

Original Article (short paper)

Effect of salbutamol on the cardiovascular response in healthy subjects at rest, during physical exercise, and in recovery phase: a randomized, double-blind, crossover study

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Abstract — Aim: To evaluate the effect of the short-acting beta agonists (SABAs) salbutamol on cardiovascular response rest, exercise and recovery phase. **Methods:** This study was conducted as a randomized, double-blind, placebo controlled, crossover study in 15 healthy adults, with a mean age of 30.2 ± 6.6 years. Participants underwent a maximal effort test on two non-consecutive days with 400 mcg of salbutamol or placebo. Throughout the protocol, the variables HR, blood pressure (BP), perceived rate of effort (modified Borg scale) and peak expiratory flow (PEF) were monitored. **Results:** After salbutamol, baseline HR and PEF had increase from 71 ± 8 to 80 ± 11 bpm ($p < 0.05$) and 454.0 ± 64.5 to 475.3 ± 71.4 L/min ($p < 0.05$), respectively. The variables HR, BP and Borg were similar between interventions during all the protocol phases ($p > 0.05$). **Conclusion:** Administration of salbutamol increased rest heart rate; however, did not change heart rate, blood pressure and perceived exertion during exercise or recovery. This suggests that the salbutamol administration is safe and does not affect exercise intensity prescription in healthy subjects.

Keywords: salbutamol; exercise; heart rate; blood pressure; healthy subject

Introduction

Physical exercise has been recommended by various health associations worldwide for prevention and treatment of non-communicable chronic diseases (NCCDs) for its physical, psychological and social benefit^{1,2}. Although physical exercise is highly recommended some individuals can develop exercise-induced bronchoconstriction (EIB)^{3,4,5,6}, which either impair or impedes physical activities. Exercise-induced bronchoconstriction is characterized by transient narrowing of the airways during or after physical exertion and can occur either in the presence or absence of other characteristic features of asthma^{7,8}. The prevalence of EIB varies between 5 and 20% in the general population and 40 and 90% in known asthmatics⁹.

Several classes of medications have been used in the treatment of EIB, but the most commonly recommended are the

short-acting inhaled β -adrenergic (SABA) agonists, such as salbutamol^{10,11,12}. Short-acting β -adrenergic agonists are generally well tolerated, but commonly increasing blood pressure (BP), heart rate (HR) and can have side effects as tachycardia, palpitations, and anxiety¹³. The incidence and severity of its side effects depend on the dosage, route of administration and the presence of comorbidities such as hypertension, cardiac tachyarrhythmias and coronary insufficiency¹⁴. The cardiovascular effects of SABAs at resting condition are well known; however, remains unclear its effects on the cardiovascular system during exercise and recovery phase¹⁵ or how it may alter the physical performance of healthy subjects¹⁶. Knowing the cardiovascular effects of SABAs during exercise may assist health professionals to prescribe appropriate exercises and minimize the risk of adverse events. Traditionally, the Karvonen formula has been used for the prescription of constant intensity physical exercise¹⁷. This

equation is essentially based on chronotropic behaviour during a maximal incremental exercise test. Consequently, autonomic changes due to diseases or medications may negatively influence the accuracy of exercise prescription¹⁸.

Thus, the aim of this study was to investigate the hypothesis that salbutamol increases cardiovascular responses (heart rate and blood pressure), during exercise and recovery in sedentary healthy subjects. In addition, the salbutamol effects on dyspnoea, peak expiratory flow (PEF), and physical performance (total time and work) were evaluated.

Materials and Methods

Subjects

Fifteen healthy subjects aged between 20 and 60 years were included in the study. Participants were excluded with: cardiovascular, psychiatric, other chronic lung diseases, or musculo-skeletal diseases that would impair exercise test; current use of medications that may affect the cardiovascular or respiratory response; pregnancy; current participation in an exercise programme; current smokers or ex-smokers; and subjects who answered 'yes' to any of the questions on Physical Activity Readiness Questionnaire (PAR-Q)¹⁹. The Ethics Review Board of the University approved the study (protocol 1.574.833) and all patients signed an informed consent form.

Experimental design

This was a randomized, double-blind, placebo-controlled cross-over study. Patients were selected to undergo two experimental sessions on 2 non-consecutive days. These sessions included administration of 4 "puffs" of 100 µg of salbutamol (Aerolin® spray, GlaxoSmithKline®, Brazil) or 4 "puffs" of pressurized inhaler as a placebo (Allen & Hanburys, Victoria, Australia) from identical devices. The subjects inhaled the drug with spacer device after full expiration and then hold their breath for 10 s. All tests were performed in the evening to avoid circadian effects.

Randomization was performed using the site <http://www.randomization.com>. The researcher leader prepared and supplied trial drug as two indistinguishable metered-dose inhalers labeled "white" (placebo) and "blue" (salbutamol), which were then administered according to the blinded randomization sequence. The unblinding code was held independently by a researcher uninvolved in the trial conduct, and all measurements, data collection, and data entry were completed before treatment codes were broken.

Protocol

The subjects were advised to refrain from food, tea, coffee or any other beverages eight hours prior to the test and to abstain from strenuous exercise for 24 hours before the protocol. Each experimental trial comprised the initial 10 min rest at seated position, salbutamol or placebo inhalation, a second rest of 15 min, exercise test, 2 min of active recovery, 3 minutes of passive

standing recovery and 15 minutes of passive sitting recovery. The subjects' heart rate was recorded during the entire experiment by a Polar RS800CX (Polar Electro Oy®, Kempele, Finland). The HR average in the last 5 s of each stage was used for analysis. Auscultatory BP (Becton Dickinson®, São Paulo, Brazil) was measured at the end of 10 min (first rest), at the end of 15 min after intervention (second rest), every three minutes throughout exercise, and at every 5 min throughout recovery phase. Perceived rate of effort was measured every 3 min during exercise test and at every 5 min in recovery stage with modified Borg scale from 0 to 10²⁰. PEF (72000MM, Medicate®, São Paulo, Brazil) was measured at the end of 10 min (first rest), at the end of 15 min (second rest) and at each 5 min in recovery stage. The sequence was repeated on a second day with the other intervention. The values obtained were compared with those predicted for the Brazilian population²¹.

Maximal incremental exercise test

The tests were performed at the Clinical Hospital at the Medical School of São Paulo University (HC-FMUSP) according to the guidelines of the Brazilian Society of Cardiology²². The ergometer used was the Technogym Excite Run 700 Treadmill (Technogym®, Cesena, Italy), in accordance with the adapted protocol of effort (attachment 1). The expected HR_{max} (bpm) for each individual was calculated with the formula [1]²³.

$$HR_{max} = 208 - (0.7 * \text{age}) \quad [1]$$

and the maximum power (watts) during exercise was calculated with the formula [2]²⁴.

$$\text{Power}_{max} = \text{mass(Kg)} * 9.81 * \text{sine of the angle of inclination} * \text{speed(m/s)} \quad [2]$$

Participants were encouraged to continue the test until they felt limiting symptoms, such as muscle or respiratory fatigue, even if they reached their HR_{max}. Exhaustion was the criterion for interruption of exercise. When patients expended maximum effort, the protocol parameters were adjusted. Then, the recovery phase commenced.

Target heart rate zone

The target heart rate (HR_{target}) zone was calculated by the Karvonen formula [3], using the limits of 60% and 80% intensity¹⁷.

$$HR_{Target} = (HR_{max} - HR_{rest}) * (0.6 \text{ or } 0.8) + HR_{rest} \quad [3]$$

Statistical analysis

Considering an average HR difference of 14 bpm with standard deviation of 11 bpm²⁵ and a loss of 10% of subjects during

follow-up, the sample size calculated to be 13 patients. The normality of data was assessed using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean and standard deviation (SD). To compare HR between interventions, linear regression was performed to determine the intercept and slope values for each subject. The average intercept and slope values for all participants were calculated and used to generate the regression equations relating to the experimental placebo and salbutamol sessions as described previously²⁶. The stages of the incremental test were chosen as the independent variable and HR as the dependent variable. A paired t-test was used to determine whether the intercept, slope, $HR_{\text{target } 60\%}$ and $HR_{\text{target } 80\%}$ by Karvonen formula differed between salbutamol and placebo experimental sessions. Comparisons of the systolic blood pressure (SBP), diastolic blood pressure (DBP), Borg, PEF across experimental sessions were performed using Two-way analyses of variance (ANOVA), followed by Scheffe's post hoc tests considering sessions (Salbutamol and Placebo) and stages as main factors.

The significance level was adjusted to 5% ($p < 0.05$) for all tests, and SigmaStat 3.5 software (Systat Software, Inc., San Jose, CA, USA) was used for statistical analyses.

Heart rate

Salbutamol intervention provided an average increase in resting HR of 7 ± 8 bpm, (salbutamol, 80 ± 11 bpm; placebo, 71 ± 8 bpm; $p < 0.05$). All participants took the maximal effort test on 2 days (% HR_{max} predict: salbutamol, 97.0 ± 5.8 ; placebo, 96.3 ± 4.6 ; $p > 0.05$) and there were no complications. Also, there were no differences in maximum HR (salbutamol, 180 ± 12 bpm; placebo, 179 ± 10 bpm; $p > 0.05$) or maximum power (salbutamol, 199.7 ± 48.2 Watts; placebo, 197.3 ± 46.2 Watts; $p > 0.05$) between the groups. This indicates the workload was equal in both experimental sessions. No significant difference was observed between HR interventions during the maximum incremental exercise test. The intercepts of the relationship FC/

Results

All subjects completed the test protocol without any adverse effects such as palpitation, tremor, headache and rhythm disturbance were observed. The anthropometric characteristics of participants are described in Table 1.

Table 1: Anthropometric characterization of participants

Variables	n = 15
Gender (F/M)	(10/5)
Age (yr)	30.2 ± 6.6
Mass (kg)	65.6 ± 10.4
Height (m)	1.64 ± 0.4
BMI (kg/m^2)	24.9 ± 6.8
PEF L/m	458.6 ± 73.5
PEF pred	99.0 ± 15.2

All data except gender are given as mean \pm standard deviation (SD). Abbreviations: BMI = body mass index, F = female, kg = kilograms, kg/m^2 = kilograms per square meter, M = male, n = number of participants, PEF = Peak Expiratory Flow

stage were similar between salbutamol and placebo intervention (74.2 ± 11.7 vs. 72.7 ± 8.3 , respectively), as were both the salbutamol and placebo slopes (6.86 ± 0.6 vs. 6.82 ± 0.9 , respectively) (Figure 1). During post-exercise recovery, HR was equivalent between the salbutamol and placebo interventions (Figure 2). Both interventions had a reduction of more than 12 bpm in the first minute of recovery (salbutamol, 31 ± 9 bpm; placebo, 26 ± 9 bpm; $p > 0.05$). This suggests the kinetic behaviour of HR was similar between interventions during all stages of exercise. $HR_{\text{target } 60\%}$ and $HR_{\text{target } 80\%}$ were similar between salbutamol and placebo intervention ($HR_{\text{target } 60\%} = 140.1 \pm 10.3$ vs. 137.2 ± 6.8 bpm; $p > 0.05$) and ($HR_{\text{target } 80\%} = 160.5 \pm 11.0$ vs. 158.3 ± 7.7 bpm; $p > 0.05$), respectively (Figure 3).

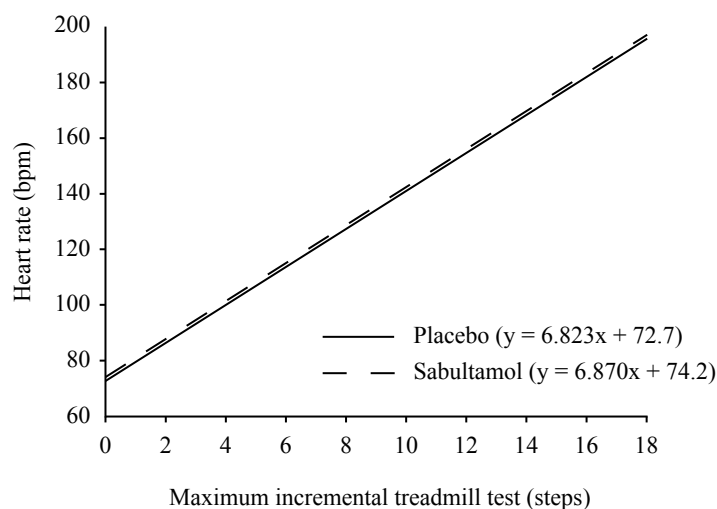


Figure 1. The mean value of the slope and the intercept obtained from the linear regressions of all individuals. Note the absence of differences between linear regressions ($p > 0.05$). Abbreviations: bpm = beats per minutes

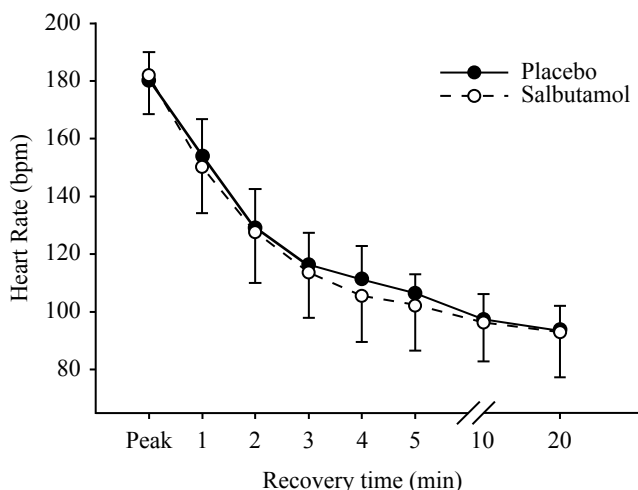


Figure 2. Heart rate recovery in the active (2 min) and passive (2 min to 20 min) phases. Abbreviations: min = minutes; bpm = beats per minutes.

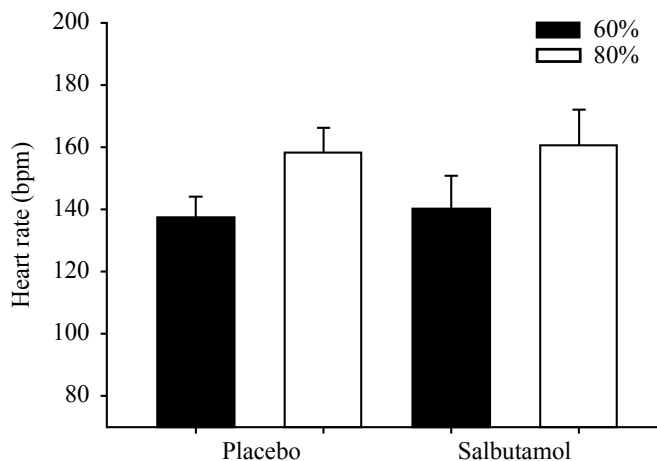


Figure 3. Mean and SD of HR_{target} 60% and HR_{target} 80% by Karvonen formula.

Blood pressure, dyspnoea and peak expiratory flow

SBP, DBP, and perceived exertion were similar in the rest phase, during exercise, and in the recovery phase between experimental

sessions (Tables 2 and 3, p > 0.05). Peak Expiratory Flow significantly increased in the salbutamol protocol, from 454.0 ± 64.5 L/min to 475.3 ± 71.4 L/min and remained elevated during all the protocol phases (Table 2, p < 0.05).

Table 2: Resting data at 10 min before (baseline) and 15 min after placebo and salbutamol interventions, and passive recovery phase at 5, 10, 15, and 20 min after the maximal stress test.

Outcomes	Rest		Passive recovery			
	Baseline	15 min after intervention	5 min	10 min	15 min	20 min
HR (bpm) placebo	78 ± 15	71 ± 8	105 ± 6	97 ± 9	93 ± 8	91 ± 8
HR (bpm) salbutamol	78 ± 14	80 ± 12*	104 ± 13	96 ± 13	93 ± 15	90 ± 14
SBP (mmHg) placebo	103.8 ± 10.4	107.7 ± 9.3	113.3 ± 14.3	110.0 ± 13.4	110.7 ± 11.9	100 ± 12.5
SBP (mmHg) salbutamol	106 ± 12.1	101.5 ± 14.6	108.4 ± 11.7	108.4 ± 10.9	103.8 ± 18.2	104 ± 17.0
DBP (mmHg) placebo	70.0 ± 12.9	67.7 ± 10.9	69.2 ± 9.9	69.2 ± 9.9	70.0 ± 9.1	68.6 ± 9.1
DBP (mmHg) salbutamol	70.8 ± 9.2	70.0 ± 9.6	73.1 ± 10.7	71.5 ± 7.7	70.8 ± 8.3	70.6 ± 8.5
PEF (L/min) placebo	440.6 ± 81.4	458.6 ± 77.6	463.3 ± 71.9	464.0 ± 66.9	467.3 ± 76.4	468.4 ± 82.1
PEF (L/min) salbutamol	454.0 ± 64.5	475.3 ± 71.4*†	470.7 ± 65.8†	472.0 ± 61.8†	481.3 ± 67.8†	480.8 ± 72.8*†
Borg placebo	0 ± 0	0 ± 0	2.7 ± 1.8	1.2 ± 0.7	0.6 ± 0.5	0.2 ± 0.4
Borg salbutamol	0 ± 0	0 ± 0	2.8 ± 1.3	1.6 ± 1.1	1.0 ± 0.8	0.4 ± 0.5

All data are given as mean ± standard deviation (SD). Abbreviations: HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, PEF = peak expiratory flow, Borg = Borg Rating of Perceived Exertion. Symbols: *placebo vs. salbutamol; p < 0.05. † Compared with pre-salbutamol; p < 0.05.

Table 3: Blood pressure response and perceived rate of effort (modified Borg scale) during maximal incremental exercise test.

Outcomes	Maximal incremental exercise test				
	3 min	6 min	9 min	12 min	Peak
SBP (mmHg) placebo	110.6 ± 11.6	112.0 ± 10.1	118.6 ± 12.5	131.5 ± 19.5	132.0 ± 26.5

SBP (mmHg) salbutamol	108.0 ± 11.7	110.6 ± 13.8	119.3 ± 15.6	125.7 ± 21.6	130.0 ± 23.9
DBP (mmHg) placebo	67.3 ± 9.6	69.3 ± 8.8	68.0 ± 9.4	71.5 ± 12.1	71.3 ± 13.5
DBP (mmHg) salbutamol	70.7 ± 9.2	73.3 ± 8.6	71.3 ± 10.8	74.2 ± 11.6	72.8 ± 12.0
Borg placebo	0.7 ± 0.8	1.6 ± 0	2.9 ± 1.6	5.5 ± 2.4	7.6 ± 1.7
Borg salbutamol	0 ± 0	0 ± 0	2.9 ± 1.3	5.2 ± 2.4	8.1 ± 1.1

All data are given as mean ± standard deviation (SD). Abbreviations: SBP = systolic blood pressure, DBP = diastolic blood pressure, Borg = Borg Rating of Perceived Exertion.

Discussion

The study aimed to evaluate the effect of salbutamol on the cardiovascular system in healthy subjects at rest, during exercise, and during recovery. The main results of the study were: 1) a significant increase in HR in the experimental salbutamol session only in relation to the rest period; 2) similar cardiovascular responses and perceived exertion between salbutamol and placebo during the exercise and recovery phases.

In this study, it was observed that the use of salbutamol significantly increased resting HR by an average of 9 ± 11 bpm. These results were similar to those found by Cekici, Valipour, Kohansal, Burghuber²⁵, where observed an average increase in HR of 13 bpm in healthy subjects after administration of 200 µg of salbutamol²⁵. Edgell, Moore, Chung, Byers, Stickland¹⁵ reported an average increase in resting HR of 8 bpm after administration of 400 µg of salbutamol¹⁵. Salbutamol is a β_2 agonist that also activates the β -adrenergic receptors in the cardiovascular system. Consequently, it promotes positive chronotropism and inotropism by a reduction of the parasympathetic nervous system and an increase of the sympathetic nervous system²⁷ that can explain these results.

The cardiovascular effects of SABAs at resting condition are widely known; however, SABAs effects on HR and BP during exercise and recovery remains poorly understood. We are aware of only one study that evaluated the influences of albuterol (similar salbutamol) on cardiovascular response in healthy subjects during exercise, and observed that salbutamol have no influences in HR and BP²⁸. Although our results show similar effects of salbutamol on HR and BP during exercise, in the present study salbutamol were delivered via metered-dose inhaler (MDI) in sample of men and women, while Freeman et al., albuterol was delivered via nebulizer only in men²⁸. The pressurized MDI is small, portable, can be used very quickly, have high lung deposition fraction and is less expensive than nebulizer²⁹. Because of these features, it is the preferred device. Our finds showed that the use of the Salbutamol does not compromise the relationship between the chronotropic response and the load, even with changes in resting heart rate values. In this way, the prescription of the physical exercise based on the Karvonen formula seems to us adequate and safe.

In addition we analysed, for the first time, the influences of salbutamol on heart rate recovery and observed that the decrease in HR during the recovery phase in the first minute was greater than 12 bpm for all participants and did not differ between placebo and salbutamol intervention. This indicates that the use

of salbutamol does not adversely affect HR recovery, which is closely linked to risk of cardiovascular disease and to mortality in various diseases^{30,31,32}.

Systolic and diastolic blood pressure was similar after placebo and salbutamol administration. This was also found in studies by Edgell, Moore, Chung, Byers, Stickland¹⁵ Cekici, Valipour, Kohansal, Burghuber²⁵, Jarti, Kaila, Tahvanainen, Kuusela, Vanto, Valimaki²⁷, Antonelli et al.²⁹, and Snyder, Wong, Foxx-Lupo, Wheatley, Cassuto, Patanwala^{15,25,27,29,33}. Blood pressure and perception of effort during exercise and recovery did not change significantly between interventions that are similar to the results observed by Freeman et al.²⁸. As in previous studies, salbutamol induced significant bronchodilation in healthy subjects^{34,35,36}. However, this improvement have no ergogenic effect³⁷. This is probably due to cardiovascular, but not respiratory, limitations observed in healthy individuals exposed to high-intensity exercise under normoxic conditions³⁸.

In practical terms, this study indicates that administration of salbutamol to healthy subjects does not affect HR during exercise and recovery. Thus, HR does not need to be adjusted for exercise intensity after administration of salbutamol. In addition, the responses of blood pressure at rest, during exercise, and during recovery were similar between experimental sessions, indicating that the use of salbutamol is considered safe from the point of view of cardiovascular risk in healthy subjects.

The study has some limitations that must be highlighted. The study analysed the acute effects of salbutamol on the cardiovascular system only. Future studies should assess the chronic effects of this medication. The study included only healthy subjects without a history of EIB. In addition, only an ergometric test was administered and cardiopulmonary exercise test could provide a better characterization of the ventilatory and cardiopulmonary responses during exercise after administration of salbutamol.

Conclusion

Administration of salbutamol increased rest heart rate; however, did not change heart rate, blood pressure and perceived exertion during exercise or recovery. This suggests that the salbutamol administration is safe and does not affect exercise intensity prescription in healthy subjects.

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Appendix 1.

Stage (min)	Speed (km.h ⁻¹)	Grade (%)
1	1.7	0
2	3.5	0
3	4	2
4	4	4.5
5	4.8	0
6	5	3
7	5.5	4
8	5.5	8
9	5.5	12
10	5.8	14
11	6.2	15
12	6.6	15
13	6.8	15
14	7.2	15
15	7.8	15
16	8.3	15
17	8.8	15
18	9.2	15
Recovery		

1	2.4	2.5
2	2.4	2.5
3	0	0
4	0	0
5	0	0

Figure 1. Incremental protocol test. Abbreviations: km = kilometre; min = minutes; h = hour; % = percentage.

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