Acute effect of salbutamol on the cardiovascular system during exercise in patients with moderate or severe asthma: a randomized, double-blind, and cross-over study

Efeito agudo do salbutamol no sistema cardiovascular durante o exercício físico em pacientes com asma moderada ou grave: estudo aleatorizado, duplo–cego e cruzado

Efecto agudo del salbutamol en el sistema cardiovascular durante el ejercicio físico en pacientes con asma moderada o grave: estudio aleatorizado, doble ciego y cruzado

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ABSTRACT | Salbutamol is a β_2-agonist of short duration commonly used in patients with asthma to prevent symptoms during or after exercise. Hemodynamic changes at rest are well described. However, there is little data on the effects on heart rate (HR) and blood pressure (BP) during exercise and recovery phase in patients with moderate or severe asthma A randomized, double-blind, cross-over study was conducted, including 15 individuals with moderate and severe asthma, mean age 46.4±9.3 years. Patients underwent a maximal 2-day exercise test with 400 mcg salbutamol or 4 placebo puffs. Throughout the protocol, HR, BP, perceived exertion and peak of expiratory flow (PEF) were monitored. After the use of salbutamol, the PEF value increased by a mean of 28.0±47.7L/m, remaining increased at 5, 10 and 15 minutes of passive recovery compared to placebo (p<0.05). The HR, BP and effort perception variables were similar across interventions at all stages of the protocol (p>0.05). These results suggest that the use of salbutamol is safe and that HR does not need to be adjusted to prescribe exercise intensity following salbutamol administration in subjects with moderate or severe asthma.

Keywords | Asthma; Albuterol; Exercise; Heart Rate; Blood Pressure.

RESUMO | Salbutamol é um β_2-agonista de curta duração frequentemente utilizado em pacientes com asma para prevenir os sintomas durante ou após exercício físico. Alterações hemodinâmicas em repouso estão bem descritas. Contudo são escassos os dados sobre os efeitos na frequência cardíaca (FC) e pressão arterial (PA) durante o exercício e na fase de recuperação em pacientes com asma moderada ou grave. Foi realizado um estudo aleatorizado, duplo-cego e cruzado, em que foram inclusos 15 indivíduos com asma moderada e grave, com média de idade de 46,4±9,3 anos. Os pacientes realizaram um teste de esforço máximo em dois dias não consecutivos, com administração de 400mcg de salbutamol ou 4 "puffs" de placebo. Durante todo o protocolo foi monitorada a FC, a PA, a percepção de esforço e o pico de fluxo expiratório (PFE). Após o uso do salbutamol, o valor do PFE aumentou em média 28,0±47,7L/m, permanecendo maior nos tempos de 5, 10 e 15 minutos de recuperação passiva em relação ao placebo (p<0,05). As variáveis FC, PA e percepção de esforço foram semelhantes entre as intervenções em todas as fases do protocolo (p>0,05). Esses resultados sugerem que o uso de salbutamol é seguro, e que a FC não necessita de ser ajustada para prescrever a intensidade do exercício após a administração de salbutamol em indivíduos com asma moderada ou grave.

Descritores | Asma; Albuterol; Exercício; Frequência Cardíaca; Pressão Arterial.

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RESUMEN | Salbutamol es un agonista β_2 de corta duración frecuentemente utilizado en pacientes con asma para prevenir los síntomas durante o después del ejercicio físico. Los cambios hemodinámicos en descanso están bien descritos. Sin embargo, son escasos los datos sobre los efectos en la frecuencia cardíaca (FC) y la presión arterial (PA) durante el ejercicio y en la fase de recuperación en pacientes con asma moderada o grave. Se realizó un estudio aleatorizado, doble ciego y cruzado, donde fueron incluidos 15 individuos con asma moderada y grave, con una media de edad de 46,4 ± 9,3 años. Los pacientes realizaron una prueba de esfuerzo máximo en 2 días no consecutivos, con administración de 400mcg de salbutamol o 4 «puffs» de placebo. Durante el protocolo se supervisaron la FC, PA, percibe el esfuerzo y el Pico flujo espiratorio (PEF). Después del uso del salbutamol, el valor del PFE aumentó en promedio de 28,0 ± 47,7 L/m, permaneciendo mayor en los tiempos 5, 10 y 15 minutos de recuperación pasiva con relación al placebo (p < 0,05). Las variables FC, PA y percepción de esfuerzo fueron similares entre las intervenciones en todas las etapas del protocolo (p > 0,05). Los resultados sugieren que el uso de salbutamol es seguro y que la FC no necesita ser ajustada para prescribir la intensidad del ejercicio después de la administración de salbutamol en individuos con asma moderada o grave.

Palabras clave | Asma; Albuterol; Ejercicio; Frecuencia Cardíaca; Presión Arterial.

INTRODUCTION

Asthma is a chronic disease consisting of the inflammatory disorder of the airways, where there is a broad and complex spectrum of interaction between cells and inflammatory mediators, leading to bronchial hyperresponsiveness[1]. The acute and unexpected attacks of shortness of breath are a constant threat to asthmatics and have a deleterious effect on the physical, emotional, and social aspect, impairing the quality of life[2]. The main objective of the treatment of patients with asthma is to promote the control of their symptoms through education, environmental control and individualized pharmacotherapy[3]. Besides pharmacological treatment, studies have shown that the addition of exercise as an adjuvant therapy improves clinical control[4], psychosocial aspects[5] and bronchial hyperresponsiveness[6]. However, it is a challenge for asthmatics to practice physical activity because of the frequent symptoms triggered during and after exercise. The symptoms are particularly important in those who develop Exercise-Induced Asthma (EIA), affecting as many as 90% of asthmatics[7].

To allow asthmatics to perform physical exercise with fewer symptoms, the prescription of short- acting β-2 agonists is common, salbutamol being the most frequently used agent[8]. The systemic absorption of the bronchodilator results in significant hemodynamic changes, such as increased heart rate (HR) and blood pressure (BP)[9] and may lead to side effects such as tachycardia, palpitations and anxiety[10]. These hemodynamic effects are well known during rest in subjects with mild asthma and a sedentary lifestyle[3,9], but little is known about the effects of salbutamol on these variables during exercise and post exercise recovery in patients with moderate or severe asthma. Considering that physical exercise is important for asthmatic individuals and that β2-agonist is often used to perform these activities, it is necessary to know the behavior of HR and BP with the bronchodilator during exercise and recovery for a correct prescription of training intensity and to minimize cardiovascular risks. This study was designed to evaluate the effects of salbutamol on HR (primary endpoint), BP, peak expiratory flow (PEF) and dyspnea (secondary endpoints) during rest, exercise and recovery in patients with moderate or severe asthma.

METHODOLOGY

Subjects

A randomized, double-blind, cross-sectional study was performed and registered at clinicaltrial.gov under number NCT03044938. A sample of 15 patients with moderate or severe asthma was randomly recruited from the Pulmonology Asthma Outpatient Clinic of the University of São Paulo Medical School (FM – USP). Patients with a diagnosis of moderate or severe asthma were included according to the clinical criteria described in GINA[1]. Patients should be between 20 and 59 years of age, undergoing treatment at the outpatient clinic for at least 3 months, with a stable clinical picture for at least 30 days and using the optimized drug. Individuals with regular physical

activity (> 1/week), smokers, pregnant women or those with locomotor disorders, or with diagnoses of diseases known to influence cardiovascular parameters were not included in the study (Figure 1). All patients read and signed the Free and Informed Consent Form, previously approved by the ethics committee of UNIB (nº 1,574,833).
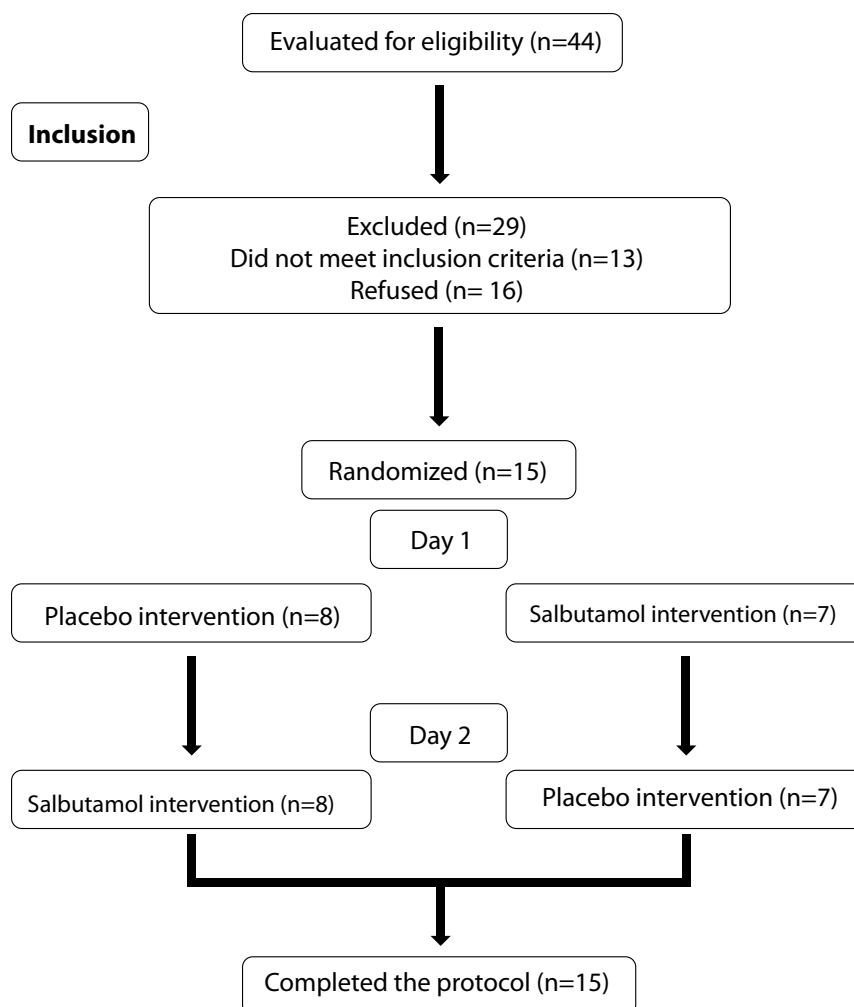
Evaluated for eligibility (n=44)

Inclusion

Excluded (n=29)
Did not meet inclusion criteria (n=13)
Refused (n= 16)

Randomized (n=15)

Day 1

Placebo intervention (n=8)

Salbutamol intervention (n=7)

Day 2

Salbutamol intervention (n=8)

Placebo intervention (n=7)

Completed the protocol (n=15)

Figure 1. Diagram of the selection and randomization of patients

Experimental design

Prior to the first experimental session, patients were submitted to the Asthma Control Questionnaire (ACQ-7), duly validated[11] to assess the effectiveness of asthma control[12]. Patients were selected to perform 2 distinct experimental sessions on 2 nonconsecutive days. These sessions were: Salbutamol session (SS), in which 4 puffs of 100 μg salbutamol (Aerolin® spray, GlaxoSmithKline®, Brazil) were administered and a placebo (PS) session, in which 4 puffs of placebo inhaler was administered (Allen & Hanburys, Victoria, Australia) containing only propellant gas (Norflurane HFA 134A)[13], both with identical devices.

The randomization was performed through the website http://www.randomization.com. The lead investigator prepared and supplied the two inhalers and labeled the devices with the "white" (placebo) and "blue" (salbutamol) codes, which were then administered according to the blind randomization sequence. The intervention was performed by a researcher who did not know the codes, and all measurements, data collection and data tabulation were completed before codes were disclosed.

Protocol

Patients were instructed to maintain the use of their inhaled medications routinely. Each experimental trial

consisted of 10 min initial rest in a sitting position, inhalation with salbutamol or placebo, a second 15 min rest, exercise test, 5 min active recovery, and then 15 min passive recovery. Heart rate was monitored on a beat-to-beat basis using a Polar heart rate monitor (Electro Oy®, Kempele, Finland) throughout the protocol. The mean HR in the last 5s of each stage was used for analysis. BP was measured at the end of 10 min (first rest), 15 min after the intervention (second rest), every 3 min throughout the exercise, and every 5 min during the recovery phase. Perceived exertion was measured every 3 min during the test and every 5 min in the recovery phase by the modified Borg scale from 0 to 10[14]. The 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 every 5 min in the recovery phase. The sequence was repeated on a second day with the other intervention.

Maximum effort test

All tests were performed in the afternoon to avoid circadian alterations. The ergometric treadmill Technogym Excite Run 700 (Technogym®, Cesena, Italy) was used according to the incremental stress protocol[15].

The predicted HR_{max} (bpm) of each patient was calculated using the following formula [1][16]:

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

The $Power_{max}$ (watts) during exercise was calculated using the following formula [2] [17]:

$Power_{max}=weight(kg) \times 9.81 \times sine\ of\ angle\ of\ slope \times speed(m/s)$ [2]

Statistical analysis

Considering a mean HR difference of 14 bpm with standard deviation of 11 bpm and considering the 10% follow-up attrition[9], a sample of 13 patients was calculated. The normality of the data was checked by the Kolmogorov-Smirnov test. Data were expressed as mean and standard deviation. Linear regression was used to compare HR between the interventions to determine the intercept and slope values for each subject. Subsequently, the mean values were calculated and used to generate the regression equations related to SS and PS as previously described[17]. The stages of the incremental test were chosen as the independent variable and HR as the dependent variable. The paired

T-test was used to determine whether the intercept, slope, systolic BP, diastolic BP, Borg's subjective effort scale, PFE, Asthma Control Questionnaire (ACQ) and maximum work power differed between SS and PS. The comparison of the variables during the interventions was assessed through analysis of variance (ANOVA) followed by Scheffe's post hoc. The level of significance was adjusted to 5% and the Sigma Stat 3.5 program was used.

RESULTS

Subjects

Fifteen subjects were selected for the study and their baseline characteristics are expressed in Table 1. All subjects completed the test protocol without any adverse effects.

Table 1. Anthropometric data

Variables	N=15
Anthropometric	
Gender (F/M)	7/8
Age (years)	46.4±9.3
Weight (kg)	74.6±6.5
Height (m)	1.64±0.1
BMI (kg/m²)	28.4±4.1
ACQ-7	
Score Placebo day	1.7±1.0
Score Salbutamol day	1.8±1.0
Daily medication	
Corticoid (µg.day^{-1})	451.7±119.7
Beta-2 long duration (µg.day^{-1})	18.6±16.2
Spirometry	
FEV$_1$ (L)	2,4±0,6
FEV$_1$ pred (%)	77,2±10,8
FVC (L)	3,2±0,7
FVC pred (%)	87,9±7,5
FEV$_1$/CVF	73,6±6,7
PEF (L/m)	378,7±87,4
PEF pred (%)	94,7±20,7

Data are expressed as mean and standard deviation (SD)
F: female; M: male; BMI: body mass index; ACQ: Asthma Control Questionnaire 7

Heart rate

Patients reached mean maximum HR of 168±18 bpm during the physical test, which corresponds to 103% of the maximum HR predicted by age. The resting HR did not change after the use of salbutamol (Table 2; p> 0.05). The intercept of the HR/stage ratio in SP (80.8±8.7) and SS (80.0±10.0) were similar, as well as the slope of SP (6.3±1.3) and SS (6.5±1.2) (Figure 2-A), indicating that HR was similar between interventions during all stages of exercise. During recovery, the post-exercise HR was similar between PS and SS (Figure 2-B). Both interventions resulted in a reduction of less than 12 bpm in the first minute of recovery.
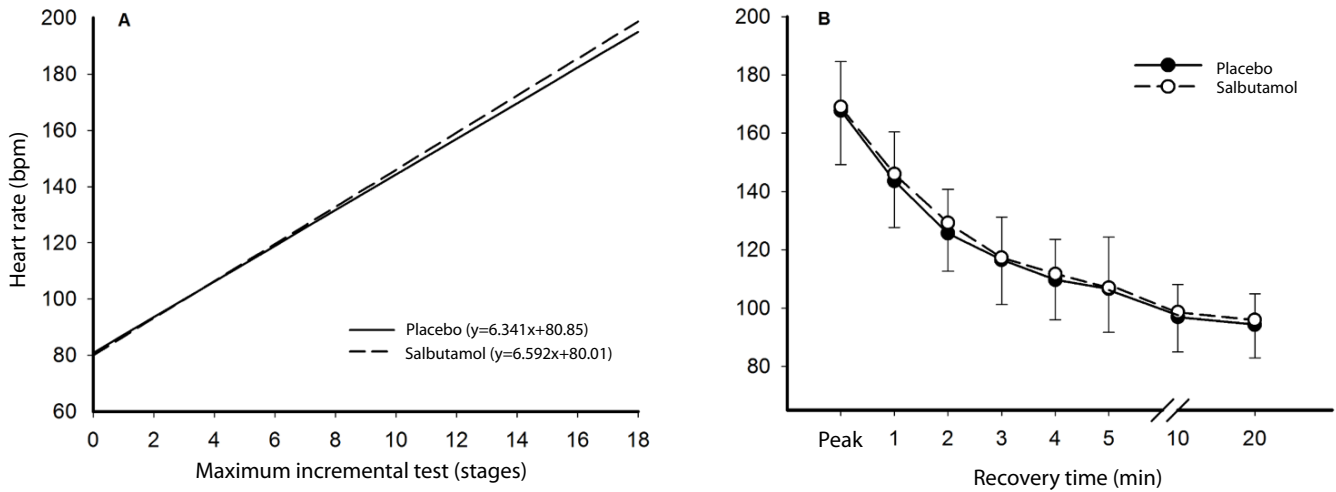

Figure 2. (A) Mean value of intercept and slope obtained by linear regression analysis of all patients. (B) Heart rate recovery during active (peak until min 5) and passive (from min 5 to 20) phases

Note the absence of significant differences between placebo versus salbutamol intervention (p>0.05) in A and B
bpm: beats per minute; min: minutes

Table 2. Resting data (baseline), 15 minutes after intervention with placebo or salbutamol and passive recovery after maximal incremental test

Variables	Home		Passive recovery			
	Basal	15 min post intervention	5 min	10 min	15 min	20 min
FC (bpm) placebo	80.5±7.5	80.8±7.5	105.8±15.3	98.6±13.7	95.9±13.0	94.5±11.9
FC (bpm) salbutamol	81.7±8.0	80.3±7.5	103.2±13.1	96.9±11.1	94.3±10.6	91.9±10.5
SBP (mmHg) placebo	117.3±8.8	120.0±10.0	135.3±20.3	126.7±18.4	124.0±13.0	118.7±9.9
PAS (mmHg) salbutamol	116.0 9.9	121.3±5.5	133.3±19.1	120.0±12.0	120.0±12.0	118.0±12.1
PAD (mmHg) placebo	74.7±11.3	74.7±15.1	75.3±9.2	77.3±11.6	76.7±12.3	78.7±10.6
PAD (mmHg) salbutamol	75.3±9.9	80.0±10.7	78.7±15.5	78.7±14.1	79.3±12.8	80.7±11.0
PEF (L / min) placebo	383.7±81.2	378.7±87.4	346.0±59.0	339.3±67.8	352.7±77.7	371.3±75.3
PEF (L / min) salbutamol	376.3±87.3	403.3±83.2 *	388.7±69.4 *	380.7±61.7 *	384.0±63.9 *	390.0±66.3
Borg placebo	0±0	0±0	2.9±1.7	1.4±1.0	0.6±0.7	0.3±0.6
Borg salbutamol	0±0	0±0	3.1±1.9	1.5±1.1	0.6±0.9	0.4±0.7

Mean and standard deviation (SD)
HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; PEF: peak expiratory flow; Borg: Borg subjective perception scale
* placebo vs. salbutamol; p<0.05. † compared to pre-salbutamol; p<0.05

Blood pressure

Similar responses of systolic and diastolic BP were observed in both experimental sessions at rest (p> 0.05, Table 2), exercise (p> 0.05, Table 3) and recovery (p> 0.05; Table 2).

Table 3. Data on systolic blood pressure, diastolic blood pressure and Borg subjective perception during maximal incremental test

	Maximum incremental exercise test				
Variables	3 min	6 min	9 min	12 min	Peak
SBP (mmHg) placebo	126.4±10.5	128.6±11.0	136.2±17.2	144.4±15.1	153.3±19.1
SBP (mmHg) salbutamol	120.7±5.9	128.7±16.8	139.3±22.0	138.9±10.5	155.3±20.3
DBP (mmHg) placebo	77.9±12.1	77.1±12.2	80.0±13.3	83.3±12.2	80.0±13.1
DBP (mmHg) salbutamol	78.7±7.4	79.3±8.8	85.0±10.9	80.0±10.0	81.3±11.9
Borg placebo	0.5±0.6	1.3±1.0	3.7±2.0	4.8±1.9	8.1±1.7
Borg salbutamol	0.7±0.9	1.4±1.1	3.1±2.4	4.9±2.3	7.5±2.1

Mean and standard deviation (SD)
SBP: systolic blood pressure; DBP: diastolic blood pressure; Borg: Borg subjective perception scale
* placebo vs. salbutamol; p<0.05

Peak expiratory flow

After the use of Salbutamol, PEF increased 28.0±47.7L/m, (9.1±15.6%). During the recovery phase, its value remained higher at 5, 10 and 15 minutes of passive recovery in PS (p<0.05; Table 2). At 20 minutes the values were the same between the experimental sessions (Table 2).

Subjective perception of Borg

Participants' perception of effort (Borg) was similar between the experimental sessions throughout the protocol (Table 2 and 3).

DISCUSSION

The main findings of the present study were: 1) the use of salbutamol does not affect HR and BP during rest, exercise and recovery phase in individuals with moderate or severe asthma. 2) PEF increased at rest and remained elevated in exercise recovery, but there were no differences in perceived exertion and maximum workload.

The effect of salbutamol on HR and BP at rest is in agreement with the study by Andrade Capuchinho-Junior et al.[18] who used the same dosage of salbutamol in mild asthmatic subjects and did not demonstrate changes in HR, systolic BP and diastolic BP during rest. In contrast, Eryonucu et al.[19] found that 200mcg of salbutamol increased HR by 4 bpm in average in individuals with a recent diagnosis of asthma and without drug treatment. Similarly, Cekici et al.[9] and Feitosa et al.[15] showed a healthy increase in mean HR of 13 bpm and 8 bpm, respectively. These different results can be explained by the characteristics of the populations studied. Our population was composed of patients with moderate or severe asthma who used chronic long-acting β2-agonists. In addition, we instructed all patients to maintain their routine medication during the test period, as the purpose of the study was to check the effect of salbutamol under actual clinical conditions of a pulmonary rehabilitation program. Chronic use of β2 -adrenergic can lead to greater hemodynamic tolerance with lower repercussions on HR and PA[20], which may explain our results.

To date, we found only one study[21] that evaluated the effect of salbutamol on the cardiovascular system during exercise in asthmatic patients. As in the present study, the authors found that administration of 5mg of nebulized salbutamol did not alter HR at rest and during exercise. However, unlike our results, they found an increase in systolic BP and a reduction in diastolic BP after the use of salbutamol at the beginning of the exercise. The study by Freeman et al.[21] differs from the present study in that it was composed of mild asthmatic patients who practiced regular physical activity, and a dosage of 5mg of salbutamol in nebulized form was applied. The present study included patients with moderate or severe asthma, who are the most indicated for pulmonary rehabilitation[22]. Also, we included only sedentary patients, which is the most prevalent lifestyle in this population. In addition, we use inhaled medication, which is the most recommended form currently, because it has less systemic effects, is more practical and has a lower cost[23]. In healthy subjects, Feitosa et al.[15] found that the use of 400mcg of salbutamol did not alter the response of the cardiovascular system during and after

exercise. Taken together, these results suggest that the use of salbutamol in the prevention or treatment of respiratory symptoms resulting from exercise does not affect the cardiovascular response during and in the recovery phase of physical exercise.

HR recovery after exercise is a strong predictor of morbidity and mortality and is altered in several diseases[24-26]. Sympathomimetic or sympatholytic drugs as well as physical training may interfere significantly with the behavior of HR[25,27]. In an unprecedented way, we also found that HR during recovery did not change with the use of salbutamol, and that the decrease was greater than 12 bpm in the first minute after maximal exercise. This indicates that the use of salbutamol does not adversely affect HR recovery.

Salbutamol also promoted an increase in PEF of 27L/min (9.1%). In addition, we found that in the recovery phase the largest difference between PEF in the salbutamol versus placebo session was 12.3% and occurred at 5 minutes. These effects were not accompanied by less dyspnea during and after exercise and also did not affect the maximal ability to perform exercise. Three aspects may justify these results: i) a maximal exercise test was used and all patients were encouraged to perform the test until exhaustion, consequently no differences in dyspnea rates were expected during exercise; ii) we instructed all patients to maintain their routine medication during the test period, which reduces the bronchodilator effect; iii) clinical improvements are only observed in the case of increases of 20% in PEF[1], and in the present study no increases of this magnitude were observed. To our knowledge, only one study with 8 patients evaluated the ergogenic effect of 300μg of salbutamol in patients with moderate or severe asthma[28]. In this study, salbutamol did not improve exercise capacity or reduce dyspnea. Similar studies in asthmatic athletes[29] and subjects with mild asthma[21] also showed that the acute use of salbutamol has no ergogenic effect.

This study presents as limitations: i) Ergospirometry could provide a better characterization of the ventilatory response and oxygen consumption during exercise; ii) FEV^1 is most commonly used to identify airflow limitation after medication and exercise; however, studies indicate that PEF also has good specificity and sensitivity[30]; iii) The present study does not allow generalization of the findings for patients with mild asthma and/or who do not use chronic medication.

CONCLUSION

Administration of salbutamol had a bronchodilator effect, but did not affect HR and BP during rest, exercise and recovery and did not improve dyspnea and maximal exercise capacity. These results suggest that the use of salbutamol is safe and that the prescription of exercise intensity based on HR can be used without complementary adjustments in individuals with moderate or severe asthma.

ACKNOWLEDGMENTS

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