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Effects of age on aerobic capacity in heart failure patients under beta-blocker therapy: Possible impact in clinical decision-making?

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Abstract

Background: *Heart failure (HF) is associated with impaired maximal aerobic capacity as indicated by decreases in peak oxygen uptake (peak VO_2). Considering that aging by itself has a negative effect on this variable, the evaluation of maximum capacity is often questioned because current predicted peak VO_2 is based on subjects without heart disease or β-blocker therapy. In contrast, if decline in predicted and attained peak VO_2 were age-related, proportionally, loss of aerobic function (predicted peak VO_2, %) would remain stable over time in these patients. The purpose of this investigation is to assess the effects of age on peak VO_2 in HF patients taking β-blockers.*

Methods: *We retrospectively evaluated 483 (132 female) patients (aged 20–88 years, LVEF 31 ± 11%) with non-ischemic (n = 362), ischemic (n = 74) and Chagas-related HF (n = 47) who had been submitted to an incremental cardiopulmonary exercise testing on a motorized treadmill. Linear regression was used to develop the equation to predict peak VO_2, based on age.*

Results: *Peak VO_2 decreased 0.9 mL/min/kg per age-decade, maximum HR also decreased with aging and VE/VCO_2 slope was similar among all decades. The predicted new β-blocker equation to peak VO_{2bb} was 20.934 – 0.092 × age.*

Conclusions: *Clinical interpretation of aerobic capacity impairment is influenced by aging in HF patients. This evidence must be considered when using peak VO_2 for prognostic stratification and clinical decision-making in patients with HF under β-blocker therapy.* (Cardiol J 2013; 20, 6: 655–661)

Key words: aging, β-blocker therapy, cardiopulmonary exercise test, cardiorespiratory fitness, heart failure

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Introduction

Chronic heart failure (HF) is an increasingly common disorder in population, which causes high mortality and morbidity, despite modern developments in medical therapy [1–4]. The primary symptoms of chronic HF are exertional fatigue and dyspnea due to a reduction in exercise tolerance [1]. Additional traits, as age, gender, weight, body surface area and muscle mass, can also be correlated to functional capacity in patients with HF [5, 6].

Indeed, performing the cardiopulmonary exercise testing (CPX) became increasingly important in order to provide objective and reproducible measurement of exercise limitation [1] and to identify individuals suffering from HF with poor prognosis [1, 6]. Among exercise variables, the strongest and most consistent predictors of death are peak oxygen consumption (peak VO_2) [1, 4, 6], VO_2 at the ventilatory threshold, percentage of age-predicted maximal heart rate (HR) and VE/VCO_2 slope [6, 7].

These data have also influence on the chosen treatment. In the early 90's, it was shown that patients with severe left ventricular dysfunction and peak VO_2 < 14 mL/min/kg would benefit from cardiac transplantation [1, 8]. More recently, a lower cutoff for peak VO_2 (< 12.5 mL/min/kg) has been identified as predictor of mortality in patients with HF, taking β-blocker agents [9].

Nevertheless, a progressive decline in cardiovascular system occurs with advancing age [10]. Age itself is an independent morbidity and mortality risk factor for a long list of diseases, hospitalization and length of hospitalization [11]. Physiological changes that occur during the aging process regarding quality of life and functional independence are muscle intrinsic abnormalities, low muscle mass or muscle perfusion [3], declining in muscle strength and in aerobic capacity, indexed as peak VO_2 [5, 12, 13].

A few studies demonstrated that longitudinal rate of declining in peak VO_2 is on average 8% to 10% per decade in the general population and, at the age of 60, it is approximately two-thirds of that at 20 [10, 14]. Recently it has been reported that peak VO_2 decreases with age in HF patients, however, these reports came from studies with patients classified as young, middle-aged and older, and the peak VO_2 was assessed using either a treadmill or cycle ergometer CPX [15, 16]. On the other hand, there are no trials showing the effect of age by decade on peak VO_2 in HF patients. It is possible that age can influence the peak VO_2, as well as the cutoff point for cardiac transplant in patients suffering from HF. The purpose of this investigation is to assess the effects of age on peak VO_2 in HF patients taking β-blockers.

Methods

Population and study design

A retrospective analysis was performed in consecutive patients with systolic HF referred to heart transplant, from 1999 to 2009. Inclusion criteria included clinical and pharmacological stability for at least 3 months prior CPX, age ≥ 20 years, left ventricular ejection fraction (LVEF) < 45%, New York Heart Association functional class I–III and no participation in regular physical activity (≥ 30 min 3 times a week). Patients with cardiac device system (pacemaker or implantable defibrillator), CPX interrupted due to hemodynamic or electrocardiographic complications, respiratory exchange ratio (RER) < 1.0, neuromuscular or respiratory limitations were excluded from the study.

A total of 655 clinically and pharmacologically stable HF patients underwent CPX during this period. One hundred seventy two patients were excluded from analysis because they were, either, under regular physical activity (n = 40), were under 20 years old (n = 25), had no optimized drug therapy (n = 10), or interrupted test due to hemodynamic or electrocardiographic complications (n = 40), respiratory limitations (n = 10), LVEF ≥ 45% (n = 10), atrial fibrillation (n = 20), and pacemaker or implantable defibrillator (n = 15). The final sample included 483 patients with systolic HF aged from 20 to 88 years, with stable dose of β-blocker for more than 3 months prior to the CPX. The patients were enrolled in six age groups ranging from 20 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69 and ≥ 70 years old. Clinical characteristics are listed in Table 1.

The review board of the ethical committee at our institution had approved the study and it is in accordance with the declaration of Helsinki.

Exercise testing

All referred patients had undergone maximal exercise testing using a modified Naughton protocol and a metabolic cart. CPX had been carried out on a programmable treadmill (TMX425 Stress Treadmill; TrackMaster, Newton, KS, USA) in a controlled-temperature room (21–23°C) with monitoring of cardiac rhythm (CardioSoft 6.5; GE Medical Systems IT, Milwaukee, WI, USA) and blood pressure (Tango Stress BP; SunTech Medical

Table 1. Baseline characteristics according to age decade.

	20–29 (n = 28)	30–39 (n = 67)	40–49 (n = 152)	50–59 (n = 143)	60–69 (n = 75)	≥ 70 (n = 18)
Sex (male/female)	19/9	49/18	114/38	96/47	60/15	12/6
Body mass index [kg/m^2]	23 ± 4	26 ± 5	25 ± 4	26 ± 5*	27 ± 5*	27 ± 4
Hemoglobin [g/dL]	13.6 ± 1.4	13.7 ± 1.4	13.5 ± 1.8	13.6 ± 1.6	13.8 ± 1.3	13.7 ± 2.2
LVEF [%]	27 ± 8	30 ± 10	28 ± 11	30 ± 13	30 ± 12	25 ± 7
Heart rate rest [bpm]	86 ± 21	79 ± 15	76 ± 15*	75 ± 15*	76 ± 18*	79 ± 12
Etiology:						
Idiophatic	23	48	114	107	62	10
Ischemic	3	13	23	22	8	5
Chagas	2	8	15	14	5	3
Medication [%]:						
Beta-blocker	100	100	100	100	100	100
Diuretics	76	73	70	69	72	77
ACE-I/ARB	86	87	80	81	79	88
Digoxin	43	38	41	40	37	38
Aldosterone	46	40	39	37	40	42
Nitrate	2.5	2.1	3.2	3.3	2.8	2.1
Amrinone	1	1.8	2.1	2.0	1	1
Anticoagulants	0	1.5	2.3	2.5	1	0

[a]Significant difference in relation to age group 20–29 (p = 0.01); LVEF — left ventricular ejection fraction; ACE-I — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker

Inc, Morrisville, NC, USA) as previously described [17]. The 12-lead electrocardiogram and HR had been monitored in the standing position before and throughout the exercise and recovery period. Ventilation (VE), oxygen uptake (VO_2) and carbon dioxide output (VCO_2) had been measured breath-by-breath using a computerized system (Vmax Encore29; SensorMedics Corp., Yorba Linda, CA, USA). The RER had been recorded at each average sample obtained during each stage of the protocol. The highest VO_2 uptake level (1 min mean) at the end of exercise was considered the peak VO_2, and the VE/VCO_2 slope was calculated by automatic linear regression fitting with the breath-by-breath values obtained throughout the whole exercise. Patients had been instructed and encouraged to exercise to their maximum capacity.

The predicted peak VO_2 was calculated according to normative values to age, sex and body weight by Wasserman et al. [18]. 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 it by 100. Predicted maximum heart rate (HR_{max}) was determined by the equation $HR_{max} = 164 - (0.7 \times \text{age})$, which was validated for patients receiving β-blocker therapy [19].

Statistical analysis

All data are reported as means ± standard deviation and the statistical program SPSS 13.0 for Windows (SPSS Inc, Chicago, IL, USA) was used to perform 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 subject's characteristics at baseline. Bonferroni *post hoc* analysis was used to determine significance of data that was indicated by one-way ANOVA. Pearson correlation was used to assess the relationship between age and both peak VO_2 and HR_{max}, and between age and percent predicted for them. Linear regression was used to generate equation to predict peak VO_2 from age for HF patients receiving β-blocker therapy. Then, we calculated the predicted peak VO_2 using this linear regression for patients taking β-blocker agents (VO_{2bb}). The significance level was set at $p < 0.05$.

Results

The comparisons of clinical characteristics of categorized patients by age decades are listed in Table 1. The percentage of subjects with non-

Table 2. Cardiopulmonary exercise test variables according to age decade.

	20–29 (n = 28)	30–39 (n = 67)	40–49 (n = 152)	50–59 (n = 143)	60–69 (n = 75)	≥ 70 (n = 18)
HR_{max}	129 ± 29	124 ± 27	123 ± 23	117 ± 24	116 ± 27	114 ± 19
% HR_{max}	89 ± 19	88 ± 20	93 ± 17	93 ± 19	97 ± 22	103 ± 17
peak VO_2	18.8 ± 6.5	17.5 ± 5.7	16.7 ± 5.0	16.2 ± 4.5	14.9 ± 4.2[a, b]	13.0 ± 2.4[a,b,c]
% VO_{2pred}	46 ± 14	43 ± 13	44 ± 11	48 ± 11	48 ± 12	46 ± 8
peak VO_{2bb}[d]	18.5 ± 0.27	17.7 ± 0.27	16.8 ± 0.25	15.9 ± 0.26	15.0 ± 0.27	13.9 ± 0.45
% $VO_{2predbb}$	101 ± 35	99 ± 32	100 ± 30	102 ± 30	99 ± 28	94 ± 18
RER	1.06 ± 0.05	1.05 ± 0.05	1.07 ± 0.06	1.07 ± 0.07	1.06 ± 0.06	1.03± 0.02
VE/VCO_{2slope}	35 ± 15	35 ± 13	35 ± 8	36 ± 10	35 ± 9	35 ± 9

HR_{max} — maximum heart rate [bpm]; % HR_{max} — percent-predicted HRmax; peak VO_2 — peak oxygen consumption [mL/kg/min]; % VO_{2pred} — percent-predicted peak VO_2; peak VO_{2bb} — peak VO_2 estimated by 20.934 – 0.092 × age [mL/kg/min]; % $VO_{2predbb}$ — percent-predicted peak VO_2 using predicted peak VO_{2bb}; RER — respiratory exchange ratio; significant differences between age group: [a]20–29, [b]30–39, and [c]40–49; [d]significant differences among all decades

-ischemic HF etiology, as well as male subjects was greatest in all decades. The body mass index was significantly lower in the 20–29 year group when compared to patients in the 50's and 60's decades. The resting HR was significantly higher in the 20's decade in relation to the 40's, 50's and 60's. LVEF and HF pharmacological therapy were not different among the groups. All patients were taking β-blockers (carvedilol 80%, bisoprolol 15% and metaprolol 5%) at maximum tolerated dose at the discretion of the treating physician.

Cardiopulmonary exercise test data are shown in Table 2. None of the exercise tests were terminated secondary to electrocardiogram criteria and all patients stopped it by fatigue symptoms. The peak VO_2 was significantly lower among patients in the 60's and 70's decades in relation to the 20's, 30's and 40's. We also observed that peak VO_2 decreased approximately 0.9 mL/kg/min by decade in this population. However, the percentage of the predicted peak VO_2 and, the peak RER were similar in all groups, as well as their maximum and percentage of maximum HR. The other variable that was similar in all decades was VE/VCO_2 slope.

The linear regression analysis of peak VO_2 vs. age is shown in Figure 1. The intercept and slope were 20.93 ± 0.95 and –0.092 ± 0.018, respectively. So, the equation for estimated peak VO_{2bb} to HF patients in β-blocker therapy is 20.934 – 0.092 × × age for whole population.

Table 2 shows the results of the new β-blocker prediction equation for peak VO_{2bb} using a computerized system in HF patients receiving β-blockers therapy underwent treadmill exercise testing. The peak VO_{2bb} was not significantly different from the peak VO_2 measured in all age-decades. However, the peak VO_{2bb} was significantly different among all groups. The Figure 2 shows the interrelation between age, HR_{max} and peak VO_2.

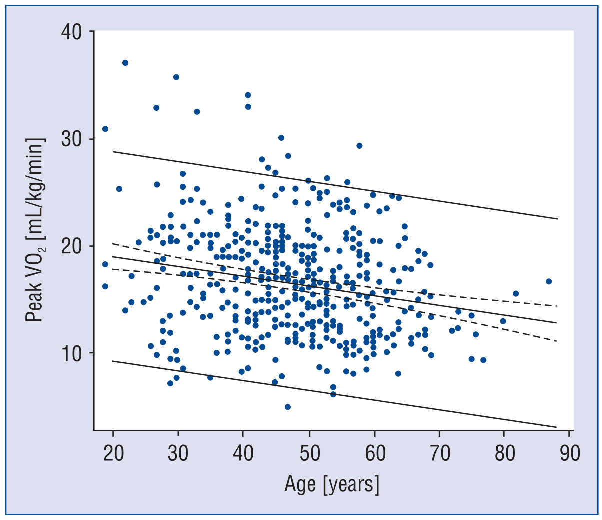

Figure 1. Linear regression equation of peak exercise oxygen consumption (peak VO_2) versus age. Dashed line represent 95% confidence interval of the mean. From these data, a new equation was proposed: VO_{2bb} = = 20.934 – 0.092 × age.

The correlations between age and peak VO_2 (r = 0.21, p < 0.0001), and HR_{max} (r = 0.16, p = = 0.0007) were weak although statistically significant (Fig. 3). The analysis for VE/VCO_2 slope did not show correlation with age (r = 0.01, p = 0.6).

Discussion

The primary finding of the present study was that peak VO_2 decreased 0.9 mL/kg/min for every 10-year increment in age in HF patients taking β-blockers. Additionally, our results show that aerobic function

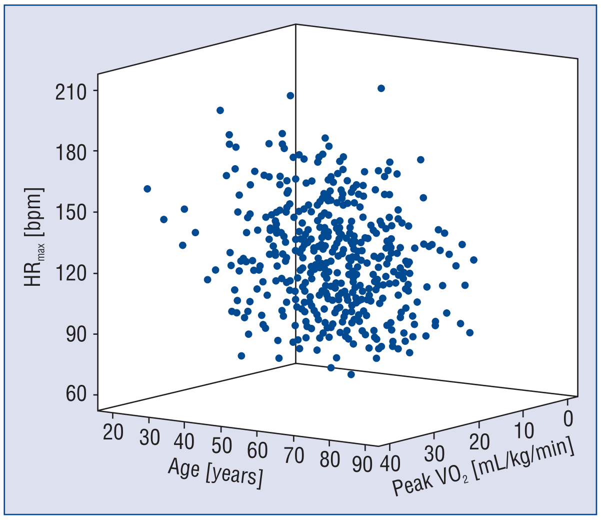

Figure 2. Interrelation among age, peak exercise oxygen consumption (peak VO_2) and maximum heart rate (HR_{max}).

(% predicted) did not differ among young, middle-aged and older patients with HF. The other finding in this investigation is that the new β-blocker equation for predicted peak VO_{2bb} in this specific population between 20 and 88 years old corresponds to 20.934 – – 0.092 × age. To the best of our knowledge, this is the first study to determine an equation to predict peak VO_2 and compare the effects of age on physical capacity among different decades in HF patients undergoing a CPX performed on a treadmill in all cases.

Two previous studies that have investigated the effect of age in HF patients showed a reduction in aerobic capacity [16, 17]. However, these authors analyzed these effects within broad aged groups and the exercise testing was completed using both treadmill and upright cycle ergometer. In spite of methodological differences, the decrease in value of peak VO_2 was 1.0 mL/kg/min for every 7 years [16], which was similar to the findings in our study. The functional capacity is associated with age and begins to decline after age 30, with a more exponential decrease in cardiorespiratory fitness and muscle strength after the age of 50 in apparently healthy individuals [20, 21]. This represents a decline in peak VO_2 on average of 8% to 10% per decade [10–12]. Hence, age itself is an independent predictor for peak VO_2. In previous specific investigations about aerobic capacity and aging in HF [16, 17] it was reported that physiologic reserve in HF is very reduced, which is supported by our results. Progressive decline in peak VO_2 reflects the degree of disease's severity and provides prognostic information in patients with HF [22].

However, our results demonstrated that the mean percent-predicted peak VO_2 value for all groups was 45.8%, which may suggest that these patients are already in their comfort zone, considering age-decades. On the other hand, when new β-blocker equation for predicted peak VO_{2bb} was used this reduction disappears. The peak VO_{2bb} calculated by equation did not differ from the actual peak VO_2 measured, so the percentage of predicted peak VO_{2bb} is around 100%. This finding itself indicates that both aerobic capacity and aerobic function, when adjusted by the equation, are in closer relationship with age than disease's severity in patients with HF. Moreover, VE/VCO_2 slope did not change among the

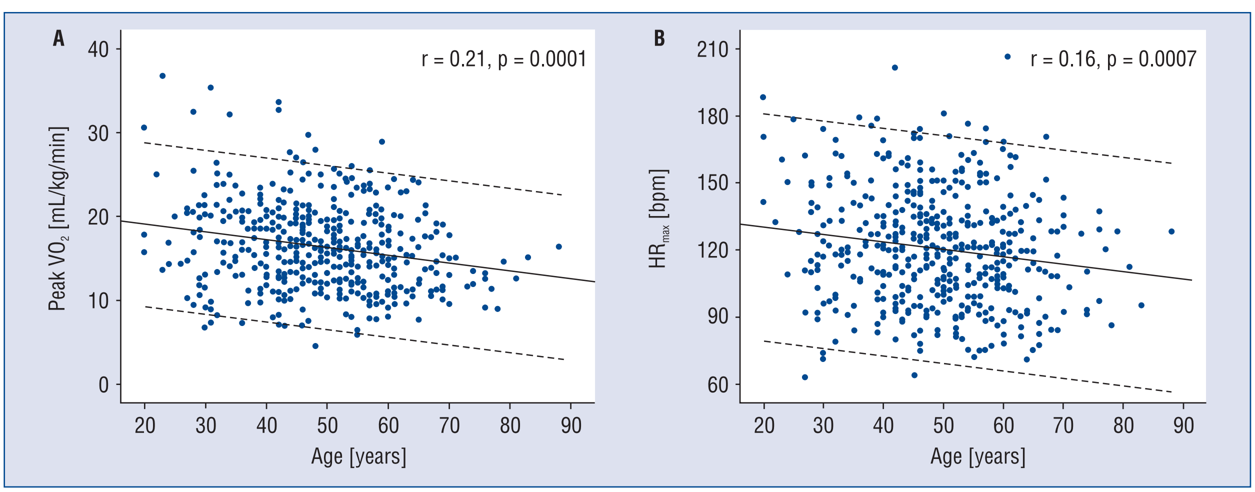

Figure 3. Relationship between age and: **A.** Peak exercise oxygen consumption (peak VO_2); **B.** Maximum heart rate (HR_{max}). There was a significant correlation between age and both **A** and **B**. Dashed lines represent 95% prediction interval.

age-decades, reinforcing the theory that the fall in peak VO_2 is not related to worsening of HF.

The results of the present study are according to our previous investigation, which showed a cutoff point for peak VO_2 of 12.5 mL/kg/min in HF patients undertaking β-blockers as better midterm prognosis [8].

The effects of physiologic aging are associated to declining in exercise capacity, HR_{max} and peak VO_2 [11]. Although it was reported that the decline in peak VO_2 seems to be primarily by reduction in HR_{max} [23], there was no significant difference in HR_{max} during age-decades among the groups.

The β-blocker therapy has become a primary pharmacologic intervention in patients with HF [24]. Previous report has shown that the maximal age-predicted HR depends on optimization of β-blocker dosing in HF patient [2, 25]. In our study, the HR in maximal effort evaluation was 93.8 ± 4.9% of the predicted in the whole sample, estimated by the specific equation to predict HR_{max} in patients receiving this therapy [18]. Despite the tendency to HR decline during age-decades, the percentage of β-blocker predicted HR_{max} in middle-aged and older tends to be higher, which may suggest reduced in chronotropic reserve over the years in HF patients taking β-blockers [26].

Limitations of the study

This is a retrospective study using selected patients with HF referred to heart transplant of a single center. All patients underwent a single treadmill CPX to assess aerobic capacity. Even though data collection is not planned and statistical analysis is exploratory, all patients underwent testing on the same equipment and by the same team, which eliminates the differences in data collection and conduction. Considering the high morbidity and mortality in this population, the functional capacity decrease is probably higher over time, since decompensated patients or with excessive limitation cannot be evaluated by exercise testing. However, our results are applicable to clinical setting where peak VO_2 is an important prognostic parameter. Since present guidelines recommend cardiac rehabilitation for stable HF patients, excluding from analyses patients undergoing regular physical activity is a limitation. However, the inclusion of small number of patients undergoing regular physical activity could bias study results. Future studies focused in analyzing how age affects stable HF patients compliant to exercise/cardiac rehabilitation guidelines are thus necessary. The number of patients between 20–29 and ≥ 70 years was relatively small in comparison to the other groups, but the analysis showed that the sample size was sufficient to detect difference. Values of peak VO_2 are lower for women than men [27], however we did not analyze it separately due to the small number of women in the sample. Finally, the new equation for predicted peak VO_2 in HF patients undertaking β-blockers is based on treadmill only and cannot be extrapolated to upright cycle ergometer exercise test.

Clinical implication

The present finding shows an inverse and decreased association between aerobic capacity and aging in HF patients taking β-blockers. This association derives from patients who underwent a treadmill CPX. The finding suggests that a reduction in peak VO_2 higher than 0.9 mL/kg/min per decade may indicate a significant worsening in aerobic capacity and may not reflect the expected decline in aerobic function in HF patients. The similarity between measured and calculated peak VO_2 in all age-decades suggests that there is no functional physiologic reserve associated to aging in HF. Peak VO_2 is used for clinical decision-making regarding the need for cardiac transplantation in all age-decades. However, the cutoff value was determined in middle-aged HF patient predominantly. Therefore, we may speculate that age-decades difference in peak VO_2 could be an important factor for clinical decision-making in patients with HF.

Conclusions

In summary, this investigation suggests that age-adjusted peak VO_2 may describe more accurately the degree of aerobic capacity impairment in HF patients. This evidence should be considered when using the peak VO_2 for prognostic stratification and clinical decision-making in patients with HF.

Acknowledgements

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Conflict of interest: none declared

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