Original Article

Prognostic Value of Chronotropic Incompetence in Elderly Patients Undergoing Exercise Echocardiography

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Abstract

Background: Chronotropic incompetence (CI), defined as failure to achieve less than 80% of age-expected heart rate, is a predictor of mortality and adverse cardiovascular events and may confer a worse prognosis in elderly diabetic individuals.

Objective: To evaluate the prognostic value of chronotropic incompetence (CI) in elderly diabetic patients considering endpoints with acute myocardial infarction (AMI), cerebrovascular disease (CVD) and overall mortality and compare clinical and echocardiographic characteristics between patients with and without CI.

Method: A total of 298 elderly diabetic patients undergoing exercise echocardiography (EE) were studied from January 2001 to December 2010. Of these, 109 were chronotropic incompetent (group 1) and were compared with the chronotropic competent ones (group 2) regarding the occurrence of cardiovascular events, clinical and echocardiographic characteristics.

Results: Chronotropic incompetents patients showed a higher frequency of cerebrovascular disease (9.2% vs. 3.2, p = 0.027) and higher mortality was observed in those who had cerebrovascular disease or acute myocardial infarction. The presence of typical angina and dyspnea prior to the performance of EE and male gender were more frequent in group 1. Rest and exercise left ventricular wall motion score index, rate of left ventricle mass and left atrium diameter were higher in chronotropic incompetent individuals.

Conclusion: Chronotropic incompetence was independently associated with the occurrence of cerebrovascular disease in elderly diabetic individuals (Arq Bras Cardiol. 2013; 100(5):429-436).

Keywords: Demographic Aging; Diabetes Mellitus; Echocardiography; Stress, Mechanical; Heart Failure.

Introduction

The rapid population aging that occurs mainly in developing countries such as Brazil is associated to the increased prevalence of chronic diseases, such as diabetes mellitus (DM) and cardiovascular diseases[1]. The main causes of death in both elderly and in diabetic individuals are coronary artery disease (CAD) and cerebrovascular disease (CVD)[2].

Chronotropic incompetence (CI) is characterized as the incapacity to achieve, on exertion, 80% of heart rate reserve for age and is a predictor of mortality and adverse cardiac events, even in healthy populations[3-8]. Nevertheless, the CI is yet to be used in clinical practice and its prognostic implications are underestimated[9]. Although its underlying mechanism is not well defined, some hypotheses have been proposed, among them the autonomic dysfunction[10].

To obtain the diagnosis and risk stratification of cardiovascular diseases, the rational use of imaging exams with proven accuracy is necessary, especially exercise echocardiography (EE)[11]. EE, a diagnostic methodology introduced in 1979, has progressively and significantly evolved in recent decades and has fundamental importance in the noninvasive diagnosis of ischemia and myocardial viability, risk stratification and prognosis of patients with established CAD[12,13]. The exercise stress test is indicated as first choice for patients with preserved physical capacity[12,14,15].

Several authors have demonstrated that EE has a similar sensitivity to that of myocardial perfusion scintigraphy, but with greater specificity, as it also has greater sensitivity and specificity than the conventional exercise testing[9].

This study aims to assess elderly diabetics undergoing EE with CI and compare them with chronotropic competent ones, with the objective of evaluating the prognostic value of CI in this population, considering as outcome: acute myocardial infarction, cerebrovascular disease, overall death and cardiovascular death.

Methods

Study design and population

This is a retrospective cohort study of 298 elderly and diabetic patients undergoing EE, between January 2001 and December 2010, at the Echocardiography Laboratory of

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Hospital São Lucas (Ecolab). Follow-up was carried out by telephone every two years from 2005. In cases where the patient or family had reported the occurrence of the outcome over the phone, the information was confirmed through test results and respective conducts or chart review; death was ratified at the information system of the State Health Secretariat. We excluded patients with poor imaging quality, significant valvular heart disease, atrial fibrillation, or incapable to be reached by telephone.

The database was filled out with information obtained from a structured questionnaire containing clinical, echocardiographic parameters (EE results) and information about events. The study was carried out by two observers from the same service with extensive experience in EE, following the same protocol. For the analysis, the 298 patients were divided into two groups: group G1, with 109 patients who were unable to reach 80% of HR reserve for estimated age during the EE and therefore met the criteria for CI; G2, with 189 patients who achieved 80% of HR reserve for estimated age and were, therefore, considered the control group patients. The groups were compared regarding clinical features, echocardiographic and cardiovascular events.

The ethical principles required for human experimentation were thoroughly followed and, prior to completion of EE, all patients signed an informed consent form authorizing the use of data contained in the questionnaire for performing the research and subsequent data publication. The study was approved by the Research Ethics Committee of the Universidade Federal de Sergipe.

Clinical features

Clinical data were collected and recorded through interviews before the procedure. A structured questionnaire assessing height, weight, symptoms, medications, risk factors for CAD and history of heart disease was used. Obesity was defined as body mass index > 27 kg/ m^2. Additionally, the results of previous laboratory tests were recorded.

Hypercholesterolemia was defined as the serum level of total cholesterol > 200 mg/dL (after 12-h fasting) and hypertriglyceridemia as triglyceride levels > 150 mg/dL (after 12-h fasting) or the use of antilipemic agent (statin and/or fibrate). Systemic arterial hypertension was considered when patients reported having received this diagnosis (blood pressure measured in the arm at rest, ≥ 140 × 90 measured by the attending physician) or when they were taking antihypertensive medication.

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

AMI was defined as the increase and decrease characteristic of specific markers for detection of myocardial injury associated with at least one of the following: a) ischemic symptoms indicative of ischemia (elevation or depression of the ST segment), b) development of pathologic Q waves in electrocardiogram; c) other suggestive ECG alterations.

Myocardial infarction was identified by clinical history, previous complementary examinations (electrocardiography, echocardiography and/or angiography) or respective medical conducts. Old infarction was considered if the event occurred prior to the performance of EE and new events, those occurring subsequent to the examination.

According to the criteria of the World Health Organization, CVD is a clinical syndrome consisting of neurological deficit of vascular origin and rapid development that persists for 24 hours or leads to death, in the absence of other diseases that could explain the symptoms. The event was confirmed by medical chart review or complementary examination of brain imaging.

Exercise Stress Echocardiography

For the echocardiography recording, patients were placed in the left lateral position for echocardiographic reading using parasternal and apical acoustic windows. Echocardiographic images were obtained using Hewlett Packard / Phillips SONOS 5500 equipment with a 2.5 MHz transducer and recorded on videocassette or DVD (Digital Video Display). The classic techniques described by Schiller et al. were used. All patients were submitted to the standard Bruce protocol during the exercise test; HR was continuously monitored and patients were encouraged to reach their peak physical effort. The occurrence of horizontal or downward ST segment depression ≥ 1 mm for men and ≥ 1.5 mm for women at 0.08 s from the J point was called ischemic electrocardiographic alteration at exertion.

The regional left ventricular motion was accessed semi-quantitatively by an experienced echocardiographist, with level III training, as recommended by the American Society of Echocardiography. Motility at rest and at exertion was graded 1 to 5 (1 = normal), according to the 16-segment model. The left ventricular wall motion index (LVWMI) was determined at rest and immediately after exercise, and obtained by adding the scores given to each of the 16 segments divided by the number of studied segments.

Left ventricular systolic function was studied based on ejection fraction (using the Teicholz and Simpson methods), as well as by LVWMI, according to which patients were classified as normal (= 1), with mild ventricular dysfunction (1.01 - 1.60), moderate ventricular dysfunction (1.6 to 2.0) and severe ventricular dysfunction (> 2.0). The development of wall motion abnormalities induced by stress was considered an indicator of myocardial ischemia[16].

Chronotropic Incompetence

To avoid age and resting HR biases of each individual, chronotropic incompetence was defined as the incapacity to achieve 80% of heart rate reserve predicted by age, calculated by the following equation:

$$[(\text{HR stage} - \text{HR rest})/(220 - \text{age} - \text{HR rest})] \times 100$$

The collected information was stored in the database created using SPSS for Windows software. Statistical analyses were processed using the SPSS release 17.0 and STATA release 10.0 (trial versions).

Statistical Analysis

Quantitative variables were characterized as mean and standard deviation, while categorical variables were described by simple frequency number and percentage.

The groups were compared using Student's *t* test or Mann-Whitney test for quantitative variables and Chi-square (χ^2) for categorical variables. A multivariate analysis to identify independent factors was performed by Poisson regression model. The level of statistical significance for all tests was set at $p = 0.05$. Event-free survival analysis was performed using Kaplan-Meier curves.

Results

A total of 298 elderly diabetics, aged 60-91 years (mean of 67.4 years) were evaluated. Of these, 36.6% (109) were allocated to group G1. Mean follow-up was 53.7 ± 32.5 months.

In the selected sample, the analysis groups (G1 and G2) were similar regarding cardiovascular risk factors (hypertension, physical inactivity, alcohol consumption, smoking, BMI, family history and age); however, typical angina and dyspnea prior to EE performance and male gender were more frequent among chronotropic incompetent patients (Table 1).

Regarding the echocardiographic variables, G1 showed higher frequency of dyspnea during EE, lower resting, peak and final heart rate, lower peak systolic blood pressure, higher initial systolic blood pressure, greater left atrial diameter and higher LV mass index. The presence of myocardial ischemia, quantitatively represented by the LVWMI, demonstrated that the CI patients, even at rest, are more ischemic than the control group patients (Table 2).

The observation of outcome occurrence showed higher frequency of CVD among chronotropic incompetent patients. There was no difference between patients with and without CI for the outcomes acute myocardial infarction and all-cause death (Table 3).

The univariate analysis of the factors possibly associated with CVD found an association only with the variable CI ($p = 0.02$) (Table 4).

The multivariate analysis by Poisson regression to evaluate the association between the independent variable CVD and the dependent variables CI, stress LVWMI and ejection fraction (EF), showed a strong association between CI and CVD ($p = 0.04$) (Table 5).

When comparing patients who developed CVD and those who did not, there was a higher mortality rate in G1 compared to G2 ($p = 0.004$) (Table 6). Similarly, when comparing patients who developed AMI with those who did not, there was a higher rate of mortality in the group of chronotropic incompetent patients ($p = 0.015$) (Table 7). Therefore, it can be observed that the CI patients had higher cardiovascular mortality than those in the control group. The G2 group had higher survival free of CVD outcomes (Figure 1).

Discussion

In the selected sample, the study groups (G1 and G2) were similar in relation to cardiovascular risk factors (hypertension, physical inactivity, alcohol consumption, smoking, BMI, family history and age); however, typical angina and dyspnea prior to the performance of EE and male gender were more frequent among chronotropic incompetent ones. The analysis of echocardiographic variables showed that LVWMI at rest and after exercise, the LV mass index and LA diameter were higher in G1. The occurrence of the outcomes analyzed showed

Table 1 - Clinical and anthropometric findings in elderly diabetic patients with and without chronotropic incompetence

Variables	G1 n = 109 (36,6%)	G2 n = 189 (63,9%)	p
Numerical* (mean ± SD)			
Age (in years)	67.6 ± 6	67.3 ± 6.2	0.72
BMI (kg/m²)	28.1 ± 3.9	27.9 ± 3.7	0.66
Categorical† n (%)			
Male gender	68 (62.4)	88 (46.6)	0.01
Asymptomatic	34 (32.1)	81(43.1)	0.06
Typical angina	18(17.0)	15 (8.0)	0.02
Atypical angina	46 (43.4)	88 (46.8)	0.57
Dyspnea	8 (7.5)	4 (2.1)	0.02
Dyslipidemia	82 (75.2)	125(66.5)	0.11
SAH	89 (81.6)	147(77.8)	0.43
Smoking	6 (5.5)	7 (3.7)	0.47
Sedentary life style	36 (64.3)	54 (51.4)	0.09
Alcohol consumption	40 (72.7)	71 (73.2)	0.95
Family history	71 (65.1)	108 (57.1)	0.18
Beta-blocker	32 (29.6)	43 (23.4)	0.23

G1: chronotropic incompetence, G2: chronotropic competence, SD: Standard deviation; BMI: body mass index, SAH: systolic hypertension. T test for independent data. †Chi-square test. Source: Data collected by the author.*

Table 2 - Echocardiographic variables in elderly diabetics with and without chronotropic incompetence

VarVariables (mean ± SD)	G1 n = 109 (36.6%)	G2 n = 189 (63.9%)	p
Numerical* (mean ± SD)			
METS achieved	6.84 ± 2.91	7.126 ± 2.28	0.56
Ejection fraction	0.65 ± 0.06	0.66 ± 0.05	0.76
Resting LVWMI	1.07 ± 0.18	1.03 ± 0.12	0.04
Stress LVWMI	1.11 ± 0.20	1.05 ± 0.16	0.004
Left atrium (cm)	4.10 ± 0.48	3.90 ± 0.45	0.02
Aorta (cm)	3.28 ± 0.38	3.18 ± 0.32	0.08
LV mass index	101.82 ± 28.56	95.16 ± 26.43	0.05
Relative LV thickness	32.25 ± 6.47	32.62 ± 6.03	0.62
Final HR (bpm)	82.23 ± 12.00	95.77 ± 13.58	< 0.0001
Rest HR (bpm)	74.90 ± 12.50	79.31 ± 12.82	0.04
Peak HR (bpm)	123.15 ± 13.03	151.17 ± 9.80	< 0.0001
Final DBP (mmHg)	78.46 ± 9.99	77.26 ± 9.79	0.32
Peak DBP (mmHg)	85.35 ± 8.90	85.44 ± 7.93	0.93
Initial DBP (mmHg)	82.31 ± 6.74	81.23 ± 6.23	0.16
Final SBP (mmHg)	150. 79 ± 20.97	151.30 ± 22.94	0.85
Peak SBP (mmHg)	187.02 ± 18.72	196.13 ± 19.24	0.0001
Initial SBP (mmHg)	135.57 ± 15.06	131.76 ± 12.79	0.02
Categorical† n (%)			
BP ≥ 220/100 mmHg	16 (14.7)	30 (15.9)	0.78
Dyspnea	20 (18.3)	11 (5.8)	0.001
Simple arrhythmia	30.3 (11.1)	30.2 (19.1)	0.98

*G1: chronotropic incompetent; G2: chronotropic competent; SD: Standard deviation; LVWMI: Left ventricular wall motion Index; LV: left ventricle; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; METS: metabolic equivalents. *Numerical variables. †Categorical variables. Source: Data collected by the author.*

Table 3 - Comparison of acute myocardial infarction, cerebrovascular disease, and death events in elderly diabetics with and without chronotropic incompetence

Variables	G1 n = 109 (36.6%)	G2 n = 189 (63.9%)	p
Categorical* n (%)			
Death	13(11,9)	14 (7,4)	0,19
CVD	10 (9,2)	6 (3,2)	0,027
AMI	12 (11,0)	10 (5,3)	0,069

*CVD: cerebrovascular disease; AMI: acute myocardial infarction; G1: chronotropic incompetence; G2: chronotropic competence. Value expressed as n (%)² = Chi-square test. * Categorical variables. Source: Data collected by the author.*

higher frequency of CVD among chronotropic incompetent patients. This study found no difference between patients with and without CI for AMI and overall death outcomes. However, it is noteworthy that among patients who had myocardial infarction or CVD, death was more common among those who were CI.

It was observed that the analyzed groups were similar regarding cardiovascular risk factors, which supports the role of the CI by reducing the influence of other variables and the confounding bias, in the occurrence of cardiac outcomes studied. The higher presence of typical angina and dyspnea prior to the performance of EE and male gender in G1 associates CI with a higher prevalence of CAD, similar to that found by Travassos et al[15], who showed that individuals who did not increase HR proportionally to physical exercise were more symptomatic.

Table 4 - Analysis of factors associated with cerebrovascular disease

Variables	CVD Present = 16	CVD Absent = 82	p
Numerical* (mean ± SD)			
LV mass index	96.5 ± 24.2	97.66 ± 27.58	0.873
Left atrium (cm)	3.92 ± 0.41	3.99 ± 0.47	0.72
Rest LVWMI	1.05 ± 0.10	1.05 ± 0.15	0.93
Stress LVWMI	1.12 ± 0.16	1.05 ± 0.15	0.35
Ejection fraction	0.65 ± 0.07	0.66 ± 0.06	0.36
Age	67.3 ± 4.9	67.4 ± 6.2	0.94
Categorical† n (%)			
SAH	13 (81.3)	223 (79.1)	0.835
Dyslipidemia	11 (68.8)	196 (69.8)	0.933
Male sex	8 (50)	148 (52.5)	0.85
CI	10 (62.5)	99 (35.1)	0.027

*CVD: cerebrovascular disease; SAH: systemic arterial hypertension; SD: Standard deviation; CI: chronotropic incompetent; LV: left ventricle; LVWMI: LV wall motion score index; G1: chronotropic incompetence; G2: chronotropic competence. * Numeric variables. † Categorical variables. Source: Data collected by the author.*

Table 5 - Multivariate analysis of factors associated with cerebrovascular disease in elderly diabetic patients

Variables	Relative Risk	95%CI	p
Categories* n (%)			
CI	2.89	1.05 − 7.95	0.04

*Multivariate analysis by CI: Poisson regression including the following variables; CI: Chronotropic incompetence, stress LV WMSI and ejection fraction. 95%CI: 95% confidence interval. * Chi-square test. Source: Data collected by the author.*

Table 6 - Death rates among patients that had cerebrovascular disease with and without chronotropic incompetence

Variables			CVD present n = 16 (5.4%)	CVD absent n = 282 (94.6%)	p
G1	Death n(%)	Yes	4 (40.0)	9 (.9.1)	0.004
		No	6 (60.0)	90 (90.9)	
G2	Death n(%)	Yes	0	14 (7.7)	0.481
		No	6 (100)	169 (92.3)	

CVD: cerebrovascular disease; G1: chronotropic incompetence; G2: chronotropic competence. Source: data collected by the author.

Table 7 - Comparison of death rates among patients that had acute myocardial infarction with and without chronotropic incompetence

Variables			AMI Present n = 22 (7.4%)	AMI absent n = 276 (92.6%)	p
G1	Death n(%)	Yes	4 (33.3)	9 (.9.3)	0.015
		No	8 (66.6)	88 (90.7)	
G2	Death n(%)	Yes	1 (10.0)	13 (7.3)	0.75
		No	9 (90.0)	166 (92.7)	

AMI: acute myocardial infarction; G1: chronotropic incompetence; G2: chronotropic competence. Source: data collected by the author.

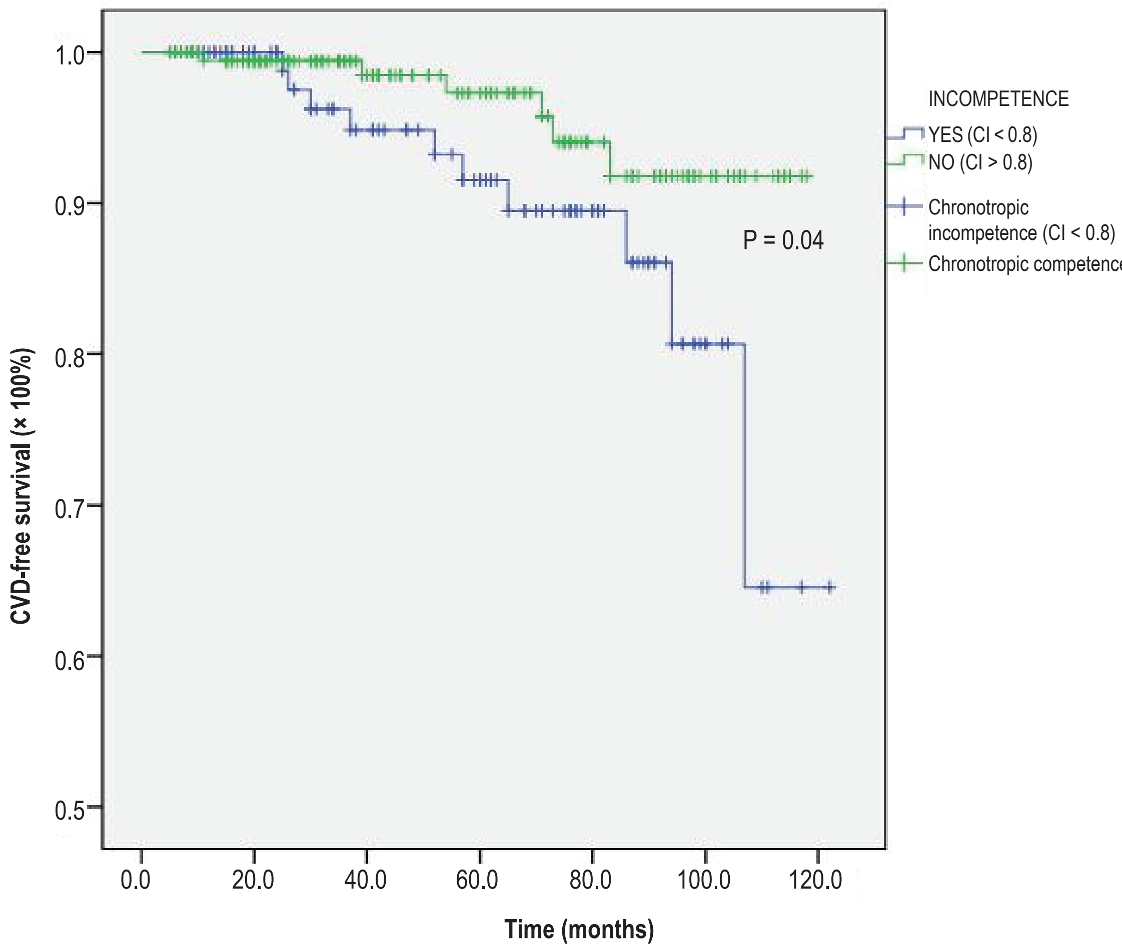

Figure 1 – *Kaplan Meier curve. CVD: cerebrovascular disease. Source: data collected by the author.*

Regarding echocardiographic parameters, it was observed that the LVWMI at rest and after exercise was higher in the CI group, corroborating the findings by this same study group, published in 2007[9], in which we evaluated the additive value of CI during EE in CAD diagnosis, demonstrating the association of CI with ischemic heart disease. Similarly, LV mass index and LA diameter (left atrium) were higher in the group of chronotropic incompetent patients, suggesting an association between CI and structural cardiac alterations; this corroborates a recent study by Secundo et al[17], carried out with 1,798 nonelderly patients, which showed an association between CI and LV mass index, demonstrating the importance of HR attenuation at physical exercise with structural heart abnormalities, even in nonelderly patients.

The relevant results of this study consist in corroborating that older diabetics with CI have a higher frequency of CVD and increased cardiovascular mortality. When hypothesizing the reason for these findings, autonomic disorders may be the answer. Systemic involvement of DM, such as cardiovascular autonomic neuropathy, can play an important role in the development of cerebrovascular complications. Cerebral autoregulation in normal humans in the awakening state is greatly dependent on vascular tone and constitutes a mechanism that ensures constant cerebral blood flow (CBF) and thus, a sufficient oxygen source, despite variations in blood pressure. This mechanism is due to normal baroreflex function[18,19].

Patients with diabetes are more likely to not being able to maintain stable cerebral blood flow throughout the day. Reasons for this association could be disturbances in cerebral blood flow caused by decreased baroreceptor sensitivity due to autonomic dysfunction[19]. It is hypothesized that the brain susceptibility to hypoperfusion and infarction is one of the explanations for the association between autonomic neuropathy and increased risk of CVD in patients with DM[19].

Although the etiology of CI is yet to be fully understood, studies have suggested that it may be related to autonomic disorders[6]. It is thought, therefore, that both CI and the increased occurrence of CVD in elderly diabetic individuals may be related to the same physiopathogeny: autonomic dysfunction. Nevertheless, methodologically well-designed studies must be carried out to test this hypothesis.

Unlike other studies, there was no difference between those with and without CI for the outcome AMI; perhaps, with a larger sample size, this association would show statistical significance. Anjos-Andrade et al[8], between 2000 and 2008, while studying 610 patients with ischemia on EE, found that CI is a marker of severe CAD and ischemia. This finding was similar to that from a prior study by Oliveira et al[9], from the same group that performed the first study, in which 4042 patients were followed between 2000 and 2006, and observed that CI is associated with increased frequency of myocardial ischemia during EE, supporting the concept that it is a marker of myocardial ischemia severity. In another study by the same group (Oliveira et al[14], carried out from December 2000 to July 2003, with 285 elderly individuals submitted to EE, it was demonstrated that CI was associated with ischemic heart disease and thus, it should not be underestimated or considered physiological in the elderly.

Unlike most studies, no difference was found between the groups regarding the all-cause death outcome. However, it is noteworthy to point out that among the patients who had myocardial infarction or CVD, the death outcome was more frequent among patients with CI, that is, there was a higher cardiovascular mortality in this group.

The study by Kiviniemi et al[7] showed that the CI is a powerful predictor of cardiac mortality and provides important information, in addition to ejection fraction, in patients with AMI. Therefore, it suggests that AMI patients should be assessed during the follow-up regarding heart rate behavior and, therefore, considers that the CI is important for risk stratification after myocardial infarction. Similar to a study published by Melzer Dreger in 2010[20], we concluded that there is an association between the incapacity to increase HR proportionally to exercise and increased mortality in patients with CAD.

Increased cardiovascular mortality and higher incidence of CVD among chronotropic incompetent patients indicate the need for further studies investigating this association, as well as to test hypotheses for possible related mechanisms.

It can be observed that, although CI has well-established clinical implications, many possibilities remain to be investigated. This study shows interesting data, making room for new studies in search of more knowledge about the prognostic implications of CI and the possible use of this predictor in medical practice protocols. One of its limitations was the small number of cardiovascular outcomes in this population.

Conclusions

Chronotropic incompetence was independently associated with the occurrence of cerebrovascular disease in elderly diabetic patients and increased cardiovascular mortality in these patients.

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Author contributions

Conception and design of the research and Analysis and interpretation of the data: Santana JS, Franco Filho JCS, Sá Neto AA, Santana NO, Oliveira JLM; Acquisition of data: Barreto ATF, Melo LD, Oliveira JLM; Statistical analysis: Melo EV; Writing of the manuscript: Santana JS, Franco Filho JCS, Sá Neto AA, Santana NO, Barreto ATF, Melo LD; Critical revision of the manuscript for intellectual content: Santana JS, Barreto Filho JA, Sousa ACS, Oliveira JLM.

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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