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Lack of protective effect of tiotropium vs induced dynamic hyperinflation in moderate COPD

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Summary
Study objective: Novel evaluation of protective effect of tiotropium against induced dynamic hyperinflation (DH) during metronome paced hyperventilation (MPH) in moderate COPD.
Methods: Prospective, randomized, double-blind, placebo control, crossover study. Lung function measured pre/post MPH at 30 breaths/min for 20 s in 29 (18M) COPD patients (GOLD Stage 2) age 70 ± 9 yr (mean ± SD) before and after 30 days of 18 μg tiotropium bromide vs placebo. Lung CT scored for emphysema (ES).
Results: At baseline post 180 μg aerosolized albuterol sulfate, FEV_1: 1.8 ± 0.6 L (69 ± 6%pred) and ≥60% predicted in all, and 14 of 29 had FEV_1 (L) ≥70% predicted with FEV_1/FVC 58 ± 8%. After 29 days + 23 h post tiotropium (trough) there was significant decrease only in FRC/TLC% ($p = 0.04$); after 30 days + 2 h post tiotropium (peak) significant increase only in FEV_1 (L) ($p = 0.03$) compared to placebo. Results post MPH induced DH at baseline and after 30 days and 2 h post placebo or tiotropium were similar with decrease in IC 0.44 ± 0.06 L ($p < 0.001$). Correlation between ES and increased FEV_1 (L) at peak tiotropium: $r = 0.19$, $p = 0.96$ and decreased FRC/TLC% at trough tiotropium: $r = -0.26$, $p = 0.36$.
Conclusion: In moderate COPD, tiotropium did not reduce MPH induced DH and reduction in IC. However, at peak tiotropium, there was significant bronchodilation in FEV_1 (L) and at trough a decrease in FRC/TLC% compared to placebo despite varying emphysema.

Abbreviations: IC, inspiratory capacity; MPH, metronome paced hyperventilation; DH, dynamic hyperinflation; FEV_1, forced expiratory volume (L) in 1 s; FRC, functional residual capacity (L); TLC, total lung capacity (L).

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Introduction

In moderate-to-severe COPD, FEV_1 (L) % predicted correlated poorly with clinical symptoms, exercise endurance and response to bronchodilators. Alternatively, exercise testing using constant or incremental cycle ergometry with repeated measurements of inspiratory capacity (IC) has been used to detect dynamic hyperinflation and evaluate the response to bronchodilators.[1]

O'Donnell et al.[2] have reported that Borg dyspneic ratings and inspiratory capacity (IC) and endurance time during submaximal cycle exercise testing were highly reproducible and responsive to intervention in moderate-to-severe COPD. Repeated measurements of IC during exercise reflect changes in end-expiratory lung volume[3–5] since total lung capacity remains constant after acute bronchodilation and during exercise.[6,7] Additionally, peak values of inspiratory esophageal pressures used as a surrogate to estimate effort, are relatively constant and correlated with breathing frequency at a given tidal volume during multiple measurements of exercise IC.[8,9]

Reduction in IC during exercise, reflects dynamic hyperinflation (DH), and correlates with decreased exercise endurance, and increased exertional dyspnea as well as breathing frequency in COPD patients.[5] We previously reported the reduction in IC with metronome paced hyperventilation (MPH), a relatively simple procedure, was similar to decrease in IC following incremental symptom-limited cycle ergometry in moderate-to-severe COPD.[1] We also noted 54 μg of inhaled ipratropium bromide (IB) failed to blunt the decrease in IC.[1] Previously, O'Donnell et al.[2] noted greater bronchodilation with much larger doses of nebulized IB (500 μg) when compared to usual doses of inhaled albuterol sulfate in patients with COPD. Subsequently, using constant cycle ergometry, O'Donnell et al.[10] reported 18 μg tiotropium in patients with moderate-to-severe COPD improved IC, exercise endurance and exertional dyspnea.

We previously reported in moderate-to-severe COPD patients, tiotropium did not reduce DH induced by MPH.[11] However, tiotropium induced bronchodilation with increase in IC and decrease in end-expiratory lung volume was in part compensatory and helped blunt dynamic hyperinflation.[11] Moreover, tiotropium induced bronchodilation was independent of the extent of lung CT scored emphysema in moderate-to-severe COPD[12] (GOLD Stage 2 and 3).[13]

The primary co-end points of the current novel study were to evaluate: (1) trough and peak bronchodilator role of tiotropium and (2) its ability to blunt MPH induced DH in moderate GOLD Stage 2 COPD patients.[13] The secondary endpoints were to correlate primary physiologic responses with varying extent of lung CT scored emphysema.[14]

Methods

We recruited 30 patients with smoking history >20 pack yr with documented GOLD Stage 2 moderate COPD[13] who were clinically stable for at least 6 weeks prior to the present study and were not on oxygen or oral corticosteroid. This was a prospective, randomized, double-blind, placebo control, tiotropium crossover pilot study. History of wheezing and/or responsiveness to aerosolized albuterol were not specific inclusion or exclusion criteria. Quality of life was graded using established SGRQ criteria.[15] Patients were instructed to continue all their usual medications, but to withhold short-acting aerosolized $beta_2$-agonists and/or ipratropium bromide for 6 h and long-acting inhaled $beta_2$-agonists (salmeterol or formoterol in all patients) for 48 h prior to initial baseline testing. Volunteer patients for this study were required to be off tiotropium for at least 4 weeks or be tiotropium naïve prior to initiating the study. During the study only short-acting aerosolized $beta_2$-agonist was permitted.

Informed patient consent and approval from the University of Toronto Medical Center, Ontario, Canada and Western Institutional Review Board, Olympia, Washington was obtained and this study was registered with NCT: 00569270. Patients underwent lung function studies before and after 180 μg of aerosolized albuterol sulfate via MDI using techniques and predictive values previously described in detail.[1,11,12] We used a spirometer (Model Vmax29), and pressure-compensated flow plethysmograph (Model 6200), both from SensorMedics, CareFusion, Yorba Linda, California.

Subsequently, on separate days, MPH was obtained (Vmax29) using previously described methods[1,11,12] in 30 COPD patients. The goal was to achieve respiratory rate twice baseline rate for 20 s, which was immediately followed by sequential measurement of inspiratory capacity, expiratory spirometry, and within 30 s plethysmographic measurement of functional residual capacity. While no attempt was made to control end tidal carbon dioxide, patients were coached to maintain a respiratory rate synchronous with the metronome. Near-constant dynamic tidal volume during MPH was achieved by having patients observe a graphic display of their breathing pattern, however no attempt was made to blunt any increase in ventilation synchronous with the metronome. Patients were studied at baseline and subsequently randomized to either 30 days of 18 μg tiotropium or 30 days of placebo and then intervention crossed. Technicians who performed these studies were blinded as were treating physicians and patients to their medication. The technique for measuring inspiratory capacity has been previously described.[1,2,4]

High-resolution thin-section CT of lung

High-resolution, thin-section scans of the lung were obtained using a helical 64 slice multi detector-row CT (Siemens Model Sensation 64, Malverne, PA) were obtained in a subset of 19 patients. Images were obtained at 5 mm collimation at intervals of 6 mm using 120 kVp and varying mA dependent upon patient size. Reconstructured 1 mm slices were obtained every 9 mm using window width of 850 HU and level of −600 HU with edge enhancing algorithm. Images were scored by a radiologist (Mark J. Schein MD, Department of Radiology, Lakewood Regional Medical Center, Lakewood, California) 0 to 100, none to worst emphysema, using picture templates, we previously validated using inflated whole lung specimens.[14]

Statistical analysis

Statistical analyses was performed by Fernando Camacho (Damos Inc., Toronto, Ontario, Canada.) Since a crossover design was used, the *p*-value for a given variable was

obtained using a Mixed model with the variable as the response and with treatment including placebo and tiotropium, period and sequence as dependent variables. The Mixed model properly takes into account that patients were measured in both sequences of the study. The reported *p*-values reported are the nominal values without Bonferroni correction for multiple tests. Analysis was done using a statistical software package (S+ version for Windows, Tibco Software, Palo Alto, California). Statistical significance was $p < 0.05$. Based on our earlier study in patients with moderate-to-severe COPD with GOLD[13] Stage 2 and 3 we calculated we needed a cohort of 29 patients with moderate COPD consistent with GOLD[13] Stage 2 for this pilot study. We wanted to achieve a power of 80% at a significant alpha level of 5% using projected sample inspiratory capacity of 2.23 ± 0.5 L (mean ± SD) post tiotropium compared to baseline inspiratory capacity 2.0 ± 0.5 L.

Results

Baseline studies (29 patients) (Table 1)

We initially studied 30 moderate GOLD Stage 2 COPD patients but one patient violated the treatment protocol. This report includes data from 29 (18 men) age 70 ± 9 yr (mean ± SD) with past smoking history of 42 ± 20 pack yr (mean ± SD). Twenty three patients were studied in Lakewood and 6 patients in Toronto and there were no significant site differences in age, gender, and smoking history. At baseline, routine lung function studies were similar in patients from the two sites and the combined data is described in Table 1 and is consistent with moderate GOLD Stage 2 COPD.[13] Following 180 μg of aerosolized albuterol sulfate, FEV_1 increased 13 ± 12%. All patients had a post 180 μg albuterol by MDI, FEV_1 (L) ≥60% predicted, and 14 of 29 had FEV_1 (L) ≥70% predicted. Quality of life SGRQ score ranged from 30–45.[15]

Table 1 Baseline Results of Lung Function Studies (mean ± SD) in 29 Moderately Severe COPD[13] Patients Age 70 ± 9 years (mean ± SD) prior to starting tiotropium.

Test	Observed	% Predicted
FVC (L)	2.9 ± 1.2	86 ± 17
FVC (L) post 180 μg albuterol sulfate MDI	3.3 ± 1.2	95 ± 16
FEV_1 (L)	1.6 ± 0.6	61 ± 8
FEV_1 (L) post 180 μg albuterol sulfate MDI	1.8 ± 0.6	69 ± 6
FEV_1/FVC (%)	56 ± 8	
SGaw Lps/cmH_2O/L	0.10 ± 0.08	
FRC (L)	3.9 ± 0.8	138 ± 29
RV (L)	2.9 ± 0.1	131 ± 37
TLC (L)	5.9 ± 1.3	109 ± 16
D_LCO_{SB} (ml/min/mmHg)	14 ± 5	69 ± 23

FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; FRC = functional residual capacity; RV = residual volume; SGaw = specific airway conductance; TLC = total lung capacity; D_LCO_{SB} = single-breath diffusing capacity. Predicted values were previously described.[1,11,12]

Primary end point: bronchodilator response after 30 days of tiotropium versus placebo (29 patients) (Table 2)

After 18 μg of inhaled tiotropium daily for 30 days, the changes in lung function studies at 1 h pre-dose (trough) and 2 h post tiotropium dose (peak) appear in Table 2. There was a significant ($p = 0.04$) decrease only in FRC/TLC% at trough, and increase in FEV_1 (L) at peak tiotropium, compared to placebo. Baseline FEV_1 was 1.6 ± 0.6 L, and it increased 0.08 ± 0.03 L, $p = 0.03$ above placebo at 2 h post dose. No significant changes were noted in total lung capacity. In this crossover placebo/drug study, there was no variable effect of treatment period and sequence.

Co-primary end point: metronome paced hyperventilation (mph) induced dynamic hyperinflation (dh) at baseline and after tiotropium versus placebo (29 patients) (Table 3)

Following MPH there was a significant decrease in IC (L) at baseline as reported in Table 3. Resting respiratory rate was 15 ± 0.6 bpm (mean ± SE) and post 20 s MPH it was 31 ± 0.2 bpm, $p < 0.0001$, whereas resting tidal volume was 0.90 ± 0.04 L and post 20 s MPH it was 0.76 ± 0.04 L, $p = 0.001$. Resting IC was 2.09 ± 0.83 L and post 20 s MPH it was 1.76 ± 0.07, $p < 0.0001$. There was no change in total lung capacity. The magnitude of the decrease in IC correlated modestly with decrease in tidal volume during MPH (Spearman rho = 0.45, $p = 0.0003$).

After 30 days and 2 h post placebo, as well as after 30 days and 2 h post tiotropium, following MPH, the magnitude of the changes in IC, respiratory rate, and tidal volume were similar to baseline MPH induced DH results prior to initiation of tiotropium (see Table 3).

Table 2 Net change in lung function studies (mean ± SE) from baseline to trough (−1 h) and peak (+2 h) after 30 days of tiotropium versus placebo in 29 moderate COPD patients.

Variable	Mean difference of tiotropium minus placebo	SE	*t* value	*p*-value
Peak FEV_1 (L)	0.08	0.03	2.33	0.027
Peak FRC (L)	−0.08	0.08	−1.02	0.318
Peak FVC (L)	0.10	0.05	1.83	0.078
Peak IC	0.12	0.03	1.91	0.067
Peak FRC/TLC%	0.01	0.03	0.51	0.615
Peak TLC (L)	−0.13	0.12	−1.00	0.325
Trough FEV_1 (L)	0.02	0.03	0.96	0.345
Trough FRC (L)	−0.17	0.09	−1.90	0.068
Trough FVC (L)	0.03	0.05	0.55	0.589
Trough IC (L)	−0.00	0.03	−0.10	0.922
Trough FRC/TLC%	−0.02	0.01	−2.18	0.038
Trough TLC (L)	−0.13	0.09	−1.47	0.15

Same as Table 1.
After 29 days of tiotropium, compared to placebo, mean changes in lung function parameters from baseline were significant at 23 h (trough) for decrease in FRC/TLC% and 30 days plus 2 h post (peak) tiotropium for increase in FEV_1 (L).

Table 3 Decrease in inspiratory capacity (IC) (mean ± SE) (L) following metronome paced hyperventilation induced dynamic hyperinflation at baseline and post 30 days plus 2 h of 18 μg tiotropium and post 30 days plus 2 h of placebo. Change in TLC (L) is increase.

Test	Change	Time	*p*-value
IC (L)	0.303 ± 0.05	Baseline	<0.0001
IC (L)	0.321 ± 0.06	2 h post placebo	<0.0001
IC (L)	0.439 ± 0.06	2 h post tiotropium	<0.0001
TLC (L)	0.05 ± 0.0	Baseline, post placebo and tiotropium	ns

Same as Tables 1 and 2.
There was no significant difference ($p = 0.12$) between decrease in IC following MPH induced DH at 2 h post placebo versus 2 h post tiotropium. The *p*-value refers to the decrease in IC (L) following MPH induced DH under varying study conditions compared to resting IC.

Secondary end point: correlation of tiotropium induced bronchodilation and extent of lung ct scored emphysema (19 patients)

There was no correlation between high-resolution thin-section lung CT scored extent of emphysema[14] obtained in 19 patients and magnitude of increase in FEV_1 (L) from baseline to peak tiotropium (Spearman rho = 0.19, $p = 0.96$) or decrease in FRC/TLC% at trough tiotropium (Spearman rho = −0.26, $p = 0.36$).

Co-secondary end point: correlation between decrease in inspiratory capacity post mph induced dh and extent of lung ct scored emphysema (19 patients)

Following MPH induced DH the decrease in IC did not significantly correlate with high-resolution thin-section lung CT scored extent of emphysema[14] obtained in 19 patients (Spearman rho = 0.20, $p = 0.4$).

Discussion

Twenty-nine GOLD Stage 2, moderate COPD patients[13] with varying lung CT scored emphysema, completed a prospective, randomized, double-blind, placebo control, tiotropium crossover study. There was a significant decrease from baseline in FRC/TLC% at trough and increase from baseline in FEV_1 (L) at peak tiotropium after 30 days, compared to placebo arm. Furthermore, there was no correlation between bronchodilation and extent of lung CT scored emphysema. The current observations in moderate COPD with GOLD[13] Stage 2 patients with post albuterol FEV_1 69 ± 6% (mean ± SD) predicted extend our previous results in moderate-to-severe COPD, GOLD[13] Stage 2 and 3 patients with FEV_1 63 ± 6% predicted.[11,12]

Metronome paced hyperventilation (MPH) at twice resting respiratory rate for 20 s to induce dynamic hyperinflation (DH) resulted in similar significant decrease in inspiratory capacity (IC) in tiotropium versus placebo. Furthermore, the decrease in IC was irrespective of the extent of lung CT scored emphysema, similar to our previous observations in moderate-to-severe GOLD Stage 3 COPD.[11,12] However, since tiotropium is a potent bronchodilator, there was a significant increase in peak FEV_1 (L) and decrease in trough FRC/TLC% compared to baseline. This would help blunt the subsequent dyspneic and physiologic challenge of MPH induced DH, by increasing exercise time, as reported by O'Donnell et al.[10] and Maltais et al.[16] using constant-load cycle ergometry.

The rationale to measure IC during exercise is that among all variables studied, changes in IC (baseline and peak exercise) not only showed good reproducibility, but correlated best with changes in Borg dyspnea scale.[2,3,15] Furthermore, since previously TLC did not change during exercise[1,6,7,11,12] as well as in the present study, any increase in IC must reflect a decrease in dynamic hyperinflation in peripheral airways.

It is important to compare our current and prior results[11] before and after tiotropium intervention during MPH induced DH. The mean increase in FEV_1 post 30 days plus 2 h of tiotropium in the present study was 170 cc (78 cc above placebo); and in our previous study post 30 days and 1.5 h was 150 cc[11] compared to results in other studies of 220 cc post 42 days plus 1.3 h[10] and 260 cc post 42 days plus 1.3 h tiotropium.[16] At similar time thresholds as above, in the current study, the mean increase in IC was 150 cc; and previously 180 cc[11] compared to 250 cc[10] and 220 cc.[16] The decreased magnitude of our current and past response[11] compared to previous studies[10,16] may be related to moderate expiratory airflow limitation at baseline.

In the current study, the mean ± SE *decrease* in IC immediately following MPH was 303 ± 50 cc at baseline; 321 ± 60 cc post 30 days plus 2 h of placebo; and 439 ± 60 cc post 30 days plus 2 h tiotropium. In our previous study[11] IC *decrease* was 370 ± 40 cc at baseline and 350 ± 30 cc post 1.5 h tiotropium for 30 days. This compares to mean *decrease* in IC following constant-load ergometry of 410 cc at both baseline and post tioropium[10] and 410 cc at baseline versus 490 cc post tiotropium.[16] In above studies[10–12,16] the magnitude of *decrease* in IC following MPH induced DH and constant-load ergometry was similar pre and post tiotropium. However, because of tiotropium induced bronchodilation and reduction in resting operational lung volumes both at rest and during exercise (increased IC), patients noted improvement in exertional dyspnea and exercise endurance.[10,16] These and other physiologic results[17–19] support the observation of improved clinical outcomes in both moderate and severe, GOLD Stage 2 and 3 COPD patients on long-term tiotropium.[20]

As emphasized in our previous study[12] normal resting airway smooth muscle tone is mediated primarily by the parasympathetic cholinergic system[21,22] via post ganglionic acetylcholine on three muscarinic subtype receptors: M_1, M_2, and especially M_3.[23] Tiotropium achieves bronchodilation in COPD safely through antagonism of the contractile effects of normal or increased cholinergic innervation[24–27] through prolonged inhibition of M_3-receptors in large and small airways leading to smooth muscle relaxation.[21,23,28,29] Furthermore, in alveolar walls only M_1-receptors are present.[28] Current FEV_1 (L) and FRC/TLC% observations reinforce our initial IC results[12] that the bronchodilator effect of tiotropium appears to be independent of the extent of lung CT scored emphysema in moderate and severe GOLD[13] 2 and 3 COPD phenotypes.

Moreover, any increase in expiratory airflow from relaxation of increased cholinergic tone in COPD,[24–26] would be incrementally greater in critically narrowed small airways compared to normals.[30]

The relative phenotypic contribution of emphysema versus intrinsic small airway disease in COPD is highly variable.[12] The severity of lung CT scored emphysema varies widely among COPD cohorts despite similar extent of symptoms, response to aerosolized albuterol sulfate, extent of expiratory airflow limitation and exercise tolerance.[14,31–38] We have previously reported in a pathologic-physiologic correlative study in 81 COPD patients with FEV_1 <50% predicted that severe lung CT scored emphysema ≥60 (scale 0–100 worst)occurred only in 30%.[14] Therefore, lung CT scored extent of emphysema should not be used to initiate or obviate tiotropium from the therapeutic regimen for COPD. There have been numerous studies evaluating the relationship between lung CT scoring techniques, especially objective densitometry masks, to reproducibly quantify the extent and distribution of emphysema and its functional consequences.[31–44] However, there has been only limited corroboration with morphologic whole lung inflated specimens.[14,38,43] The visual lung CT technique to score emphysema in the present study has been shown to have a strong correlation with inflated whole lungs and provides a reliable CT lung assessment of extent of morphologic emphysema.[14] The current lung CT results reinforce our earlier lung CT similar observations in cohort of 29 COPD patients.[12] Additional similar studies with larger cohort size will be needed to further evaluate COPD emphysema phenotypes and efficacy of therapeutic intervention including combinations of tiotropium, inhaled corticosteroids and long-acting $beta_2$-agonists.

Results in the present study of 29 patients, demonstrate significant improvement only in tiotropium trough FRC/TLC % and peak FEV_1. The limited number of patients in this underpowered study was based on initial over-estimated IC and can lead to a type 2 error. Had the same results been observed in a study with double the number of patients ($n = 58$), more comparisons would have become significant including increase in tiotropium peak FEV_1 (L) ($p = 0.01$); FVC (L) (0.04); IC (L) (0.03); and decrease in trough FRC (L) ($p = 0.03$); and FRC/TLC% ($p = 0.02$).

In summary, in GOLD Stage 2 moderate COPD, tiotropium did not reduce MPH induced DH and reduction in IC despite varying extent of lung CT scored emphysema. However, despite an underpowered study, tiotropium induced significant bronchodilation, with significant decrease in trough FRC/TLC% and increase in peak FEV_1 (L), independent of varying lung CT emphysema. This should help buffer the effects of exercise intolerance in these patients.

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Conflict of interest

The authors have no other financial conflicts of interest to declare. Registration: NCT00569270.

References

1. Gelb AF, Gutierez AC, Weisman AM, et al. Simplified detection of dynamic hyperinflation. *Chest* 2004;**126**:1855–60.
2. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation and endurance during exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**158**:1557–65.
3. Belman MJ, Botnick WC, Shin JC. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**153**:967–75.
4. Dodd DS, Brancatisano T, Engel LA. Chest wall mechanics during exercise in patients with severe chronic airflow obstruction. *Am Rev Respir Dis* 1984;**12**:33–8.
5. O'Donnell DE, Webb KA. Exertional breathlessness in patients with chronic airflow limitation: the role of lung hyperinflation. *Am Rev Respir Dis* 1993;**148**:1351–7.
6. Stubbing DG, Pengelly LD, Morse JLC, et al. Pulmonary mechanics during exercise in subjects with chronic airflow obstruction. *J Appl Physiol* 1980;**49**:511–5.
7. Duranti R, Filipelli M, Bianchi R, et al. Inspiratory capacity and decrease in lung hyperinflation with albuterol in COPD. *Chest* 2002;**122**:2009–14.
8. O'Donnell DE, Chau LKL, Bertley JC, et al. Qualitative aspects of exertional breathlessness in chronic airflow limitation: pathophysiologic mechanisms. *Am J Respir Crit Care Med* 1997;**155**:109–15.
9. Yan S, Kaminski D, Sliwinski P. Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;**156**:55–9.
10. O'Donnell DE, Fluge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea, and exercise tolerance in COPD. *Eur Respir J* 2004;**23**:832–40.
11. Gelb AF, Taylor CF, McClean PA, et al. Tiotropium and simplified detection of dynamic hyperinflation. *Chest* 2007;**131**:690–5.
12. Gelb AF, Taylor CF, Cassino C, et al. Tiotropium induced bronchodilation and protection from dynamic hyperinflation is independent of extent of emphysema in COPD. *Pulm Pharmacol Ther* 2009;**22**:237–42.
13. Rabe KF, Hurd S, Anzueto A, et alFor the GOLD Scientific Committee. Global initiative for Chronic Obstructive Lung Disease (GOLD). *Am J Respir Crit Care Med* 2008;**176**:532–55.
14. Gelb AF, Hogg JC, Muller NL, et al. Contribution of emphysema and small airways in COPD. *Chest* 1996;**109**:353–9.

15. Meguro M, Barley EA, Spencer S, et al. Development and validation of an improved COPD-specific version of the St. George Respiratory Questionaire. *Chest* 2007;**132**:456—63.
16. Maltais F, Hamilton A, Marciniuk D, et al. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest* 2005;**128**:1168—78.
17. Casaburi R, Conoscenti CS. Lung function improvement with once-daily tiotropium. *Am J Med* 2004;**117**(Suppl. 12A):33s—40s.
18. VanNoord JA, Aumann JL, Janssens E, et al. Effect of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with chronic obstructive pulmonary disease. *Chest* 2006;**129**:509—17.
19. Celli B, ZuWallack R, Wang S, et al. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased lung volumes. *Chest* 2003;**124**: 1743—8.
20. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;**359**: 1543—54.
21. Nadel JA, Barnes PJ. Autonomic regulation of the airways. *Annu Rev Med* 1984;**35**:451—67.
22. Cabezas GA, Graf PD, Nadel JA. Sympathetic versus parasympathetic nervous regulation of airways in dogs. *J Appl Physiol* 1971;**31**:651—5.
23. Witek Jr TJ, Disse B. Inhaled anticholinergic therapy: applied pharmacology and interesting developments. *Curr Opin Investig Drugs* 2001;**2**:53—8.
24. Gross NJ, Co E, Skorodin MS. Cholinergic bronchomotor tone in COPD. Estimates of its amount in comparison with that in normal subjects. *Chest* 1989;**96**:984—7.
25. Gross NJ, Skorodin MS. Role of parasympathetic system in airway obstruction due to emphysema. *N Engl J Med* 1984;**311**:421—5.
26. Gross N. Ipratropium bromide. *N Engl J Med* 1988;**319**:486—94.
27. Michele TM, Pinhero S, Iyasu S. The safety of tiotropium-the FDA's conclusion. *N Engl J Med* 2010;**363**:1097—9.
28. Mak JC, Barnes PT. Autographic visualization of muscarinic receptor subtypes in humans and guinea pig lung. *Am Rev Respir Dis* 1990;**141**:1559—68.
29. Hanania NA, Donohue JF. Pharmacologic intervention in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2007;**4**:526—34.
30. Barnes PJ, Thomson NC. Neural and humoral control. In: Barnes PJ, Drazen JM, Rennard S, Thomson NC, editors. *Asthma and COPD: basic mechanisms and clinical management*. London, England: Academic Press; 2002. p. 323—40.
31. Makita H, Nasuhara Y, Nagai K, et alHokkaido COPD Cohort Study Group. Characterization of phenotypes based on severity of emphysema in chronic obstructive pulmonary disease. *Thorax* 2007;**62**:932—7.
32. Hersh CP, Jacobsen FL, Gill R, et al. Computerized tomography phenotypes in severe, early onset chronic obstructive pulmonary disease. *COPD* 2007;**4**:331—7.
33. Eda S, Kubo K, Fujimoto K, et al. The relations between expiratory chest CT using helical CT and pulmonary function tests in emphysema. *Am J Respir Crit Care Med* 1997;**155**:1290—4.
34. Fujita E, Nagasaka Y, Kozuka T, et al. Correlation among the indices of high-resolution computed tomography, pulmonary function tests, pulmonary perfusion scans and exercise tolerance in cases of chronic pulmonary emphysema. *Respiration* 2002;**69**:30—3.
35. Crausman RS, Ferguson G, Irvin CG, et al. Quantitative chest computed tomography as a means of predicting exercise performance in severe emphysema. *Acad Radiol* 1995;**2**:463—9 [Erratum in: Acad Radiol 1995;2:870].
36. Kitaguchi Y, Fujimoto K, Kubo K, et al. Characteristics of COPD phenotypes classified according to the findings of HRCT. *Respir Med* 2006;**100**:1742—52.
37. Holme J, Stockley RA. Radiologic and clinical features of COPD patients with discordant pulmonary physiology: lessons from alpha$_1$-antitrypsin deficiency. *Chest* 2007;**132**:909—15.
38. Washko GR, Criner GJ, Mohsenifar Z, et al. Computed tomographic-based quantification of emphysema and correlation to pulmonary function and mechanics. *COPD* 2008;**5**:177—86.
39. Malinen A, Erkinjuntti-Pekkanen R, Partanen K, et al. Reproducability of scoring emphysema by HRCT. *Acta Radiol* 2002; **43**:54—9.
40. Friedman PJ. Imaging studies in emphysema. *Proc Am Thorac Soc* 2008;**5**:494—500.
41. Revel MP, Faivre JB, Remy-Jardin M, et al. Automated lobar quantification of emphysema in patients with severe chronic obstructive pulmonary disease. *Eur Radiol* 2008;**18**:2723—30.
42. Desai SR, Hansell DM, Walker A, et al. Quantification of emphysema: a composite physiologic index derived from CT estimation of disease extent. *Eur Radiol* 2007;**17**:911—8.
43. Litmanovich D, Boiselle PM, Bankier AA. CT of pulmonary emphysema-current status, challenges and future directions. *Eur Radiol* 2009;**19**:537—51.
44. Coxson HO, Rogers RM, Whithall KP, et al. A quantification of the lung surface area in emphysema using computed tomography. *Am J Respir Crit Care Med* 1999;**159**:851—6.