High doses of inhaled terbutaline enhance muscle strength and exercise capacity and elevate inflammatory response in patients with chronic obstructive pulmonary disease

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Abstract

Introduction: Many patients with chronic obstructive pulmonary diseases (COPD) have a subjective effect of beta2-agonist, despite the effect on lung function being limited. The subjective effects of beta2-agonists in patients with COPD may be related to systemic effects of the drugs substance. Here, we investigated the effect of high-dose inhaled terbutaline on exercise capacity, inflammatory response and muscle strength in patients with severe COPD.

Methods: Eight patients with severe COPD (FEV1<50% pred.) participated in a randomized, placebo-controlled, crossover study with inhaled terbutaline. The participants attended four visits. At visit one and two, participants' basic characteristics and maximal oxygen uptake (VO2max) were measured. At the third and fourth visit, 40 puffs of terbutaline (20 mg) or placebo were inhaled after which participants' maximal voluntary contraction (MVC) of m. quadriceps was determined, followed by two incremental exercise tests to exhaustion on a bike ergometer. After the second incremental test, MVC, maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were measured. Before, during and after the exercise test, blood samples were collected to evaluate glucose, potassium, lactate, interleukine-6 (IL-6), interleukine-8 (IL-8), tumor necrosis factor-alpha (TNF-α), surfactant protein D (SP-D) and high-sensitivity C-reactive protein (HsCRP) levels.

Results: Terbutaline improved ($P < 0.05$) MVC with a mean value of 401 N (121) vs. placebo 362 N (125), respectively. Time to exhaustion was on the first incremental test 431s (114) terbutaline and 400s (104) with placebo($p<0.05$), IPPO went from 117.8(28.4) on terbutaline against 110(26) with placebo($p<0.05$) and VO2max increased with terbutaline 1461 ml/min (345) against 1369 ml/min(2999) with placbo ($P < 0.05$) during both incremental tests compared with placebo and IL-6 increased during exercise with terbutaline compared with placebo ($p<0.05$).

Conclusion: High doses of inhaled terbutaline benefit respiratory function, exercise endurance and muscle strength in patients with severe COPD. Seemingly, terbutaline induces il-6 response during exercise.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading chronic diseases worldwide and is predicted by the World Health Organization (WHO) to increase in the coming decades[1]. The most common symptoms of COPD are dyspnea, cough, phlegm, and reduced exercise capacity. First-line treatment in any degree of COPD is either short-acting beta2-agonists (SABA), or short-acting muscarinic antagonist (SAMA), and long-acting beta2-agonists (LABA), ultra-long-acting beta2-agonists (LABA) or long-acting muscarinic antagonist (LAMA)[2 3].

Patients with COPD often complain of exercise intolerance due to airway obstruction and dyspnea. There is sparse evidence for the use of SABA in either stable COPD or during exacerbations of COPD (AECOPD); nevertheless, SABA are generally recommended when "required" to relieve acute dyspnea[2]. Several studies have investigated the effect of SABA on exercise tolerance. The results have been contradictory and no improvement in maximal oxygen uptake (VO2max)[4] has been shown. However, most patients with COPD report benefits from inhalation of SABA during physical activity or exacerbations, even though lung function is generally unaffected [5 6]. A recent study has demonstrated that high doses of beta2-agonists increase muscle strength and enhance supra-maximal exercise performance in healthy young men,[7] albeit no improvement in VO2max was shown. During AECOPD it is not unusual to administer high doses of SABA, and the presumed effect on muscle strength could contribute to some of the benefits patients with COPD. To our knowledge, this has not been investigated in COPD patients.

Although COPD is characterized as an inflammatory disease of the airways, recent research has shown that patients with COPD also have a low-grade systemic inflammation. An elevated level of systemic inflammation correlates with higher risks of AECOPD[8]. Cross-sectional studies have shown that healthy individuals who are physical active have a lower grade of systemic inflammation compared with inactive individuals[9]. Strenuous exercise induces an inflammatory response in patients with COPD[10], but it is unknown whether a high dose of beta2-agonists affects the inflammatory response to exercise.

Thus, the aim of the present study was to investigate pulmonary and systemic effects of high-dose inhaled terbutaline in patients with COPD and whether this could alter the inflammatory response during exercise.

Material and Methods

Basic parameters

After screening, 11 patients were included in the study; 3 of whom were excluded due to an exacerbation, malfunction of the investigational tools and nausea after the incremental test, respectively. Accordingly, 8 patients completed the cross-over study. Patients had a mean age of 65.2 (3.4) years, a body mass index (BMI) of 24.5 (4.6) and a total CAT score of 9.3 (2.9). Number of pack-years was 44 (14.9). Of the 11 participants, 3 were current smokers. FEV1 was 41.9 (10.1)% of predicted value with an FEV1/FVC ratio of 47.3 (9.8) (Table 1).

Table 1

Screening characteristics of the patients included

Screening Characteristics	Mean	SD
Age	65.2	3.4
Smoking history(pack years)	44	14.9
BMI	24.5	4.6
CAT	9.3	2.9
mMRC	0	0
FEV1(L)	1.37	0.7
FVC(L)	3.0	0.7
FEV1/FVC (%)	47.3	9.8
FEV1 (%)	41.9	10.1
FVC(%)	73.4	13.0
RV(%)	175.2	46.1
TLC(%)	122.1	15.8
DCO/VA(%)	68.2	26.0
VO2MAX	1533.5	384.15
VO2MAX/ml/kg	19.5	5,4

FEV1: Forced expiratory Volume in 1 second, FVC: Forced Vital Capacity, RV: Residual Volume, TLC: Total Lung Capacity, DLCO/VA: Diffusing capacity of the lung for carbon monoxide/alveolar Volume, BMI: Body Mass Index, CAT: COPD Assessment Test, mMRC: modified Medical Research Council scale, MVC: Maximal Voluntary Contraction of the quadriceps muscle, VO2max: Maximal oxygen Consumption.

Study design

The study was a randomized, placebo-controlled, crossover study conducted in collaboration with the local unit for Good Clinical Practice (GCP).The study consisted of four visits: two screening visits, and two intervention visits with inhalation of either placebo or 40x0.5 mg of terbutaline. Each visit was separated by 5–10 days.

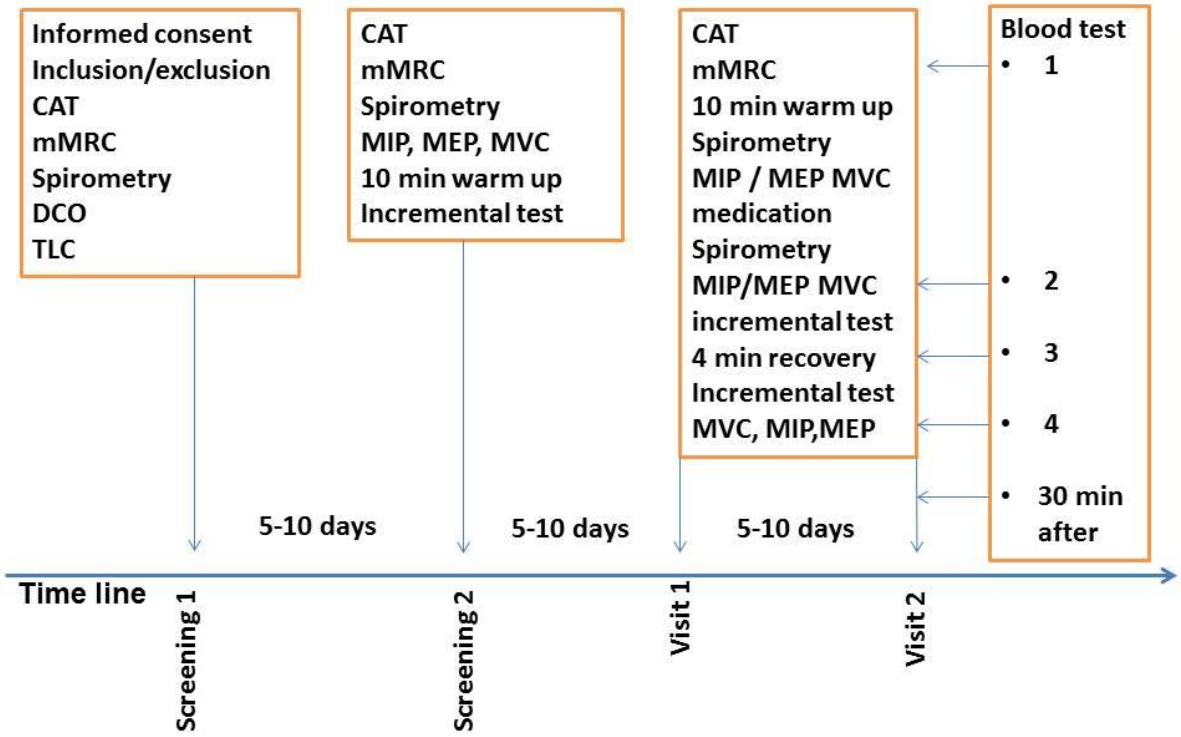
At the first screening visit, participants completed two self-administered disease-specific questionnaires, the COPD Assessment Test (CAT) and the modified Medical Research Council (mMRC). The dynamic lung function as forced expiratory volume (FEV1), forced vital capacity (FVC), total lung capacity (TLC) by body plethysmography and diffusion lung transfer of carbon monoxide (DLCO) were then determined.

At the second screening visit, participants performed the incremental cycling test and all the study procedures to familiarize themselves with the procedures.

At the two intervention visits, the participants filled out the CAT and mMRC before any of the study procedures. Then tested for maximal inspiratory and expiratory mouth pressures (MIP/MEP) and maximum voluntary contraction of the quadriceps muscle (MVC). They performed two incremental exercise tests on a bike ergometer separated by 4 min of passive recovery. The primary end-point was the time to exhaustion and the maximum oxygen consumption (VO2Max) at each incremental test. The two intervention visits took place at the same time of the day and participants were instructed not to eat or drink, but this was not checked, and, if possible, to use the same amount of inhaled medicine on the day of testing. Terbutaline was administered using a 0.5 mg turbohaler, the placebo used was a Bricanyl turbohaler dummy. Patients were informed about relevant side effects such as tremor and tachycardia. Medication was administered 20 minutes before the incremental test but after 10 minutes' warm up at 20 watt. Spirometry, MIP, MEP and MVC were performed before and after medication. MIP, MEP and MVC were performed just after the second exercise bout. Blood samples were collected before and after medication, after the first and second exercise bout and 30 minutes after the second exercise bout. Informed consent was obtained at screening before the individuals enrolled in the study. The consent and all procedures were approved by the local ethics committee of

Copenhagen, Denmark (H-1-2011-080) and by the Danish Health and Medicines Authority (EudraCT nr 2011-002987-26).

Flowchart



Inclusion and exclusion criteria

The study comprised 11 participants with an FEV1 less than 50% of predicted value, an FEV1/FVC ratio less than 0.7 and a smoking history of more than 20 pack-years. The participants were recruited from the pulmonary outpatient clinic at Bispebjerg University Hospital, Copenhagen, Denmark. Participants were excluded if they had pulmonary diseases other than COPD, such as fibrosis, asthma, tuberculosis; required domiciliary oxygen; or had a history of cancer 5 years prior to the study. Participants were also excluded if they had an exacerbation of COPD within 6 weeks of study entry; if they were participating in a pulmonary rehabilitation program; or if they had cardiovascular disease contradictive of strenuous exercise, for example, heart failure, atrial fibrillation or conditions treated with beta blockers.

Questionnaires: All patients completed the COPD Assessment Test (CAT) and the modified Medical Research Council dyspnea (mMRC). The tests were performed prior to any study procedures all visits to ensure that the patients were stable and did not have large day-to-day variations.

Dynamic and static lung function testing: Spirometry was performed using EasyOne spirometer (Spiropharma®) and the percentage of predicted normal values of FEV1 (FEV1%), FVC of predicted normal value (FVC%), and the FEV1/FVC ratio were calculated according to ATS/ERS (2005) guidelines.

DLCO: This was measured using a Jaeger MS-PFT Analyzer Unit according to ATS/ERS guidelines[11].

TLC: Total Lung Capacity and functional residual capacity (FRC) were measured using a Jaeger Masterscreen Body Plethysmograph according to ATS/ERS guidelines[12].

Maximal Expiratory Pressure (MEP) and Maximal Inspiratory Pressure (MIP): These were measured using a manovacuometer (MicroRPM, CareFusion®). The manovacuometer was used according to the manufacture's guidelines (ATS/ERS 2002). During each measurement the participant held the maximum pressure for approximately one second[13]. MIP was measured four times, always before measurement of MEP. The mean value of

the two highest values was noted. If the variation for the two highest measurements was more than 10%, additional measurements were performed.

Determination of VO2max: An incremental bike test with breath-by-breath measurements was performed. Pulmonary oxygen uptake (VO_2) was measured using a gas analyzing system (JAEGER MasterScreen CPX; Viasys Healthcare GmbH, Hoechberg, DE). Calibration was done with a 3-l syringe and with gasses of known O_2 and CO_2 concentrations. Patients were instructed to pedal with a cadence of 60–90 revolutions per minute (rpm). The test stopped when pedaling frequency fell below 50 rpm for more than 5s. VO2max was determined as the highest value over 30s.

Incremental exercise tests: Two incremental exercise tests were performed seperated by 4 minutes' passive recovery. Both tests started at 10W and increased 15W each minute until exhaustion. Breath-by-breath measurements were taken during both tests.

Maximal voluntary isometric contraction (MVC): MVC of m. quadriceps was measured with the participant sitting on a table with the right leg fixed and flexed in a knee joint angle of 90°. The ankle was attached to a strain gauge (Tedea-Huntleigh, United Kingdom) proximal to the malleoli. To ensure the participant remained in the same position during the MVC, three Velcro strips were secured around the chest, hip and thighs. To reduce day-to-day variation, the individual's exact body position was registered and used throughout the entire experiment. The maximal force developed during the MVC was defined during a 3-second plateau. The highest value was defined as the individual's MVC. The force transducers were connected to an amplifier (Powerlab/16SP og Octal bridge AMP model ML 228) linked to a personal computer (labchart 7.0) to display force signals for off-line analysis.

Incremental Peak Power Output (IPPO): The maximum W achieved divided by the total seconds used.

VE: Ventilation in liters per minute measured at exhaustion during the incremental exercise tests.

Blood analysis: Blood analyses for lactate, glucose and potassium were done using the ABL 800 flex Radiometer. Blood was drawn before the incremental test, every 2 minutes during exercise and 10 minutes after exercise and kept on ice until analyzed.

Biomarkers: IL-6, IL-8 and TNF-α were measured with Quantikine HS ELISA high sensitivity (R&D systems, Minneapolis, USA) enzyme-linked immunosorbent assay kit. Procedures were done following the protocol issued by the manufacturer and measured in duplicates. Surfactant protein D : Assay-type: Sandwich ELISA based on 2 antibodies.

HsCRP: Tna-quant cardiac C-reactive protein (latex) high sensitivity, Roche/Hitachi 904, measurement interval 0–20 mg/l. Preparation and procedures were done following the protocol issued by the manufacturer and measured in duplicates.

Statistics

Data were analyzed using the statistical IBM pack SPSS Statistics 19 for Windows (USA;2012). Data were tested for normality using a Shapiro-Wilks test and by Q-Q plots. Data were normally distributed and are expressed in mean +/- standard deviation (SD). Differences between treatments in blood markers, MIP, MEP, FEV1, IPPO, VO2 max and MVC were tested in a two-way repeated measure analysis of the variance (ANOVA). In the event of a significant ANOVA, a Bonferroni post-hoc test was used to correct for familywise errors. A p-value of < 0.05 was considered statistically significant. Differences in venous IL-6, IL-8, TNF-α, glucose, lactate and potassium were analyzed with a two-way repeated measures ANOVA (treatment x time). In the event of a significant main or interaction effect, a Student-Newman-Keuls post-hoc test was used to identify pair-wise differences.

Results

Lung function and respiratory muscle strength

FEV1 and FVC were higher (p<0.001 and P<0.05) after inhalation with terbutaline than with placebo. MIP was higher (P < 0.05) for terbutaline than for placebo before exercise (Table 2). At exhaustion, MIP had decreased for both treatments, although it was higher for terbutaline (p< 0.05). There was no difference in MEP before and after exercise in either treatment.

Table 2

Lung function values before and after administration of terbutaline / placebo and after the second incremental test.

	Terbutaline			Placebo		
	Pre	**Post**	**End**	**Pre**	**Post**	**End**
FEV1)	**1.27**	**1.47***		**1.33**	**1.31**	
FVC (l)	**2.85**	**3.01***		**2.83**	**2.88**	
MIP	**72.8**	**84.5**	**77.0**	**81.3**	**80.6**	**67.4#**
MEP	**119.1**	**112.3**	**109.5**	**110.4**	**113.4**	**103.7**

FEV1: Forced expiratory Volume in 1 second, FVC: Forced Vital Capacity, MIP: Maximal Inspirratory Pressure, MEP: Maximal Expiratory Pressure, *****P< 0.05 different from placebo # P< 0.05 different from pre and post-exercise.End= after the second incremental test

Incremental exercise performance

During both bouts, (TTE) VO2max and IPPO increased (p<0.05) with terbutaline compared with placebo (Table 3). Tidal volumes and VEmax during both exercise bouts were higher with terbutaline (p<0.05) than with placebo.

Table 3

Time to Exhaustion and respiratory parameters at first and second incremental test

Mean(SD)	First bout		Second bout	
	placebo	terbutaline	Placebo	terbutaline
TTE (s)	400(104)	431(114)*	391(98)	407(102)*
$VO2_{max}$ (ml/min)	1369(299)	1461(345)*	1377(311)	1463(320)*
VEmax (l/min)	52,5(14,1)	58,8(13,2)*	53,6(14,3)	60,6(13,2)*
BF /min	33,4(6,1)	34,4(4,6)	35,4(6,2)	35,9(4,6)
Tidal Volume L	1,58(0,2)	1,72(0,3)*	1,53(0,2)	1,69(0,2)*
IPPO W	110,0(26,0)	117,8(28,4)*	107,8(24,5)	111,6(25,6)*
SaO2 at rest	97,1(0,6)	97,0(1,2)	NA	NA
SaO_2 at TTE	91,6(2,9)#	91,9(4,3)#	91,6(3,1)#	92,5(4,6)#

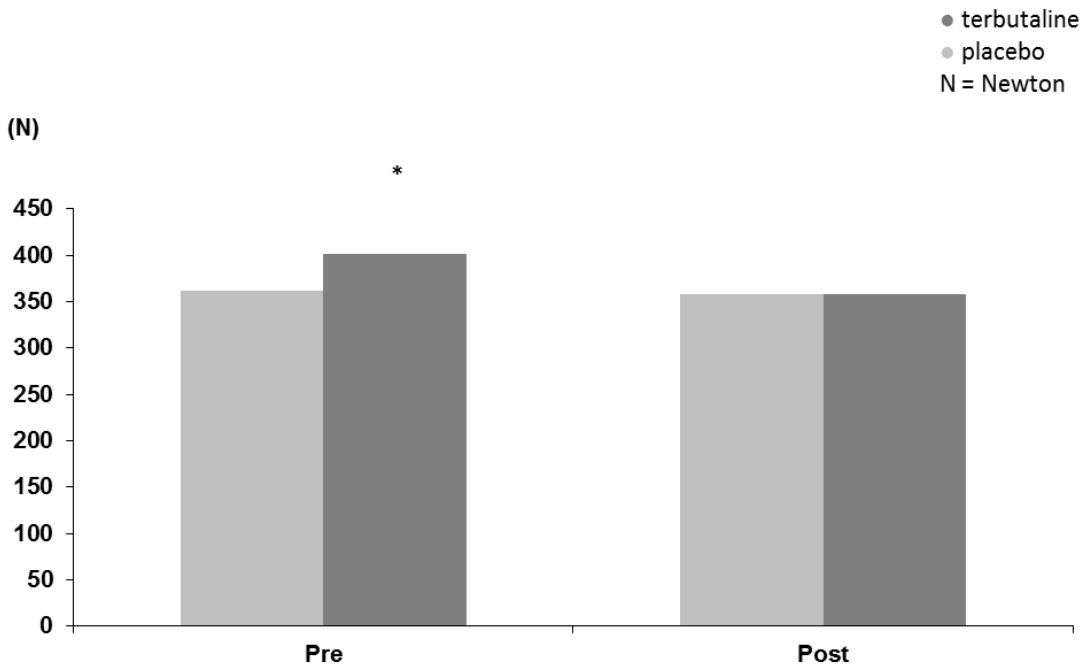
TTE, Time TO Exhaustion. VO2max, Maximal oxygen consumption. VEmax(l/min), Maximal minute ventilation. BF/min, Breath Frequency/ minute. IPPO W, Incremental Peak Power Output in Watt. SaO2, oxygen saturation. *Significant from terbutaline vs placebo $p< 0.05$ # Significant from rest to end of the incremental test.

Maximal isometric voluntary contraction of the quadriceps muscle

MVC was higher (P < 0.05) for terbutaline than for placebo with a mean value of 401 (121) vs. 362 (125), respectively, before exercise but was not different between treatments at exhaustion 358 (117) vs. 357 (129) (Figure 1).

Figure 1

Maximal voluntary isometric contraction (MVC)



Inflammatory biomarkers

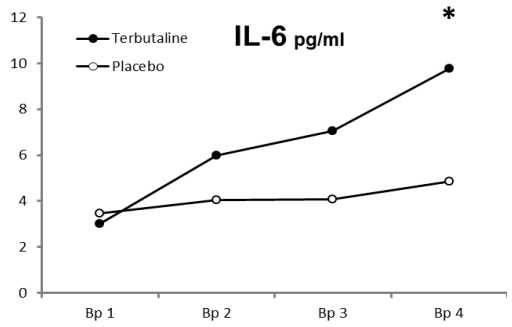
There were no differences in IL-6 concentrations between treatments at B1 and B2, but IL-6 concentrations were higher (P<0.05) for terbutaline compared with placebo at B4 and tended to be higher at B3 (p=0.07). For terbutaline, IL-6 increased (p<0.05) gradually from B1 to B4, whereas no difference was observed between any time points with placebo.

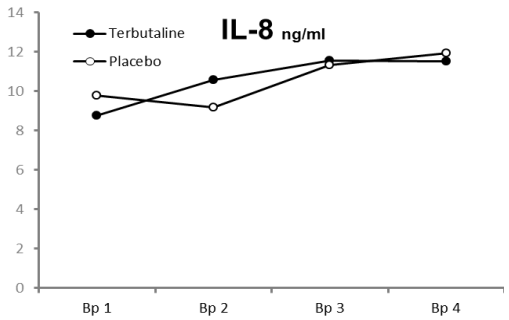
There were no differences in TNF-α, IL-8, HsCRP or SP-D concentrations between treatments or sampling points (Figure 2).

Figure 2

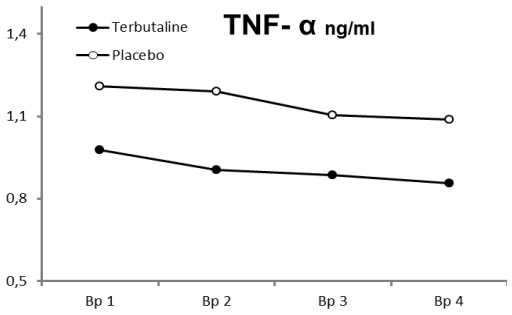
Inflammatory biomarkers

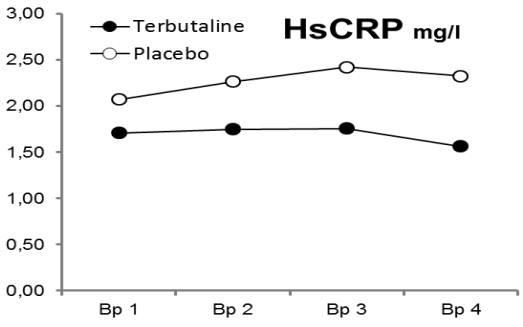
Bp 1= before first incremental test, Bp 2= after first incremental test, Bp 3= after second incremental test, Bp 4= 30 minuttes after second incremental test.

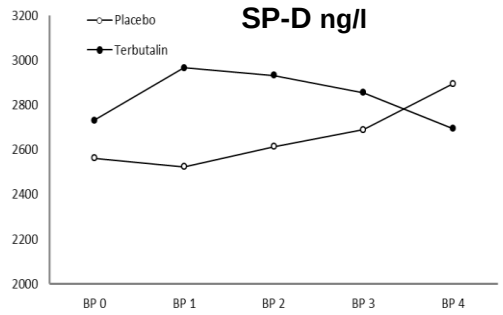




*P< 0.05





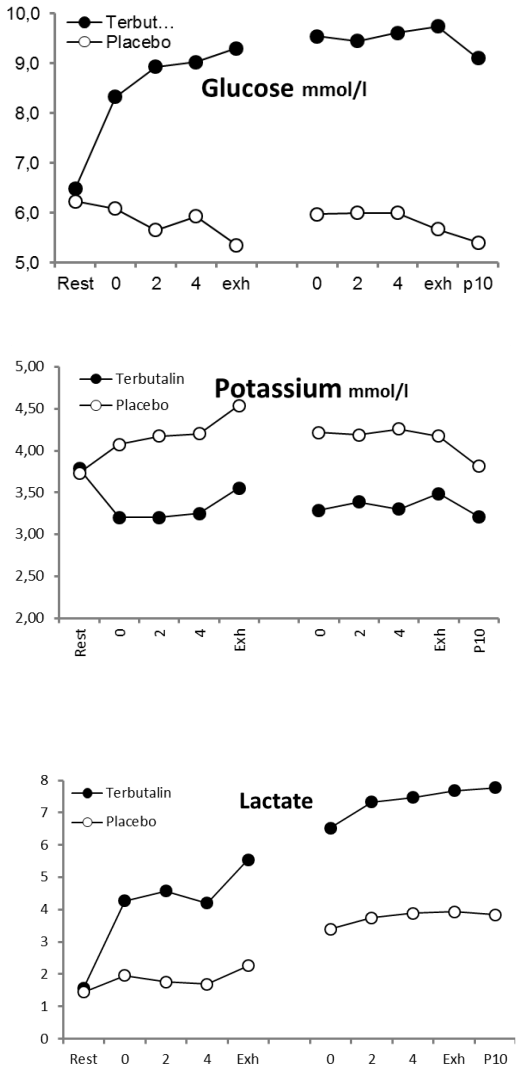


Blood samples of level of beta2-agonist, glucose, potassium and lactate

Venous glucose and lactate were higher ($p<0.05$) for all sampling points (apart from before drug administration) with terbutaline compared with placebo. Venous potassium was lower ($p<0.05$) for all sampling points (apart from before drug administration) with terbutaline compared with placebo. (Fig 3).Level of beta2-agonist was found to be higher after inhalation of terbutaline 27.13(11.21) compared with placebo 1.19 (2.10), which supported the randomization.

Figure 3

Glucose, potassium and lactate.



Discussion

The most important findings of the present study were that administration of high doses of terbutaline increased VO2max, IPPO, tidal volumes and minute ventilation as well as quadriceps muscle strength in patients with severe COPD. Additionally, terbutaline elevated plasma IL-6 during exercise.

To our knowledge, the present study is the first to investigate the effects of high doses of inhaled terbutaline on incremental exercise, muscle strength and inflammatory biomarkers in patients with severe COPD. High doses of terbutaline resulted in markedly lowered plasma K+ and elevated levels of glucose and lactate.

High-dose inhaled terbutaline improved FEV1, FVC, tidal volume and minute ventilation in both incremental tests. Likewise, performance (IPPO) was enhanced by 7.8 W with a concurrent increase in VO2max of 92 ml/min after inhalation of terbutaline. Previous studies investigating the effects of beta2-agonists on VO2max and exercise capacity in patients with COPD the results have been inconclusive, possibly due to differences in using low doses and various exercise protocols. For example, we used the CPET breath-by-breath measurement as it measures oxygen consumption both during and after exercise. However, our positive findings regarding VO2max and IPPO might be an outcome of improved lung function as both FEV1 and FVC increased with treatment of terbutaline, which was associated with an increased tidal volume and minute ventilation. It is plausible that the improved ventilation increased the supply of oxygen to the circulation and therefore improved oxygen uptake, leading to higher VO2max and IPPO. Accordingly, the reduction of the airway resistance had substantial benefits on exercise performance, which indicates that the disparity between our results and those of others could be due to our use of a markedly higher dose.

A meta-analysis of clinical trials of pulmonary rehabilitation in patients with COPD suggested a minimum clinically important difference (MCID) of 8.3 W (95% CI 2.8–16.5) in maximum exercise capacity using the incremental cycling test[14] . The IPPO of the present study was just short of that (7.8 W). However, the MCID was based on patients attending a pulmonary rehabilitation program opposed to the patients in the present study, who all had a low CAT score (9.3), thereby representing a patient subgroup not eligible for pulmonary

rehabilitation. Likewise, a meta-analysis from 2008 suggests different MCID for different disease severities when using the 6-min walking distance[15]; this should also be taken into consideration when using other exercise protocols. Our observations support the recent findings that short-acting bronchodilators as addition to regular use of LAMA or LABA therapy improve exercise tolerance[16] .

An important finding of the present study was that inhalation of terbutaline increased quadriceps muscle strength, which could be attributed to an extra-pulmonary effect. The observation of enhanced muscle strength induced by beta2-agonist is in agreement with previous studies conducted in healthy subjects[17]. The effects of beta2-agonists on muscle strength have been suggested to be mediated via cAMP-dependent PKA-phosphorylation of various proteins in skeletal muscles, including proteins involved in Ca2+ release and uptake along with proteins involved in ion homeostasis[18]. The MVC is considered as a measure independent of lung function and dyspnea, and therefore the increased muscle strength observed with terbutaline in the present study clearly shows a systemic effect of terbutaline on skeletal muscle. Despite MVC not being a good marker of aerobic exercise capacity, it cannot be excluded that increased muscle strength contributed to the improved exercise capacity. Furthermore, increased muscle strength may aid COPD patients in accomplishing daily tasks more easily and hence improve quality of life[19] . The maximal inspiratory pressure was significantly higher after exercise with terbutaline. This finding should be interpreted with caution because the inspiratory pressures could vary at different lung volumes. In patients with abnormally high lung volumes (e.g., patients with COPD), a low MIP may partly reflect the shortened inspiratory muscle fiber length with increased lung volume rather than reduced inspiratory muscle strength[20]. Inspiratory capacity (IC) as a measure of dynamic hyperinflation was not measured, but the lower tidal volumes observed at the TTE with placebo could indicate a higher residual volume, leading to a lower MIP.

To our knowledge, this is the first study to investigate the effect of beta2-agonist on inflammatory biomarkers during exercise in patients with COPD. An interesting observation is that terbutaline elevated plasma IL-6 during exercise. In support of this, IL-6 has also been shown to increase during acute exacerbations of COPD[21], where high doses of beta2-agonists are often administered. Consistent with our observations, Kalsen

and co-workers[22] observed a marked elevation in plasma IL-6 in elite swimmers after intake of beta2-agonist. The elevated plasma levels IL-6 induced with beta2-agonist may be caused through increased glycogenolysis in the skeletal muscles leading to decreased muscle glycogen, which has been shown to increase IL-6 mRNA expression[23].

IL-6 levels can increase a 100-fold during exercise in healthy individuals[24]. A similar response has not been found in COPD patients. Hannik et al. found a small but significant increase in IL-6 levels in response to a constant workload of 40W [25] opposed to our study where terbutaline induced an almost three-fold increase compared with no response with placebo. Van Helvoort found an acute systemic response to a single bout of exercise in leucocytes, but not in CRP, during an incremental cycling test of 8–12 minutes,[26] which is in line with our findings where HsCRP was unchanged at both study visits. An increase in HsCRP could have been expected because IL-6 is known to elevate the levels of HsCRP[27].

IL-8 and SP-D were unchanged during both study visits, indicating no effect of terbutaline on exercise.

Rabinovich et al. found TNF-α levels were significantly increased after exercise in COPD patients, which is in contrast to our findings[28]. The differences may be due to differences in using incremental or constant workload protocols. Our findings are in line with observations in healthy individuals, where TNF-α does not increase during exercise[29].

Strengths

All the procedures were conducted in the same manner at each study visit and the two study visits were separated by one week, which is longer than 6 times the elimination half-life of terbutaline and therefore no carry-over effect was observed. The study was monitored by the GCP (Good Clinical Practice) unit at the University of Copenhagen.

Limitations

The high doses of terbutaline we administered resulted in tremor and tachycardia, which may have influenced the blinding of the study. Because all patients were on either LAMA or LABA, an influence on FEV1 and FVC was not expected. To eliminate these differences on the study visits, we could have selected patients less responsiveness to therapeutic doses of SABA/SAMA, thereby securing better control of their regularly inhaled medication. The measuring of IC would have provided more detailed knowledge of the degree of dynamic hyperinflation during exercise. Lastly the number of participants should be taken in consideration.

Conclusion

To conclude, high doses of inhaled terbutaline increased FEV1 and FVC as well as VO2max, IPPO, tidal volumes and minute ventilation during two incremental exercise tests in patients with severe COPD. Additionally, terbutaline enhanced quadriceps muscle strength. These positive effects of high-dose terbutaline may be beneficial as an integrated tool in pulmonary rehabilitation programs where improving exercise tolerance is one of the main objectives. Moreover, we found that terbutaline elevated plasma IL-6. Whether this approach could be applied to other short-acting beta2-agonists or whether lower doses could be used should be investigated in future studies.

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