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Heart Rate Response to Graded Exercise Correlates with Aerobic and Ventilatory Capacity in Patients with Heart Failure

ALESSANDRO VALLEBONA, M.D., GUIDO GIGLI, M.D., SANDRO ORLANDI, M.D., GIORGIO REGGIARDO, PH.D.

Department of Cardiology, Heart Failure Unit, Rapallo Hospital, Rapallo (Genoa), Italy

Summary

Background: Autonomic dysfunction and reduced exercise tolerance are typical features of patients with congestive heart failure (CHF). Baro-chemoreflex balance and organ response may have a common role in conditioning exercise tolerance, ventilation, and chronotropic competence in patients with CHF.

Hypothesis: We tested the hypothesis that there is a relationship between functional capacity and chronotropic competence to exercise in CHF.

Methods: In all, 48 stable outpatients with CHF (age 65 ± 10 years, 41 men, NYHA class 2.1 ± 0, ejection fraction 31 ± 7%, peak VO_2 16 ± 4 ml/kg/min) performed cardiopulmonary exercise testing (CPX). Heart rate (HR) response to exercise was assessed by the chronotropic index (CRI). The CRI was calculated by the following formula: CRI = peak HR − rest HR/220 − age − rest HR × 100 (normal value > 80%). The relationship of CRI to peak oxygen consumption (VO_2) and ventilation/carbon dioxide production (VE/VCO_2) ratio was examined. A group of 33 healthy controls underwent CPX as well.

Results: The CRI correlated directly with peak VO_2 ($r = 0.638$, $p < 0.001$) and inversely with VE/VCO_2 ($r = -0.492$, $p < 0.001$) in patients with CHF. A CRI < 78% identified patients with CHF and a peak VO_2 < 20 ml/kg/min, area under the receiver operating curve (AUROC): 0.76, 95% confidence interval (CI) 0.60–0.92. A CRI < 74% predicted exercise hyperventilation in CHF (AUROC: 0.71 for $VE/VCO_2 > 30$, 95% CI 0.53–0.88). The CRI was not significantly related either to peak VO_2 or to VE/VCO_2 in the control group.

Conclusions: In patients with mild to moderate CHF, CRI correlates with functional capacity. This relationship adds new data on pathophysiologic grounds and supports the routine incorporation of CRI into CPX interpretation.

Key words: congestive heart failure, functional capacity, heart rate, chronotropic index

Introduction

Autonomic dysfunction and reduced exercise tolerance are typical features of patients with congestive heart failure (CHF).[1–4] Autonomic dysfunction is characterized by impaired autonomic balance, with a reduction of vagal activity and a prevalence of sympathetic activity.[5,6] Heart rate variability and chronotropic competence are blunted due to beta-adrenergic receptor downregulation and uncoupling of G proteins.[7–10] The cause of impaired autonomic balance in CHF is not clearly known. Recently, chemoreflex and baroreflex functions have been investigated. Central chemoreceptors, located in the brain stem, and peripheral chemoreceptors, located in the mural carotid and aorta, regulate ventilatory response to O_2 and CO_2 content. Chemoreflex activation increases ventilation, sympathetic activity, and pulmonic vasoconstriction.[11–13] Baroreceptors located in heart, lung, and arterial bodies modulate heart rate (HR) and blood pressure. Baroreceptorial activity is blunted in CHF, leading to a reduction in HR variability, bradycardia, and further increase in chemoreceptorial sensitivity because of the loss of antagonistic interaction on chemoreflex activity.[8,14] In CHF, there is a strong inverse relationship between chemoreflex sensitivity that is increased and baroreflex activity that is markedly depressed.[11,15] Metabolic changes during exercise activate muscular ergoreceptors that increase sympathetic, vasoconstrictive, and ventilatory activation, contributing to exercise intolerance.[16] Peak oxygen consumption (VO_2) is reduced and ventilatory response to exercise is characterized by an elevated ventilation relative to carbon dioxide production (VE/VCO_2).[17–20] Indices of functional capacity correlate poorly with central hemodynamics[21] and cardiac noradrenaline spillover,[2] suggesting that

Address for reprints:

Alessandro Vallebona. M.D.
Department of Cardiology
Heart Failure Unit
Rapallo Hospital
Piazza Molfino 10
16035 Rapallo (Genoa), Italy
e-mail: avallebona@asl4.liguria.it

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baro-chemoreflex balance and tissue refractoriness may have a role in conditioning exercise tolerance, ventilation, and chronotropic competence.[12, 22]

We tested the hypothesis that there is a relationship between functional capacity and chronotropic competence to exercise in CHF.

Methods

Subjects

Consecutive, stable patients with CHF referred for ambulatory visit between January 1999 and December 2003 were enrolled. Inclusion criteria were chronic symptomatic heart failure (New York Heart Association [NYHA] II or III), left ventricular ejection fraction (LVEF) ≤ 40%, clinical stability, and no changes in medical therapy for at least 6 months. Exclusion criteria were atrial fibrillation, beta-blocking treatment, myocardial infarction, or heart surgery or hospitalization during the preceding 6 months, effort angina, limitation to exercise because of ischemic electrocardiographic (ECG) changes, inferior limb arteriopathy, primary valvular disease, permanent pacemakers, clinically relevant pulmonary disease, anemia (hemoglobin < 12 g/dl), and neoplasia. All enrolled patients underwent echocardiography to evaluate LVEF (calculated by mean of the modified Simpson's rule).[23] A Sonos 5500® sonographer (Hewlett Packard, Andover, Mass., USA) with 2.5–3.5 MHz transducer was utilized. Patients were submitted to cardiopulmonary exercise testing (CPX) within 1 week after echocardiographic examination and stratified in Weber class A (peak VO_2 > 20 ml/kg/min), class B (16–20 ml/kg/min), and class C (< 16 ml/kg/min).[24] The etiology of heart failure was considered ischemic in patients with critical coronary stenosis at previous coronary angiography (> 50% luminal diameter) or previous myocardial infarction, and nonischemic in the others. Cardiopulmonary exercise testing was also performed in 33 body mass index-matched volunteers without history of heart or lung disease.

Cardiopulmonary Exercise Testing

All tests were performed in the morning using a bicycle ergometer. After a minute of warming up period at 0 W, a 10 W/min incremental protocol was started. Ventilation, oxygen uptake, and carbon dioxide production were monitored on line by a Jaeger Oxycon Delta® gas measuring system (version 4.3, Mijnhardt, Bunnik, The Netherlands). Calibration with reference gases was performed immediately prior to each test. A standard 12-lead ECG was recorded continuously. Patients were encouraged to exercise until they experienced limiting dispnea or fatigue. Ventilatory anaerobic threshold (VAT) was determined by the ventilatory equivalent for VO_2 or by the V-slope method.[25] Peak VO_2 was defined as the highest O_2 consumption obtained during the test, and peak VE/VCO_2 was defined as the value of the ventilatory equivalent for VCO_2 at the time of the peak VO_2. Resting HR was defined as the lowest HR recorded in the upright position before exercising and peak HR the highest HR obtained during exercise. Chronotropic index (CRI) was calculated by the following formula: CRI = peak HR − rest HR/220 − age − rest HR × 100.[26] Special effort was taken in patients to perform symptom-limited exercise testing, in controls to attain physical exhaustion. All patients underwent a preliminary CPX 2 to 60 days before the study and they were familiar with the test. Variability of peak VO_2 was < 10% compared with the preliminary test.

Statistical Analysis

Continuous variables are given as mean ± standard deviation (SD). Student's *t*-test, analysis of variance (ANOVA), and chi-square tests were used where appropriate to analyze clinical and functional patient characteristics. The relationship of CRI to peak VO_2 and VE/VCO_2 was examined by Pearson's correlation. The area under the receiver operating characteristic curve (AUROC) was utilized for discrimination of the highest accuracy with peak VO_2 < 20 ml/kg/min and VE/VCO_2 > 30 as the response variables. P values < 0.05 were considered significant. All analyses were performed with the Statistical Package for Social Sciences (SPSS) 10.0 for Windows (SPSS, Inc., Chicago, Ill., USA).

Results

Forty-eight patients with CHF (41 men, age 65 ± 10 years, NYHA class 2.1 ± 0, EF 31 ± 7%, peak VO_2 16 ± 4 ml/kg/min) were evaluated. Patients treated with beta blockers (n = 10) discontinued the treatment 1 week before enrollment. The baseline characteristics of patients and controls are shown in Table I. Clinical characteristics of patients with preserved

TABLE I Baseline characteristics of patients and controls

Patients		Controls	p Value
Number of patients	48	33	
Age (years)	65 ± 10	61 ± 8	< 0.05
Gender (M/F)	41/7	19/14	
NYHA class	2.1 ± 0		
LVEF (%)	31 ± 7		
CAD (n, %)	27 (56)		
VO_2 (ml/kg/min)	16 ± 4.0	21 ± 5.0	< 0.000
VE/VCO_2	34 ± 6.2	28 ± 3.5	< 0.000
CRI value (%)	59 ± 22	75 ± 17	< 0.01
Exercise time (min)	8 ± 3	11 ± 4.5	< 0.01
Amiodarone (n, %)	5 (10)		
Digoxin (n, %)	19 (39)		
ACE inhibitors (n, %)	46 (95)		

Abbreviations: M = male, F = female, NYHA = New York Heart Association, LVEF = left ventricular ejection fraction, CAD = coronary artery disease, VO_2 = peak oxygen consumption, VE/VCO_2 = peak ventilation/carbon dioxide production ratio, CRI = chronotropic index, ACE = angiotensin-converting enzyme.

functional capacity (Class A) and reduced exercise capacity (Classes B and C) were not significantly different (Table II). Patients in Classes B and C were more frequently unable to sustain prolonged exercise; the CRI was significantly reduced and VE/VCO_2 was higher with respect to Class A (Table III). Peak VO_2, VE/VCO_2, and CRI were significantly different in patients and controls (see Table I). No correlation of CRI with peak VO_2 ($p = 0.22$) or VE/VCO_2 ($p = 0.11$) was found in the control group. In patients with CHF, CRI directly correlated with peak VO_2 ($r = 0.638$, $p < 0.001$, Fig. 1) and inversely with VE/VCO_2 ($r -0.492$, $p < 0.001$, Fig. 2). No significant correlation of CRI was found with age (p = NS), therapy with digoxine (p = NS), or amiodarone (p = NS). Receiver operating characteristic curves (ROC) show the sensitivity and specificity of the CRI in predicting peak $VO_2 < 20$ ml/kg/min and $VE/VCO_2 > 30$. The AUROC for a CRI value < 78% was 0.76 (95% confidence interval [CI]: 0.60–0.92) showing a sensitivity of 100% and a specificity of 63% for predicting peak $VO_2 < 20$ ml/kg/min (Fig. 3). For predicting $VE/VCO_2 > 30$ with a CRI value < 74%, the AUROC was 0.71 (95% CI: 0.53–0.88), still demonstrating good discriminatory power (sensitivity 72%, specificity 69%, see Fig. 4).

TABLE II Clinical characteristics of patients according to functional class

	Class A	Class B	Class C	p Value
VO_2 (ml/kg/min)	23 ± 2	17 ± 1	12 ± 2	(A vs. B + C)
Patients (n)	8	24	16	
Age (years)	58 ± 9	67 ± 11	64 ± 10	NS
Gender (M/F)	8/0	20/4	13/3	NS
NYHA	2 ± 0	2 ± 0	2.2 ± 0.4	NS
LVEF (%)	37 ± 4	31 ± 7	28 ± 8	0.04
CAD (n, %)	3 (37)	14 (58)	10 (62)	NS
Amiodarone (n, %)	0	1 (0.4)	4 (25)	NS
Digoxin (n, %)	2 (25)	10 (41)	7 (43)	NS
ACE inhibitors (n, %)	8 (100)	23 (95)	15 (93)	NS

Abbreviations as in Table I.

TABLE III Functional characteristics of patients according to functional class

	Class A	Class B	Class C	p Value
VAT reached (n,%)	7 (87)	17 (70)	9 (56)	NS
VE/VCO_2 (ratio)	28 ± 3.7	33 ± 5.8	40 ± 5.7	< 0.001
Exercise time (min)	12 ± 2.2	9 ± 2.6	6 ± 2.3	< 0.001
CRI value (%)	83 ± 10	72 ± 17	49 ± 23	< 0.01

Abbreviation: VAT = ventilatory anaerobic threshold.
Other abbreviations as in Table I.

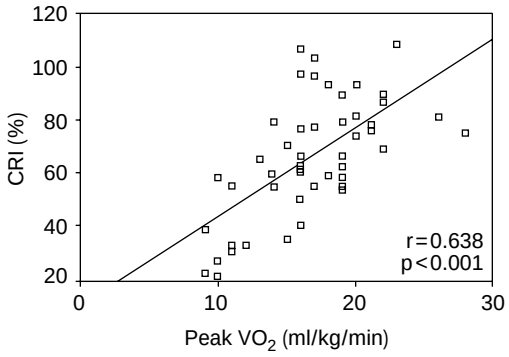

FIG. 1 Correlation between chronotropic index (CRI) and peak oxygen consumption (VO_2).

Discussion

Our data demonstrate that the CRI is significantly related to peak VO_2 and VE/VCO_2 in patients with CHF. In healthy adults, the normal CRI value is 1.00, and chronotropic incompetence has been defined by a CRI value < 0.80.[27] On the basis of our data, in stable moderately symptomatic patients

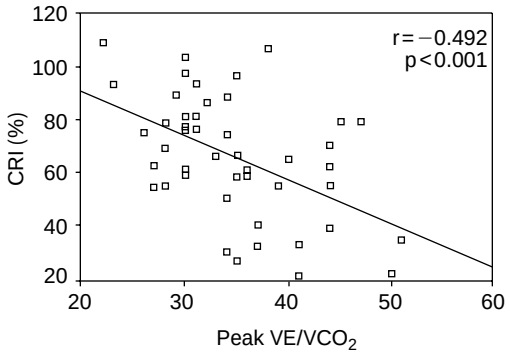

FIG. 2 Correlation between chronotropic index (CRI) and peak ventilation/carbon dioxide production (VE/VCO_2).

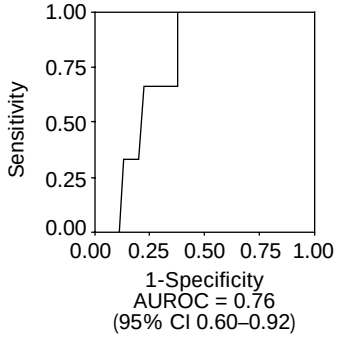

FIG. 3 Receiver operating characteristic curve of CRI < 78% for the determination of peak $VO_2 < 20$ ml/kg/min. AUROC = area under the receiver operating characteristic curve, CI = confidence interval. Other abbreviations as in Figure 1.

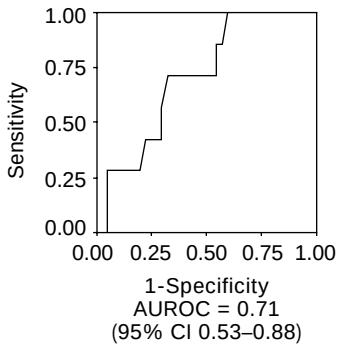

FIG. 4 Receiver operating characteristic curve of CRI < 74% for the determination of $VE/VCO_2 > 30$. Abbreviations as in Figures 2 and 3.

with CHF, a CRI value < 78% is associated with impaired functional capacity (peak VO_2 < 20 ml/kg/min), whereas a CRI < 74% is associated with a minimally increased ventilatory response (VE/VCO_2 > 30). The direct relationship of chronotropic response to exercise with oxygen uptake could be mostly explained by the direct relationship between cardiac output and HR. In the failing heart, because the increase in cardiac output is largely dependent on an increase in HR, chronotropic incompetence will produce severe limitation to effort capacity.[28] On the other hand, the relationships of CRI with VO_2 and VE/VCO_2 in CHF support the hypothesis that the autonomic nervous system has a role in conditioning both functional impairment and chronotropic incompetence. An important contribution to the increase in HR during exercise has been demonstrated to be of neural origin.[29] The sympathetic activation, more than sustaining cardiac output and maintaining an efficient peripheral circulation when pump failure occurs, ends by exhausting target organs as well as the cells of the sinus node. The elevated levels of VE/VCO_2 have been explained by two principal mechanisms: an increase in dead space relative to tidal volume because of pulmonary hypoperfusion, ventilation/perfusion mismatching, and lung restrictive changes, and the increased production of CO_2 due to buffering of lactic acid by HCO_3.[19, 30] However, the increased ventilatory drive could be a response to an abnormal stimulus rather than merely a consequence of pulmonary involvement.[31] Increased chemoreflex sensitivity is a common finding in CHF, and activation of chemoreceptors increases ventilation and pulmonic vasoconstriction.[11, 13] According to Clark *et al.*,[31] excessive ventilation could be a cause and not a consequence of increased dead space. The relationship between ventilatory competence, chronotropic response, and aerobic capacity that we observed supports the hypothesis of a unique pathophysiologic model driven by autonomic dysfunction. The inappropriate hyperventilatory response associated with the inappropriately low chronotropic response may represent the worsening of CHF, characterized by exhaustion of autonomic compensatory mechanisms and organ refractoriness as a consequence of sustained sympathetic and chemoreflex overactivity.

Study Limitations

The study included patients on therapy with digoxin and amiodarone; however, no correlation of the CRI was found with treatment. Furthermore, chronotropic competence was assessed by an index that is unrelated to age and physical fitness and takes resting HR into account.[26, 27]

To compare all indices at peak exercise, the VE/VCO_2 ratio was analyzed at peak and not at anaerobic threshold;[32] however, peak and VAT values of VE/VCO_2 have been found to correlate strongly.[26]

Patients were primarily in mild to moderate heart failure, based on their oxygen consumption; consequently, the CRI discriminated well the mildly reduced peak VO_2 (< 20 ml/kg/min). Further studies are needed on patients with advanced heart failure.

Conclusions and Clinical Implications

In CHF, the chronotropic response to exercise correlates with functional capacity: the greater the reduction in CRI, the greater the impairment in functional capacity (peak VO_2 < 20 ml/kg/min). Reduced CRI likely expresses the progression of autonomic dysfunction and the worsening of heart failure. The relationship adds new data on pathophysiologic grounds, supporting the hypothesis that the autonomic nervous system has a role in conditioning functional impairment of CHF and confirming chronotropic competence as one of the major mechanisms to preserve exercise capacity in these patients. Functional evaluation of CHF should include an analysis of HR response to exercise. If our observations will be confirmed and the prognostic power of CRI extended, another interesting, simple, and powerful index will be available for risk stratification in patients with CHF.

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