Echocardiographic predictors of chronotropic incompetence to exercise in patients with heart failure with preserved ejection fraction

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Objective: Exercise intolerance in patients with heart failure with preserved ejection fraction (HFpEF) is most often attributed to diastolic dysfunction (DD); however, chronotropic incompetence (CI) could also play an important role. We intended to examine if there are predictive echocardiographic parameters of DD for impaired chronotropic response to exercise.

Methods and Results: Patients (n=143) with unexplained dyspnea and/or exercise intolerance who fulfilled clinical and echocardiographic criteria of HFpEF presence underwent symptom-limited exercise test using treadmill (ETT) according to Bruce protocol. CI was defined as achieved heart rate reserve (HRR) of ≤ 80%. Comparison of the groups with (n=98) and without CI (n=45) didn't show any statistical significant difference regarding demographic and clinical characteristics except for use of beta blockers (BB) that were more frequently present (p=0.012) in patients with CI in comparison with those without. Patients with CI had a higher mean E-wave velocity, E/A ratio, increased E/E' septal, lateral as well as average ratio and abnormal IVRT/$T_{E-e'}$ index all consistent with elevated LV filling pressures. E/E' average ratio > 15 was statistically insignificantly more frequently present in patients with CI. In addition, by multivariate stepwise regression analysis value of E' septal (β=3.697, 95%CI 0.921-6.473, p=0.009) along with use of BB, current smoking and basal heart rate appeared as statistically significant independent predictors of lower HRR %.

Conclusion: Patients with HFpEF frequently have chronotropic incompetence to graded exercise which may partly be predicted with echocardiographic parameters that are consistent with elevated LV filling pressures.

Keywords: heart failure with preserved ejection fraction; diastolic dysfunction; left ventricular filling pressure; chronotropic incompetence

Introduction

Chronotropic response to exercise and its impairment reflected as chronotropic incompetence (CI) are under-appreciated and often overlooked in clinical practice. [1-3] CI is common in patients with cardiovascular disease, produces exercise intolerance, and is an independent predictor of major adverse cardiovascular events and overall mortality even in patients taking drugs that interfere with CI such as beta blockers, [4-6] CI is often present in patients with HF especially in those with preserved ejection fraction (HFpEF), even compared with older, age-matched controls and independent of rate-slowing medication use, and contributes to their prominent exertional symptoms, lower exercise capacity and reduced quality-of-life. [7-10] Because exercise requires coordinated changes in ventricular function, arterial tone, endothelial function, venous return, and autonomic signaling, CI as one of the mechanisms that are impaired in patients with HFpEF contributing in coordinate fashion to depressed reserve capacity that produce exercise limitation. [9, 11] However, recent clinical studies also observed a significant correlation between exercise capacity and diastolic function parameters, i.e. exercise capacity being worse in patients with marked diastolic dysfunction, [12, 13]

Understanding the pleiotropic nature of exercise capacity limitation in patients with HFpEF, we intended to examine if there are predictive echocardiographic parameters of diastolic dysfunction for impaired chronotropic response to exercise, which would result in more tailored therapy for individual patient.

Methods

Study Population

This was a prospective cross-sectional study conducted between November 2012 and Mart 2014 examining 143 consecutive patients with multiple atherosclerotic risk factors who were referred for cardiology assessment to Special Hospital "Acibadem-Sistina" and/or University Clinic of cardiology in Skopje for unexplained dyspnea and/or exercise intolerance and who fulfilled clinical and/or echocardiographic criteria of HFpEF presence: dyspnea, preserved left ventricular ejection fraction (LVEF>50% or LVEDVI< 97 ml/m^2) and diastolic dysfunction along with elevated LV filling pressure (E/E' > 15). [14] In patients with intermediate E/E' average ratio between 8 and 15, additional parameters of diastolic dysfunction was implemented. These included an E/A ratio < 0.5 and /or deceleration half-time (DT) > 280 ms in patients over 50 years, and/or a duration difference of atrial reverse pulmonary vain flow and atrial mitral valve flow (Ar-A) > 30 ms, and/or a left atrial volume index (LAVI) >40 ml/m^2, and/or and increased LV mass index (LVMI: men >149 g/m^2, women >122 g/m^2). [14- 16]

Data on the presence of hypertension, diabetes mellitus, dyslipidemia, smoking, and family history of premature coronary artery disease (CAD) were collected prospectively by questioning the patients at the time of echocardiography. To be eligible for the study, patients had to have a sinus rhythm, normal lung function tests and normal blood counts. Patients with a history of recent (≤6 months) acute coronary syndrome, coronary artery bypass grafting, more than moderate mitral regurgitation or more than mild disease of the other valves, hypertrophic obstructive cardiomyopathy, atrial fibrillation, pulmonary disease, or anemia were excluded. Patients with a history of coronary artery disease, post-percutaneous coronary intervention (>6 months), or postmyocardial infarction (>6 months) were not excluded if they showed preserved LV ejection fractions and had no significant coronary artery stenosis. Patients were studied on chronic medications, including beta-blockers or nondihydropyridines calcium blockers. The study protocol was approved by the Medical Ethics Committee of involved institutions, and informed consent was obtained from patients.

Echocardiography

Standard assessment of LV dimensions, wall thickness, and mass were performed in standard views on commercially available equipment (Vivid 7, GE) according to the joint recommendations of the European Association of Echocardiography, the American College of Cardiology, and the American Heart Association. [17] LV volumes and ejection fraction were calculated using the biplane method of disks (modified Simpson's rule). [17] Left atrial volume was derived by the biapical area-length method and indexed to body surface area (LAVI). [17] Mitral flow using pulsed-wave Doppler was recorded as recommended and early (E) and late (A) transmitral inflow velocities as well deceleration time (DT) were measured. [16] Pulmonary venous flow using pulsed-wave Doppler was recorded and peak systolic (S), diastolic (D) and atrial reversal flow including its duration were measured as recommended. [16] Pulse-wave tissue Doppler imaging was performed in the apical 4-chamber view to assess annular early and late diastolic velocities. [16] The recording was performed at a sweep speed of 100 mm/s at end-expiratory apnea. The septal, lateral, and average early diastolic velocity (E′) were recorded, and the ratio of mitral flow E wave to E′ for each of these annular velocities was calculated as well as the time interval between the onsets of mitral inflow velocity (E) and mitral annulus velocity ($T_{E-e'}$). IVRT/$T_{E-e'}$ index was measured and calculated. Tissue Doppler was not performed in patients with dense mitral annular calcification. The average of 3 consecutive cardiac cycles was taken for measurement of each echocardiographic index.

Exercise testing

Symptom-limited exercise test using treadmill (ETT) was conducted according to Bruce protocol as recommended. [18, 19] During each exercise and recovery stage, symptoms, blood pressure, heart rate, cardiac rhythm, ST-segment displacement and metabolic equivalents were recorded. Testing was terminated because of fatigue, dyspnea, leg discomfort, chest pain, achievement of maximal predicted heart rate, exaggerated hypertensive response (systolic blood pressure >250 mm Hg or diastolic blood pressure >115 mm Hg) or drop in systolic blood pressure of more than 10 mmHg, severe arrhythmias including second- or third-degree atrioventricular (AV) block, or marked ST-segment displacement. [19] After peak exercise, the test was almost immediately terminated, and measurements were taken while the patients were in the standing position.

Chronotropic incompetence

Chronotropic incompetence (CI) was defined to be a diminished heart rate (HR) response to exercise on the basis of the following two criteria [4, 18, 20-24]: failure to achieve 85% of the maximum age-predicted heart rate (%Max PHR) were %Max PHR was calculated as 220 – age (years) [23] and percentage of HR reserve (%HRR) of ≤ 80% which was calculating using following equation: (HR at peak exercise - resting HR)/[(220 - age) - resting HR)] [4, 20-24]. We decided in our study to use latter criteria because it outweigh the possible confounding effects of age, physical fitness and resting HR.

Statistical analysis

Categorical parameters were summarized as percentages and continuous parameters as mean ± SD. Comparison between two groups was based on Mann-Whitney test for continuous parameters and Pearson’s chi-square test for categorical parameters. Assessment of correlation of various factors was done using Spearman correlation analysis. Multiple regression analysis was performed in stepwise order to determine independent predictors among set of predictor parameters of presence of chronotropic incompetence.

All data analysis was performed using the Statistical Package for Social Sciences software (SPSS 15.0, SPSS Inc., and Chicago, IL, USA) and a p-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics of the patients

Inclusion criteria were fulfilled by 143 patients (62.15 ± 10.0 y), 56 man and 87 women with body mass index (BMI) 29.60 ± 4.09 kg/m^2. Hypertension was present in 96.5%, dyslipidemia in 95.8% and diabetes mellitus in 50.3% of all patients. 46.9% of patients were taking beta blockers (BB). Patients had a mean New York Heart Association class of 1.52 ± 0.5. Out of all 60 (42.0%) patients failed to reach %Max PHR and 98 (68.5%) patients had low %HRR. When we divided patients according to the BB presence, 53.7% patients on BB failed to reach %Max PHR and 79.1% had low HRR.

Baseline characteristics of the study patients according to CI presence assessed by %HRR are shown in Table 1. Comparison of the groups with and without CI didn't show any statistical significant difference regarding demographic and clinical characteristics except for BB which were significantly more frequently present (p=0.012) in patients with CI in comparison with those without. There was significant negative relation between %HRR and current smoking (r=-0.222; p=0.008) as well as with use of BB (r=-0.210; p=0.013). The OR for having CI with using BB was 2.58 (95%CI 1.22-5.46).

Echocardiographic data

Echocardiographic data are provided in Table 2. Patients with and without CI had similar values for LVEF, LAVI and LV mass indexed to body surface area. The average value of duration of reverse pulmonary vain atrial systole flow-mitral valve wave flow was normal in both groups with and without CI. Patients with CI had a higher mean E-wave velocity, E/A ratio, increased E/E' septal, lateral as well as average ratio and abnormal IVRT/$T_{E\text{-}e'}$ index all consistent with elevated LV filling pressures. Elevated LV pressure represented with E/E' average ratio > 15 was statistically insignificantly more frequently present in patients with CI (Table 2). The OR for having CI with E/E' average ratio > 15 was 2.35 (95%CI 0.89-6.19). There was significant positive relation between %HRR and value of E' septal and E' avarage (r=0.191, p=0.022;r=0.181, p=0.030; respectivelly) and weak negative relation with E/E' septal ratio (r=-0.158, p=0.060).

Exercise test data

Exercise test responses are showed in Table 3. Patients with CI showed statistically insignificant lower exercise capacity and METs achieved, had shorter exercise duration (min) and more frequently symptoms (angina or fatigue) during exercise (Table 3). Those with CI had statistically significantly lower peak HR achieved (p=0.0001) and increase in HR (p=0.0001) as well as they achieved significantly lower %Max PHR (p=0.0001) and lower %HRR (p=0.0001). Correlation analysis of %HRR with exercise duration, METs achieved and exercise capacity didn't showed any significant relation except for symptoms which were significantly negatively related to %HRR (r=-0.193, p=0.021).

In order to define the role of CI in limitation of exercise capacity, echocardiographic parameters of diastolic function along with along with parameters of CI (%Max PHR and %HRR) were put in multiple stepwise regression analysis. The results showed (Table 4) that parameters of CI during exercise didn't appear as independent predictors of exercise capacity limitation, whilst echocardiographic parameters that represent extensive diastolic dysfunction and symptoms mostly of angina or fatigue during exercise appeared as significant independent predictors of lower exercise capacity.

Prediction of chronotropic incompetence

Multiple stepwise regression analysis of demographic, clinical and echocardiographic data significantely related with CI revealed (Table 5) that current smoking, use of beta blockers, basal HR and myocardial early diastolic velocity at septal mitral annulus assessed by TDI (E'septal) appeared as independent significant predictors of CI existence represented by

%HRR. Taking all parameters together model showed that are responsible for 41.0 % of the lower %HRR. As for echocardiographic parameter, it means that with every one cm/s of E'septal decline, the %HRR decline by 3.697% with significance of p=0.009.

Discussion

Chronotropic incompetence (CI) defined as failure to achieve 85% of the age-predicted maximum heart rate (%Max PHR) was present in 60 (42.0%) patients and/or heart rate reserve of ≤ 80% (%HRR) in 98 (68.5%) patients out of 143 patients with HFpEF that were subject of this study which was in concordance with other authors. Phan *et al.* [8] found that 34% of patients with HFpEF have CI during maximal exercise when defined by %Max PHR and 63% when defined by %HRR. In order to avoid age, functional capacity and resting HR biases of each individual [1, 4, 5, 20- 24], for comparison analysis of patient data we have used %HRR. It is now well known that both parameters of CI were associated with adverse risk profile, whereby %HRR represents an isolated measure of chronotropy that appeared as independent predictor of mortality. [4, 5, 24]

Comparison of the groups with and without CI didn't show any statistical significant difference regarding demographic and clinical characteristics except for use of beta blockers (BB) which were significantly more frequently present in patients with CI in comparison to those without. Multivariate stepwise regression analysis of demographic and clinical data revealed that along current smoking, use of beta blockers and basal HR appeared as independent significant predictors of CI existence represented by %HRR. The majority of earlier studies, concerning the relationship between chronotropic response and exercise capacity, were carried out when such therapy was not a part of standard management. However, studies on patients with chronic heart failure (CHF) which were on optimal medical therapy concordant with the current guidelines showed that there is no significant difference in the rates of CI between patients receiving and not receiving BB agents. [20, 25,26] A previous study by Witte *et al.* [26], conducted on a total of 237 CHF patients, evaluated CI and showed a 32% and 64% prevalence of CI according to the %Max PHR and %HRR, respectively, whereas in patients on BB therapy these percentages were 49% and 75%. Our data are in line with those of Witte (53.7% and 79.1, respectively). Similarly, Jorde *et al.* [27] found CI in >70% of patients with advanced systolic CHF irrespective of BB use and confirmed that BB had no impact on the relationship between exercise time and HR during treadmill exercise testing.

In the present study, cigarette smoking was more common in patients with CI. In addition multivariate stepwise regression analysis showed (Table 5) that current smoking appeared as independent significant predictors of CI existence represented whether by %HRR. Lauer et al. [28, 29] reported a similar result that CI was associated with smoking in a healthy, population based cohort and revealed that the association is not just a reflection of impaired exercise capacity as well as associations persisted after accounting for a number of potential confounders. However, the mechanisms linking smoking to CI remains unclear. There are a number of potential mechanisms including endothelial dysfunction, increased ischemic burden, increased peripheral vascular resistance, autonomic dysfunction and/or downstream deficits in beta-adrenergic stimulation [21, 28, 29], all mechanisms which are inevitably connected to HFpEF.

Regarding echocardiographic parameters we found that patients with CI had insignificantly higher indexes that are consistent with elevated LV filling pressures. E/E' average ratio > 15 was also insignificantly more frequently present in patients with CI. Using multivariate stepwise regression analysis, E'septal appeared as statistically significant independent echocardiographic predictor of lower %HRR. Hense, the more prominent is diastolic dysfunction the more frequent is CI which confirmed their relation. A number of recent studies have revealed the existence of depressed chronotropic reserve in patients with HFpEF even compared with older, age-matched controls and independent of rate-slowing medication use. [7-11, 30] Similar to CHF, this is likely related to downstream deficits in beta-adrenergic stimulation and/or autonomic dysfunction. [7, 8] Data on the relation between extent of diastolic dysfunction and CI in patients with HFpEF are limited. Thus, Grewal *et al.* [13], in their study on patients with symptoms of dyspnea, multiple risk factors and preserved LVEF, found that chronotropic response to exercise is only modestly associated with diastolic function and filling pressures. Clearly, the mechanisms underlying relationships of heart rate with exercise capacity are complex and cannot be entirely explained by diastolic dysfunction parameters.

Because exercise requires coordinated changes in ventricular function, arterial tone, endothelial function, venous return, and autonomic signaling, CI as one of the mechanisms that are impaired in patients with HFpEF contributing in coordinate fashion to depressed reserve capacity that produce exercise limitation. [7-9, 11] The results of our study showed that patients with HFpEF and CI presence had statistically insignificant lower exercise capacity and METs achieved, had shorter exercise duration and more frequently symptoms (angina or fatigue) during exercise. Recent clinical studies also observed a significant relation between exercise capacity and diastolic function parameters, i.e. exercise capacity being worse in patients with marked diastolic dysfunction. [12, 13, 31]

In order to define the role of CI in exercise capacity limitation we performed multiple stepwise regression analysis (Table 4), but parameters represented CI didn’t appear as independent predictors of lower exercise capacity, whilst echocardiographic parameters that represent extensive diastolic dysfunction, higher LV filling pressure and symptoms mostly of dyspnea or fatigue during exercise appeared strongly associated with exercise capacity limitation. Although CI didn’t appear strongly associated with exercise capacity limitation, it does exist more frequently in patients with more pronounced diastolic dysfunction.

Conclusion

Patients with HFpEF frequently have chronotropic incompetence to graded exercise which may partly be predicted with echocardiographic parameters that are consistent with elevated LV filling pressures. Although CI didn't appear strongly associated with exercise capacity limitation as were extensive diastolic dysfunction, higher LV filling pressure and symptoms mostly of dyspnea or fatigue during exercise, it does exist more frequently in patients with more pronounced diastolic dysfunction.

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Резиме

Основи: Неподносливоста на оптоварување кај пациенти со срцева слабост со сочувана лево коморна ејекциона фракција (ССсЕФ) најмногу се должи на дијастолната дисфункција (ДД); сепак, и хронотропната инкомпетенција (ХИ) би можела да има важна улога. Нашата цел беше да истражиме дали постојат ехокардиографски параметри за ДД кои би биле предиктивни за постоење на ХИ.

Метод и резултати: Пациенти (n=143) со необјаснива диспнеа и/или неподносливост на оптоварување кој ги исполнија клиничките и ехокардиографски критериуми за постоење на ССсЕФ беа подложени на симптом-ограничувачки тест на оптоварување по протоколот на Bruce. Пациентите беа поделени според присуството на ХИ која беше дефинирана како резерва на срцева фреквенција од ≤ 80% (%РСФ). Споредбата на групите со (n=98) и без (n=45) ХИ не покажа каква било статистички значајна разлика во однос на демографските и клинички карактеристики освен за употребата на бета блокатори (ББ) во терапија која беше значајно почеста (p=0.012) кај пациентите со во однос на оние без ХИ. Пациентите со ХИ имаа повисока средна вредност на брзината на Е бранот, Е/А односот, зголемен Е/Е' септален, латерален и просечен однос и абнормален IVRT/$T_{E-e'}$ индекс, сите вредности кои се во согласност со постоење на зголемен ЛК притисок на полнење. Е/Е' просечен однос од > 15 беше статистички несигнификантно почесто присутен кај пациентите со ХИ. Натаму, со употреба на мултиваријантната постепена регресиона анализа, вредноста на Е' на ниво на септум (β=3.697, 95%CI 0.921-6.473, p=0.009) заедно со употребата на ББ, активното пушење и базаланата срцева фреквенција се покажаа како значајни ехокардиографски независни предиктори за пониска %РСФ.

Заклучок: Пациентите со ССсЕФ имаат често ХИ за време на постепено оптоварување чие што постоење би можело делумно да биде предвидено со

ехокардиографските параметри кои се во согласност со постоење на зголемен ЛК притисок на полнење.

Клучни зборови: срцева слабост со сочувана ејекциона фракција; дијастолна дисфункција; хронотропна инкомпетенција.

Table 1. Basal characteristics of patients divided according to chronotropic incompetence presence.

Parameters	Group with CI (n=98)	Group without CI (n=45)	p
Age (years)	61.44±10.63	63.69± 8.38	0.135
Man/women (%)	36.7/63.3	44.4/55.6	0.382
BMI (kg/m2)	29.54±4.21	29.74±3.86	0.692
NYHA class	1.54±0.50	1.49± 0.51	0.565
Resting HR (beats/min)	74.80±9.48	78.93±11.37	0.069
Resting systolic BP (mmHg)	141.47±16.55	143.89±15.84	0.525
Current smoking (%)	27.6	15.6	0.119
Hypertension (%)	96.9	95.6	0.677
Dyslipidemia (%)	96.9	93.3	0.320
Diabetes mellitus (%)	48.0	55.6	0.400
Coronary heart disease (%)	17.3	15.6	0.791
Serum hemoglobin (g/L)	143.24±11.94	142.91±14.56	0.649
Use of beta blockers (%)	54.2	31.8	0.012

BMI= body mass index; BP= blood pressure; CI=chronotropic incompetence; HR= heart rate; NYHA=New York Heart Association.

Table 2. Comparison of echocardiographic parameters of patients divided according to chronotropic incompetence presence.

Parameters	Group with CI (n=98)	Group without CI (n=46)	p
LVEF (%)	65.84±6.99	65.62±7.15	0.782
LAVImax (ml^2/m^2)	36.83±10.39	37.88±10.23	0.520
LV mass index (g/ m^2)	131.85±28.62	131.57±30.93	0.838
E (cm/s)	77.44±20.13	75.71±14.41	0.969
E/A ratio	0.92±0.34	0.84±0.21	0.299
DT (ms)	209.30±52.16	205.29± 42.31	0.931
IVRT (ms)	105.76±25.14	100.26± 20.84	0.314
Ar-A (ms)	-5.22±20.68	2.25±20.23	0.036
E' septal (cm/s)	5.36±1.31	5.63±1.33	0.253
E'lateral (cm/s)	6.91±1.66	7.40±1.76	0.077
E' avarage (cm/s)	6.13±1.26	6.51±1.34	0.054
E/E' septal ratio	14.98±4.58	13.91±3.29	0.172
E/E' lateral ratio	11.86±4.94	10.90±4.31	0.131
E/E' avarage ratio	12.94±3.91	12.09±3.40	0.117
IVRT/E-e' avarage	0.43±16.32	4.59±35.60	0.489
E/E' > 15 ratio (%)	26.5	13.3	0.080

A= late filling velocity of transmitral flow; Ar= Atrial retrograde velocity of flow in pulmonary veins; CI=chronotropic incompetence; DT= deceleration time of mitral early filling velocity; E= early filling velocity measured by PW Doppler; E'= myocardial early diastolic velocity by TDI at mitral annulus; E/A = transmitral early to late filling velocity by CW-Doppler; E/E'= transmitral early diastolic velocity by CW-Doppler to myocardial early diastolic velocity of mitral annulus by TDI; EF=ejection fraction; IVRT=isovolumic relaxation time; IVRT/E-e'=tau index; LAVI= left atrial volume index; LV=left entricular.

Table 3. Comparison of exercise test characteristics of patients divided according to chronotropic incompetence presence.

Parameters	Group with CI (n=98)	Group without CI (n=46)	p
Exercise capacity (%)	104.34±24.30	107.95±21.02	0.473
METs achieved	7.29±1.80	7.45±1.67	0.536
Exercise duration (min)	5.60±1.95	5.79±1.79	0.448
Peak HR (beats/min)	130.24±14.55	156.27± 10.97	0.0001
Increase in HR (beats/min)	48.05±13.18	65.20± 14.44	0.0001
Max PHR (%)	82.17±7.65	100.07± 6.24	0.0001
HRR (%)	63.30±14.18	101.48± 15.25	0.0001
Peak systolic BP (mmHg)	184.64±26.75	191.28± 19.43	0.127
Increase in systolic BP (mmHg)	40.05±20.43	43.22±16.76	0.328
Increase in diastolic BP (mmHg)	3.36±9.09	6.91±11.53	0.015
Symptoms during exercise (%)			0.235
Angina	10.2	0	
Fatigue	34.7	33.3	
Dispnea	1.4	0	

BP=blood pressure; CI=chronotropic incompetence; HR=heart rate; %HRR= percent of heart rate reserve; %Max PHR= Proportion of predicted HR achieved; MET= metabolic equivalent.

Table 4. Multivariate stepwise regression analysis of echocardiographic and exercise parameters in prediction of exercise capacity.

Parameters	β Unstandardised (SE)	β Unstandardised 95%CI	β Standardised	P value
	Exercise capacity in metabolic equivalents achieved			
Symptoms*	-1.658 (0.248)	-2.149 to -1.167	-0.466	0.0001
E/E' avarage	-0.124 (0.033)	-0.190 to - 0.058	-0.266	0.0001
E/A ratio	1.188 (0.411)	0.376 to 2.00	0.206	0.004
	Exercise capacity in minutes of exercise			
Symptoms*	-1.941 (0.261)	-2.467 to -1.425	-0.505	0.0001
E/E' avarage	-0.137 (0.035)	-0.206 to - 0.067	-0.271	0.0001
E/A ratio	1.161 (0.431)	0.308 to 2.014	0.186	0.008
	Percent exercise capacity			
Symptoms*	-15.321 (3.757)	-22.749 to -7.893	-0.325	0.0001

* Symptoms of angina or fatigue during exercise; E/A = transmitral early to late filling velocity by CW-Doppler; E/E'= transmitral early diastolic velocity by CW-Doppler to myocardial early diastolic velocity of mitral annulus by TDI.

Table 5. Multivariate stepwise regression analysis of demographic, clinical and echocardiographic parameters in prediction of chronotropic incompetence presence represented by %HRR.

Parameters	β Unstandardised (SE)	β Unstandardised 95%CI	β Standardised	P value
Use of BB	-8.366 (3.665)	-15.614 to -1.118	-0.183	0.024
Current smoking	-13.021 (4.206)	-21.339 to - 4.704	-0.244	0.002
Basal HR	0.484 (0.187)	0.114 to 0.854	0.209	0.011
E’ septal	3.697 (1.404)	0.921 to 6.473	0.207	0.009

BB=beta blockers; CI=chronotropic incompetence; E’= myocardial early diastolic velocity by TDI at mitral annulus; HR=heart rate; %HRR= percentage of HR reserve.