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Tiotropium improves walking endurance in chronic obstructive pulmonary disease

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ABSTRACT

Rationale : The primary objective of this study was to evaluate the effects of a 3-week treatment with tiotropium on walking capacity in chronic obstructive pulmonary disease (COPD).

Methods: After familiarization with study procedures, 36 patients were randomized to receive tiotropium 18 µg OD or matching placebo in a double-blind and parallel-group study. Pre (trough) and 2-hour post-dose pulmonary function was measured. An endurance shuttle walk was then completed. The same procedures were repeated after 3 weeks of treatment. Ventilatory parameters were monitored during exercise.

Results: At 3 weeks, tiotropium significantly improved walking endurance time over placebo with a between-group difference of 128 ± 141 sec, $p = 0.017$. At 3 weeks, trough values for FEV_1 and FVC were significantly improved with tiotropium in comparison to placebo. The post-dose response to tiotropium was statistically superior to placebo after the first dose and after 3 weeks of treatment for FEV_1, FVC and inspiratory capacity. Ventilation and tidal volume at the end of walking were significantly improved with tiotropium.

Conclusion: Three weeks of tiotropium resulted in a greater walking endurance in patients with COPD. Improvements in FEV_1, maximal ventilation and tidal volume may contribute to this enhanced exercise capacity.

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INTRODUCTION

Long-acting bronchodilators such as tiotropium, aclidinium, salmeterol and formeterol are effective in improving exercise tolerance in patients with chronic obstructive pulmonary disease (COPD). In well-designed, randomized, placebo controlled trials, these bronchodilators have been convincingly shown to improve endurance time, dyspnea and hyperinflation during constant-load cycling endurance tests in COPD[1-5]. Although the symptomatic and functional benefit associated with these drugs is felt to be clinically relevant, important issues remain to be resolved in this regard. For instance, we do not know whether the observed improvement in cycling capacity translates into better performance in different activities of daily living such as walking.

We recently documented, in clinical trials, the responsiveness of the endurance shuttle walk test (ESWT) to detect improvement in functional status following the administration of ipratropium bromide[6] and salmeterol[7] in patients with COPD. The ESWT appears as an exercise testing modality that is particularly well suited to evaluate the efficacy of pharmacotherapy in COPD because it is more responsive than the 6-minute walking test in this context[8] and may be more relevant to activities of daily living compared to cycling. Based on these observations, we reasoned that tiotropium should also improve walking time during an ESWT in COPD.

The primary objective of this study was to compare, at three weeks, the efficacy of tiotropium to improve walking endurance time in comparison to placebo in patients with COPD. Secondary objectives were to assess changes in endurance time after the first dose of study medication as well as the changes in pulmonary function after the first dose of study medication and at 3 weeks in comparison to baseline. We also assessed the impact of study treatment on the physiological responses to exercise at 3 weeks in comparison to baseline.

MATERIALS AND METHODS

Study population

Subjects included in this study were clinically stable patients with COPD aged 50 years or older with a forced expiratory volume in one second (FEV_1) ≤ 70% of the predicted value, a FEV_1/forced vital capacity (FVC) < 70% and a smoking history of ≥ 10 pack-years. Exclusion criteria were as follows: (1) COPD exacerbation in the last 2 months, (2) history of asthma, (3) supplemental oxygen therapy or significant O_2 desaturation (SaO_2 < 85%) at rest or during exercise. Patients with a history of left ventricular dysfunction (left ventricular ejection fraction < 50%), a diagnostic of cancer within the past 5 years, neuromuscular or locomotive impairment affecting the ability to walk were also excluded. In case of COPD exacerbation during the study protocol, patients were treated as recommended by the investigator and withdrawn from the study. This was done because patients would not have time to fully recover before the assessment of the primary endpoint in this 3-week duration study. Patients were not involved in pulmonary rehabilitation at the time of the study. The research protocol was approved by the institutional ethics committee, and a signed, informed consent was obtained from each subject.

Study design

This single centre, double-blind, randomized, parallel-group study required 5 visits to the research facility. All study procedures, including the recruitment of patients, were performed at the *Institut Universitaire de cardiologie et de pneumologie de Québec*, a tertiary care hospital which is the referral hospital for respiratory diseases in the eastern part of the province of Quebec in Canada. The first visit included review of the consent form, pulmonary function testing and one maximal incremental shuttle walk test (ISWT). The following two visits were used to familiarize participants to the ESWT and establish their baseline endurance time. The goal of the familiarization was to reduce the learning effect that typically occurs when an individual completes the same endurance test several times[9]. One additional ESWT could be performed on a subsequent visit in case of non-reproducibility of their endurance time (difference > 2 minutes or 10%) on visits 2 and 3. If reproducibility was not reached despite this

supplementary visit, the patient was excluded. If the endurance time was longer than 20 minutes at the maximal walking speed, the patient was also excluded.

At visit 4, patients were randomized to receive one of the following two treatments for 3 weeks: placebo or tiotropium (Spiriva®) 18 μg once daily, in a double-blind fashion using the HandiHaler® device (Boehringer Ingelheim), which was identical in appearance between the placebo and the active medication. Randomization was performed by the study pharmacist using a randomization table. The study medication was provided by the pharmacist who ensured concealment of allocation and kept a log of the allocation group for each recruited patient. Pulmonary function testing was performed before (pre-dose) and 120 ± 20 minutes after (post-dose) inhalation of the first study dose. An ESWT was then performed. Patients were provided enough medication for the study duration and discharged. The same procedures were completed three weeks later, at visit 5.

The following medications were allowed throughout the study if used for at least 4 weeks before the trial: as-needed short-acting β_2-agonists (stopped 6 hours preceding visit 2 to 5), long-acting β_2-agonists (stopped 48 hours preceding visit 2 to 5), inhaled corticosteroids and combination of long-acting β_2-agonists and inhaled corticosteroids (stopped 48 hours preceding visit 2 to 5). Patients on tiotropium were switched to ipratropium bromide 40 μg QID at least 4 weeks prior to the trial. Ipratropium bromide was not taken in the 6-hour period preceding visit 2 and 3 and its use was not allowed starting 6 hours prior to visit 4 and for the remaining of the study. Theophyllines were not allowed.

The sponsor (Boehringer Ingelheim and Pfizer) was not involved in the study design, data collection, analysis or interpretation. The sponsor had the opportunity to read and comment on the manuscript with no obligation for the authors to incorporate any suggestion into the final version.

Outcome variables

The primary outcome of this study was the change in endurance time at 3 weeks (visit 5) versus baseline (the last familiarization ESWT). Secondary outcomes

included: *i)* change in endurance time after the first dose of study medication (visit 4) versus baseline, *ii)* trough (pre-dose) pulmonary function at 3 weeks (visit 5) in comparison to baseline (pre-dose values at visit 4), *iii)* changes in pulmonary function after the first dose of study medication (visit 4) and after the last dose of study medication in comparison to baseline, and *iv)* impact of study treatment on the physiological response to exercise at 3 weeks in comparison to baseline.

Study procedures

Pulmonary function testing. Standard pulmonary function testing, including spirometry, lung volumes and diffusing capacity of the lung for carbon monoxide (DL_{CO}) were measured at the first visit according to previously described guidelines[10-12]. Results were compared with predicted normal values from the European Community for Coal and Steel/European Respiratory Society[13]. Spirometry and lung volumes measurements were repeated before and 120 ± 20 minutes after inhalation of study medication at visits 4 and 5.

Incremental shuttle walk test. Peak walking capacity was determined with the incremental shuttle walk test. As originally described by Singh and colleagues[14], the test was performed in an enclosed corridor on a flat 10 meters long course. The course was identified by two cones, each positioned 0.50 meters from either end to allow patients to walk in a circle and avoid the need for abrupt changes in direction. Patients walked at a predetermined rhythm, as dictated by an audio signal emitted at each end of the course. Walking speed was initially set at 0.50 m/sec and then increased by 0.17 m/sec every minute until the patient reached a symptom-limited maximal capacity. Patients received standardized instructions to walk for as long as possible. Encouragement was provided to ensure maximal performance during the test.

Endurance shuttle walk test. Endurance walking capacity was determined with the endurance shuttle waking test (ESWT). It was performed on the same course as the incremental shuttle walk test in accordance with published guidelines[15]. After 90 seconds of warm-up, walking speed was set at the speed corresponding to 80% of peak $\dot{V}O_2$, as predicted from the incremental shuttle walk test. Before each ESWT, patients

received standardized instructions to walk for as long as possible although there was a pre-determined 20-minute maximum. Since the effects of encouragement on walking performance have been demonstrated[16], no encouragement was given to patients throughout the test. Reproducibility criteria were set at ≤ 2 minutes or 10% between consecutive ESWT. The final measure was endurance time, expressed in seconds, excluding the 90 seconds warm-up period. The ESWT was supervised without knowledge of the spirometry results. The proposed minimal important difference for this test is 65 sec [95% CI 45 - 85][17].

Physiological measures. During each exercise test, cardiac and ventilatory parameters (heart rate, pulse oxygen saturation (SpO_2), respiratory rate, ventilation and gas exchange) were measured and recorded using a portable metabolic system (Oxycon Mobile, Jaeger, Viasys Healthcare GmbH, Germany). This system, both light and compact, allows breath-by-breath measurement of pulmonary gas exchange parameters during exercise. It consists of a facemask, electrocardiogram recording, pulse oximeter, battery, transmitting unit and receiving unit. The volume sensor and gas analyzers were calibrated before each test. The intensity of dyspnea and perception of leg fatigue were evaluated at rest and at end-exercise using the modified 10-point Borg scale[18]. The intensity of dyspnea was also evaluated with this scale at two-minute intervals during the exercise tests. At the end of each test, patients were asked to identify the main reason for stopping the test.

Statistical analysis

Results are reported as means ± standard deviations, except in the figures were standard errors are used for clarity purposes. The sample size calculation was based on the premise that the improvements in the walking endurance time with tiotropium should be of similar magnitude to that seen with ipratropium bromide in a previous study (164 sec) with a similar standard deviation (177 sec)[6]. It was calculated that 17 patients in each treatment arm would be necessary for this study to reach a power of 0.80 at the 0.05 level of significance with a two-tailed statistical test. Taking into account a 25% attrition rate, we planned to recruit 45 patients for this study. Between-group comparisons for baseline characteristics were performed using unpaired *Student t-tests*. The *chi-square* test was used for categorical variables. Normality assumption

was verified with the *Shapiro-Wilk*'s test. Between group differences were calculated when appropriate. The effects of treatment on walking endurance time were analyzed with a repeated measures ANOVA in which a heterogeneous residual variance model specific to time of measurements was adjusted. The changes in pulmonary function parameters and in physiological variables during exercise were also analysed with a repeated measures ANOVA model. Isotime was defined as the latest exercise time that was reached both at baseline and at three weeks (visit 5) during the ESWT. Significance level was set at the 0.05 level for all analyses.

RESULTS

Subjects

The study flow-chart is presented in figure 1. Sixty-eight patients were screened, with 32 were excluded due to various ineligibility reasons. Thus, 36 patients were randomized in a 1:1 ratio to tiotropium or placebo at visit 4. One patient in each group failed to complete the protocol because of a COPD exacerbation. Thus, 34 patients constituted analysis set; 17 in the tiotropium arm and 17 in the placebo arm. Subject characteristics are presented in Table 1. About 70% of participants were males. Patients had, on average, moderate to severe airflow obstruction with mild hyperinflation, gas trapping and reduction of DL_{CO} at rest. Peak symptom-limited $\dot{V}O_2$ was reduced, averaging only 17 $ml \cdot kg^{-1} \cdot min^{-1}$, and the ventilatory reserve was reduced with a $\dot{V}_E$/MVV ratio above 90%. Baseline endurance time to constant-load cycling exercise was 390-400 sec. Apart from body mass index which was higher in the tiotropium group in comparison to the control group, the two groups were well matched for baseline characteristics.

Endurance time and walking distance

Group mean changes in walking endurance time after the first study dose of study medication and after three weeks of treatment are shown in figure 2, panel A, while the individual changes in walking endurance time at three weeks are provided in figure 2, panel B. After the first dose, there was no significant change in walking endurance time compared to baseline in either the tiotropium group (38 ± 142 sec) or the placebo group (-29 ± 124 sec). After 3 weeks of treatment, tiotropium was associated with a significant improvement in walking endurance time compared with baseline (132 ± 166 sec, $p < 0.001$) with no change in the placebo groups (4 ± 111 s). The between group difference (tiotropium – placebo) amounted to 128 ± 141, $p = 0.017$. Twelve patients out of 17 (71%) of the active treatment group improved their walking endurance time beyond the minimal important difference for this outcome parameter (65 sec) while this magnitude of improvement was seen in only 4/17 (24%) patients of the placebo group ($p = 0.006$).

Pulmonary function testing

The comparative effects of tiotropium and placebo on pulmonary function are provided in figure 3. At three weeks, the trough values for FEV_1 and FVC were significantly improved with tiotropium in comparison to placebo (tiotropium – placebo): 80 ± 111 ml, p = 0.05 and 174 ± 264 ml, p = 0.043. The reduction in trough functional residual capacity (FRC), residual volume (RV) and total lung capacity tended to be larger with tiotropium compared to placebo but the between-group comparison did not reach statistical significance. The post-dose response to tiotropium was statistically superior to placebo after the first dose of study medication and after three weeks of treatment. The between-group differences at three weeks amounted to: FEV_1 (129 ± 131 ml, p = 0.002), FVC (295 ± 292 ml, p = 0.008), inspiratory capacity (151 ± 217 ml, p = 0.03) and RV (-287 ± 500 ml, p = 0.06). The post-dose reduction in FRC at three weeks with tiotropium compared to placebo was numerically important (-199 ± 547 ml) but this difference did not reach statistical significance. The changes in total lung capacity throughout the study were small and not statistically significant.

Physiological response during ESWT

Changes in physiological response to exercise after three weeks of treatment (visit 5) in comparison to baseline values in both study groups are reported in table 2. In general, the changes were small and not statistically significant. Ventilation and tidal volume at the end of the ESWT were significantly improved at three weeks in the tiotropium group in comparison to placebo. Borg dyspnea score did not change significantly in either group at isotime or peak exercise. Symptoms responsible for exercise limitation were not modified; at baseline 14 patients (83%) of the tiotropium group and 13 patients (76%) in the placebo group stopped because of dyspnea. After three weeks of treatment, 14 patients (83%) in each group stopped because of dyspnea.

DISCUSSION

This study is an additional confirmation that the ESWT enables the detection of functional changes after bronchodilation in patients with COPD. Tiotropium, a long-acting anticholinergic bronchodilator, significantly improved walking capacity in patients with moderate to severe COPD after three weeks of treatment. It also significantly increased expiratory flows and inspiratory capacity while promoting lung deflation. This study provides the first confirmation that tiotropium improves walking capacity beyond the minimal important difference for this outcome in patients with COPD.

The ESWT is a simple field exercise test that was initially developed to assess exercise capacity in patients with COPD[15]. More recently, we assessed the evaluative properties of this exercise testing modality[6-8]. We demonstrated that the ESWT was more sensitive than the constant-load cycling exercise test to detect an improvement in functional status following bronchodilation in patients with COPD[6]. This observation that walking is a well-suited exercise modality to detect improvement in functional status following bronchodilation was further corroborated by other investigators[19]. One likely mechanism for this observation is that walking, as opposed to cycling, induces significantly less quadriceps fatigue[6,20], which is a phenomenon that prevents bronchodilation to fully translate into better exercise capacity[21,22]. The relative magnitude of improvement in walking capacity with tiotropium was larger with the endurance shuttle walking test (32%) than that reported for the incremental shuttle walking test (11%)[23]. This is in keeping with the notion that constant-load based exercise protocols are more responsive than incremental maximum tests[24].

Another attractive feature of the ESWT is that walking is an activity relevant to daily living. Previous studies have documented the ability of tiotropium to improve the 6-min walking distance[25] and the incremental shuttle walking distance[23] but the magnitude of these improvements were small and of unclear clinical significance[26,27]. In contrast, the 128-sec improvement in walking endurance after three weeks of tiotropium in comparison to placebo is clinically important as it was recently suggested that a 65 sec [95% CI 45 - 85] change in the ESWT endurance time is likely to be perceived by patients[17]. In this context, the present study provides clinically relevant

information about the impact of tiotropium on walking capacity. We also noted that the improvement in walking capacity was small after the first dose of tiotropium. This is in conformity with the pharmacology of this medication and with previous studies showing that the exercise enhancing effects of tiotropium are modest after a single dose and increase progressively over a 3-6 week period[1,3,23,25].

The effects of tiotropium on lung function seen in the present study were generally consistent with the expected improvement in expiratory flows reported for this bronchodilator. However, the magnitude of lung deflation was somewhat smaller than in two studies where patients were selected on the basis of a FRC $\geq$ 120% predicted[1,3] and in which the mean FRC was 160-170 % predicted. In the present study, baseline hyperinflation was not a prerequisite for participation and the mean FRC was 135% predicted; as such, the possibility to observe pronounced lung deflation was likely to be reduced.

Monitoring the physiological responses during walking using a portable metabolic system makes it possible to explore the mechanisms of improvement in walking capacity with bronchodilation. In this study we observed, after three weeks of treatment with tiotropium, a significant increase in ventilation and in tidal volume at end-exercise of the ESWT. These improvements were likely to be associated with an improved maximum voluntary ventilatory capacity, a consequence of both bronchodilation with improved maximal expiratory flows and increased inspiratory capacity due to reduced air trapping[28]. A fundamental benefit of bronchodilation is the reduction of operating lung volumes during exercise[28,29]. Although we did not measure inspiratory capacity during exercise, the improved inspiratory capacity at rest prior to exercise indicates that patients were breathing at lower lung volumes at the beginning of exercise, an advantage expected to be maintained throughout the exercise duration[28]. Also the expansion in tidal volume at isotime and end-exercise is a likely reflection of a reduced mechanical constraint and operating lung volumes during exercise[28]. This effect on tidal volume is important given its association with improved exercise tolerance[28].

Some methodological comments should be made about our study to help in its interpretation. Although our experience with the ESWT in assessing the response to

bronchodilation is favourable[6-8], these studies were conducted in a single center and the feasibility of this exercise testing modality in a multicentre setting remains to be confirmed as it was previously done for the endurance cycling exercise test[1,3,5,30]. The measurement of inspiratory capacity is also more challenging during a walking test where the patient is not stationary[7]. This may be viewed as a potential limitation of a walking test as an outcome measure in an exercise study for which a thorough physiological assessment is considered an important objective. The study sample size was too small to fully explore the sensory responses during exercise. A reduction in isotime dyspnea would be an expected consequence of the improved ventilatory mechanics that were observed with tiotropium, but this could not be confirmed in the present study. However the similar dyspnea score at end-exercise between the two groups, in spite of the increased endurance time with tiotropium, may suggest that the rate of increase in dyspnea during walking was reduced following treatment with tiotropium. A larger clinical trial will be useful to address the impact of tiotropium on dyspnea during walking. We did not perform a true intent-to-treat analysis since two patients who presented an exacerbation of their disease were excluded from the analysis, as pre-specified by the study protocol. This analysis strategy is in keeping with studies evaluating the effects of bronchodilation on exercise tolerance in COPD[3,5]. Although the sample size was adequate to provide a clear answer to the research question, it was not sufficiently large to explore the exercise enhancing effects of tiotropium in various subgroups of patients with COPD. We acknowledge the short-term duration of our study. Considering that tiotropium maintains its bronchodilatory properties over time{Tashkin, 2008 #2924}, we suspect that the exercise enhancing effects of this drug should also persist on the long-term. However, a study properly designed to evaluate the long-term impact of tiotropium on walking capacity in COPD will be necessary to address this issue.

In conclusion, the present study demonstrates the ability of tiotropium to significantly improve walking capacity in patients with chronic obstructive pulmonary disease after three weeks of treatment. Reduction of airway obstruction leading to lung deflation and enhanced maximal ventilation and end-exercise tidal volume contribute to this enhanced exercise capacity. This study supports the role of the endurance shuttle walking test in evaluating functional gain and physiological impact of interventions in patients with COPD.

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LEGENDS FOR FIGURES

Figure 1. Study flow. SpO_2: pulse oxygen saturation; FEV_1: forced expiratory volume in one second.

Figure 2. *Group mean changes ± SEM in walking endurance time after the first dose and after 3 weeks of treatment compared to baseline value (panel A) and individual changes in walking endurance time at three weeks (panel B). The grey and black horizaontal lines on panel B represent the group mean change seen in the placebo and tiotropium group, respectively while the dash line represents the minimal important difference for the endurance shuttle waking time (65 sec). The between group difference in the improvement in walking endurance time was statistically significant at 3 weeks whereas it was not after a single dose (p = 0.12). * between-group comparison p = 0.017.*

Figure 3. Mean changes ± SEM in resting pulmonary function. The trough responses at 3 weeks (V5) in comparison to baseline (panel A) and the post study medication responses after the first dose (V4, panel B) and after 3 weeks (V5, panel C) in comparison to baseline are represented. * p = 0.05, † p < 0.05, ‡ p < 0.01, ¶ p = 0.06.

Table 1. Subject characteristics at baseline*

	Placebo n = 17	**Tiotropium n = 17**
Males, n (%)	11 (65%)	12 (71%)
Age, yrs	66 ± 8	64 ± 7
Body mass index, $kg \cdot m^{-2}$	26.0 ± 3.0	29.4 ± 4.4
FEV_1, L	1.42 ± 0.47	1.53 ± 0.51
FEV_1, % of predicted	54 ± 12	53 ± 12
FVC, % of predicted	102 ± 18	99 ± 15
FEV_1/FVC, %	41 ± 10	44 ± 11
FRC, % of predicted	138 ± 22 (n=16)	132 ± 31 (n=16)
TLC, % of predicted	116 ± 12 (n=16)	111 ± 15 (n=16)
RV, % of predicted	148 ± 28 (n=16)	138 ± 37 (n=16)
IC, % of predicted	91 ± 15	86 ± 17
DL_{CO}, % predicted	57 ± 13	56 ± 19
Peak $\dot{V}O_2$, $ml \cdot kg^{-1} \cdot min^{-1}$	17.1 ± 4.4	16.9 ± 4.0
Peak $\dot{V}_E$, $L \cdot min^{-1}$	47.2 ± 17.5	52.0 ± 16.0

Peak $\dot{V}_E$/MVV, %	92 ± 12	94 ± 14
Peak SpO_2 (%)	92 ± 3	91 ± 3
Peak heart rate, beats·min^{-1}	127 ± 14	126 ± 19
Endurance time, sec	391 ± 81	404 ± 114
Respiratory medication, n (%)		
Short-acting ß2 agonists	12 (71)	13 (76)
Long-acting ß2 agonists	3 (18)	3 (18)
Short-acting anticholinergics	1 (6)	1 (6)
Long-acting anticholinergics	6 (35)	6 (35)
Inhaled corticosteroids	2 (12)	1 (6)
Long-acting ß2 agonists/inhaled corticosteroids	7 (41)	12 (71)

*Values are mean ± SD. Definition of abbreviations: FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FRC: functional residual capacity; TLC: total lung capacity; RV: residual volume; IC: inspiratory capacity; DLco: single-breath diffusing capacity of the lung for carbon monoxide; $\dot{V}O_2$: oxygen uptake; $\dot{V}_E$: minute ventilation; MVV: maximum voluntary ventilation; SpO_2: pulse oxygen saturation.

Table 2. Changes in physiological responses to exercise at three weeks compared to baseline *

	Placebo n = 17	**Tiotropium n = 17**	**p†**
$\dot{V}_E$ **, L/min**			
Rest	-0.2 ± 4.1	-0.6 ± 5.2	0.783
Isotime	-0.6 ± 2.6	1.18 ± 5.4	0.240
Peak	-1.2 ± 2.5	2.9 ± 4.2	0.002
RR, breaths/min			
Rest	1.1 ± 4.8	-2.3 ± 5.5	0.064
Isotime	0.8 ± 2.9	-0.8 ± 5.2	0.283
Peak	-0.3 ± 2.6	0.7 ± 3.4	0.319
V_T, ml			
Rest	-70 ± 210	0 ± 320	0.228
Isotime	-40 ± 120	80 ± 200	0.032
Peak	-30 ± 100	60 ± 130	0.026
$\dot{V}O_2$ **, L/min**			
Rest	0.01 ± 0.11	0.00 ± 0.12	0.851
Isotime	-0.02 ± 0.07	0.00 ± 0.11	0.503
Peak	-0.02 ± 0.07	0.02 ± 0.11	0.258
$\dot{V}CO_2$ **, L/min**			
Rest	0.00 ± 0.09	0.04 ± 0.18	0.372
Isotime	-0.05 ± 0.08	0.00 ± 0.15	0.288
Peak	-0.08 ± 0.12	0.04 ± 015	0.023
Dyspnea, Borg			
Rest	0.2 ± 0.7	-0.2 ± 0.7	0.162
Isotime	-0.5 ± 2.0	-0.9 ± 1.7	0.586
Peak	-0.1 ± 0.7	0.1 ± 1.3	0.521
SpO_2			
Rest	0 ± 2	1 ± 1	0.252
Isotime	1 ± 2	2 ± 2	0.281
Peak	1 ± 2	1 ± 2	0.923
Heart rate			
Rest	-3 ± 13	-6 ± 7	0.516
Isotime	-4 ± 10	-3 ± 7	0.886
Peak	-2 ± 17	-1 ± 8	0.751

*Values are mean ± SD. Definition of abbreviations: $\dot{V}_E$: minute ventilation; RR: respiratory rate: $\dot{V}O_2$: oxygen

uptake; $\dot{V}CO_2$: carbon dioxide excretion; SpO_2: pulse oxygen saturation; HR: heart rate. Isotime was defined as the latest exercise time that was reached both at baseline and at three weeks during the ESWT
† between-group comparisons.

Figure 1. Study flow-chart

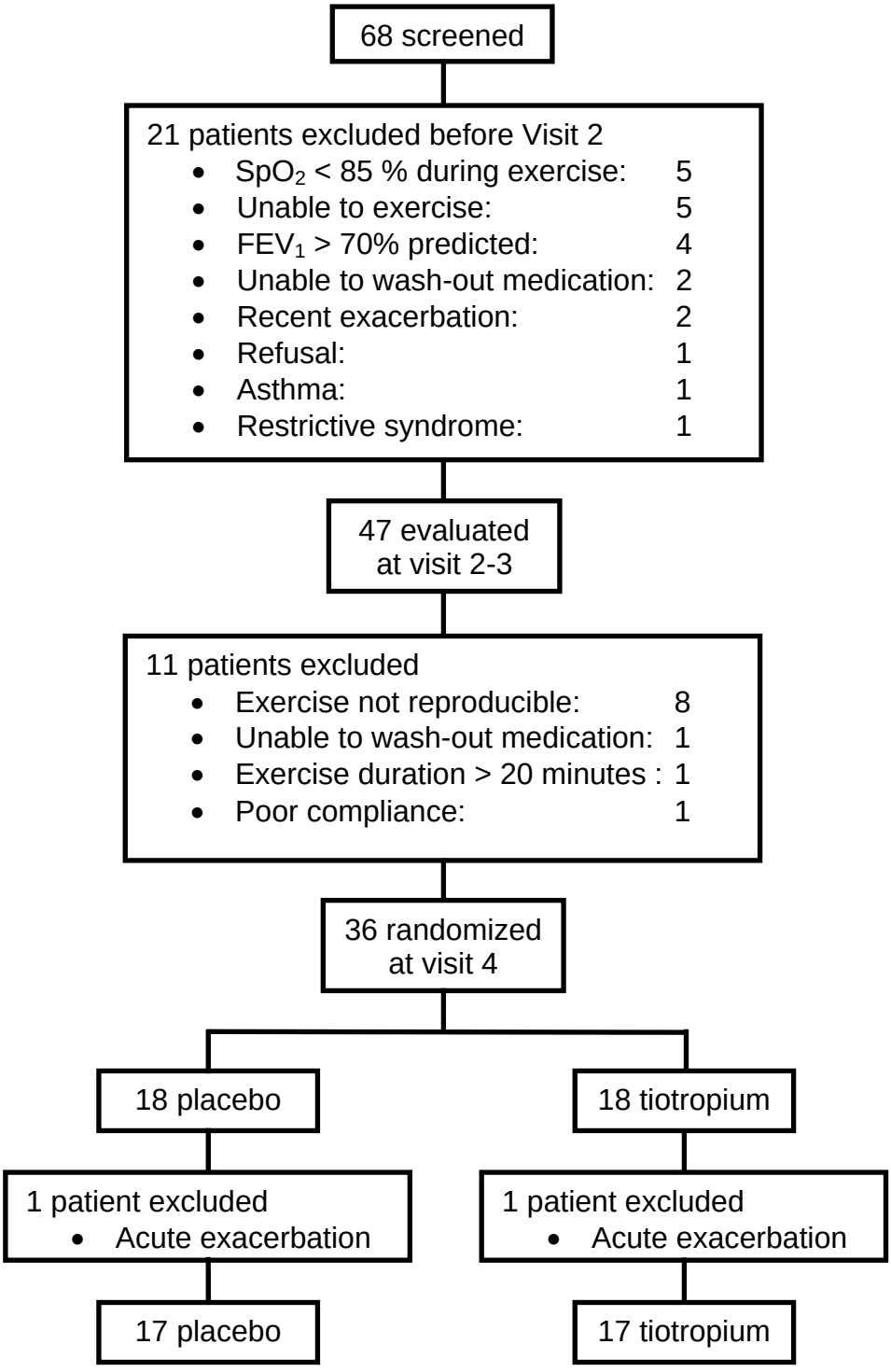


Figure 2. Mean change in endurance time

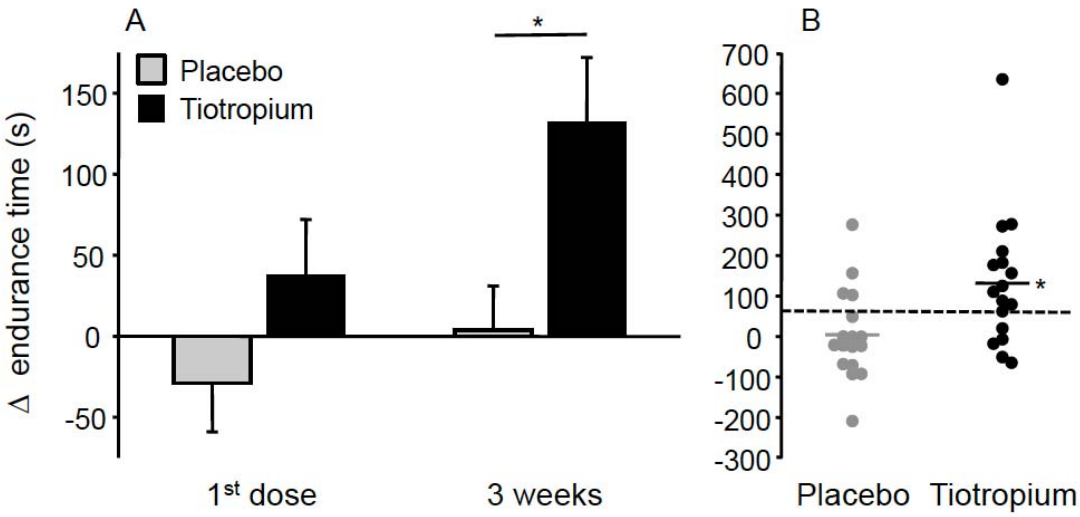
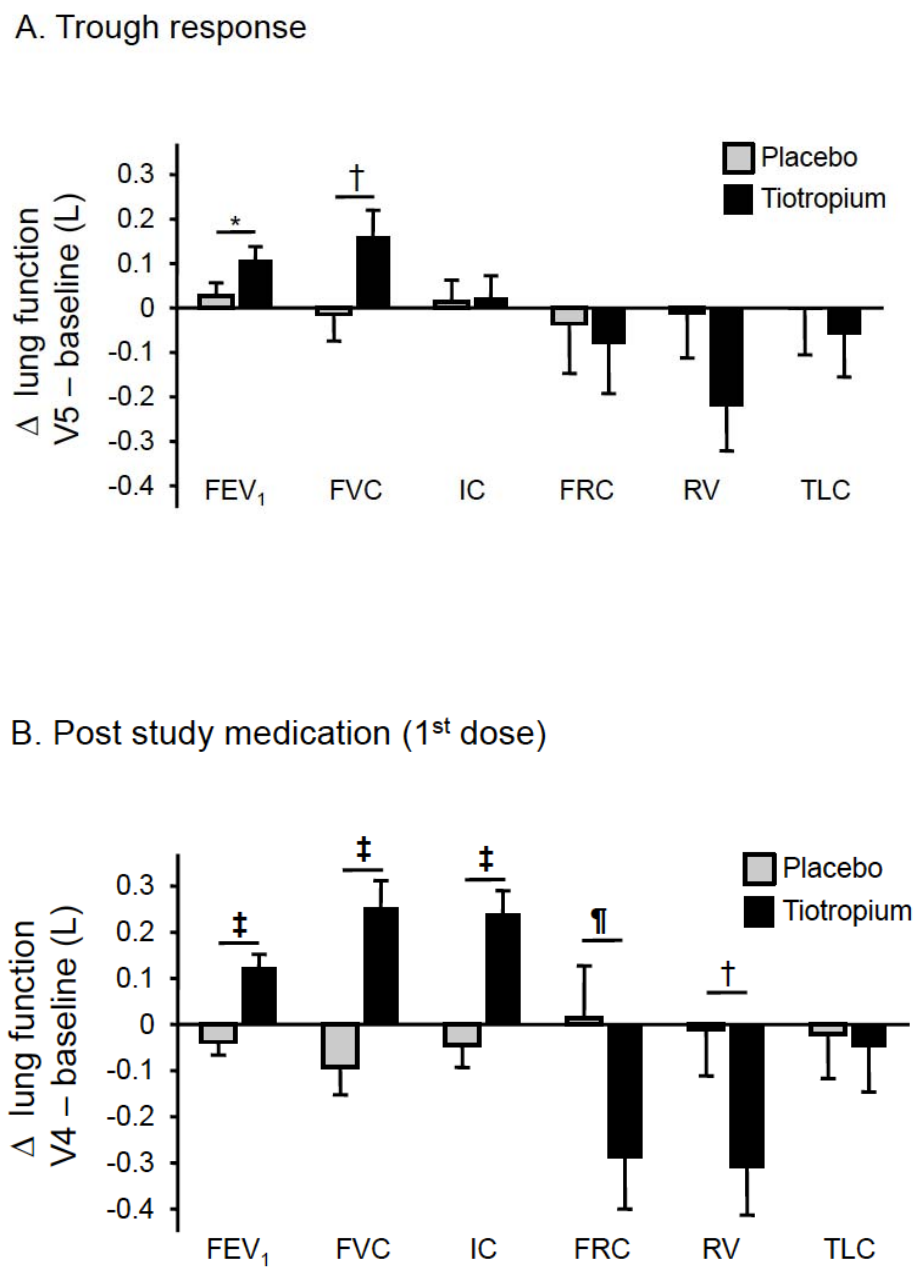


Figure 3. Mean changes in resting pulmonary function.



C. Post study medication (3 weeks)