

# The effect of left ventricular dysfunction on right ventricle ejection fraction during exercise in heart failure patients: Implications in functional capacity and blood pressure response

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## Abstract

**Background:** *The aim of this study was to assess the effect of left ventricular dysfunction on right ventricular ejection fraction during exercise in heart failure patients and its implications in functional capacity and blood pressure response.*

**Methods:** *In a cross-sectional study 65 patients with heart failure were included. Left and right ventricular ejection fractions were evaluated by radio-isotopic ventriculography. All subjects underwent an exercise treadmill test (Bruce modified protocol). Systolic and diastolic blood pressures were also recorded.*

**Results:** *From the total population, 38 (58.46%) showed a significant increase ( $\geq 5\%$ ) in left ventricular ejection fraction (LVEF) and 27 (41.5%) showed a significant decrease in LVEF ( $\geq 5\%$ ) after the stress test. Patients with a significant reduction in LVEF during stress had lower exercise tolerance ( $4.1 \pm 2.5$  vs.  $6.1 \pm 2.5$  METs,  $p = 0.009$ ) compared to those who showed an increase in LVEF. Diastolic blood pressure was higher at rest among those who had a reduced LVEF during stress ( $83 \pm 12.2$  vs.  $72.6 \pm 12.2$  mm Hg,  $p = 0.035$ ) and during exercise ( $95 \pm 31.3$  vs.  $76.9 \pm 31.3$  mm Hg,  $p = 0.057$ ), as well as mean arterial pressure in the same group ( $97.1 \pm 11.6$  mm Hg,  $p = 0.05$ ). In addition, this group decrease of  $-8.8 \pm 51.6\%$  in the right ventricular ejection fraction after exercise compared to an increase of  $27.3 \pm 49.1\%$  ( $p = 0.007$ ) among the patients with an increase in LVEF.*

**Conclusions:** *Biventricular systolic dysfunction during exercise is associated with higher rest and stress blood pressure and worse functional capacity. (Cardiol J 2009; 16, 2: 127–132)*

**Key words:** biventricular dysfunction, functional capacity, blood pressure

## Introduction

Many studies have addressed the clinical implications of left-sided systolic heart failure (HF); nonetheless, right ventricular (RV) involvement has been historically underestimated [1]. However, RV dysfunction may develop in association with left ventricular (LV) dysfunction via multiple mechanisms: LV failure increases pulmonary circulation pressure, thus increasing RV afterload [2]; ventricular interdependence due to septal dysfunction [1]; LV dilation in a limited pericardial compartment modifies diastolic function of both ventricles [3]; the common coronary arteries are associated with simultaneous right-left ischemic compromise [1]; later on, RV failure to supply an adequate left side pre-load jeopardizes cardiac output [1].

Also, recent studies have shown that RV failure is associated with a poor prognosis and is an independent survival predictor in several heart conditions such as ischemic heart failure [4, 5], myocarditis [6], or idiopathic dilated cardiomyopathy [7, 8]. On the other hand, RV function preservation improves survival [9], exercise tolerance, and functional class [10].

It is known that survival, symptoms, and ejection fraction are worse in patients with dilated cardiomyopathy with angiographically documented biventricular dysfunction, and they also have a higher New York Heart Association (NYHA) functional class and higher %VO<sub>2</sub> [11] compared to those with LV dysfunction alone [1]. The latter had better survival rates, as well as lower post-exercise NYHA functional classes and lower %VO<sub>2</sub> [11]. It should also be taken into account that, additionally, peripheral circulatory and muscular factors appear to play a role in the limitation of exercise tolerance of HF patients. Contrary to that found in normal subjects, vasodilatory reserve is altered in HF patients [12]. In fact, in some patients systolic function appears normal at rest; however, inappropriate blood pressure response and limited vasodilatory reserve increase cardiac work [13, 14].

The aim of the study was the evaluation of LV and RV ejection fraction at rest and during exercise in HF patients, and their relation with functional capacity and blood pressure response.

## Methods

In this cross-sectional study 65 patients with chronic heart failure (CHF) were included. They were stable outpatients in NYHA functional class I–III attending the Heart Failure Clinic at the In-

stituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ). They were consecutively included from December 2005 to November 2007 if they were more than 18 years old, with confirmed HF diagnosis (defined as systolic and/or diastolic dysfunction by an echocardiogram; and if signs and symptoms of HF developed) [15, 16]. Subjects were excluded if they had hypertrophic or restrictive cardiomyopathies, pericardial constriction, unstable ischemic heart disease (unstable angina and/or acute myocardial infarction), recent myocardial revascularization procedures (percutaneous transluminal coronary artery angioplasty and/or aortic coronary bypass grafting in the last 3 months), or life threatening arrhythmias.

All patients were on standard HF therapy: diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, aldosterone receptor blockers, digitalis and beta-adreno-receptor blockers.

All participants underwent a multistage exercise treadmill test according to the Bruce modified protocol. Systolic and diastolic blood pressures were recorded by cuff when the subject was standing immediately before testing and during the last minute of the last exercise stage. Subjects exercised until reaching an age-specific target heart rate or until the development of symptoms necessitating termination of the test or high blood pressure. Functional capacity was recorded in metabolic equivalents (METs).

The study was approved by the local bioethical committee and all patients gave their informed consent.

## Radio-isotopic ventriculography technique

Left and right ventricular functions were evaluated by radio-isotopic ventriculography, which is one of the simplest techniques to perform an initial functional evaluation among HF patients [17–19].

The procedure was performed at rest in the supine position with use of *in vivo* red blood cell labelling with <sup>99m</sup>Tc by standard methods [20].

The patients were required to fast for 4 hours prior to the study, and refrained from caffeine for 24 hours. They were injected with 40 mg of stanous pyrophosphate in 1.5 mL saline. Ten minutes later, the patients were positioned on the bed of the camera with the detector in the right anterior oblique (RAO) position. A rapid bolus of 20 mCi technetium-<sup>99m</sup> pertechnetate was given intravenously, together with the start of a list mode acquisition. Following the first pass study and after time for equilibration in the blood volume, a standard

**Table 1.** Demographic characteristics.

Variables	LVEF increase $\geq$ 5% (n = 38)	LVEF decrease $\geq$ 5% (n = 27)	p
Gender — male (%)	56.4	57.1	0.9
Age (years)	57.9 $\pm$ 16.8	63.7 $\pm$ 14.1	0.15
Body mass index	27.4 $\pm$ 5.3	28.4 $\pm$ 6.5	0.5
Hand grip strength [kg]	24.7 $\pm$ 9.9	20.98 $\pm$ 8.7	0.11
Hypertension (%)	63.2	64.3	0.9
Diabetes mellitus (%)	41	50	0.5
Ischemic cardiopathy (%)	64	47.6	0.3
Atrial fibrillation (%)	7.7	10.7	0.6
Edema (%)	41	42.9	0.88
NYHA I	60.5	45.9	0.3
NYHA II	28.9	35.7	
NYHA III	10.5	21.4	
Beta-blocker (%)	87.2	88.9	0.8
ACE inhibitors (%)	43.6	25.9	0.14
Angiotensin receptor blockers (%)	66.7	81.5	0.18
Thiazide diuretics (%)	58.3	48.1	0.6
Asa diuretics (%)	23.1	44.4	0.07
Spironolactone (%)	65.8	77.8	0.3

LVEF — left ventricular ejection fraction; ACE — angiotensin converting enzyme; NYHA — New York Heart Association functional class

gated cardiac blood pool study was acquired in the left anterior oblique (LAO) and left lateral projections. The R to R interval was divided into 16 frames, not greater than 0.04 s in length. Multigated acquisition was recorded for 900 s in a 64  $\times$  64 matrix. Both phases, rest and stress, were performed on the same day. Quantization was performed on the LAO view. Processing and measurements were made according to the American Society of Nuclear Cardiology Society guidelines.

Contractile reserve preserved was defined as the difference between the left ventricular ejection fraction (LVEF) obtained at peak effort during exercise and the resting values (changes were considered significant if an increase or decrease equal to or more than 5% was recorded).

### Statistical analysis

Continuous variables are given as mean  $\pm$  standard deviation (SD), and categorical variables are presented as absolute and relative frequency. Comparisons among groups were made with Pearson's  $\chi^2$  for categorical variables and unpaired *t*-test for continuous variables. A *p* value  $<$  0.05 was considered statistically significant. Analyses were performed using a commercially available package (SPSS for Windows, Rel. 15.0 1999 Chicago SPSS Inc).

### Results

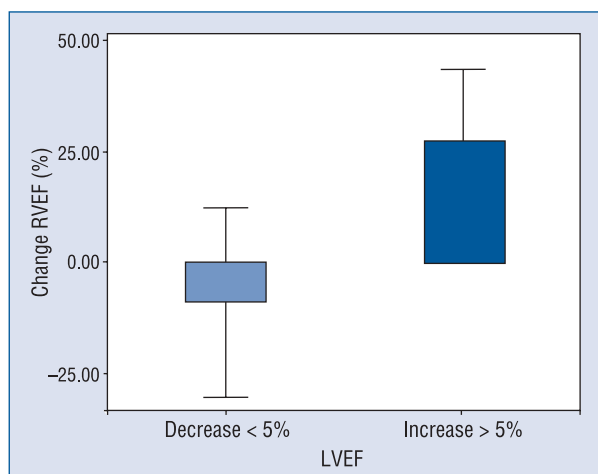
We analyzed 65 patients with left ventricular dysfunction. Thirty-eight (58.4%) showed a significant increase ( $\geq$  5%) in LVEF and 27 (41.5%) showed a significant decrease in LVEF ( $\geq$  5%) after the stress test. We also compared the general characteristics of our population (Table 1) according to the stress LVEF. Table 2 shows that patients with a significant reduction in LVEF during stress had lower exercise tolerance (4.1  $\pm$  2.5 *vs.* 6.1  $\pm$  2.5 METs, *p* = 0.009) compared to those that showed an increase in LVEF. Diastolic blood pressure was higher at rest among those who had a reduced LVEF during stress (83  $\pm$  12.2 *vs.* 72.6  $\pm$  12.2 mm Hg, *p* = 0.035). These numbers were still higher after exercise (95  $\pm$  31.3 *vs.* 76.9  $\pm$  31.3 mm Hg, *p* = 0.057), as well as mean arterial pressure in the same group (97.1  $\pm$  11.6 mm Hg, *p* = 0.05).

Figure 1 shows the percentage change in the right ventricular ejection fraction (RVEF) stress according to the stress LVEF. It can be seen that the group with a LVEF reduction during stress has a  $-8.8 \pm 51.6\%$  in the RVEF, compared to an increase of  $27.3 \pm 49.1\%$  in RVEF (*p* = 0.007) among the patients that had an increase in LVEF.

**Table 2.** Resting and exercise characteristics of study population.

Variables	LVEF increase $\geq$ 5% (n = 38)	LVEF decrease $\geq$ 5% (n = 27)	P
Age (years)	57.9 $\pm$ 16.8	63.7 $\pm$ 14.1	0.15
Resting SBP [mm Hg]	116.7 $\pm$ 20.1	125.3 $\pm$ 13.2	0.19
Peak exercise SBP	135.3 $\pm$ 20.1	148.0 $\pm$ 26.6	0.16
SBP change (%)	16.87 $\pm$ 11.38	17.9 $\pm$ 15.8	0.8
Resting DBP [mm Hg]	72.6 $\pm$ 12.9	83 $\pm$ 12.2	0.035
Peak exercise DBP [mm Hg]	76.9 $\pm$ 15.5	95 $\pm$ 31.3	0.057
DBP change (%)	5.9 $\pm$ 12.2	14.1 $\pm$ 32.0	0.4
Mean blood pressure [mm Hg]	87.3 $\pm$ 14.5	97.1 $\pm$ 11.6	0.056
Resting heart rate [bpm]	74.7 $\pm$ 20.1	68.5 $\pm$ 12.9	0.29
Peak exercise heart rate [bpm]	130.2 $\pm$ 22	119.9 $\pm$ 21.3	0.19
Heart rate change (%)	80.2 $\pm$ 36.6	79.7 $\pm$ 36.8	0.9
Functional capacity [METs]	6.1 $\pm$ 2.5	4.0 $\pm$ 2.5	0.009
Resting DP [mm Hg]	8750.6 $\pm$ 3272.9	8337.4 $\pm$ 1487.6	0.7
Peak exercise DP [mm Hg]	14232 $\pm$ 5337.7	17373.5 $\pm$ 4072.1	0.096
DP change (%)	75.2 $\pm$ 78.4	114.4 $\pm$ 64.1	0.17
Rest LVEF	31.1 $\pm$ 12.9	34.7 $\pm$ 17.3	0.33
Rest RVEF	26.8 $\pm$ 10.8	30.3 $\pm$ 14.5	0.28
Stress RVEF	32.1 $\pm$ 12.7	26.1 $\pm$ 15.2	0.08

SAP — systolic blood pressure; DBP — diastolic blood pressure; DP — double product; LVEF — left ventricle ejection fraction; RVEF — right ventricle ejection fraction; bpm — beats per minute



**Figure 1.** Right ventricular ejection fraction (RVEF) percentage of change from rest to stress, according to change in left ventricular ejection fraction (LVEF); p = 0.007.

### Discussion

In this study, we found that patients with LV dysfunction and significant decrease of LVEF during stress had higher diastolic blood pressure at rest and during stress, poor functional capacity, and a decrease in RVEF during exercise. Regarding systolic blood pressure, it only showed a tendency

towards significance. It is possible that peripheral vasoconstriction attributable to neurohumoral activation in heart failure, exercise-induced stress, and a sub-optimal blood pressure control (two thirds of our population are hypertensive) are responsible for the higher ventricular afterload. This could explain why in a rest state LVEF can remain around 45% but during exercise-induced stress a lack of vasodilatory response can diminish the ejection fraction [12].

Contractile reserve is always reduced in HF patients nonetheless; during exercise end-systolic pressure also increases among them, even if the rise is smaller than in healthy subjects [12, 21].

In patient with HF, systemic vascular resistances are higher at rest than normal subjects. During exercise, they decline markedly, and the reduction in peripheral resistances during exercise is only slightly less marked than in normal people [22, 23] Nevertheless, resistances always remain higher than in normal subjects at a given load; contrary to healthy subjects, they plateau at approximately 75% of maximal effort, muscle blood flow then becoming exclusively dependent on perfusion pressure [24].

In this series, both patients with increased diastolic blood pressure at rest or during stress developed a reduction in ejection fraction, suggesting that this sort of fixed intrinsic peripheral vascular

resistance is badly tolerated by HF patients, and thus their ejection fraction decreases, as other authors have noted [25].

Neurohormonal over-stimulation with a predominance of vasoconstrictor and antinatriuretic systems (sympathetic nervous system, renin–angiotensin–aldosterone system, endothelin, vasopressin, constrictive prostaglandins) over vasodilatory or natriuretic systems (natriuretic factor, dilative prostaglandins) is well documented in HF and contributes to the rise in peripheral resistance [12].

An initial approach would be to justify an increase of the doses of ACE inhibitor or angiotensin blocker receptors in order to decrease the over-activation of the renin–angiotensin–aldosterone system, and thus to improve vasoconstrictive status; however, the use of these kinds of drugs does not normalize metabolic vasodilatation, and despite a substantial reduction in plasma angiotensin II and noradrenalin, maximal muscle blood flow does not increase, indicating that the blockade of these systems does not interfere with blood flow towards active muscles during exercise in CHF. Nonetheless, several months of ACE inhibitors and angiotensin receptor blocker treatment can increase the femoral blood flow during exercise, as well as increase the maximal local oxygen consumption [12].

The endothelium plays an important role in the control of vascular tone, not only at the conductive vessels level but also at the resistive vessels level. Tissue perfusion is mainly regulated by resistive vessels, where nitric oxide is continuously released in systemic and pulmonary territories that have been implicated in muscle perfusion, exercise capacity, and ejection fraction preservation [26].

As has been described, right ventricular function is a determinant of functional capacity and prognosis [1, 2, 6]. In our population, we found differences in effort tolerance between groups related to an increase or decrease in LVEF. Those with LVEF decline also showed a simultaneous decrease in RVEF during exercise, as opposed to those that showed a biventricular increase. In this group, even if the RVEF was lower at rest, exercise-induced inotropic response was higher than in those with reduced LVEF. In absolute terms, RVEF was lower, but the percentage of change was statistically significant. Is possible that chronic right ventricular overload plays a very important role in effort tolerance in the setting of depressed LVEF.

The function and size of the right ventricle are not the only indicators of severity and chronicity of pulmonary hypertension, which implies an additional cause of symptoms and reduced longevity.

In fact, right ventricular function is the most important determinant of longevity in patients with pulmonary arterial hypertension [1, 27].

In addition, both ventricles share vascular territories, thus increasing MVO<sub>2</sub> after physical stress. It is thought that a reduced coronary reserve induces myocardial dysfunction, as has been demonstrated in chronic pulmonary hypertension secondary to obstructive sleep apnea syndrome, in which a really ischemic phenomenon was observed during apnea period [28].

Larger studies are required to know the prevalence of mixed forms of ventricular dysfunction, and tools for a more specific evaluation of systolic function than ejection fraction are needed to evaluate biventricular dysfunction and possible treatment strategies.

### Limitations of the study

We did not perform volume-pressure curves, O<sub>2</sub> consumption, quantification, invasive determinations of pulmonary artery pressure, or ventricular perfusion studies.

### Conclusions

In heart failure patients, right systolic dysfunction is highly prevalent and associated with higher rest and exercise diastolic blood pressure levels. The association of left sided systolic dysfunction and decrease of right ventricular ejection fraction was present in those with worse functional capacity.

### Acknowledgements

The authors do not report any conflict of interest regarding this work.

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