Original Article

Clinical and Echocardiographic Parameters Associated with Low Chronotropic index in Non-Elderly Patients

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Abstract

Background: **Despite abundant evidence of increased morbidity and mortality, chronotropic incompetence (CI) is not a routine diagnosis well defined in protocols of cardiac evaluation and its clinical importance is still underestimated.**

Objective: **To evaluate the clinical and echocardiographic parameters associated with HF in non-elderly patients submitted to stress echocardiography (SE).**

Methods: **One thousand seven hundred ninety-eight patients with a mean age of 48.4 ± 7.5 years, who underwent SE between January/2000 and August/2009 were evaluated. Patients with chronotropic index smaller than 0.8 were considered chronotropic incompetent as compared to competent patients as to clinical and echocardiographic characteristics.**

Results: **The duration of the exercise was 9.3 ± 2.4 minutes on average. Two hundred and seventy (15%) patients were chronotropic incompetent. The chronotropic index of this group was 0.7 ± 0.1 vs. 1.0 ± 0.1 for competent patients. Multivariate logistic regression analysis identified the following parameters as independently associated with HF: dyspnea on examination [odds ratio (OR) = 4.27, p <0.0001], previous chest pain on medical history (OR = 1.51; p = 0.0111), higher left ventricular mass rate in incompetent patients (LVMI) (OR = 1.16, p = 0.0001), metabolic equivalents (METs) (OR = 0.70, p = 0 , 0001), ST segment depression (OR = 0.58, p = 0.0003) and high systolic blood pressure (ΔSBP) (OR = 0.87, p = 0.0011). Myocardial ischemia was not associated with HF.**

Conclusion: **HF is associated with functional parameters, such as dyspnea on exertion, history of chest pain and lower METS. It is also associated with structural benchmark index of left ventricular mass. In addition, chronotropic incompetence does not appear to increase the chance of myocardial ischemia in non-elderly patients. (Arq Bras Cardiol 2012;98(5):413-420)**

Keywords: **Physical exertion; heart rate; exercise test; echocardiography, stress; exercise tolerance.**

Introduction

Attenuation of increase in heart rate (HR) during exercise, known as chronotropic incompetence (CI), has been associated with myocardial ischemia and CAD even in healthy patients[1-5]. Nevertheless, it is not a routine diagnosis well defined in cardiac evaluation protocols. Its pathophysiological mechanisms are unknown and clinical implications are underestimated.

The exercise testing (ET) is presented as a well established methodology in the diagnosis and risk stratification of patients with CAD[6,7]. Patients unable to reach submaximal HR are classified as incompetent in chronotropic terms and qualify the test as "ineffective", but not necessarily abnormal, since no increase in HR may limit the appearance of ST segment changes, which constitutes a potential limitation of this method[8,9].

Stress echocardiography (SE) is a noninvasive method well established in the diagnosis of myocardial ischemia and viability, risk stratification and prognosis of CAD[10]. Moreover, it is confirmed to present diagnostic accuracy superior to that of the ET, especially in patients with HF[11].

In Brazil, the value of pharmacological stress echocardiography is well defined[12-16]. However, studies on SE are scarce. It has been demonstrated in an unselected population, including patients with prior CAD, that HF is associated with an increased frequency of myocardial ischemia on SE[11]. The same authors studied only the elderly and found that HF in this group is also associated with higher frequency of contractile alterations and adds to a positive predictive value to SE in identifying patients with obstructive CAD[17].

Since the general population and the elderly have been analyzed for factors associated with HF, particularly ischemia, this study aims to evaluate the clinical and echocardiographic characteristics independently associated with HF in nonelderly patients without previous CAD and under no use of beta-blockers and calcium antagonists submitted to SE.

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Methods

Study population: Patients under the age of 60 years who underwent SE in the Echocardiography Laboratory of Clínica e Hospital São Lucas (Aracaju, SE) between January 2000 and August 2009 were deemed potentially eligible for analysis. We excluded those who had: inability to reach the second stage of the standard Bruce protocol; typical angina manifestation during SE; use of beta-blockers, nitrates and/or calcium channel antagonist; confirmed previous CAD (acute myocardial infarction, coronary artery bypass grafting and/or percutaneous coronary intervention), valvular heart disease, heart failure, congenital heart disease and/or left bundle branch block. Muscle fatigue and dyspnea on SE did not exclude patients, as these limitations are characteristic of the procedure. Where there were repeated examinations during this period, only the first examination was used for analysis.

One thousand seven hundred ninety-eight patients were able to participate in the analysis. The ethical principles governing human experimentation were followed closely, and all patients signed an informed consent. The study was approved by the Ethics and Research of the Universidade Federal de Sergipe.

Chronotropic incompetence: To avoid biases in age, physical ability and resting HR of each individual, chronotropic incompetence was assessed by the chronotropic index. According to Wilkoff[18,19], the index is described as the ratio between reserve HF and the metabolic reserve used during peak exercise.

For any stage of the exercise, the percentage of reserve HR reached is:

[(stage HR - resting HR)/(220 - age - resting HR)] x 100

The percentage of metabolic reserve is:

[(stage METs - resting METs) / (peak METs - resting METs)] x 100

Where METs refer to metabolic equivalents measured by gas analysis, stage refers to any stage of exercise, and peak refers to the peak of exercise.

When considering the chronotropic index at peak, by definition, the metabolic reserve rate at this stage has a value of one (100% of the metabolic reserve). Under these conditions, the index should be at the rate of reserve HR used, based only on variables of resting HR, peak HR and age. Chronotropic index smaller than 0.8 defines chronotropic incompetence[18-21]. Based on this index, patients were divided into incompetent group (IG) and competent group (CG).

Clinical characteristics: Clinical data were collected and recorded through interviews held before the procedure. We used a structured questionnaire investigating weight, height, symptoms, medications, risk factors for CAD, history of heart disease. We defined obesity as body mass index greater than 30 kg/m^2. Moreover, the results of previous laboratory tests were recorded.

Hypercholesterolemia was defined as total serum cholesterol above 200 mg/dL (after fasting for 12 hours) and hypertriglyceridemia as serum triglycerides above 150 mg/dL (after fasting for 12 hours) or use of antilipidemic agent (statins and/or fibrates). We considered hypertension when blood pressure levels measured in the upper limb at rest were greater than or equal to 140 x 90 mmHg, or when making use of antihypertensive medication.

Diabetes mellitus was defined by fasting glucose above 126 mg/dL, or use of insulin or oral hypoglycemic agents.

We defined old myocardial infarction by clinical history and/or previous exams, such as electrocardiogram (ECG), echocardiogram and/or coronary artery angiography.

Stress test: First, the protocol consisted of twelve-lead ECG and echocardiography at rest after the clinical investigation. Then, physical exertion was made on a treadmill, and soon after, echocardiographic images were taken.

All patients underwent a standard Bruce protocol exercise testing. We performed continuous monitoring of HR, and patients were encouraged to reach their peak physical effort. For metabolic calculations, the volume of inspired oxygen at peak exercise (VO_{2max}) was obtained indirectly using the following formula: $VO_{2max} = 14.76$ to $1.379\ t + 0.451t^2 - 0.012t^3$, where t is the duration in minutes[22]. The load was expressed as metabolic equivalents, in which 1 MET corresponds to 3.5 mL/kg·min VO_2 inspired, referring to rest[21]. During testing, the individuals were continuously monitored with three-lead ECG.

Ischemic electrocardiographic abnormalities on exercise were considered to be horizontal or downsloping ST segment depression ≥ 1 mm for men and ≥ 1.5 mm for women at 0.08 second from the J point[6].

Stress Echocardiography: To record echocardiography at rest and immediately after exercise, patients were accommodated in the left lateral position for echocardiographic reading on parasternal and apical acoustic windows. Echocardiographic images were obtained through the equipment Hewlett Packard/Phillips SONOS 5500 with 2.5 MHz transducer and recorded on VCR or Digital Video Display. The classic techniques described by Schiller et al[23] were adopted.

The left ventricular wall motion was accessed semiquantitatively by an experienced echocardiographer with level III training as recommended by the American Society of Echocardiography. Wall motion at rest and on exercise was scored 1-5 (1 = normal) according to the 16-segment model[23]. Left ventricular wall motion score index (MSI) was determined at rest and immediately after exercise and expressed as the sum score of segments divided by the number of segments viewed.

Furthermore, left ventricular systolic function was also studied. Based on the MSI, patients were classified as normal (equal to 1), with mild ventricular dysfunction (between 1.01 and 1.6), with moderate ventricular dysfunction (between 1.61 and 2) and severe ventricular dysfunction (greater than 2).

The development of segmental wall motion abnormalities induced by stress was considered an indicator of myocardial ischemia.

Statistical analysis: Categorical variables were analyzed using Pearson's chi-square test ($\chi 2$) or Fisher's exact test (as indicated). For continuous variables, we used the Student t test. We considered $p < 0.05$ as statistically significant.

To identify the parameters independently associated with chronotropic incompetence, a logistic regression model was determined. Variables that presented p <0.25 in the univariate analysis were included in the multivariate analysis. A variable selection backward procedure was used. p <0.05 was adopted as a criterion for keeping variables in the model. The capacity to discriminate the final model between competent and incompetent patients was evaluated using the area under the curve (AUC) of a receiver operating characteristic, and model fit was assessed by the Hosmer-Lemeshow test (p> 0.05). All calculations were carried out using the Statistical Package for Social Sciences version 17 (SPSS 17, Chicago IL).

Results

Clinical characteristics: We studied 867 (48.2%) men and 931 (51.8%) women with a mean age of 48.4 ± 7.5 years (ranging between 21-59 years). Among the 1798 patients eligible for the study, the IG was composed of 270 (15%) patients and the CG, 1528 (85%).

Comparing the groups (IG vs. CG), some clinical variables showed a higher frequency in IG. These variables include history of chest pain and coronary risk factors, such as systemic hypertension, smoking, family history and obesity (Table 1).

Stress test: The duration of the exercise was 9.3 ± 2.4 min on average. It is important to ratify that only patients who reached the second stage of the Bruce protocol participated in the study. The average chronotropic index was 0.9 ± 0.1.

There was no significant difference in resting HR, reactive hypertension and arrhythmias between the groups. However, the elevation of systolic blood pressure (ΔSBP) during peak exercise was higher in the CG (p < 0.001). These patients were able to achieve, with statistical significance, a higher speed and a greater Bruce stage. This same group also showed higher frequency of ischemic electrocardiographic abnormalities (p < 0.001) during the test than the IG. On the other hand, the GI presented a higher frequency of dyspnea than the GC (p < 0.001) (Table 2).

Stress Echocardiography: The test was positive for myocardial ischemia in 151 patients (8.4%). There was a higher prevalence of ischemic individuals among incompetent patients (15.2% vs. 7.2%, p < 0.001).

Wall motions, which defined the MSI, revealed a higher rate in IG on echocardiography performed immediately after exercise (p < 0.001). With regard to left ventricular (LV) systolic function, only a mild dysfunction was observed among ischemic individuals. Furthermore, there was a greater mass index in these patients (p < 0.001). There was no significant difference in LV relative wall thickness among the groups (Table 3).

There were differences between the groups only on changes in the inferior wall and LV inferior septum, with greater frequency in incompetent patients (p <0.001 and p = 0.003, respectively) (Table 4).

Logistic Regression Analysis: After performing the test to account for the possible confounding factors in the model, only six variables were independently associated with HF. There were no interactions between the variables analyzed (Table 5).

On the Hosmer-Lemeshow test, p = 0.531 was observed, therefore, the final model was considered appropriate. AUC of 0.78 (95% CI, 0.75 to 0.81, p < 0.001) was observed, and the capacity of discrimination of the final model was considered reasonable (Chart 1).

Discussion

This study evaluated the clinical and echocardiographic parameters associated with HF, according to the chronotropic index in nonelderly patients. Out of the 1798 patients evaluated, 270 (15%) were chronotropic incompetent. Prior history of chest pain, dyspnea on examination and higher left ventricular mass indexes (LVMI) were shown to be independently associated with increased odds of HF. Higher values of METs and ΔPAS and ST segment depression were independently associated with lower odds of HF.

Table 1 - **Clinical characteristics**

DATA	*IG (n = 270) (15%)	CG†(n = 1528) (85%)	p
Age (years)	48.2 ± 7.5	48.4 ± 7.5	0.745
Gender (M)	86 (31.9%)	781 (51.1%)	<0.001
Asymptomatic	64 (23.8%)	586 (38.6%)	<0.001
Previous chest pain	199 (74%)	904 (59.6%)	<0.001
Previous dyspnea	6 (2.2%)	29 (1.9%)	0.728
Hypertension	151 (55.9%)	644 (42.1%)	<0.001
Dyslipidemia	158 (58.5%)	889 (58.2%)	0.927
Smoking	21 (7.8%)	73 (4.8%)	0.040
Diabetes mellitus	24 (8.9%)	91 (6.0%)	0.070
Family history	156 (57.8%)	734 (48.1%)	0.003
Obesity	89 (35%)	336 (22.9%)	<0.001

M - Male; (*) Patients with chronotropic index <0.8; (†) Patients with chronotropic index ≥ 0.8; (‡) Evaluated in only 52% of the population; (§) Evaluated in only 26% of the population.

Table 2 - **Clinical, hemodynamic and ECG findings during exercise**

DATA	IG* (n = 270) (15%)	GC†(n = 1528) (85%)	p
Chronotropic index	0.69 ± 0.11	0.99 ± 0.08	<0.001
HR (bpm)			
Rest	78.7 ± 14.0	77.1 ± 13.0	0.064
Peak	143.2 ± 11.9	170.5 ± 9.7	<0.001
ΔSBP (mmHg)	59.7 ± 19.2	67.0 ± 17.9	<0.001
Duration (min)	7.4 ± 2.3	9.6 ± 2.2	<0.001
Maximum speed (mph)	3.4 ± 0.7	4.0 ± 0.7	<0.001
Maximum Stage (Bruce)	3.1 ± 0.8	3.8 ± 0.8	<0.001
VO_{2max} (mL/kg·min)	25.4 ± 7.7	33 ± 8.5	<0.001
METs achieved	7.2 ± 2.2	9.4 ± 2.4	<0.001
Reactive hypertension	43 (15.9%)	243 (15.9%)	0.996
Arrhythmias	49 (18.1%)	270 (17.7%)	0.850
Dyspnea	35 (13.1%)	31 (2.0%)	<0.001
ST segment depression	138 (51.1%)	987 (64.6%)	<0.001

HR - heart rate; ΔSBP - high systolic blood pressure; METs - metabolic equivalents; VO_{2max} - volume of oxygen inspired at peak exercise; (*) Patients with chronotropic index <0.8; (†) Patients with chronotropic index ≥ 0 8.

Table 3 - **Echocardiographic parameters obtained by SE**

DATA	IG* (n = 270) (15%)	CG†(n = 1528) (85%)	p
EF at rest	0.67 ± 0.05	0.67 ± 0.05	0.625
LFMI			
Rest	1.0	1.0	-
Post-exercise	1.014 ± 0.037	1.006 ± 0.026	0.001
LVMI (g/m2)	83.5 ± 21.5	78.6 ± 17.7	0.001
LVRT (%)	31.5 ± 5.5	31.0 ± 5.0	0.132
Ischemia	41 (15.2%)	110 (7.2%)	<0.001

EF - ejection fraction; SE - stress echocardiography; LVWM - left ventricular wall motion; LVMI - left ventricular mass index; LVRT - left ventricular relative thickness; (*) Patients with chronotropic index < 0.8; (†) Patients with chronotropic index ≥ 0.8.

Table 4 - **Location of segmental left ventricular changes on SE**

DATA	IG* (n = 270) (15%)	GC†(n = 1528) (85%)	p
Front wall	10 (3.7%)	40 (2.6%)	0.320
Inferior wall	11 (4.1%)	17 (1.1%)	0.001
Sidewall	7 (2.6%)	23 (1.5%)	0.199
Posterior wall	1 (0.4%)	0 (0%)	0.151
Anterior septum	5 (1.9%)	12 (0.8%)	0.160
Inferior septum	13 (4.9%)	28 (1.9%)	0.003
Apical septum	6 (2.2%)	25 (1.7%)	0.451

SE - stress echocardiography; (*) Patients with chronotropic index <0.8; (†) Patients with chronotropic index ≥ 0.8.

Table 5 - Multivariate logistic regression with parameters associated with HF

Parameter associated	Crude Odds Ratio	Odds ratio adjusted	CI 95%	p
Previous chest pain	1.93	1.51	1.10 to 2.09	0.0111
Dyspnea examination	7.2	4.27	2.41 to 7.55	0.0000
METs	0.65	0.70	0.65 to 0.75	0.0000
LVMI (10 g/m2)	1.14	1.16	1.08 to 1.25	0.0001
ΔSBP (10 mmHg)	0.78	0.87	0.80 to 0.95	0.0011
ST segment depression	0.57	0.58	0.43 to 0.78	0.0003

Hosmer-Lemershow test (p = 0.531); METs - metabolic equivalents; LVMI - LV mass index; ΔSBP - high systolic blood pressure; ST segment depression - ST segment depression.

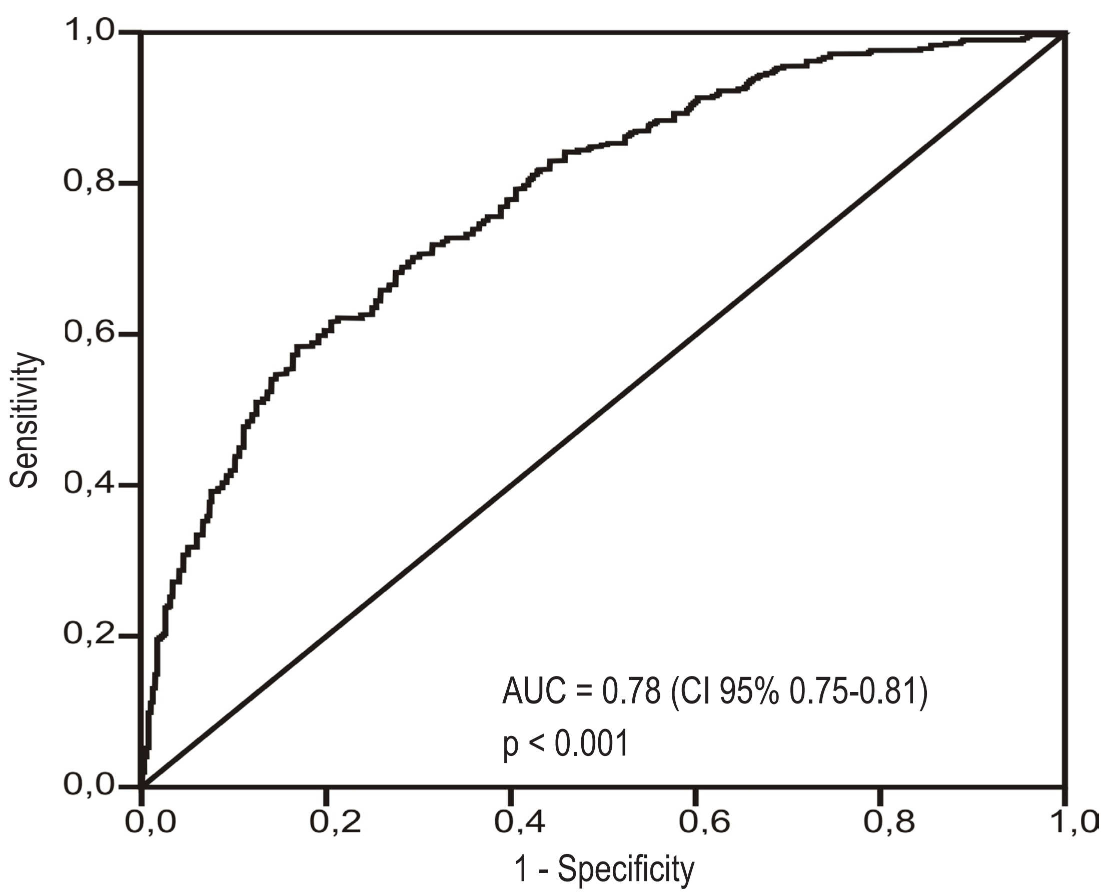

Chart 1 - *Discrimination capacity of the final model.*

The prevalence of HR varies according to the population studied and the defining criterion of incompetence. In this study, we found a prevalence of HR similar to data from previous studies in which the prevalence ranged from 15 to 25%[24].

Multivariate logistic regression analysis identified dyspnea on exertion as a parameter associated with HF. The presence of this symptom represents four-fold greater odds of being incompetent (p <0.0001). When evaluating patients with HF, studies in the literature report the symptom but do not examine its independent association regarding the abnormality of HR. The manifestation of dyspnea during stress testing for cardiac evaluation is of great prognostic relevance. The presence of this symptom on exertion is associated with a risk of death from cardiac causes four times higher than in asymptomatic patients and two-fold higher compared to those presenting typical angina, as demonstrated in a large population of patients with unknown history of CAD[25,26].

With regard to physical capacity, incompetent individuals had a lower tolerance to stress. For each increment of three units in the METs, the odds of incompetence is reduced by 66% ($p < 0.0001$). Similar results were found by other studies that confirm the inverse relationship between the presence of incompetence and physical capacity[11,18,20,21,27,28]. In a comparative study among users of pacemaker with fixed ventricular rate and variable rate during exercise, it was observed that the first group, which behaves like HF patients, presented worse tolerance to exertion[29].

The analysis of ST segment depression is still a major marker of ischemia induced by exercise[30,31]. However, the accuracy of ST in patients with HF has been questioned; the examination is often characterized as ineffective or not diagnostic[8,9]. Although there is an association between incompetence and myocardial ischemia[11], the imbalance between oxygen supply-consumption in incompetent patients would not be so encouraged to the point of developing electrocardiographic abnormalities suggesting ischemia, as typically occurs in competent patients, which would decrease the sensitivity of ST in incompetent patients. In this study, the higher incidence of ST-segment depression was associated with lower odds of HF (OR = 0.58; $p = 0.0003$), similar to what was described by Cay et al[32]. Maddox et al[33] found ischemia on ECG in only 17% of incompetent patients, and Dresing al[27], in 52% versus 65% of competent patients. Oliveira et al[11] described 30% of abnormalities in the incompetent group versus 43% in the competent group ($p < 0.0001$). Thus, these data should not be interpreted as an attempt to study the association between myocardial ischemia and heart failure, but as a reflection of the interference of HF in the manifestation of the marker of myocardial ischemia on ST (ST segment depression). Hence, there is a lower incidence of ST segment depression among incompetent patients not because of a lower frequency of myocardial ischemia in this group, but due to a lower frequency of electrocardiographic manifestation in the incompetent group. Therefore, stress electrocardiogram does not seem to be a good parameter to assess ischemia in incompetent patients, even in non-elderly patients.

ΔSBP during ET has been related to left ventricular performance[34]. Patients with good ventricular function were less likely to have HF (OR = 0.87, $p = 0.001$). At each increment of 10 mmHg, the odds of being incompetent are reduced by 13%. Similarly, Elhendy et al[18] described a smaller ΔSBP in incompetent patients (35 ± 30 vs. 50 ± 24, $p = 0.0001$). In other studies, we evaluated the systolic pressure at peak exercise, which also proved lower in these patients[11,20,21,27,28,35].

Not only functional variables were associated with HF. The highest values of LVMI were associated with inadequate chronotropic response on exercise even after multivariate analysis. Because it is a measure at rest, it is suggested that incompetent patients, even the non-elderly ones, have structural cardiac changes, rather than simply functional changes, such as a smaller capacity to raise heart rate on exertion. At each increment of 10 g/m^2 in LVMI, the odds of being incompetent is increased by 16% ($p = 0.0001$). These results were also found by Lauer et al[36] in middle-aged asymptomatic individuals, where increased left ventricular mass and dilation of this heart chamber represented greater likelihood of reduced chronotropic response to exercise. Another study described a higher LV mass index in incompetent patients with a trend towards statistical significance ($p = 0.06$)[20]. In addition, left ventricular hypertrophy has been associated with a decreased probability of reaching the heart rate predicted for age in men and women[37].

Although in the univariate analysis alone the index score of left ventricular wall motion, which represents ischemia on SE, was higher in patients with HF, this was not independently associated with HF in nonelderly patients. Nevertheless, in the literature, there are reports of HF as an important factor associated with myocardial ischemia and cardiovascular death[11,18,21,25,27,35]. However, these surveys either relied on univariate analysis or did not perform multivariate analysis with control for the variables used in this study, especially those related to the stress test.

Although myocardial ischemia is not independently associated with HF in this study, on multivariate analysis, the presence of previous chest pain raised 51% the odds of incompetence ($p = 0.0111$). There are other similar reports in the literature: Elhendy et al[18] described the increased presence of typical angina in incompetent patients (25% vs. 13%; $p < 0.001$), as well as Oliveira et al[11] (18% vs. 7%, $p < 0.0001$). This attenuation of heart rate increase during exercise may be, through unknown pathophysiological means, a protection mechanism intended to reduce myocardial oxygen demand. Thus, HF would be associated with symptomatic ischemia (patients with chest pain) rather than myocardial ischemia per se. Further studies with control for confounding factors are needed to elucidate the presumed association between heart failure and myocardial ischemia in non-elderly patients.

The limitations of this study include the metabolic evaluation performed using the indirect method of calculation VO_{2max}. In future studies, we would need to evaluate patients by cardiopulmonary exercise testing to confirm the association between HF and reduced exercise tolerance. Because it is a cross-sectional study, the findings do not allow diagnostic and predictive conclusions. Therefore, additional studies addressing the longitudinal design of HF are needed. As a highly selected sample was analyzed, we must be cautious in extrapolating the results found to other populations, such as elderly patients or patients with established CAD.

HF is still an underestimated diagnosis in clinical practice whose significance remains unclear, and may even be multifactorial. This study identified some factors associated with HF in the subgroup of nonelderly patients and may serve as a starting point for further pathophysiological or prognostic studies. But the most interesting point of attention for clinicians facing a non-elderly patient with chronotropic incompetence is to consider him/her as an individual with a potentially abnormal left ventricular mass index with chest pain and dyspnea on exertion and therefore monitoring him/her in greater detail.

Conclusion

HF is associated with the structural parameter of left ventricular mass index and functional parameters, such as dyspnea on exertion, history of chest pain and lower values of METS. In addition, chronotropic incompetence does not appear to increase the chance of myocardial ischemia in non-elderly patients.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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