RESEARCH

Cardiovascular Therapeutics

Effects of Beta-Blockade on Exercise Performance at High Altitude: A Randomized, Placebo-Controlled Trial Comparing the Efficacy of Nebivolol versus Carvedilol in Healthy Subjects

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Keywords
Autonomic nervous system; Beta receptor; Adrenergic receptor blockade; Cardiopulmonary exercise test; Carvedilol; Clinica trial; Hypoxia; Nebivolol.

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This work was performed at the Capanna Regina Margherita, a shelter on top of Monte Rosa, Italian-Swiss Alps, at 4559 m above sea level, and at the S. Luca Hospital, IRCCS, Istituto Auxologico Italiano; Via Spagnoletto, 3. 20149, Milan, Italy. †Giulio Savia MD passed away on February 2009.

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SUMMARY

Aims: Exposure to high altitude (HA) hypoxia decreases exercise performance in healthy subjects. Although β-blockers are known to affect exercise capacity in normoxia, no data are available comparing selective and nonselective β-adrenergic blockade on exercise performance in healthy subjects acutely exposed to HA hypoxia. We compared the impact of nebivolol and carvedilol on exercise capacity in healthy subjects acutely exposed to HA hypobaric hypoxia. **Methods:** In this double-blind, placebo-controlled trial, 27 healthy untrained sea-level (SL) residents (15 males, age 38.3 ± 12.8 years) were randomized to placebo (n = 9), carvedilol 25 mg b.i.d. (n = 9), or nebivolol 5 mg o.d. (n = 9). Primary endpoints were measures of exercise performance evaluated by cardiopulmonary exercise testing at sea level without treatment, and after at least 3 weeks of treatment, both at SL and shortly after arrival at HA (4559 m). **Results:** HA hypoxia significantly decreased resting and peak oxygen saturation, peak workload, VO_2, and heart rate (HR) ($P < 0.01$). Changes from SL (no treatment) differed among treatments: (1) peak VO_2 was better preserved with nebivolol (–22.5%) than with carvedilol (–37.6%) ($P < 0.01$); (2) peak HR decreased with carvedilol (–43.9 ± 11.9 beats/min) more than with nebivolol (–24.8 ± 13.6 beats/min) ($P < 0.05$); (3) peak minute ventilation (VE) decreased with carvedilol (–9.3%) and increased with nebivolol (+15.2%) ($P = 0.053$). Only peak VE changes independently predicted changes in peak VO_2 at multivariate analysis ($R = 0.62$, $P < 0.01$). **Conclusions:** Exercise performance is better preserved with nebivolol than with carvedilol under acute exposure to HA hypoxia in healthy subjects.

Introduction

In a normoxic environment, treatment with β-blockers, either nonselective (such as propranolol [1]) or selective (such as bisoprolol [2], and metoprolol [3]) is known to decrease exercise capacity in healthy subjects. This is chiefly achieved by a reduction in peak heart rate (HR) and cardiac output (CO) [1,2] and in locomotor blood flow [3], both CO and blood flow to the exercising muscles being the main determinants of peak oxygen consumption (VO_2) in normoxia [4]. β-blockers may also impair exercise performance by affecting ventilation (VE) control, mitochondrial function, and lung gas diffusion. Although early data report no discernible changes of ventilatory control during exercise in subjects receiving propranolol [5], recent ones suggest that either β1-selective [2] or nonselective β-blockade [6] is associated with a decreased ventilatory response to exercise at any level of VO_2 and CO_2 production (VCO_2). Moreover, as the skeletal muscle predominantly expresses β2-adrenoreceptors (which mediate the mitochondrial activity in the exercising muscle), nonselective β-blockers may impair exercise capacity also by attenuating

mitochondrial adaptation to exercise [7]. Finally, β-blockers, especially nonselective ones, may, at least in the case of lung fluid increase, affect exercise performance also by impairing alveolar-capillary membrane diffusion: in fact, over 90% of lung β-adrenoreceptors belong to the β-2 type and are expressed on the alveolar surface, whereas only 10% belong to β-1 type and are expressed on the airways [8].

Acute exposure to high altitude (HA) hypoxia increases minute VE and pulmonary artery pressure (PAP). Moreover, it decreases peak exercise VO_2, CO, and HR. Such a decrease is proportional to the decrease of inspired O_2 pressure and arterial O_2 content [9,10].

To our knowledge, the effects of β-adrenoreceptor inhibition on hypoxic exercise were addressed in healthy subjects in very few investigations in which nonselective β-adrenoreceptor blockade was achieved by means of propranolol only [11–13]. Such studies report that acute exposure to hypoxia decreases exercise performance and that β-sympathetic inhibition by this compound does not further impair maximal O_2 uptake despite significantly decreasing peak HR and CO. Taken all together, these studies suggest that, unlike with normoxic exercise, peak HR and peak CO play a minor if any role in preserving exercise performance at HA. Thus other factors, such as changes in VE control, mitochondrial function, lung gas diffusion, and the consequent levels of blood oxygen saturation, might be involved in determining functional capacity during hypoxic exercise at HA. These observations, however, are based on the results obtained by the administration of the first-generation nonselective β-blocker propranolol, only. To our knowledge, no studies have compared the effects of vasodilatory β-blockers, characterized by different cardioselectivity and ancillary properties, on cardiorespiratory responses to HA hypoxic exercise in healthy subjects. In fact, the available evidence comparing the effects of vasodilatory β-adrenergic receptor blockers [14,15] like carvedilol and nebivolol on cardiorespiratory responses to exercise is limited to patients treated with these drugs for chronic heart failure (HF) [16]. The primary objective of this study was thus to fill this gap, and to compare, in healthy subjects, the effects of carvedilol (nonselective) and nebivolol (highly β1-selective) on cardiorespiratory responses to exercise performed under conditions of HA hypoxia.

Methods

Study Subjects

Out of 35 screened, 27 adult, nonsmoking healthy volunteers taking no medications were recruited by advertisement (15 males, 12 females, mean age 39.1 $\pm$ 12.7, range 26–62 years, body weight 66.4 $\pm$ 13.3 kg, BMI 22.0 $\pm$ 3.3 kg/m^2). They were all SL residents not engaged in regular endurance exercise training (Figure 1).

Study Design

On enrollment, at SL, subjects underwent general laboratory investigations, Doppler heart ultrasound, and cardiopulmonary exercise test (CPET), the latter performed for safety and familiarization with the procedure. Subjects were then double-blindly and randomly assigned to placebo (n = 9, one tablet b.i.d.), carvedilol (n = 9, one 25 mg tablet b.i.d.), or nebivolol (n = 9; one 5 mg tablet in the morning, one placebo tablet in the evening). Drugs were taken for 3 weeks before and throughout HA exposure. Three additional CPETs, each one preceded by systolic PAP measurements by echo-Doppler, were performed: under no treatment at SL (CPET 1), under treatment at SL (CPET 2), and under treatment within the first 2 days of HA exposure (CPET 3). As previously described [17,18], all subjects ascended in less than 30 h to the Regina Margherita hut (Monte Rosa, altitude 4559 m), where they did not perform any relevant physical activity before CPET 3. Occurrence and severity of acute mountain sickness was explored by computing in each subject the Lake Louise Score (LLS).

Study Outcomes

Primary endpoint was change in peak exercise VO_2 observed between SL under no treatment (CPET 1) and HA exposure under treatment (CPET 3). Additional endpoints were the changes, between the same conditions, in peak exercise VE; the absolute peak values of VO_2, VE, HR, and SpO_2, achieved in the various study conditions; PAPs values; and LLS at HA.

Cardiopulmonary Exercise Test

All CPETs were performed using the same cyclo-ergometer (Ergometrics 100, Ergoline, Bitz, Germany) and metabolic cart (Oxycon Mobile software v. 4.6, VIASYS Healthcare GmbH, Wurburg, Germany). The exercise protocol included 10 min of monitored sitting rest, followed by 3 min of unloaded pedaling and by 30 W load increments every 2 min up to exhaustion. Breath-by-breath VE, respiratory gases, one-lead ECG, and pulse oxymetry (SpO_2) were recorded throughout each test. Arterial blood pressure (BP) was measured with the auscultatory method by a mercury sphygmomanometer in duplicate at the end of the resting phase, at the end of each 30 W step, and at peak exercise.

CPETs were blindly and independently evaluated by two expert readers (D.M., P.A.). The anaerobic threshold was identified by the standard technique [19]. The VE/VCO_2 slope was calculated as the slope of the linear relationship between VE and VCO_2 measured up to the respiratory compensation point. The experimental protocol was approved by the Ethics Committee of the Istituto Auxologico Italiano. All subjects signed written informed consent.

Echocardiographic and Doppler Study

All echographic-Doppler examinations were performed by the same operators (M.R., G.B.) using a portable device (Vivid I, GE Ultrasound) according to the current guidelines [20].

Lake Louise Score (LLS)

The severity of acute mountain sickness was quantified by the LLS, based on response to a specific questionnaire [21].

Statistical Analysis

Normally distributed variables are reported as means $\pm$ SD. For all parameters during CPET, mean values were computed over 20 seconds. Differences among groups, changes over time within each group (time effect), and any interaction (differing trends over

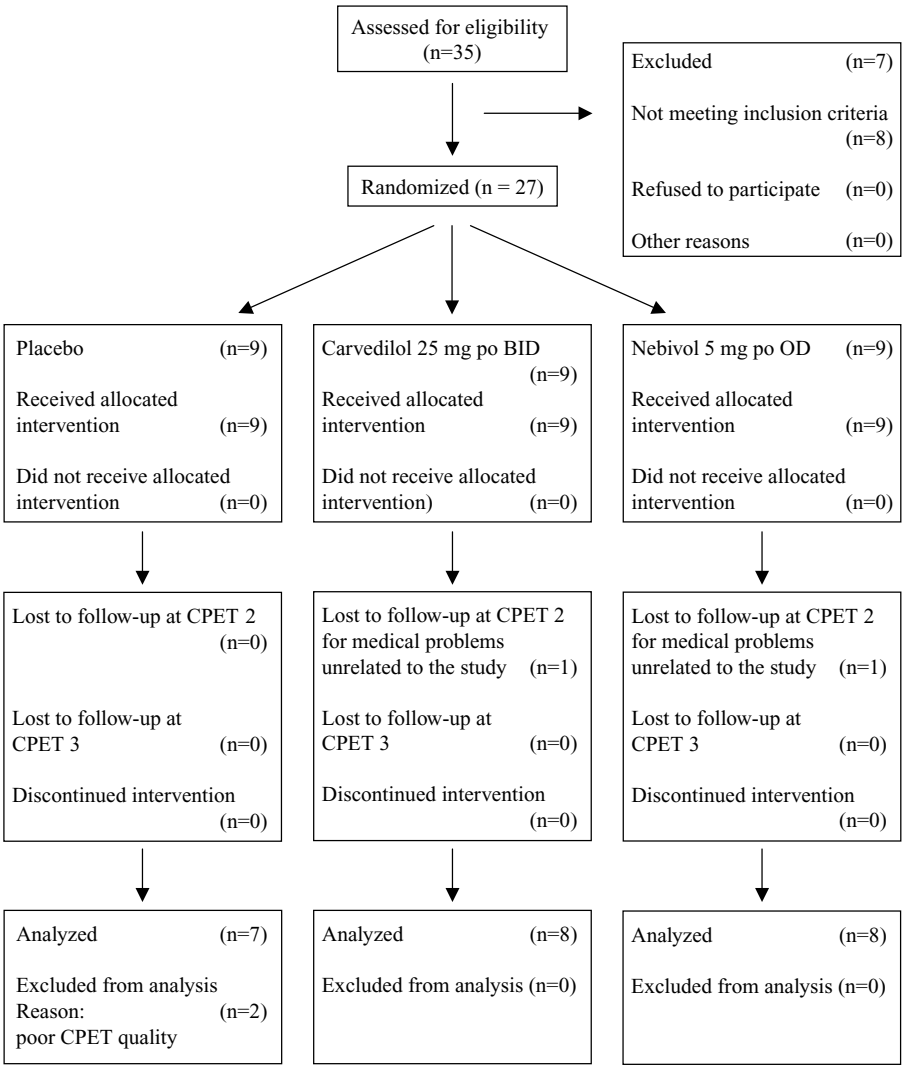

Figure 1 Flow of participants through each stage.

time among groups) were assessed by two-way repeated measures ANOVA. Post hoc analysis was performed with paired Student's *t*-test with Bonferroni correction for within-group comparisons; unpaired Student's *t*-test with Bonferroni correction was performed for between group comparisons. Spearman correlation was used to assess the relationship between peak VO_2 and other variables at altitude. Independent predictors of peak VO_2 were evaluated by multivariate regression analysis including all variables found to be statistically significant at univariate analysis. Data management and analysis was performed with SPSS version 13.0 (SPSS Inc, Chicago, IL, USA). A P level of < 0.05 was considered statistically significant.

Given the lack of previous data comparing the effects of non-selective and selective β-adrenergic blockers on cardiorespiratory responses to exercise in hypoxia, calculation of sample size was made by means of an "educated guess" of the clinically relevant difference between treatments in changes of peak VO_2 from baseline SL to altitude hypoxia (i.e., 5 ± 3 mL/kg/min). With a two-sided 5% significance level, a power of 90%, and equal sized groups, the requested sample size was 8.6 subjects per group. Such a size was also compatible with the demanding conditions of our study at HA.

Results

All subjects took the target doses of the investigational drugs over the entire duration of the study. CPETs and PAPs measurements of satisfactory quality were obtained in all but two female subjects randomized to placebo, who were therefore excluded from data analysis. CPET 2 in two other subjects (one male randomized to carvedilol, one female to nebivolol) was not performed because of incident medical problems unrelated to the study (Figure 1). No difference at baseline was observed among treatment groups with

respect to gender distribution, age, BP, HR, and anthropometric data as well as PAPs in subjects included in the final analysis. Table 1 summarizes peak CPET data of subjects performing all three tests.

- *CPET 1 (no treatment, SL)*. All subjects performed a maximal or near-maximal exercise as inferred by the peak respiratory exchange ratio (RER), with results in the normal range and with no differences among treatment groups.
- *CPET 2 (on treatment, SL)*. None of the treatments at SL had any effect on resting and peak VO_2 (Figure 2(A) upper panel), VE (Figure 2(A), mid panel), respiratory rate (RR) (Figure 2(A), lower panel), SpO_2 (Figure 3(A), upper panel), peak workload and peak O_2 pulse (Table 1). Both β-blockers induced a comparable reduction in resting HR (from 79.3 ± 10.8 to 67.9 ± 8.7 bpm for carvedilol, $P < 0.01$; from 82.8 ± 12.1 to 67.5 ± 12.9 bpm for nebivolol, $P < 0.01$) (changes from CPET 1 in Figure 3(A), mid panel). They also similarly decreased peak HR (from 173.4 ± 17.4 to 149.0 ± 17.3 bpm for carvedilol, $P < 0.001$; from 180.4 ± 9.3 to 166.8 ± 11.4 bpm for nebivolol, $P < 0.05$) (Figure 3(A), lower panel). There was no significant difference between carvedilol and nebivolol in HR peak as well as in HR reserve (peak exercise-resting HR) at SL. At SL, with carvedilol treatment resting systolic (S) BP and diastolic (D) BP changed from 118 ± 11 to 109 ± 10 mm Hg, $P < 0.05$, and from 78 ± 8 to 74 ± 11 mm Hg, NS, respectively. With nebivolol, SBP changed from 112 ± 10 to 105 ± 11 mm Hg, NS, and DBP from 75.9 ± 7.1 to 68.1 ± 8.0 mm Hg, $P = 0.01$. Both SBP and DBP at peak of exercise were not affected by any of the treatments (Table 1).

  Mean PAPs values did not differ among groups (20.6 ± 2.8, 16.8 ± 2.9, and 19.1 ± 3.9 mm Hg for placebo, carvedilol and nebivolol, respectively).
- *CPET 3 (on treatment, HA)*. Compared to CPET 1, exposure to hypoxia decreased resting SpO_2 (from 98.3 ± 0.8 to 87.3 ± 2.6% for placebo, from 98.4 ± 0.7 to 84.4 ± 4.4% for carvedilol, and from 98.9 ± 0.8 to 84.8 ± 2.7% for nebivolol), and peak exercise workload (Table 1) ($P < 0.001$ for all), with no difference among treatments. In all groups peak VO_2 significantly decreased, compared to both CPETs 1 and 2 ($P < 0.01$). Reductions in peak VO_2 between CPETs 1 and 3 differed among treatments (ANOVA, $P < 0.05$), being lower with nebivolol (–22.5 ± 8.0%) than with carvedilol (–37.6 ± 8.2%) ($P < 0.01$ for percent changes, $P < 0.05$ for absolute changes, Figure 2(B) upper panel). The change with placebo was –32.7 ± 11.0%. Resting VE similarly changed at HA in all groups between CPETs 1 and 3 (from 12.7 ± 3.0 to 14.7 ± 5.0 L/min with placebo; from 12.8 ± 5.1 to 13.5 ± 2.8 L/min with carvedilol; from 13.7 ± 2.1 to 13.7 ± 2.7 L/min with nebivolol). Unlike resting VE, peak VE changes between CPETs 1 and 3 differed among treatments ($P < 0.05$), being reduced (–9.3 ± 13.3%) with carvedilol, and increased (+15.2 ± 17.1%) with nebivolol ($P = 0.05$). No significant difference in peak VE changes was observed between placebo (0.7 ± 20.2%) and any of the β-blockers (Figure 2(B), mid panel). Resting RR at HA increased only in the placebo group ($P < 0.01$ vs. CPET 1, $P = 0.01$ vs. CPET 2). Peak RR increased at HA only with nebivolol ($P < 0.01$ vs. CPET 1), such a change

Table 1 Peak CPET data collected from subjects who performed all of the three tests. Data are presented as mean ± SD

		CPET 1			CPET 2			CPET 3		
		Placebo N = 7	Carvedilol N = 8	Nebivolol N = 8	Placebo N = 7	Carvedilol N = 8	Nebivolol N = 8	Placebo N = 7	Carvedilol N = 8	Nebivolol N = 8
PEAK	VO_2 (mL/kg/min)	33.9 ± 10.4	37.6 ± 4.3	38.0 ± 8.7	33.9 ± 9.4	36.2 ± 3.9	39.7 ± 8.6	22.9 ± 8.7[a,b]	24.0 ± 4.1[a,b]	28.8 ± 5.1[a,b]
	VCO2 (mL/kg/min)	39.4 ± 10.8	44.9 ± 5.7	46.2 ± 12.1	40.8 ± 11.7	45.2 ± 7.9	49.6 ± 10.2	26.2 ± 8.6[a,b]	28.4 ± 6.3[a,b]	35.6 ± 7.2[a,b]
	RER	1.17 ± 0.06	1.20 ± 0.05	1.20 ± 0.15	1.20 ± 0.06	1.24 ± 0.11	1.26 ± 0.10	1.16 ± 0.09	1.18 ± 0.09	1.23 ± 0.07
	VE (l/min)	93.9 ± 29.1	90.3 ±21.8	81.8 ± 24.4	95.6±29.9	89.6 ± 22.2	83.8 ± 25.2	90.3 ± 19.9	84.5 ± 27.4	92.0 ± 20.7
	RR (breaths/min)	37.8 ± 7.0	34.7 ± 4.1	38.2 ± 4.7	37.0 ± 5.2	35.9 ± 4.4	42.1 ± 8.1	41.3 ± 7.9	36.5 ± 6.4	45.9 ± 8.5[c]
	SpO2 (%)	96.9 ± 1.3	97.5 ± 1.8	98.1 ± 1.9	97.9 ± 0.7	97.3 ± 1.0	97.6 ± 1.4	79.3 ± 2.8[a,b]	75.8 ± 3.0[a,b]	75.9 ± 2.0[a,b]
	HR (beats/min)	161.0 ± 13.8	173.4 ± 17.4	180.4 ± 9.3	163.9 ± 12.9	149.0 ±17.3[a]	166.8 ± 11.4[e]	142.1 ± 21.4[c,d]	128.6 ± 22.0[a,d]	153.6± 15.5[a]
	%HR predicted	92.9 ± 6.4	94.9 ±7.7	95.9 ±5.2	95.0 ± 4.8	82.4 ± 11.0[@]	89.2 ± 8.6	82.0 ± 7.6	70.6 ± 9.7[°]	82.0 ± 7.8[^]
	O2 pulse (mL/min)	15.5 ± 4.9	14.8 ± 4.0	13.0 ± 4.7	15.3 ± 4.5	16.4 ± 3.8	14.4 ± 4.5	11.7 ± 3.3[a,b]	12.8 ± 3.8[b,c]	11.5 ± 3.8[c]
	SBP (mm Hg)	199.0 ± 24.0	183.2 ± 32.0	177.0 ± 15.0	185.7 ± 23.0	175.3 ± 31.6	163.6 ± 24.3	182.9 ± 22.9[f]	152.3 ± 17.4[c,d]	158.8 ± 18.9
	DBP (mm Hg)	97.4 ± 10.8	85. 6± 7.3	87.8 ± 4.5	94.4 ± 12.4	83.8 ± 14.1	79.9 ± 9.2	99.3 ±8.4[c,d]	81.8 ± 10.5	83.8 ± 7.0

RER = respiratory exchange ratio; VE, minute ventilation; RR, respiratory rate; SpO_2, oxygen saturation; HR, heart rate; O_2 pulse, oxygen pulse; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a] $P \leq 0.001$ versus CPET 1, [b] $P \leq 0.001$ versus CPET 2, [c] $P \leq 0.01$ versus CPET 1, [d] $P \leq 0.01$ versus CPET 2, [e] $P < 0.05$ versus CPET 1, [f] $P < 0.05$ placebo versus carvedilol in CPET 3.
[@] $P < 0.05$ placebo versus carvedilol in CPET 2, [°] $P = 0.05$ placebo versus carvedilol in CPET3, [^] $P < 0.05$ nebivolol versus carvedilol CPET3.

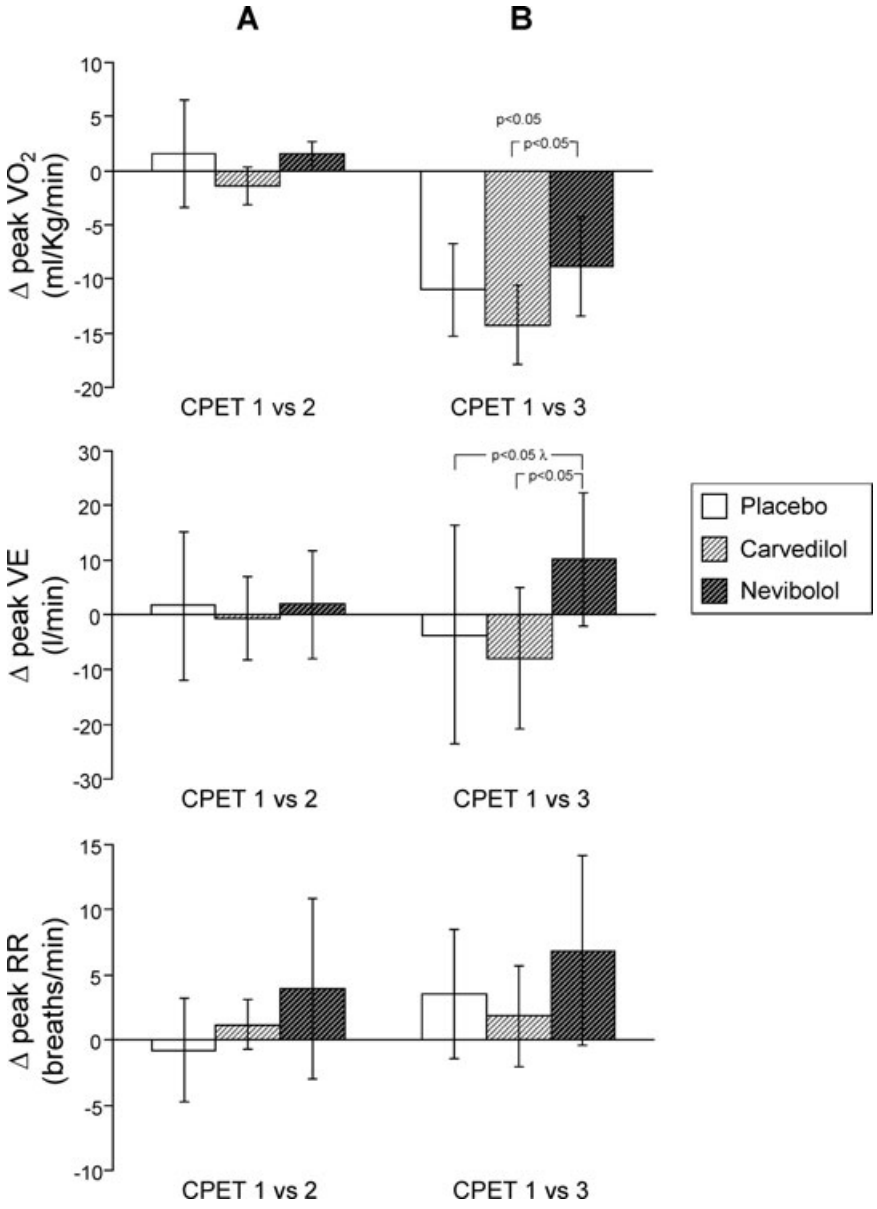

Figure 2 Upper panel: delta VO_2 at peak of exercise CPET 1 versus 2 (**A**), CPET 1 versus 3 (**B**). Middle panel: delta VE at peak of exercise CPET 1 versus 2 (**A**), CPET 1 versus 3 (**B**). Lower panel: delta RR at peak of exercise CPET 1 versus 2 (**A**), CPET 1 versus 3 (**B**). Data are presented as mean ± SD.

being marginally greater than that with carvedilol ($P = 0.07$) (Figure 2(B), lower panel). Peak SpO_2 significantly decreased in CPET 3 compared to CPETs 1 and 2 in all groups, although such a decrease tended to be more pronounced with carvedilol compared to placebo ($P = 0.05$). Changes in peak SpO_2 between CPETs 1 and 3 differed among treatments ($P < 0.05$), being more pronounced with carvedilol (–22.2 ± 3.7%) than with placebo (–17.6 ± 1.9%, $P < 0.05$). In the nebivolol group it was –21.2 ± 3.5% (Figure 3(B), upper panel).

The reduction in resting HR observed at SL with carvedilol persisted at HA, while it was less pronounced with nebivolol ($P <$ 0.01 CPET 2 vs. CPET 3). The difference between carvedilol and nebivolol in HR reserve at HA was not statistically significant being 64.0 ± 14.5 bpm for placebo, 55.0 ± 12.4 bpm for carvedilol and 71.7 ± 16.0 bpm for nebivolol. Changes in peak HR between CPETs 1 and 3 differed among treatments ($P < 0.01$), being significantly higher with carvedilol (–43.9 ± 11.9 beats/min) than with both nebivolol (–24.8 ± 13.6 beats/min) ($P < 0.05$) and placebo (–18.9 ± 14.9 beats/min) ($P < 0.01$). No significant difference was observed between placebo and nebivolol (Figure 3(B), lower panel). At CPET 3, HR at peak exercise, reported as percentage of predicted, was lower with carvedilol compared to nebivolol (Table 1).

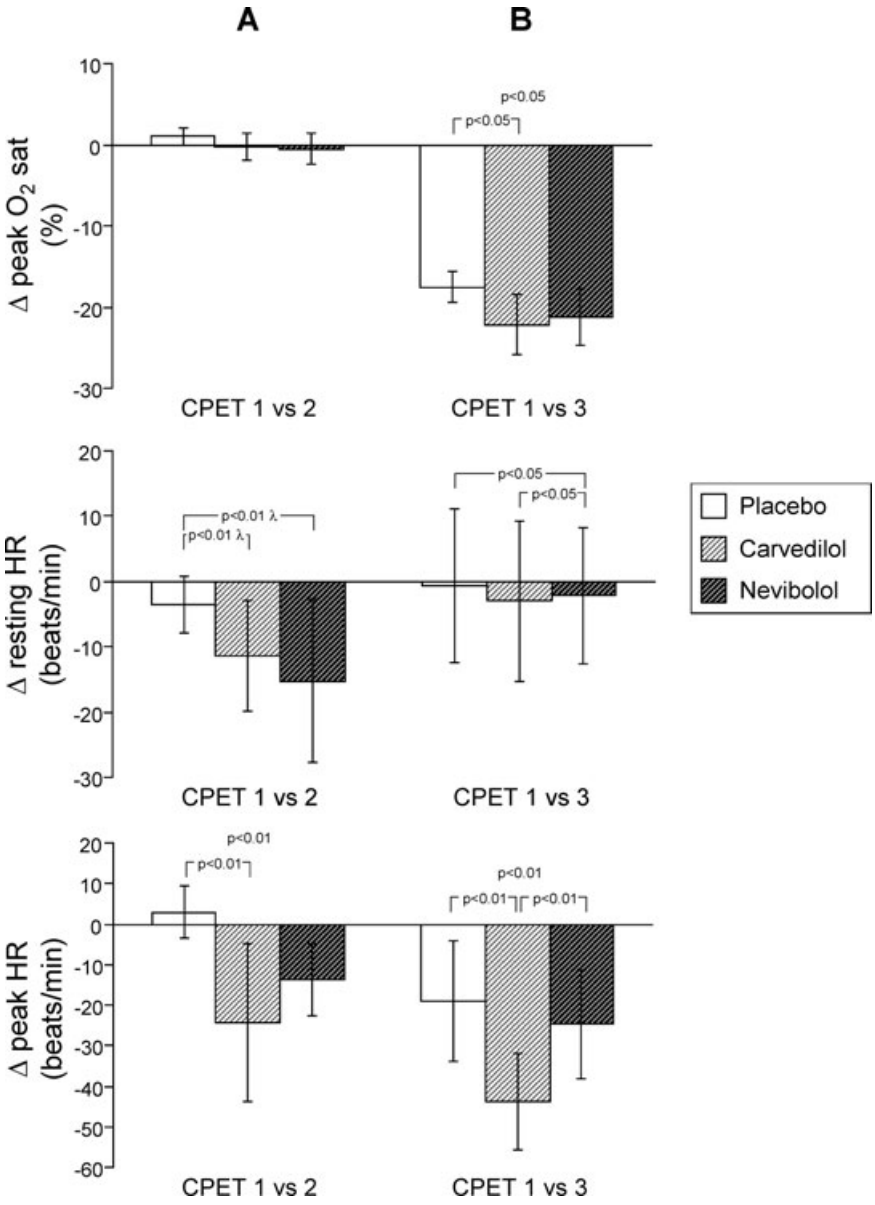

Figure 3. Upper panel: delta sat O_2 at peak of exercise CPET 1 versus 2 (**A**), CPET 1 versus 3 (**B**). Middle panel: delta resting HR in CPET 1 versus 2 (**A**), CPET 1 versus 3 (**B**). Lower panel: delta HR at peak of exercise CPET 1 versus 2 (**A**), CPET 1 versus 3 (**B**). Data are presented as mean ± SD.

Resting SBP decreased with carvedilol at SL and did not further change at HA (from 108.9 ± 10.5 to 111.2 ± 7.6 mm Hg). Peak SBP, unaffected by carvedilol at SL, decreased at HA ($P < 0.01$ vs. both CPETs 1 and 2), such a decrease being larger than that with placebo ($P < 0.05$). In the nebivolol and in the placebo group both baseline and peak SBP did not change at HA.

The VE/VCO_2 slope as well as the VE/VO_2 ratio at the anaerobic threshold (Table 2) increased at HA ($P < 0.001$) with no treatment effect as a result of an increase in VE.

The decrease in peak VO_2 observed at HA correlated in univariate analysis with the decrease in peak VE (r = 0.60, $P < 0.01$), peak RR (r = 0.51, $P < 0.01$) and peak HR (r = 0.52, $P < 0.01$) and with the increase in peak O_2 pulse (r = – 0.62, $P = 0.001$). At multivariate regression analysis, the variation in peak VE (standardized beta = 0.619, $P = 0.001$) was the only independent predictor of changes in peak VO_2 observed from CPET 1 to CPET 3.

Mean PAPs increased at HA ($P < 0.01$) with no difference among groups (29.7 ± 4.2 for placebo, 27.4 ± 4.6 mm Hg for carvedilol, and 29.3 ± 4.6 mm Hg for nebivolol).

The LLS was equally low in all groups, being 1.6 ± 1.81 on placebo, 3.6 ± 1.81 on carvedilol, and 2.7 ± 2.06 on nebivolol, with a nonsignificant tendency to be worse in subjects randomized to β-blockade.

Table 2 *VE/VCO2* slope values, *VE/VCO2* and VE/VO_2 ratios at the AT in the three experimental conditions by treatment. Data are presented as mean ± SD

	CPET 1			CPET 2			CPET 3			*P* (time)
	Placebo	Carvedilol	Nebivolol	Placebo	Carvedilol	Nebivolol	Placebo	Carvedilol	Nebivolol	
VE/VCO2 slope	26.6 ± 2.5	24.7 ± 2.8	24.1 ± 3.8	25.3 ± 1.9	23.4 ± 3.8	21.5 ± 2.9	37.6 ± 4.1[a,b]	35.5 ± 4.9[a,b]	34.9 ± 4.7[a,b]	<0.001
VE/VCO2 ratio at AT	30.0 ± 3.5	29.0 ± 2.6	29.0 ± 5.4	30.1 ± 3.0	29.0 ± 4.7	29.5 ± 5.1	43.0 ± 4.21[a,b]	40.8 ± 4.3[a,b]	40.6 ± 6.4[a,b]	<0.001
VE/VO_2 ratio at AT	27.7 ± 3.7	27.4 ± 2.5	28.4 ± 6.6	28.7 ± 3.4	27.0 ± 2.9	26.5 ± 5.0	41.3 ± 5.4[a,b]	38.1 ± 4.1[a,b]	39.8 ± 6.5[a,b]	<0.001

AT, anaerobic threshold; CPET, cardiopulmonary exercise test.
[a] $P \leq 0.001$ versus CPET 1, [b] $P \leq 0.001$ versus CPET 2. *P* nonsignificant for time * treatment model.

Discussion

Under acute exposure to HA hypoxia exercise performance is better preserved with nebivolol than with carvedilol, despite similarly increased PAPs and comparable LLS. This represents novel information, our study being the first to compare the effects of different vasodilatory β-blockers on cardiopulmonary exercise testing at an altitude above 4500 m in healthy subjects.

Several studies have demonstrated that exposure to altitude hypoxia decreases peak VO_2 proportionally to the decrease of inspired O_2 pressure and arterial O_2 content [9–13]. Acute exposure to altitude hypoxia stimulates the sympathetic nervous system which, in turn, elicits an increase in resting BP, HR [22], and CO [23,24] and in pulmonary vascular resistances [25]. Most [11,26] but not all of the studies [27] also reported a decrease in peak exercise HR and peak CO [11]. Although tachycardia has been hypothesized as an important mechanism to preserve peak VO_2 at HA as in normoxic environment [12], some studies have demonstrated that maximal HR and CO are not the main determinants of peak VO_2 at HA [11,12,28]. In a few investigations peak VO_2 decreased in healthy subjects exercising in hypoxia but such a change was not affected by nonselective β-adrenergic blockade with propranolol [11–13] despite a significant decrease in peak HR and CO. These results suggest that other factors, such as changes in VE control, pulmonary pressure during exercise, peripheral blood flow, mitochondrial function, lung gas diffusion, and the consequent levels of blood oxygen saturation, affecting O_2 delivery and O_2 availability at the tissue level, might be involved in determining peak VO_2 during hypoxic exercise at HA [28,29].

The results of our study support this suggestion. Since at HA muscle metabolism is even more dependent on O_2 availability than at SL, exercise capacity might have been affected by the amount of O_2 made available to the mitochondria [29–31]. The greater the VE during exercise, the greater the oxygen flow to the mitochondria and the VO_2. When VE becomes unable to maintain arterial HbO_2 saturation, reducing the O_2 flow to the mitochondria, subjects have to stop exercising. Indeed, at multivariate analysis, the reduction in peak VO_2 at HA was independently predicted only by changes in peak VE. Furthermore, despite comparable resting VE among groups in the three testing conditions, in the treatment group with best preserved exercise capacity under hypoxia the best exercise VE was observed. Finally, as the skeletal muscle predominantly expresses β2-adrenoreceptors and as such receptors mediate both the mitochondrial biogenesis and activity triggered by exercise, a nonselective β-blocker like carvedilol might have affected exercise capacity also by attenuating such mitochondrial adaptations [7].

Exercise ventilatory inefficiency, reflected by an increased VE/VCO_2 slope, is a typical manifestation of HF, carrying prognostic value [32] independently from VO_2, i.e., from CO reduction. Several interventions, including β-blockade, may improve the VE/VCO_2 slope in HF patients, in parallel with clinical benefits [33–35], although increases in maximal exercise performance and VO_2 are not constantly demonstrated. It has been suggested that the beneficial effect of β-blockade may also depend on an improvement in ventilatory efficiency during exercise [36–38], although a specific comparison between the effects of different β-blockers in this regard is not available. However, whereas a

decrease of exercise-induced hyperventilation can be beneficial in normoxia, it may be counterproductive when exercising in hypoxia [6,29]. Although at HA we observed a similar increase in ventilatory inefficiency among treatments, nebivolol-treated subjects showed a better preserved exercise performance (higher peak VO_2), which was associated with higher peak VE.

Our data also show, however, that carvedilol administration at HA was associated with a greater decrease in peak HR compared to both nebivolol and placebo. In univariate analysis, the higher peak VO_2 observed with nebivolol than with carvedilol was associated with higher peak HR during exercise under HA hypoxia, the relation between peak VO_2 and peak HR being however no longer significant at multivariate analysis. This emphasizes importance of the observed association between better exercise performance and achievement of a higher peak exercise VE in subjects receiving nebivolol. Moreover, the differences in exercise performance among groups were neither related to differences in mountain sickness symptoms nor to differences in PAPs. It remains to be determined, however, whether a lower CO at peak of exercise, as inferable from a lower peak HR, might be the cause of a lower VE, VE being flow dependent during exercise [2].

Due to the unique experimental setting, the results of our study may not apply to conditions characterized by longer HA permanence. Experiments were performed in a laboratory inside Capanna Regina Margherita at controlled temperature, a condition not fully representative of outfield at HA, where low temperature, dry air, and UV exposure may further influence exercise capacity. Moreover, to properly assess the different effects of carvedilol and nebivolol on peak exercise HR, administration of different drug doses in different subjects might have been needed. However, in our study we used standard clinical doses of both β-blockers, because, for logistic difficulties, it was not possible in our experimental conditions to individually titrate drug dosages. Thus, the degree of β-adrenergic receptor blockade might have been different in each subject and between drugs. Indeed peak exercise HR was different at HA altitude between carvedilol and nebivolol. Finally, because carvedilol and nebivolol have properties other than beta adrenergic receptor blockade, such as alpha-blocking action for carvedilol and an NO-releasing action for nebivolol, some of the reported effects of these drugs at HA might be related to these specific properties.

In conclusion, our observations show that functional differences during exercise occur under conditions of HA hypoxemia in healthy subjects treated with carvedilol as compared to nebivolol. Our data might also be clinically relevant in selecting the type of β-blocker to be used in cardiac patients, especially if traveling to altitude. Based on our data, nebivolol may be preferred to carvedilol whenever hybobaric hypoxia exposure is expected. This suggestion may also apply at SL, in the case of significant lung diffusion impairment [37,39] secondary to interstitial edema, when preserving β-2 mediated alveolar fluid clearance is crucially important [39].

Conflict of Interest

The authors have no conflict of interest.

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