic function evaluation.[1-5]

Little is known of the short-term effects of therapy with carvedilol on left atrial volume, cardiac adrenergic activity and systolic function in patients with HF.

This study aims to evaluate the behavior of echocardiographic indexes, scintigraphic indexes and left atrial volume before and after three months of therapy with carvedilol in patients with HFREF, New York Heart Association (NYHA) FC II and III.

Methods

This study is an echocardiographic substudy of a cohort of patients from an outpatient clinic specializing in heart failure from Hospital Universitário Antônio Pedro (HUAP), Universidade Federal Fluminense, diagnosed with HF without prior use of beta-blockers. These patients were selected from those who did admission echocardiography before and after therapy with carvedilol.

The work is part of the study approved by the Research Ethics Committee from HUAP under no. 014/06, including Informed Consent Form. It was also submitted to the Scientific Committee of Hospital Pró-Cardíaco.

Echocardiography was used as a screening and follow-up test of patients with systolic heart failure for a thesis project on HFREF. All patients were clinically evaluated using a standardized anamnesis protocol from the HF/Cardiology clinic.

Electrocardiography (ECG), chest X-ray, laboratory tests and standard echocardiography were used for research, which evaluated LV ejection fraction using the Simpson's method. All patients considered for the study, that is, in NYHA FC II and III, and ejection fraction ≤45%, were invited to participate in the study, after signing the Informed Consent.

The study included patients with heart failure NYHA FC II and III, adults, echocardiography showing EF 45% using the Simpson's method and clinical examination compatible with HF (Framingham and Boston criteria). Exclusion criteria adopted: pregnant or breastfeeding women, atrial fibrillation, pacemaker, organic mitral valvulopathy of moderate or significant degree/alcohol abuse (frequent), systolic blood pressure <85 mmHg and >160 mmHg, heart rate <60 bpm, prior use of beta-blockers, 2nd or 3rd atrioventricular block, history of bronchospasm, blood glucose >125 mg/dL, signs and symptoms of neurological disease (Parkinson's disease), patients with NYHA FC I and IV, presence of other diseases affecting the sympathetic nervous system.

Doppler echocardiography tests were performed in Niterói, at HUAP, on an echocardiographic device VIVID 3 (GE, Massachusetts, USA) and analyzed by an experienced echocardiographer without prior knowledge of the results of other tests. The parameters of cardiac function were estimated by the average of three consecutive heartbeats according to the protocols of the recommendations of the American Society of Echocardiography (ASE)/European Association of Echocardiography.

Results

The study included 19 patients, 12 (63.2%) of whom were male, 11 (57.9%) in FC II and 8 (42.1%) in FC III. The variables evaluated in the pre-treatment showed reduced EF values both on echocardiography (0.28) and on radionuclide ventriculography (0.29). Mean baseline heart rate was 84 bpm.

Plasma catecholamine was, on average, within the normal range: NE=199.2 pg/mL (normal up to 370 pg/mL), DOP=142.6 pg/mL (normal up to 200 pg/mL) and EPI=106.9 pg/mL (normal up to 150 pg/mL). The variables that assess diastolic function, time to peak filling (TPF) and peak filling rate (PFR) were abnormal. The TPF measuring the time between the beginning of diastole and the maximum ventricular filling velocity was well above normal (<180 ms) and PFR was very high. For some variables, there was loss of information in the data collection: in one case, it was not possible to conduct 4-hour MIBG.

After three months of treatment with carvedilol, which in the echocardiography variables (Table 1) there was significant reduction in LAV (p=0.009), LAV index (p=0.014), LVs (p=0.016), ESV (p=0.009) and significant increase in Simpson's EF (p=0.0002).

In the scintigraphy variables (Table 2), there was a significant increase in EFVI (p=0.012) and 4-hour MIBG (p=0.049) and reduction of HR measured during scintigraphy (p=0.0001). There was no significant variation at the level of 5% on the other variables between the two periods studied.

Furthermore, according to the corrected McNemar test, there was a significant decrease (improvement) in FC after three months of treatment (p<0.0001). Table 3 shows the frequency (n) and percentage (%) of CF at baseline and three months after treatment.

The Spearman correlation coefficient (Tables 4 and 5), which measures the degree of association between two numerical variables, showed that for the LAV delta, there was a significant direct correlation with the LVd deltas (n=18; r_s=0.517; p=0.028); LV_S (n=18; r_s=0.664; p=0.003); EDV (n=17; r_s=0.564, p=0.018); ESV (n=17; r_s=0.561; p=0.019); and Peak E (n=15; r_s=0.561; p=0.030); and a significant inverse correlation with Simpson's EF delta (n=18; r_s=-0.679; p=0.002). There was no significant correlation with age (n=18; r_s=0.141, p=0.58).

For the LAV index delta, there was a significant direct correlation with the LVd deltas (n=18; r_s=0.579, p=0.012); LV_S (n=18; r_s=0.769; p=0.002); EDV (n=17; r_s=0.478, p=0.052); ESV (n=17; r_s=0.534, p=0.027); and significant inverse correlation with Simpson's EF delta (n=18; r_s=-0.695; p=0.001). There was no significant correlation with age (n=18; r_s=0.222, p=0.37).

According to multiple linear regression (MLR), ESV delta (p = 0.003) and LVs delta (p=0.009) were independent predictors to explain the LAV delta, that is, the higher the drop of LVs and ESV, the higher the expected LAV drop value (Table 6).

Similarly, it was observed that the ESV delta (p=0.003) and the LVs delta (p=0.005) were independent predictors for explaining the LAV index delta, that is, the higher the LVs and EVS drop, the higher the expected LAV index drop value (Table 7).

Table 1
Baseline echocardiography variables after three months and the corresponding absolute delta

Variables	Baseline (M1)			3 months (M2)		Delta (M2-M1)	p-value[a]
	n	mean±SD	med	mean±SD	med	mean±SE	
BS	18	1.84±0.23	1.84	1.85±0.22	1.86	0.009±0.013	0,57
Aorta (cm)	19	3.26±0.52	3.11	3.20±0.41	3.18	-0.066±0.059	0,45
LA (cm)	19	4.56±0.75	4.23	4.49±0.66	4.23	-0.077±0.117	0.59
LAV (mL)	18	83.2±33.4	69.6	73.7±29.8	65.0	-9.53±3.90	0.009
LAV index (mL/m²)	18	44.8±15.8	42.8	39.7±14.5	36.9	-5.05±2.18	0.014
Simpson's EF	19	0.271±0.078	0.28	0.342±0.087	0.37	0.072±0.021	0.0002
LVd (cm)	19	6.92±0.81	6.91	6.73±0.92	6.48	-0.195±0.105	0.22
LVs (cm)	19	5.89±0.83	5.87	5.47±1.04	5.29	-0.425±0.155	0.016
IVS (cm)	19	0.849±0.138	0.82	0.917±0.177	0.87	0.068±0.032	0.11
LVPW (cm)	19	0.868±0.125	0.82	0.899±0.184	0.82	0.031±0.033	0.61
EDV (mL)	17	205.5±66.9	192.3	185.3±68.8	169.6	-20.2±8.9	0.071
ESV (mL)	17	152.9±59.8	136.4	125.7±59.0	107.9	-27.1±10.7	0.009
LV Mass (g)	18	285.8±79.2	277.1	267.0±96.4	228.8	-18.8±15.4	0.090
LV/BS Mass (g/m²)	18	151.7±33.6	152.5	143.8±47.6	128.8	-7.93±9.13	0.14
EDT (ms)	12	153.6±61.0	140	171.9±54.1	165	18.3±16.7	0.077
E wave (m/s)	16	0.901±0.237	0.885	0.868±0.196	0.855	-0.033±0.063	0.63
A peak (m/s)	16	0.613±0.299	0.545	0.580±0.289	0.525	-0.033±0.050	0.63
E/A ratio	16	1.95±1.18	1.695	2.08±1.59	1.425	0.129±0.290	0.91
PV < 0.45 (m/s)	14	0.352±0.075	0.35	0.332±0.074	0.325	-0.020±0.023	0.39
E/PV	14	2.62±0.90	2.52	2.67±0.76	2.66	0.046±0.243	0.76
E line (m/s)	18	0.086±0.032	0.09	0.088±0.036	0.09	0.002±0.006	0.64
E/E line ratio	16	13.0±5.9	12.0	11.7±7.3	10.1	-1.24±1.25	0.40

SD – standard deviation; SE – standard error; med – median.[a] Wilcoxon signed-rank test
BS – body surface; LA – left atrium; LAV – left atrial volume; Simpson EF – ejection fraction by echocardiography; LVd – LV diastolic diameter; LVs – LV systolic diameter; IVS – interventricular septum in diastole; LVPW – LV posterior wall in diastole; EDV – LV end-diastolic volume; ESV – LV end-systolic volume; EDT – mitral flow E wave deceleration time; Peak E – mitral flow rapid filling peak diastolic velocity; Peak A – mitral flow atrial contraction peak diastolic velocity; PV – M-mode mitral inflow propagation velocity; E line – peak early diastolic myocardial velocity

Table 2
Scintigraphy variables at baseline after three months and the corresponding absolute delta

Variables	Baseline (M1)			3 months (M2)		Delta (M2-M1)	p-value[a]
	n	mean±SD	med	mean±SD	med	mean±SE	
EFVI	19	0.289±0.085	0.29	0.333±0.096	0.31	0.044±0.015	0.012
MIBG 30 min	19	1.62±0.21	1.55	1.69±0.24	1.72	0.068±0.039	0.15
4-hour MIBG	18	1.57±0.14	1.57	1.65±0.20	1.71	0.087±0.045	0.049
Washout	18	0.293±0.114	0.30	0.341±0.141	0.30	0.048±0.047	0.49
ECG HR	19	84.6±11.4	85	68.1±11.9	66	-16.6±2.9	0.0001
NE	19	199.2±101.2	188	236.8±89.1	248	37.7±22.1	0.14
DOP	19	142.6±53.7	144	154.9±46.9	152	12.3±13.7	0.40
EPI	19	106.9±39.8	115	103.8±29.0	97	-3.16±7.07	0.72
TPF	19	300.4±222.4	269	327.5±239.7	195	27.1±77.7	0.77
PFR	19	864.9±535.9	648	601.5±450.6	458	-263.4±151.7	0.10

SD – standard deviation; SE – standard error; med – median; [a] Wilcoxon signed-rank test
EFVI – ejection fraction by radionuclide ventriculography; MIBG 30 min – metaiodobenzylguanidine; Washout – uptake difference between early image and late image; HR – heart rate; NE - norepinephrine; DOP – dopamine; EPI – epinephrine; TPF – time peak filling; PFR – peak filling rate

Table 3
Functional class at baseline and after three months of treatment

FC	Baseline		3 months		p-value [a]
	n	%	n	%	
I	0	0.0	9	47.4	
II	11	57.9	10	52.6	<0.0001
III	8	42.1	0	0.0	

[a] Corrected McNemar test. FC – functional class

Table 4
Correlation between the deltas of echocardiography with the LAV delta and LAV index

Echocardiography variables delta	n	LAV delta		LAV index delta	
		r_s	p-value	r_s	p-value
BS	18	0.117	0.64	-0.132	0.60
Aorta (mm)	18	0.003	0.99	-0.053	0.84
LA (mm)	18	0.227	0.36	0.372	0.13
LAV Index	18	0.936	0.0001		
LVd (mm)	18	0.517	0.028	0.579	0.012
LVs (mm)	18	0.664	0.003	0.769	0.0002
IVS (mm)	18	-0.372	0.13	-0.235	0.35
LVPW (mm)	18	-0.284	0.25	-0.221	0.38
EDV (mL)	17	0.564	0.018	0.478	0.052
ESV (mL)	17	0.561	0.019	0.534	0.027
Mass (g)	17	0.331	0.19	0.324	0.21
Mass/BS	17	0.113	0.67	0.113	0.67
EDT	11	-0.073	0.83	-0.191	0.57
E peak	15	0.561	0.030	0.504	0.056
Peak A	15	-0.161	0.57	-0.164	0.56
E/A ratio	15	0.377	0.17	0.331	0.23
PV < 45	13	0.228	0.45	0.179	0.56
E/PV	13	0.462	0.11	0.440	0.13
E line	17	0.068	0.80	0.026	0.92
E/E line ratio	15	0.371	0.17	0.468	0.079

r_s – Spearman correlation coefficient; BS – body surface; LA – left atrium; LAV – left atrial volume; LVd – LV diastolic diameter; LVs – LV systolic diameter; IVS – interventricular septum in diastole; LVPW – LV posterior wall in diastole; VDF – end-diastolic volume of the left ventricle; VSF – LV end-systolic volume; TDE – mitral flow E wave deceleration time; Peak E – mitral flow rapid filling peak diastolic velocity; Peak A – mitral flow atrial contraction peak diastolic velocity; PV – M-mode mitral inflow propagation velocity; E line – peak early diastolic myocardial velocity

Table 5
Correlation between the scintigraphy deltas with LAV delta and LAV index

Scintigraphy variables delta	n	LAV delta		LAV index delta	
		r_s	p-value	r_s	p-value
Simpson's EF	18	-0.679	0.002	-0.695	0.001
EFVI	18	-0.293	0.24	-0.306	0.22
MIBG 30 minutes	18	-0.067	0.79	-0.241	0.34
4-hour MIBG	17	-0.075	0.78	-0.167	0.52
Washout	17	-0.338	0.18	-0.395	0.12
ECG HR	18	-0.020	0.94	-0.028	0.91
NE	18	-0.110	0.66	-0.030	0.91
DOP	18	-0.237	0.34	-0.221	0.38
PPE	18	-0.362	0.14	-0.317	0.20
TPF	18	-0.319	0.20	-0.453	0.059
PFR	18	-0.046	0.85	-0.187	0.46

r_s – Spearman correlation coefficient; Simpson's EF – ejection fraction by echocardiography; EFVI – ejection fraction by radionuclide ventriculography; MIBG – metaiodobenzylguanidine; Washout – uptake difference between early image and late image; HR – heart rate; NE – norepinephrine; DOP – dopamine; EPI – epinephrine; TPF – time peak filling; PFR – peak filling rate

Table 6
Multiple regression analysis for LAV delta

Variables	Coefficient	Standard error	p-value	Model R^2
ESV delta	0.1994	0.0565	0.003	0.803
LVs delta	11.3554	3.7732	0.009	

The selection process was stepwise forward at the level of 5%.
ESV – LV end-systolic volume; LVs – LV systolic diameter

Table 7
Multiple regression analysis for the LAV index delta

Variables	Coefficient	Standard error	p-value	Model R^2
ESV delta	0.1080	0.0304	0.003	0.817
LVs delta	6.7288	2.0301	0.005	

The selection process was stepwise forward at the level of 5%.
ESV – LV end-systolic volume; LVs – LV systolic diameter

Discussion

The results showed that in patients with heart failure with depressed systolic function, carvedilol therapy improved both ventricular systolic function and left atrial volume.[20-25]

Studies show improved left ventricular systolic function in patients with HF, NYHA FC II and III occurring after therapy with beta-blockers.[26-29] Quaife et al.[28], assessing the effects of beta-blocker therapy with carvedilol in 21 patients with HF, NYHA FC II and III, before and after four months, found significant improvement in ejection fraction of 0.22±0.02 to 0.30±0.02, assessed by radionuclide ventriculography.[28] Comparing the parameters of diastolic function,

In insufficient ventricular myocardium, beta-blockers produce benefits through multiple mechanisms, unique among the medications for heart failure. At first, beta-blockers depress myocardial function due to the withdrawal of adrenergic support to the myocardium; however, later on, they improve myocardial energy through an exchange of substrate utilization, reduces cardiomyocyte apoptosis, cancels the induction of fetal genetic program and improves intrinsic myocardial function through a time-dependent effect on insufficient cardiac muscle[21]. Based on these data, the patients' catecholamines (Nora, Dopa and Epi) were measured before and after three months of beta-blocker therapy. However, there were no significant changes in the number of cases studied. Initial dosages reveal values in a picture of relative clinical stability and its level after treatment showed no significant change. This behavior throughout cardiac MIBG shows that hemodynamic changes can occur with no changes to cardiac adrenergism.

Several randomized trials have shown improved prognosis of patients with HF after beta-blocker therapy.[22,23] The main reported benefits include improvement in symptoms and systolic function, reverse remodeling of ventricular size, and delayed HF progression.[24] Sevimli et al.[25] demonstrated significant left atrial volume reduction on transesophageal echocardiography in patients with HF after short-term therapy with carvedilol. In fact, in this study, ventricular function and left atrial volume improved, confirming previous reports of the beneficial effects of this medication on ventricular function, extending this knowledge to the left atrium.[25] Quaife et al.[28] showed improved systolic performance after treatment carvedilol but with no significant change in LV filling.[28] Pallazuoli et al.[24] demonstrated that therapy with metoprolol induces positive diastolic filling changes not only in idiopathic cardiomyopathy, but also in ischemic cardiomyopathy and HF[16]. These improvements to the Doppler parameters were only minimally attributed to reduced heart rate and blood pressure.

These findings strengthen the divergence of literature findings on the effect of carvedilol in diastolic function of patients with HF, as there was no significant improvement in diastolic function parameters derived from Doppler. There was only some tendency to reduce mitral inflow E wave deceleration time, which may be due to the small sample size. In contrast, reduction of LAV and LAV index, as shown in this study, may be associated with improved diastolic function, as the LAV and the LAV index have been considered markers of severity and duration of diastolic dysfunction.[20,26]

Despite few studies, the association between left ventricular systolic function and LAV has been discussed. Russo et al.[29] demonstrated that left atrial volume correlates both with systolic function and with diastolic function, but there is not a better association between minimum LAV (end diastole) with diastolic function, while the maximum LAV (measured in the end of systole, which is employed in this study and in most of the literature) is strongly correlated with left ventricular systolic function. According to the authors, the direct association between LAV and systolic function makes it a less precise parameter to assess the LV diastolic function.[29]

This study showed that, by multivariate analysis, the improvement in cavity volumes and diameters (ESV, LVs), considering LV systolic function, was determining to reduce LAV and LAV index after short-term therapy with carvedilol. This is partially due to improved left atrial function after therapy with carvedilol and direct action of carvedilol in the left atrial myocardium, which results from improvement of neurohumoral mechanisms. In addition, a left atrial emptying facilitated by a drop in LV filling pressures consequent to improved systolic function by carvedilol is also present.

This study has some limitations: the small sample size that is partially due to the strict inclusion criteria; and the high complexity of the study, which used advanced

technology, not available at HUAP, which would require more time to include more cases, in addition to full doses of beta-blockers.

Conclusions

There was a clear reduction of the left atrial volume, reverse remodeling, and LAV index in patients with HF, FC II and III, after three months of therapy with carvedilol; there was no significant improvement in other diastolic function indexes. Carvedilol therapy in the short term was associated with improved systolic function and that was the main determinant of LAV reduction.

Potential Conflicts of Interest
This study has no relevant conflicts of interest.

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