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Age-Related Maximum Heart Rate Among Ischemic and Nonischemic Heart Failure Patients Receiving β-Blockade Therapy

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ABSTRACT

Background: Equations to predict maximum heart rate (HR_{max}) in heart failure (HF) patients receiving β-adrenergic blocking (BB) agents do not consider the cause of HF. We determined equations to predict HR_{max} in patients with ischemic and nonischemic HF receiving BB therapy.

Methods and Results: Using treadmill cardiopulmonary exercise testing, we studied HF patients receiving BB therapy being considered for transplantation from 1999 to 2010. Exclusions were pacemaker and/or implantable defibrillator, left ventricle ejection fraction (LVEF) >50%, peak respiratory exchange ratio (RER) <1.00, and Chagas disease. We used linear regression equations to predict HR_{max} based on age in ischemic and nonischemic patients. We analyzed 278 patients, aged 47 ± 10 years, with ischemic (n = 75) and nonischemic (n = 203) HF. LVEF was 30.8 ± 9.4% and 28.6 ± 8.2% (P = .04), peak VO_2 16.9 ± 4.7 and 16.9 ± 5.2 mL kg^{-1} min^{-1} (P = NS), and the HR_{max} 130.8 ± 23.3 and 125.3 ± 25.3 beats/min (P = .051) in ischemic and nonischemic patients, respectively. We devised the equation $HR_{max} = 168 - 0.76 \times age$ (R^2 = 0.095; P = .007) for ischemic HF patients, but there was no significant relationship between age and HR_{max} in nonischemic HF patients (R^2 = 0.006; P = NS).

Conclusions: Our study suggests that equations to estimate HR_{max} should consider the cause of HF. (*J Cardiac Fail 2012;18:831–836*)

Key Words: Heart rate, exercise testing, heart failure, β-adrenergic receptor blocker.

Heart failure (HF) is a complex clinical syndrome associated with high rates of morbidity and mortality.[1] β-Adrenergic receptor blocking (BB) agents have been widely used in this condition since it was proven that they improve survival and clinical status and reduce hospitalization.[2–6]

The main clinical manifestation in these patients is exercise intolerance, and cardiopulmonary exercise testing (CPET) is a useful tool in prognostic evaluation, providing essential information when patients are considered for cardiac transplantation. In this setting, they must be evaluated with optimized clinical therapy, including BB agents.

Heart rate (HR) response is one of the parameters provided by CPET, and chronotropic incompetence (CI) has been commonly defined by incapacity to reach an arbitrary percentage of the predicted maximum HR (HR_{max}). CI has been recognized as an independent prognostic marker in patients with[7] and without[8–10] HF taking[11] or not taking[8] BB agents. However, the determination of predicted HR_{max} is usually based on the equation 220 − age,[10] which is not appropriate for patients taking BB agents.[12] Furthermore, the reported prevalence of CI in HF patients is highly variable and may reflect different criteria used to define CI as well as differences in patient characteristics.[10] Recently, an equation that predicts HR_{max} based on age, resting HR, and ergometer type was determined for patients with

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See page 835 for disclosure information.

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HF.[13] However, it did not consider the impact of the cause of HF on HR_{max}.

The purpose of the present study was to determine an equation to predict HR_{max} in patients with ischemic and nonischemic HF who are receiving BB therapy.

Methods

Population and Study Design

A retrospective analysis was performed in 655 consecutive patients with HF referred for heart transplantation from 1999 to 2010. All patients underwent CPET; they had been clinically stable before CPET. Excluded from the analysis were 377 patients because they were either participating in regular physical activity ≥30 minutes 3 times a week (n = 45), were <20 years old (n = 25), had no optimized drug therapy (n = 10), had incomplete data (n = 4) or interrupted test owing to hemodynamic or electrocardiographic complications (n = 50), or had respiratory limitations (n = 10), left ventricular ejection fraction (LVEF) ≥50% (n = 30), atrial fibrillation (n = 20), pacemaker or implantable defibrillator (n = 37), peak respiratory exchange ratio (RER) <1.00 (n = 120), or Chagas disease (n = 26). The final sample included 278 patients aged 20−76 years with systolic HF (SHF), receiving a stable dose of a BB for >3 months before the CPET. All patients were taking BBs (carvedilol 80%, bisoprolol 15%, and metoprolol 5%) at the maximum tolerated dose at the discretion of the treating physician. Furthermore, 80% of the patients were taking angiotensin-converting enzyme inhibitor (ACE-I), 21% angiotensin receptor antagonist (ARA), and 58% spironolactone. We asked them to take their medications normally, including on the day of the test. LVEF and clinical data were obtained from the last echocardiogram and the patient's medical record, respectively.

Ischemic HF was defined as SHF with past myocardial infarction or revascularization (surgical or percutaneous). The patients were enrolled in 6 age-range groups (years): 20−29, 30−39, 40−49, 50−59, 60−69, and ≥70.

The study was approved by the Institutional Review Board of the Ethics Committee, and it was in accordance with the Declaration of Helsinki.

Exercise Testing

All referred patients underwent maximum exercise testing using a modified Naughton protocol and a metabolic cart. CPET was carried out on a programmable treadmill (TMX425 Stress Treadmill; TrackMaster, Newton, Kansas, USA) in a controlled-temperature room (21−23°C) with monitoring of cardiac rhythm (CardioSoft 6.5; GE Medical Systems IT, Milwaukee, Wisconsin, USA) and blood pressure (Tango Stress BP; SunTech Medical, Morrisville, North Carolina, USA) as previously described.[14]

The 12-lead electrocardiogram and HR were monitored with the patient in the standing position before and throughout the exercise period and during recovery. Ventilation (VE), oxygen uptake (VO_2), and carbon dioxide output (VCO_2) were measured breath by breath with the use of a computerized system (Vmax Encore 29; SensorMedics Corp, Yorba Linda, California, USA). The RER had been recorded at each average sample obtained during each stage of the protocol. The highest VO_2 and HR levels (1-minute mean) at the end of exercise were considered to be the peak VO_2 and HR_{max}, respectively. The VE-VCO_2 slope was calculated by automatic linear regression fitting with the breath-by-breath values obtained throughout the whole exercise. Patients were instructed and encouraged to exercise to their maximum capacity.

The predicted peak VO_2 was calculated according to normative values for age, sex, and body weight from Wasserman et al.[15] The percentage of predicted peak VO_2 was determined by dividing the weight-normalized peak VO_2 by the predicted peak VO_2 and then multiplying by 100. Predicted HR_{max} was determined by the equation $HR_{max} = 164 - 0.7 \times age$, which was validated for patients receiving BB therapy.[12] Reserve HR was the absolute difference between HR_{max} and resting HR (HR_{rest}).

We also calculated the values of predicted HR_{max} in our sample by the equation $HR_{max} = 119 + 0.5(HR_{rest}) - 0.5(age)$, which we called "HF-pred HR."[13]

Statistical Analysis

All data are reported as mean ± SD, and the statistical program SPSS 13.0 for Windows (SPSS, Chicago, Illinois, USA) was used to perform the statistical analysis. The Kolmogorov-Smirnov test was applied to ensure a gaussian distribution of the results. One-way analysis of variance (ANOVA) was used to analyze differences in the subjects' characteristics at baseline. Bonferroni post hoc analysis was used to determine the significance of the data that was indicated by 1-way ANOVA. Pearson correlation was used to assess the relationship between age and HR_{max}. Linear regression was used to generate the equation to predict HR_{max} from age for ischemic and nonischemic HF patients receiving BB therapy. The significance level was set at $P < .05$. Bootstraping resampling based on 1,000 bootstrap samples was used for validation in each HF group (ischemic and nonischemic).

Results

Population and Study Design

The clinical baseline characteristics of the whole sample and according to the cause of HF are listed in Table 1. Most patients were male and had nonischemic HF. We observed that LVEF was lower for nonischemic than for ischemic patients.

Table 2 presents the results of linear regression model for HR_{max} in ischemic and nonischemic HF patients. We found that age is a significant but weak predictor of HR_{max} in ischemic patients only ($R^2 = 0.095$; $P = .007$) and derived an equation $HR_{max} = 168 - 0.77 \times age$. On the other hand,

Table 1. Clinical Baseline Characteristics and Comparison Between Ischemic and Nonischemic Heart Failure Patients

Parameter	Total (n = 278)	Ischemic (n = 75)	Nonischemic (n = 203)	*P* Value
Male, n (%)	207 (75)	59 (79)	148 (73)	NS
Age, y	47.2 ± 10.3	48.9 ± 9.3	46.6 ± 10.6	NS
Weight, kg	70.5 ± 16.0	70.2 ± 16.3	70.6 ± 16.0	NS
Height, cm	164 ± 10	164 ± 11	164 ± 9	NS
BMI, kg/m^2	25.8 ± 5.3	25.2 ± 5.9	26.1 ± 5.1	NS
NYHA functional class	2.2 ± 0.9	2.3 ± 0.9	2.2 ± 0.9	NS
LVEF, %	29.2 ± 8.6	30.8 ± 9.4	28.6 ± 8.2	.04
Hemoglobin, g/dL	13.6 ± 1.6	13.3 ± 1.9	13.6 ± 1.6	NS

BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction.

Table 2. Linear Regression Model for Maximum Heart Rate in Ischemic and Nonischemic Heart Failure Patients

Variable	β	SE	*P* Value	R^2	SEE
Ischemic					
Constant	168.347	13.808			
Age	−0.768	0.278	.007*	0.095	22
Nonischemic					
Constant	133.929	8.014			
Age	−0.184	0.168	NS*	.006	25

SE, standard error; SEE, standard error of the estimate.
*t test.

there was no significant relationship between age and HR_{max} in nonischemic HF patients (R^2 = 0.006; P = NS). The bootstrap resampling analysis showed bias 0.004, standard error 0.292, 95% CI −1.333 to −0.170, and P = .011 for ischemic and bias 0.005, standard error 0.176, 95% CI −0.531 to 0.179, and P = .296 for nonischemic HF patients.

Table 3 presents the exercise parameters and a comparison between ischemic and nonischemic HF patients. We found that nonischemic patients had a higher VE-VCO_2 slope. The absolute HR_{max} tended to be lower and the percentage of predicted HR_{max} was significantly lower for nonischemic patients, using the validated equations both for patients receiving BBs and for HF patients (HF-pred HR) to predict HR_{max}. We did not find any difference in peak RER, peak VO_2 (mL kg^{-1} min^{-1}), peak VO_2 (% of predicted), or reserve HR between ischemic and nonischemic patients.

We compared HR_{max} between ischemic and nonischemic HF patients in each age group, as presented in Table 4. The 20−29-year and ≥70-year groups were excluded because they included only nonischemic patients. We found that HR_{max} was significantly higher in ischemic than in nonischemic patients in the age groups 30−39 and 40−49 years, but there was no difference in the age groups 50−59 and 60−69 years. Reserve HR, HR_{rest}, and peak VO_2 were not different according to etiology in any group. Interestingly, the VE-VCO_2 slope was significantly higher and LVEF significantly lower in nonischemic HF patients only in the 40−49 group. Considering only nonischemic patients, we did not find a significant difference in any of these parameters among age groups. On the other hand, for ischemic patients, we found that HR_{max} was significantly lower in the 50−59-year than in the 30−39-year group, and peak VO_2 was lower in the 60−69-year and LVEF lower in the 50−59-year compared with the 40−49-year group.

Discussion

We have found that age-related predicted HR_{max} obtained by linear regression is different between ischemic and nonischemic HF patients. There is only a weak relationship between HR_{max} and age in ischemic patients, and age is not a significant predictor of HR_{max} in nonischemic patients. To our knowledge, this is the first study to demonstrate a difference between ischemic and nonischemic HF patients.

The equation 220 − age is a common equation used to determine the predicted HR_{max}, and it has been applied to calculate indices that have prognostic value in HF patients. However, earlier studies[12,16] indicated that this equation should not be used in patients using BB agents. Brawner et al[12] developed and validated an equation to predict HR_{max} in patients using BB agents: HR_{max} = 164 − 0.72 × age. They included patients with coronary artery disease and excluded those with HF or LVEF <50%. Interestingly, that equation is very similar to what we found for ischemic patients, suggesting that it could apply to individuals with coronary artery disease using BB agents regardless of ventricular function. Recently, Keteyian et al[13] validated a simplified equation based on age, HR_{rest}, and ergometer [HR_{max} = 119 + 0.5 × (resting HR_{rest}) − 0.5(age) for treadmill] in HF patients taking BB agents, of which 49% were ischemic.

Table 3. Exercise Parameters and Comparison Between Ischemic and Nonischemic Heart Failure Patients

Parameter	Total	Ischemic	Nonischemic	*P* Value
HR_{rest}, bpm	77.6 ± 15.3	79.6 ± 16.2	76.8 ± 15.0	NS
Equation HR_{max}		168.3 − 0.77 × age	133.9 − 0.18 × age	—
HR_{max}, bpm	126.8 ± 24.9	130.8 ± 23.3	125.3 ± 25.3	.051
Reserve HR	48.7 ± 20.8	50.9 ± 19.2	47.9 ± 21.3	NS
% HR_{max}*	97.0 ± 19.2	100.7 ± 17.0	95.6 ± 19.8	.02
% HR_{max} (HF-pred HR)†	94.0 ± 16.1	96.9 ± 14.1	92.9 ± 16.6	.02
% HR_{max} (proposed equation)‡	99.8 ± 19.3	99.7 ± 16.8	99.9 ± 20.1	NS
Peak RER	1.08 ± 0.07	1.07 ± 0.06	1.08 ± 0.08	NS
Peak VO_2, mL kg^{-1} min^{-1}	16.9 ± 5.1	16.9 ± 4.7	16.9 ± 5.2	NS
Peak VO_2 (% max pred)	46.0 ± 11.9	46.1 ± 11.4	46.0 ± 12.0	NS
VE-VCO_2 slope	35.0 ± 10.0	32.7 ± 9.5	35.7 ± 10.1	.01

LVEF, left ventricle ejection fraction; HR, heart rate; bpm, beats per minute; HR_{max}, maximum heart rate; HR_{rest}, resting heart rate; % HR_{max}, percentage of predicted HR_{max} using equation 164 − 0.7 × age; RER, respiratory exchange ratio; VO_2, oxygen uptake.
*HR_{max} was calculated by the equation 164 − 0.7 × age.[12]
†HR_{max} was calculated by the equation 119 + (0.5 × HR_{rest}) − (0.5 × age).[13]
‡HR_{max} was calculated by the derived equations proposed in this study: 168.3 − 0.77 × age for ischemic and 133.9 − 0.18 × age for nonischemic HF patients.

Table 4. Comparison of Exercise Parameters and Left Ventricle Ejection Fraction (LVEF) Between Ischemic and Nonischemic Patients Among Age Groups

Parameter	30−39 y	40−49 y	50−59 y	60−69 y
n	46	97	85	34
HR_{max}				
Ischemic	140.4 ± 25.0	135.0 ± 22.2	123.7 ± 21.8†	124 ± 22.5
Nonischemic	125.0 ± 25.0*	126.0 ± 22.9*	120.1 ± 27.0	130 ± 28.0
Reserve HR				
Ischemic	56.4 ± 16.1	53.8 ± 19.9	45.4 ± 20.7	50.7 ± 15.2
Nonischemic	46.8 ± 24.5	49.8 ± 22.1	46.7 ± 21.9	48.8 ± 17.8
HR_{rest}				
Ischemic	84.0 ± 18.4	84.4 ± 14.6	78.3 ± 15.8	74.2 ± 18.1
Nonischemic	78.2 ± 12.4	76.2 ± 11.9	73.4 ± 15.7	76.2 ± 16.9
Peak VO_2				
Ischemic	17.5 ± 4.2	17.5 ± 5.5	17.1 ± 4.4	13.7 ± 3.9‡
Nonischemic	17.4 ± 5.5	16.7 ± 5.1	16.5 ± 4.5	15.6 ± 4.4
VE-VCO_2 slope				
Ischemic	31.8 ± 15.1	31.0 ± 6.7	34.1 ± 7.4	35.4 ± 9.3
Nonischemic	35.7 ± 12.7	36.6 ± 9.1*	36.6 ± 10.5	34.1 ± 9.4
LVEF				
Ischemic	30.7 ± 7.5	34.3 ± 9.9	28.4 ± 9.1‡	28.5 ± 10.1
Nonischemic	29.4 ± 7.1	28.8 ± 8.4*	28.7 ± 9.0	27.0 ± 7.4

HR, heart rate; HR_{max}, maximum heart rate; HR_{rest}, resting heart rate; VO_2, oxygen uptake; LVEF, left ventricle ejection fraction.
*$P < .05$; nonischemic vs ischemic HF patients.
†$P < .05$ compared with 30−39-y age group among ischemic HF patients.
‡$P < .05$ compared with 40−49-y age group among ischemic HF patients.

However, both of those equations had a considerable individual variation, with a standard error of the estimate (SEE) of 18 beats/min. Many factors may have contributed to that, such as prior acute myocardial infarction, although it did not explain most of the variation in the present study. We have found that these equations seem to overestimate HR_{max} in nonischemic HF patients and that age did not influence HR_{max}, because the slope of the linear regression is not different from zero. Considering only ischemic HF patients, we have also found high individual variation (SEE 22) and weak relationship between age and HR_{max}, indicating that other factors may have influenced this variation, such as severity of the disease and individual tolerability to BB therapy.

We have found no significant difference in either reserve or resting HR according to etiology among age groups. The small number of patients in each group may have limited these results. In earlier studies, reserve HR was not a significant prognostic marker in patients receiving BBs.[7] In addition, in HF patients not receiving BBs, it was shown that even though it is a predictor of mortality in univariate analysis, reserve HR loses its prognostic value in multivariate analysis.[7,17] Although blunted HR response induced by BB agents may be responsible for its lack of prognostic value, we demonstrated that HR_{max} is influenced by age in different ways according to the cause of the heart failure.

The reasons for these differences are uncertain. Patients with HF have abnormal sympathetic function in the myocardium, characterized by a reduction in presynaptic norepinephrine (NE) uptake and postsynaptic β-adrenoceptor density.[18] Altered expression of β-adrenoceptor density was demonstrated in both ischemic and nonischemic HF patients.[19,20] It has been considered that down-regulation of β-adrenoceptor could be due to a locally increased NE concentration in the synaptic cleft.[18]

Metaiodobenzylguanidine (MIBG) is an NE analog and, likewise, is captured in the presynaptic membrane.[21−23] Its neuronal uptake reflects the distribution and integrity of the heart's sympathetic innervation.[24] Earlier studies have analyzed the prognostic value of cardiac scintigraphy with the use of MIBG labeled with iodine-123 (^{123}I-MIBG) in HF patients.[24−30] It has been found that decreased ^{123}I-MIBG uptake and increased washout rate are independent predictors of mortality in patients with HF independently from etiology.[18,31−33] On the other hand, clinical treatment including ACE-I,[34] ARA,[35] BBs,[36,37] and spironolactone[38] can improve sympathetic neuronal uptake function and could affect HR exercise response. Chizzola et al[39] found a 14% increase in MIBG uptake after 2 months of treatment with carvedilol. This indicates an improved neuronal reuptake of NE with carvedilol, preventing the down-regulation of expression of adrenergic receptors (reverse remodeling of the cardiac sympathetic nervous system). Whether a higher increase occurs in β-adrenoceptor activity after chronic treatment with BB agents for ischemic versus nonischemic patients is still uncertain. Recently, Rocha Messias et al[40] found that a group of HF patients taking BBs with an altered washout rate (≥27%) had a peak HR significantly lower than patients with a normal washout rate. Despite the small sample, that study suggests that lower peak HR is, at least in part, associated with accelerated sympathetic tone or NE spillover, leading to a down-regulation of β-adrenoceptors. Interestingly, it has been found[41] that a higher washout rate occurs in nonischemic than in ischemic patients. It may explain possible mechanisms involved in differences in peak HR that we found.

Study Limitations

This was a retrospective study using selected patients with HF referred for heart transplantation at a single center. All patients underwent a single treadmill CPET to assess aerobic capacity. Although data collection was not planned and statistical analysis was exploratory, all of the patients underwent testing on the same equipment and by the same team, which eliminates the differences in data collection and conduction. The number of patients 20−29 and ≥70 years old was relatively small, and there were only patients with nonischemic HF in those groups. Also, LVEF values were lower and VE-VCO_2 slope higher for nonischemic than for ischemic patients, especially in the 40−49-year age group. However LVEF values and VE-VCO_2 slope may have influenced our results, they are applicable to the population of patients referred for heart transplantation and may result from similar pathophysiologic pathways.

We obtained HR_{rest} with the patient in the standing position just before starting exercise, and there was no difference in HR_{rest} between groups. It is possible that the absence of a difference in reserve HR arises from an increased sympathetic drive secondary to preanticipatory response.

Finally, these findings are based on treadmill testing only and can not be extrapolated to upright cycle ergometer exercise testing.

Conclusion

This investigation found that equations to predict maximum heart rate are different between ischemic and nonischemic HF in patients receiving BB therapy. The cause of HF should be considered when interpreting the heart rate response in HF patients who undergo cardiopulmonary exercise testing on a treadmill.

Disclosures

None.

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