Beta-adrenergic Receptor Blockade Effects on Cardio-pulmonary Exercise Testing

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Research Article

Keywords: Bisoprolol, exercise aerobic capacity, chronotropic response

Posted Date: December 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1124846/v1

Version of Record: A version of this preprint was published at Sports Medicine-Open on December 20th, 2022. See the published version at https://doi.org/10.1186/s40798-022-00537-5.

Abstract

Background: Beta-blockers are increasingly prescribed while the effects of beta-adrenergic receptor blockade on cardio-pulmonary exercise test (CPET) derived parameters remain under-studied.

Methods: 21 young healthy adults repeated 3 CPET at an interval of 7 days at the same time of the day. The tests were performed 3 hours after a random, double blind, cross-over single dose intake of placebo, 2.5 mg bisoprolol or 5 mg bisoprolol. Gaz exchange, heart rate and blood pressure were measured at rest and during cyclo-ergometric CPET.

Results: Maximal workload and VO_{2max} were unaffected by the treatment, with maximal respiratory exchange ratio > 1.15 in all tests. A beta-blocker dose-dependent effect reduced resting and maximal blood pressure and heart rate and the chronotropic response to exercise, evaluated by the heart rate/VO_2 slope (placebo: 2,9 ± 0,4 beat/ml/kg; 2,5 mg bisoprolol: 2,4 ± 0,5 beat/ml/kg; 5 mg bisoprolol: 2,3 ± 0,4 beat/ml/kg, $p<0.001$). Ventilation efficiency measured by the VE/VCO_2 slope and the ventilatory equivalent for CO_2 at the ventilatory threshold were not affected by beta1-receptor blockade. Post-exercise chronotropic recovery measured after 1 min was enhanced under beta1-blocker (placebo: 26 ± 7 bpm; 2,5 mg bisoprolol: 32 ± 6 bpm; 5 mg bisoprolol: 33 ± 6 bpm, $p<0.01$).

Conclusion: The present results suggest that a single dose of bisoprolol does not affect metabolism, respiratory response and exercise capacity. However, beta-adrenergic blockade dose-dependently reduced exercise hemodynamic response by lowering the pressure and chronotropic responses.

Introduction

Beta-blockers are a class of pharmacological competitive antagonists of the adrenergic beta receptors of the sympathetic nervous system allowing for a smoothened endogenous catecholamines response. Beta-blockers are frequently prescribed in coronary artery disease (CAD), congestive heart failure (CHF) [1], cardiac arrhythmias, congenital heart disease (CHD), but also for essential tremor[2, 3].

Cardio-pulmonary exercise testing (CPET) in chronic heart disease or in apparently healthy subject with unexplained dyspnea is increasingly promoted [4]. CPET provides a quantitative and qualitative characterization of the oxygen transport system involving the pulmonary, cardiovascular and muscular oxidative systems. It allows direct measurement of variables related to survival and adverse events (Class1-evidence A) (aerobic capacity (VO_2max), minute ventilation/carbon dioxide output slope (VE/VCO_2) and exercise oscillatory ventilation (EOV)). Notwithstanding, CPET also assess important secondary variables including oxygen pulse, systolic blood pressure (BP) or the heart rate vs oxygen uptake slope (HR/VO_2). These variables are additional prognostic predictors of the risk for future adverse events in pathological conditions and in apparently healthy individuals. The chronotropic response to exercise is also widely used for exercise intensity quantification in the context of rehabilitation[5, 6].

Beta-blockers intake has unequivocally been demonstrated to produce a 20 - 30% reduction in resting and maximal HR in healthy subjects[7–10]. A compensatory increase in stroke volume through intrinsic cardiac regulation however prevents a cardiac output alteration[11–13]. An increase in arteriovenous oxygen content difference ($CavO_2$) has also been suggested to prevent a large decrease in VO_2 during exercise [11–13]. While previous studies in healthy individuals showed trivial influence of beta-blocker intake on VO_2max and on the ventilatory threshold (VT) level, controversial effects were described on CPET secondary outcome variables[9, 13–15]. The previous conflicting results in heathy subjects may be attributed to the beta-blocker agent, type, posology, intake duration, unknown pathology, fitness level or additional confounding factors.

We investigated the effects an acute administration of a selective beta-blocker (bisoprolol) in normal young subjects on secondary outcome CPET variables in a prospective double-blind cross-over observational study. We believed this is of importance since an underestimation of bisoprolol effects on CPET may lead to an inappropriate interpretation and might lead to misleading exercise prescription.

Methods

Twenty-six healthy volunteered subjects participate to the study, but five of them presenting baseline resting HR under 60 bpm or a mean BP less than 70 mmHg were refuted from the study to avoid excessive bradycardia or hypotension. The study was approved by the local Institutional Ethics Committee (P2019/504) and all participants gave their written consent. All volunteers were nonsmokers and declared themselves in good health. Their clinical examinations were unremarkable and none of them took any drugs. Their electrocardiograms were normal. Finally, twenty-one subjects were allowed to participate in the study (10 women/11 men, 23 ± 2 years, 175 ± 8 cm, weight: 70 ± 9 kg).

Participants underwent a baseline clinical examination followed by a CPET on a cyclo-ergometer on 3 occasions with minimum 5 to maximum 7 days of rest between each trial. All three tests were performed at the same time of the day. Subjects were asked to maintain their daily activity levels, maintain their habitual diet and avoid energy drinks before testing.

A randomized, double-blind, crossover, placebo-controlled design was conducted, with subjects receiving a sequence of 2,5 mg bisoprolol or 5 mg bisoprolol or placebo, strictly 3 hours before de beginning of the tests[16]. Hémifumarate of bisoprolol has been chosen for his competitive antagonist characteristics conferring a high degree of cardio-selective -adrenergic receptor blocking with maximal effect 3 hours after intake[16]. 2.5mg is the initial clinical lower dose prescribed. 5mg was also tested in our study to assess the effect of a stronger -adrenergic inhibition on CPET.

Clinical examination.

Medical history, blood pressure (sphygmomanometry) (Medisoft Ergoline 4M, Hasselt, Belgium), heart rate (electrocardiographic lead) (Strässle & CO DT100, Albstadt, Germany) and oxygen saturation (SpO_2,

pulse oximetry) (Nonin 8000S, Tilburg, The Netherlands) were monitored.

Cardio-pulmonary Exercise Testing

The cycle ergometer CPET were performed as previously reported with a warm-up of 3 minutes set at 60W for men and 30W for women and workload increased by 30 W/min for men and 20 W/min for women until volitional fatigue[17]. The recovery period consisted in pedaling at 60 round per minute at 60 W for men and 30 W for women for 2 minutes. BP was measured automatically by an electronic sphygmomanometer (Ergoselect 200, Ergoline, Bitz, Germany) at each level of exercise, HR was continuously monitored with a 12-lead electrocardiogram and oxygen saturation (SpO_2, pulse oximetry) were continuously monitored.

During the 3 exercise testing sessions, breath by breath data of VE, VO_2 and VCO_2 were collected and analyzed every 5 seconds using a metabolic recording system (HypAir, Medisoft, Dinant, Belgium) calibrated with room air and standardized gas before each test. VO_2max was considered to be achieved when two of the following criteria were met: an increase in VO_2 of less than 100 ml/min with a further increase in workload, a respiratory exchange ratio (RER) greater than 1.15 or age-predicted maximal HR. The ventilatory threshold 1 (VT1) was measured by the V-slope method. The V_E/VCO_2 ratio was measured at the VT1[18]. The VO_2/workload slope and the HR/VO_2 slope were calculated from rest to maximal exercise. The VE/VCO_2 slope was calculated from rest to the respiratory compensation point as recommended[18]. Maximal voluntary ventilation was calculated as forced expiratory volume in one second (FEV1) multiplied by 40 and was considered as the limit of the ventilatory reserve[18]. Maximal O_2 pulse was found by dividing the VO_2max by maximal HR. Chronotropic index (CI) was calculated as (HRmax – HRrest)/((220-age)-HRrest)[19]. HR recovery (HRR) was the difference between maximal HR and HR measured after one and two minutes of recovery.

Statistics

Results are presented as mean ± SD. The statistical analysis consisted of a repeated measured analysis of variance, with modified t tests (Bonferroni) to compare different -blockers doses when the F-ratio of the analysis of variance reached a $P<0.05$ critical value. Statistical analysis was performed using Statistica (Statistica version 10).

Results

Rest

The effect of placebo or different bisoprolol doses intake on resting hemodynamic parameters are shown in Table 1. 2.5mg bisoprolol intake decreased resting HR by 14 bpm and SBP by 11 mmHg with no statistical influence on DBP, while 5mg bisoprolol reduced resting HR by 20 bpm, SBP by 18 mmHg and DBP by 8 mmHg. SpO_2 remained unaffected.

Table 1
Baseline characteristics.

	Placebo	2,5mg	5 mg
Age (year)	*23 ± 2*		
Height (cm)	*175 ± 8*		
Weight (kg)	*70 ± 9*		
BMI (kg/m²)	*22,8 ± 2,4*		
HR (b/min)	*87 ± 11*	*73 ± 10****	*67 ± 8***$*
SBP (mmHg)	*115 ± 13*	*104 ± 15 ***	*97 ± 12***$*
DBP (mmHg)	*71 ± 10*	*66 ± 6*	*63 ± 9***
SpO_2 (%)	*99 ± 1*	*99 ± 1*	*99 ± 1*

BMI: Body Mass Index, HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SpO_2: Pulsed oxygen saturation.

**p<0.01, ***p<0.001 comparison bisoprolol vs placebo; $ p<0.05 comparison 2,5 vs 5 mg bisoprolol

Ventilatory threshold

As exposed in Table 2, the ventilatory threshold level did not differ between the three pharmacological conditions with unchanged workload, absolute VO_2 (L/min) or VO_2 relative to VO_2max (% VO_2max) and the ventilatory equivalent for CO_2 (VE/VCO_2 ratio). However, the intake of bisoprolol dose-dependently reduced HR, SBP and DBP at this submaximal exercise level.

Table 2
Cardio-pulmonary exercise variables after bisoprolol vs placebo.

	Placebo	**2,5mg**	**5 mg**
Ventilatory Threshold 1			
HR (b/min)	143 ± 17	119 ± 12***	111 ± 12***$$
SBP (mmHg)	151 ± 16	130 ± 21 ***	117 ± 14 ***$
DBP (mmHg)	73 ± 10	68 ± 8	64 ± 8**
VO_2 (L/min)	1,8 ± 0,5	1,7 ± 0,4	1,6 ± 0,4
$VE/VCO_{2\ ratio}$	28 ± 3	28 ± 4	28 ± 4
Maximal exercise			
RER	1,29 ± 0,09	1,27 ± 0,07	1,30 ± 0,08
HR (b/min)	183 ± 8	160 ± 11***	151 ± 12***$$
Chronotropic Index	0,87 ± 0,06	0,71 ± 0,08***	0,65 ± 0,08***$$
SBP (mmHg)	196 ± 20	179 ± 23 **	160 ± 22 ***$$
DBP (mmHg)	81 ± 13	78 ± 14	73 ± 11*
Workload (Watt)	246 ± 48	245 ± 52	238 ± 42
VO_2 (L/min)	2,7 ± 0,5	2,7 ± 0,5	2,6 ± 0,5
VO_2 (mL/kg/min)	39 ± 5	39 ± 5	37 ± 5
$O_{2\ Pulse}$ (mL/b/min)	15,0 ± 3,2	17,1 ± 3,7*	17,3 ± 3,7*
VE (L/min)	114 ± 16	105 ± 16	104 ± 21
VE/MVV (%)	78 ± 9	74 ± 9	74 ± 12
SpO_2 (%)	*98 ± 2*	*98 ± 2*	*98 ± 2*
Slopes			
VE/VCO_2	27 ± 3	26 ± 3	26 ± 4

RER: Respiratory Exchange Ratio; HR : Heart Rate ; SBP : Systolic Blood Pressure; DBP: Diastolic Blood Pressure; VO_2: Oxygen consumption; VE: Ventilation; MVV: Maximal Voluntary Ventilation; HRR: Heart Rate Recovery.

* p<0.05, **p<0.01, ***p<0.001 both measurements vs placebo; $$ p<0.01 comparison 2,5 vs 5 mg bisoprolol

	Placebo	2,5mg	5 mg
HR/VO_2 (b/mL/kg)	2,9 ± 0,4	2,4 ± 0,5***	2,3 ± 0,4***
VO_2/W (mL/min/watt)	10 ± 1	10 ± 1	10 ± 1
Recovery			
HRR 1' (b/min)	26 ± 7	32 ± 6**	33 ± 6**
HRR 2' (b/min)	45 ± 7	48 ± 6	46 ± 7
RER: Respiratory Exchange Ratio; HR : Heart Rate ; SBP : Systolic Blood Pressure; DBP: Diastolic Blood Pressure; VO_2: Oxygen consumption; VE: Ventilation; MVV: Maximal Voluntary Ventilation; HRR: Heart Rate Recovery.			
* p<0.05, **p<0.01, ***p<0.001 both measurements vs placebo; $^{\$\$}$ p<0.01 comparison 2,5 vs 5 mg bisoprolol			

Maximal exercise

All exercise tests reached a metabolic maximality with end exercise RER systematically exceeding 1,15 (Table 2).

Maximal SBP, DBP and HR were decreased by 1-receptor blockade as compared to the placebo condition with majorated effect after 5 mg of bisoprolol compared to 2,5 mg (Fig. 1). HR/VO_2 slope and CI also decreased with the use of bisoprolol (2,5 and 5 mg) (Fig. 2 and 3). 2,5mg or 5mg bisoprolol increased maximal O_2 pulse (Table 2). Bisoprolol had no effect on maximal VE, workload, VO_2, SpO_2, and on the VE/VCO_2 or VO_2/W slopes.

End exercise recovery

1-blockade had no effect on gas exchange or ventilatory parameters during the recovery period (not shown). However, enhanced chronotropic recovery was observable with the use of bisoprolol (2,5 and 5 mg) within the first minute post-exercise but returned to normal at 2 min of recovery (Table 2).

Discussion

-blocker is a commonly used drug class whose influence remains under-considered in the interpretation of CPET. In the present study, acute inhibition of cardio-specific -adrenoreceptors had no effect on aerobic capacity or ventilatory response during exercise in healthy subjects. Preserved VO_2max was possible since the -blockers negative chronotropic and inotropic effects, assessed by lower resting and maximal HR and systolic BP with a 18% reduction in the HR/VO_2 slope, was counter-balanced by increased O_2 pulse probably through intrinsic cardiac and/or peripheral adaptative mechanisms. The

present result also revealed a 23% increase in the early chronotropic recovery within the first end-exercise minute.

Hemodynamic response to exercise

As expected, smoothened chronotropic and SBP responses to exercise were observed after pharmacological blockade of 1-adrenergic receptors. This observation has consistently been reported when cardiac adrenergic stimulation is blocked. With smooth muscle cells in the peripheral vascular media rich in 2 and α1-receptors instead of 1-receptors, the SBP decrease could be attributed to a negative inotropic cardiac effect.

Aerobic capacity

Previous studies reported either an unchanged or a 5 -7% VO_2max alteration after 1 or 2 weeks of -blocker intake [14, 15]. No altered VO_2max was observed in the present study in accordance with other previous studies on healthy young subjects[20, 21], aortic aneurysm[12] or hypertension patient[22]. This general observation made in healthy or pathological conditions suggests that the negative inotropic and chronotropic effects of -blocker promote multiple compensatory dependent mechanisms, such as mechanical/intrinsic cardiac adaptation and/or according to Fick's principle enhanced O_2 extraction in exercising muscles to name a few.

Chronotropic response to exercise

HR response to exercise is multi-factorial and depends on autonomic outflows (central command), reflex responses to skeletal muscle activation (exercise pressor reflex), hemodynamic changes, sinus node function, parasympathetic withdrawal, and β-adrenoceptor responsiveness. At the onset of exercise, chronotropic response mainly depends on para-sympathetic drive reduction. Further exercising allows the catecholamines to stimulate nodal cells and cardiomyocytes 1-receptors which will in turn modify the membrane permeability to K^+ and Ca^{++} resulting in increased cardiomyocytes excitability (positive bathmotropic effect), increased frequency of cellular excitation (positive chronotropic effect), increased impulse conduction towards the contractile myocytes (positive dromotropic effect) and increased Ca++ pumping into the sarcoplasmic reticulum for relaxation (positive lusitropic effect). Pharmacological inhibition of the 1 receptors will therefore attenuate all those stimulating adrenergic response during exercise[19].

Chronotropic index

Chronotropic incompetence, defined as the inability of the heart rate to increase during exercise is diagnosed using the chronotropic index, the HR/VO2 slope or when the measured maximal HR does not

reach 80% of the predicted maximal HR[19, 23].

Numerous studies showed an altered chronotropic index under -blockers[23–25]. However, the chronotropic index has also been shown to be inversely correlated to mortality in healthy men [26], congenital heart disease[27] but also in HF treated with -blockers where a cutoff value below 0.6 showed a net increase in mortality (+17%) at 24 months[28]. As illustrated in Figure 3, 7 healthy subjects out of 21 (33%) showed a chronotropic index < 0.6 after 5mg of bisoprolol intake. Hence in some circumstances, an altered chronotropic index might be more affected by the treatment instead than the disease for which the treatment was recently initiated.

HR/VO_2 slope

The HR vs metabolism relationship, namely the HR/VO_2 or HR/MET slopes, is also used to evaluate the chronotropic response to exercise and has the advantage to be independent of the subject's physical fitness. Normal values of HR/VO_2 are between 3 to 4 b/ml/kg in healthy sedentary subjects[18] and is known to be influenced by age, sex, physical fitness or altitude[21, 29, 30]. The HR/VO_2 slope has been shown to be increased in cardiac affections such as Fontant patients or atrial septal defect and reduced in heart failure with preserved ejection fraction (HFpEF) [31–33]. The presently healthy subjects exhibited a decreased HR/VO_2 slope reaching lower limits of normal after bisoprolol intakes independent by the prescribed dose (Fig. 2). Our study highlights that a drug-related reduction in the HR/VO2 slope (average decrease of 0,5 b/ml/kg) has to be taken into account during CPET analysis, when beta blockers are prescribed, at least acutely, as in this study.

Chronotropic post-exercise kinetics

HRR is often reported as an indirect estimation of cardio-vascular fitness. Indeed, HRR is enhanced in endurance athletes as compared to resistive training athletes[19]. Conversely, a delayed HRR, particularly when <12 bpm decrease is observed during the first minute after maximal exercise, is associated with increased all-cause mortality in asymptomatic and pathological populations such as HF patients but also in chronic obstructive pulmonary disease or interstitial lung disease[5, 18, 34, 35]. Indeed, the early and rapid recovery phase during the first minute after a maximal exercise is highly dependent on the reactivation of the parasympathetic tone while the slow phase of the HRR seem to be the consequence of a combination of the roles of sympathetic tone and non-autonomic factors (α-adrenergic tone, atrial stretch or central temperature changes)[36].

However, inconsistent BB effects on HRR have been described. Pavia et al. reported a steeper slope of the decline in heart rate during recovery time in CAD taking 95 mg metoprolol vs CAD not taking BB[37]. Racine et al. demonstrated no clear impact of the altered HR recovery in CHF patients after 6 months of -blocker therapy[38].

The present results showing an increased HRR at 1 min post-exercise suggest that acute 1-adrenergic blockade may allow for an enhanced cardiac vagal reactivation. However, the involvement of non-autonomic mechanisms can not be excluded[36].

O2 pulse

In the present study, maximal O_2 pulse, a composite index reflecting maximal stroke volume and end exercise peripheral O_2 extraction, was increased by the intake of 1-blocker with no influence of the drug dose. As ventricular contraction depends on strength, velocity and time, previous studies suggested that an increased maximal stroke volume was most likely related to a lower left ventricular afterload and an increased preload with increased diastolic filling time, enhancing ventricular contractility via the Frank-Starling mechanism[10]. Increased maximal O_2 pulse may therefore reflect a decreased systemic resistance, a reduced left ventricular afterload and an intrinsic cardiac adaptation after -adrenergic receptor blockade. In our study, we used a 1 selective blocker. This is because unspecific -adrenergic blockade have been previously shown to interfere with skeletal muscle metabolism during exercise lipolysis or glycogenolysis inhibition associated to a loss of K+ during muscle contraction may affect muscular excitability, contractility and fatigability[10]. This effects is presumably 2-aderenergic dependent since no alteration was found following 1-selective blocker intake[10]. 1-selective blockade is also known to preserve the 2-receptor induced muscular vasodilation during exercise with one study reporting a 4% increase in end exercise $CavO_2$ of CAD patients[11]. This suggests that this peripheral adaptation may partially contribute to the increased maximal O_2 pulse and the VO_2max preservation under 1-blockade.

Gaz exchange and chemosensibility

The present result showed no influence of bisoprolol intake on the ventilatory response to exercise, preserving maximal ventilation but also ventilatory efficiency evaluated by $EqCO_2$ (VE/VCO_2 ratio at the ventilatory threshold) or the VE/VCO_2 slope. This suggests little or no interference of 1-adrenergic effects on central or peripheral chemo-receptors or muscle metabo-receptors during exercise[39]. However, Beloka et al. previously showed smoothened VE/VCO_2 slopes after chronic intake of bisoprolol in healthy subjects[15]. Because this was not associated with detectable changes in the sympathetic nervous system tone, metabosensitivity or chemosensitivity, the authors attributed the lower VE/VCO_2 slopes to underlying hemodynamic mechanisms. Other studies showing lower hyperventilation response under β-blockers were realized under un-specific blockade, suggesting an involvement of 2-adrenoreceptor rather than 1-receptor in the ventilatory response to exercise[39].

Limitation of the study

There are several limitations in the present study that could have affected the results or conclusions. All tested subjects were healthy active young adults. The extrapolation of the present results to older subjects or to patient with cardiac diseases remains therefore uncertain. It is also important to underly

that 5 subjects were precautionary excluded for high reactivity to bisoprolol with bradycardia and hypotension. This thus constitute an inclusion bias in the present study.

Moreover, the present observed effects are the consequence of an acute -blocker dose intake and it remains uncertain if more 1-receptors would be inhibited with a chronic -blocker treatment and if it would influence the present results.

Conclusion

In conclusion, even if acute -blocker intake has little or no influence on aerobic capacity, it however affects the chronotropic response to exercise, by lowering the chronotropic index or the HR/VO_2 slope and increasing the HR recovery during the first min post-exercise.

This should be taken into consideration during CPET interpretation for prognostic establishments, follow-up but also for HR based exercise titration. As a general recommendation, this study and previous evidence suggest CPET should be performed only under chronic stabilized betablockers therapy in order to facilitate the interpretation of the results.

Abbreviations

BMI: Body Mass Index; CAD : coronary artery disease; CavO2: arteriovenous oxygen content difference; CHD: congenital heart disease; CHF: congestive heart failure; CI: Chronotropic Index; CPET: Cardio-pulmonary exercise testing; DBP: Diastolic Blood Pressure; HR: Heart Rate; HRR: Heart Rate Recovery; MVV: Maximal Voluntary Ventilation; RER: Respiratory Exchange Ratio; SBP: Systolic Blood Pressure; SpO2: Pulsed oxygen saturation; VE: Ventilation; VO2: Oxygen consumption; VT: ventilatory threshold.

Declarations

Ethics Approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The Ethics Committees approved all experiments and procedures (Erasme Hospital Ethical Committee: P2019/504). All participants provided written informed consent.

Consent for publication

All authors have approved and consent to the publication of this article.

Availability of Data and Materials

Not applicable

Competing interests

The authors have no conflicts of interests to declare.

Funding

Dr Chaumont and Mr Gillet were supported by “Fonds Erasme pour la recherche médicale”

Authors Contributions

Significant manuscript writer: KF/VF. Significant manuscript reviewer/reviser: KF/ML/AG/MC/PV/VF. Concept and design: KF/ML/PV/VF. Data acquisition: KF/AG/MC. Data analysis and interpretation: KF/ML/AG/MC/PV/VF. Statistical expertise: KF/VF.

Acknowledgements

The authors wish to acknowledge Mr Wartel Anthony and Mr Dochen François for their help.

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Figures

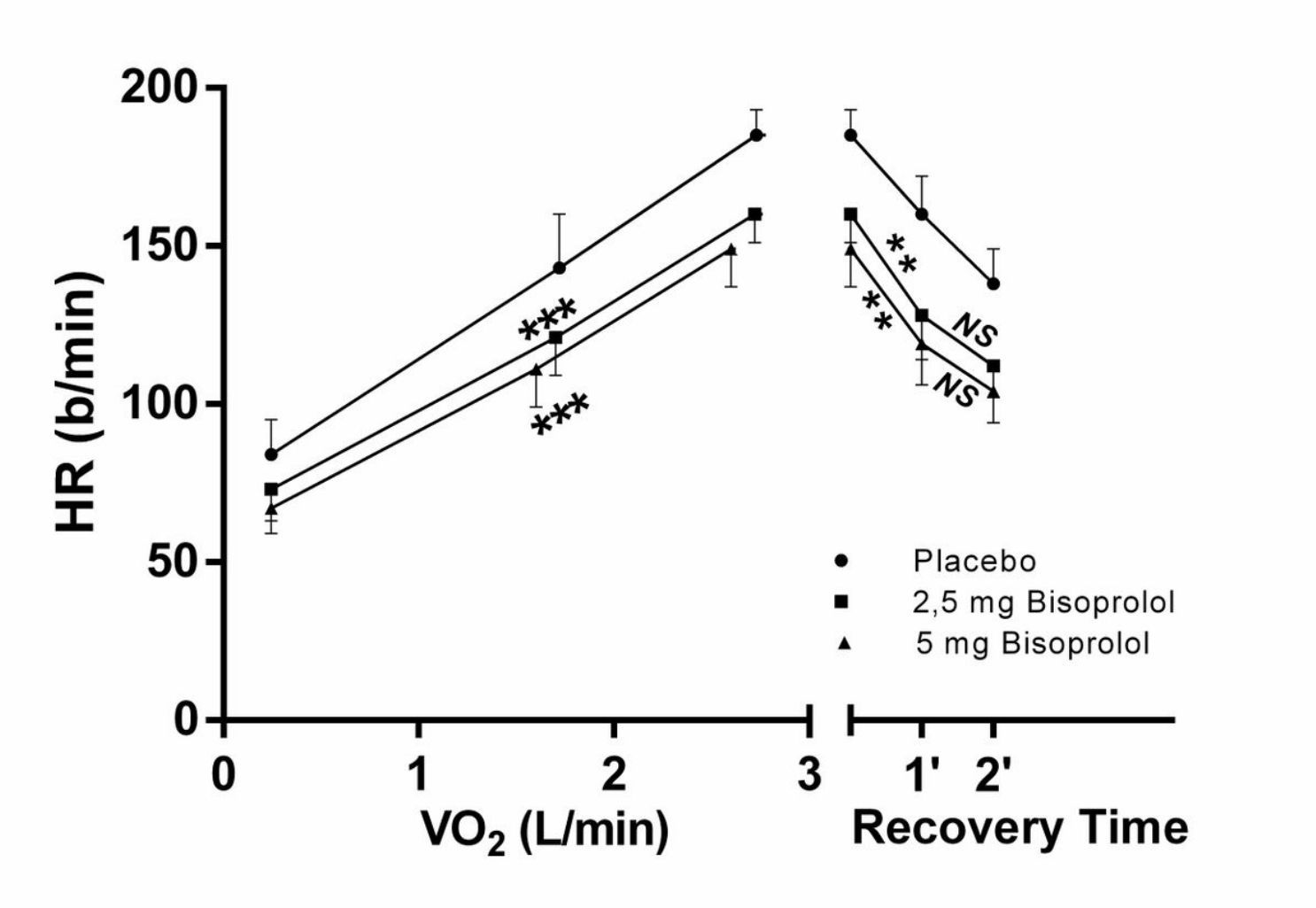

Figure 1

Chronotropic response during and after an incremental exercise. HR measurements were reported at rest, at the ventilatory threshold, at maximal exercise, after 1 and 2 minutes of recovery. The slope of the heart rate (HR) vs oxygen consumption (VO_2) measured during CPET is negatively impacted by the intake of 2,5 or 5 mg of bisoprolol. Bisoprolol also increased the HR recovery after 1 min, but not after 2 min under 1-blockade compared to placebo. No difference between 2,5 and 5 mg of acute bisoprolol intake were observable.

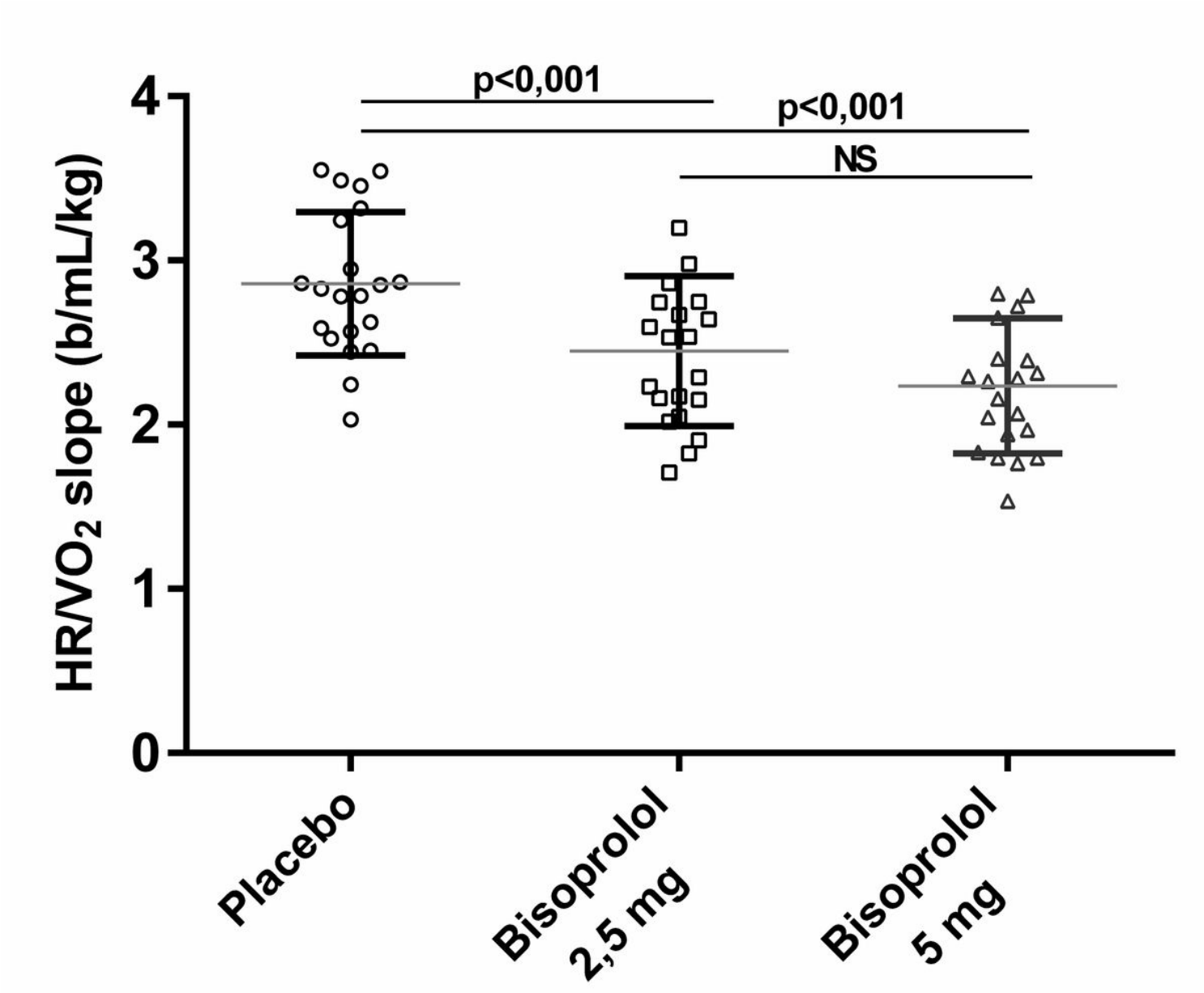

Figure 2

Individual CPET derived HR/VO2 slopes measured in healthy subjects under placebo, 2,5 mg Bisoprolol or 5mg of Bisoprolol. Mean values are represented by large horizontal bars and standard deviation by vertical bars in each condition. B1 adreno-receptors blockade negatively affected the HR/VO_2 slope.

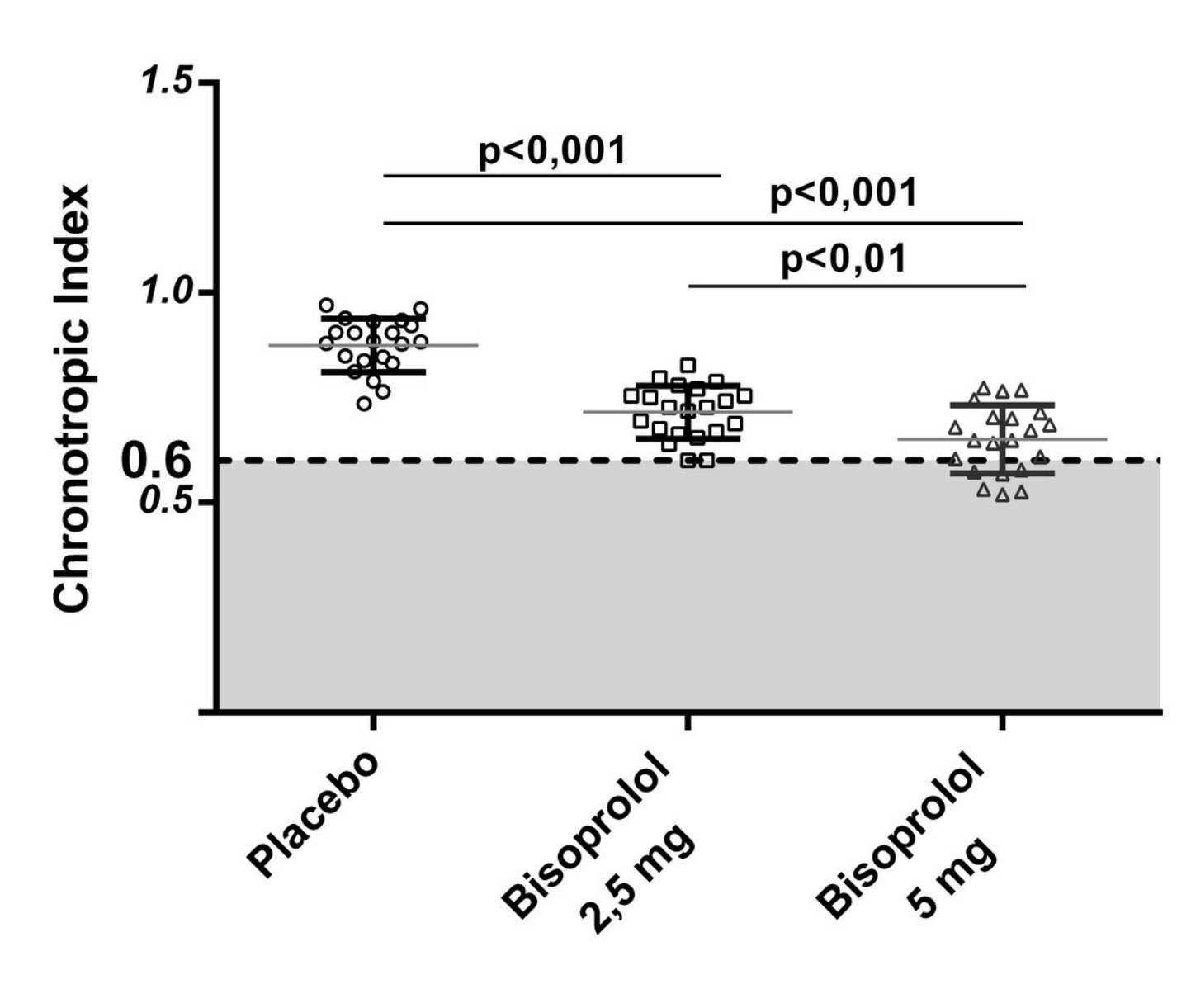

Figure 3

Calculated chronotropic index (CI) in healthy subjects under Placebo, 2,5 mg Bisoprolol or 5mg of Bisoprolol. Mean values are represented by large horizontal bars and standard deviation by vertical bars in each condition. 7 subjects out of 21 (33%) under 5 mg of bisoprolol are included in the chronotropic incompetence zone (grey zone) situated below a chronotropic index of 0.6.