

TITLE: Effects of inhaled furosemide on exertional dyspnea in
Chronic Obstructive Pulmonary Disease

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ABSTRACT

The aim of this study is to investigate the effects of inhaled furosemide on the sensation of dyspnea produced during exercise in patients with stable chronic obstructive pulmonary disease (COPD). In a double-blind, randomized, crossover study we compared the effect of inhaled furosemide on dyspneic sensation during exercise testing with that of placebo. Spirometry, incremental and constant-load exercise testing were performed after inhalation of placebo or furosemide on 2 separate days in 19 patients with moderate or severe COPD. Subjects were asked to rate their sensation of respiratory discomfort using a 100mm visual analogue scale (VAS). There was significant improvement in mean FEV₁ and FVC after inhalation of furosemide ($p = 0.038$ and 0.005 respectively) but not after placebo. At standardised exercise time during constant-load exercise testing but not during incremental exercise, the mean dyspneic VAS score was lower after inhalation of furosemide compared to placebo (33.7 ± 25.2 mm versus 42.4 ± 24.0 mm respectively, $p = 0.014$). We conclude that inhalation of furosemide alleviates the sensation of dyspnea induced by constant-load exercise testing in patients with COPD and that there is significant bronchodilation after inhalation of furosemide compared to placebo in these patients.

(Word count = 195)

Key words: exercise capacity, bronchodilation, breathlessness, exercise test, spirometry

INTRODUCTION

Dyspnea is the hallmark symptom of chronic obstructive pulmonary disease (COPD) and is a major cause of disability and anxiety associated with the disease (1). It is also the reason most patients with COPD seek medical attention (1). COPD patients are known to experience dyspnea at lower levels of exercise than unaffected individuals as a consequence of multiple pathophysiologic factors (2). Although exertional symptoms may be mild at the outset, exercise limitation is the most disabling and distressing consequence of COPD for the majority of patients.

The interest in the clinical application of inhaled furosemide has grown in the last few years. Inhalation of furosemide has been shown to have an inhibitory effect on experimentally induced cough (3) and to prevent bronchoconstriction in patients with asthma (4-6). Recently, inhaled furosemide has been observed to decrease the sensation of experimentally induced dyspnea. In a double-blind, randomized, crossover study (7) performed on 12 healthy subjects, there were remarkable prolongation of both the total breathholding time and the period of breathhold with no respiratory sensation after inhalation of furosemide. The development of respiratory discomfort induced by a combination of resistive loading and hypercapnia was also much slower and less than that observed after inhalation of placebo.

Since patients with COPD may experience, especially during exercise, dyspnea similar to that experienced by the normal subjects with resistive loading and hypercapnia in the study by Nishino et al (7), it would be reasonable to hypothesize that furosemide inhalation would also relieve dyspnea during exercise in COPD. In the present study, we performed a double blind, randomised, crossover study to investigate the effect of inhaled

furosemide on the sensation of dyspnea during exercise in patients with COPD. As it is unknown whether inhaled furosemide has any bronchodilating effects in chronic airflow limitation, a secondary aim of this study was to investigate the effects of inhaled furosemide on spirometry of patients with COPD.

METHODS

(Word count = 500)

Subjects were patients with stable COPD who satisfied the following criteria: (1) moderate to severe COPD ($FEV_1 < 70\%$ predicted) with a clinical course consistent with chronic bronchitis and/or emphysema and a long history of cigarette smoking; (2) moderate to severe chronic breathlessness (Medical Research Council Dyspnea Scale grade 4 and 5) (8); (3) age 50 years or older; and (4) clinically stable as defined by no exacerbations or hospital admissions in the preceding six weeks.

The study was conducted on two days (not more than 2 weeks apart) in a double-blind, randomized, crossover design. Eligible subjects were assigned to the order of study visits (placebo-furosemide or furosemide-placebo) using simple randomization. On each of the 2 days, baseline spirometry was performed before the patient was asked to inhale furosemide (4 ml of furosemide as a 10 mg/ml solution) or placebo (4 ml of 0.9% saline solution), administered by means of a jet nebulizer and nebulized to dryness with the subjects breathing tidally over 15 minutes.

Incremental cardiopulmonary exercise testing (CPET) was performed immediately after completion of nebulization. After recovery from exercise and at one hour after nebulization of placebo or furosemide, the patients performed another spirometry. After this, the patients rested and one hour after termination of the

incremental exercise test, they received another nebulization of furosemide or placebo (the same agent as that received earlier in the day) followed immediately by constant work rate (CWR) exercise testing at 70% of the peak work rate achieved in the initial incremental CPET. Figure 1 shows the timing of events and measurements during experimental visits.

At the beginning of every minute during exercise testing, each patient was asked to rate the intensity of sensation of dyspnea using a visual analogue scale (VAS) (9). The analogue scale consisted of a vertical straight line, 100-mm in length with 10 equally spaced markers. It was labelled 100 at the top and 0 at the bottom. Patients were instructed to point to a spot on the line indicating the sensation of respiratory discomfort at that point in time. The numerical value of zero indicated no sensation at all and 100 indicated a sensation that was intolerable. Dyspnea was defined as an unpleasant urge to breathe with no further clarification or definition given.

The primary outcome measures were dyspneic VAS scores during incremental and CWR exercise testing after inhalation of placebo or furosemide. We compared the exercise responses at standardised exercise time (SET) during incremental and during CWR exercise testing for each patient. We analyzed the data obtained during exercise testing after placebo inhalation and after furosemide inhalation using two-tailed paired *t* tests. SET was equal to the time of the highest equivalent amount of work (isoworkrate) or time (isotime) completed in the incremental or endurance exercise tests for each patient, that is, the time of the shorter of the 2 incremental or endurance tests for each patient.

Spirometry results at baseline, after placebo inhalation and after furosemide inhalation were also analyzed using two-tailed paired *t* tests.

Additional details on the method for making these measurements are provided in an online data supplement.

RESULTS

Of the 20 patients recruited, 8 were randomised to receiving placebo first and 12 to receiving furosemide first. Nineteen patients completed all the experimental protocols performed on 2 separate days. One patient developed acute wheezing and breathlessness after performing spirometry subsequent to inhalation of placebo on the first study visit and refused to participate further in the study. The data for this patient is excluded from analysis. The baseline anthropometric and pulmonary function data of the remaining 19 patients are shown in Table 1. All the patients had moderate or severe COPD as defined by the European Respiratory Society guidelines (10). Table 2 shows the spirometry results of patients before and after inhalation of placebo or furosemide and exercise testing. After inhalation of furosemide and exercise, there was significant improvement in mean FEV₁ and FVC compared to placebo ($p=0.038$ and 0.005 respectively). There was also a significant difference in the mean FEV₁ after furosemide and exercise when compared to the mean FEV₁ after placebo and exercise ($p=0.040$).

During incremental exercise testing after inhalation of placebo, 12 patients (63.2%) were ventilatory limited as they achieved all 3 of the following criteria: (1) a ratio of the $\dot{V}E$ at peak exercise ($\dot{V}E_{max}$) to the maximal voluntary ventilation (MVV; calculated as $FEV_1 \times 40$) > 0.8 , (2) $MVV - \dot{V}E_{max} < 12$ L/minute, (3) maximum heart rate (HR_{max}) $< 90\%$ predicted. Eleven (57.9 %) patients had ventilatory limitation of

exercise (VLE) after inhalation of furosemide. All patients who had VLE reported dyspnea as the limiting symptom at peak exercise. The remaining patients complained of leg fatigue as the predominant symptom limiting exercise. Overall, combining the results of incremental tests after placebo and furosemide, the mean dyspneic VAS score at peak exercise of ventilatory limited subjects was 52.1 and the mean dyspneic VAS score at peak exercise of non-ventilatory limited subjects was 35.4. The difference was statistically significant ($p = 0.043$). Four patients had significant oxygen desaturation by pulse oximetry of greater than 4% during incremental exercise after placebo compared to 6 patients who had significant oxygen desaturation during exercise after furosemide. As shown in Table 3, none of the selected variables during peak exercise were significantly different after inhalation of placebo or furosemide. In particular, the dyspneic VAS score at peak exercise was lower after furosemide than after placebo but the difference was not statistically significant ($p=0.391$). There was also no significant difference in exercise responses at SET during incremental exercise testing (see Table 4). The mean dyspneic VAS scores at SET during incremental exercise testing after inhalation of furosemide and after placebo were 35.5 ± 23.7 and 35.8 ± 22.1 respectively, $p = 0.921$).

At termination of CWR exercise testing, 16 patients reported dyspnea as the limiting symptom after inhalation of placebo while the rest reported leg fatigue only as the predominant symptom limiting exercise. During CWR exercise testing after inhalation of furosemide, 11 patients reported dyspnea as the limiting symptom while leg fatigue was the predominant symptom for the remainder. At SET during CWR exercise testing, the mean dyspneic VAS score was lower after inhalation of furosemide compared to placebo (33.7 ± 25.2 versus 42.4 ± 24.0 respectively, $p = 0.014$) (Table 5). Except for 3

patients, all other patients had lower or similar VAS scores after inhalation of furosemide compared to placebo (see Figure 2). Although the mean duration of CWR exercise achieved by patients was longer after furosemide than after placebo (619 ± 94 s versus 572 ± 90 s, respectively), the difference was not statistically significant ($p = 0.497$).

The chart of mean VAS scores over time during CWR exercise testing is shown in Figure 3. The VAS scores at the beginning, early and intermediate stages of exercise testing were similar but differed towards the end of constant load exercise testing.

The subjects and investigators in this study were successfully and totally blinded to the study drugs during the course of the study. None of the subjects noticed any differences during or after inhalation of furosemide and placebo. In particular, none of the subjects expressed a bitter taste in the throat, a known association after inhalation of furosemide, although this was not specifically asked of each subject. Only one patient reported a desire to urinate after incremental exercise testing following inhalation of furosemide. No other systemic or adverse effects of furosemide were noted during the study.

DISCUSSION

The main findings of this study are that inhalation of furosemide alleviates the sensation of dyspnea induced by constant-load exercise testing in patients with COPD and that there is significant bronchodilation after inhalation of furosemide compared to placebo in these patients. The finding of reduction in dyspneic sensation after inhalation of furosemide is consistent with the findings of Nishino and co-workers (7) who demonstrated that inhaled furosemide greatly alleviates the sensation of dyspnea induced experimentally by breathholding and by a combination of resistive loading and

hypercapnia in normal subjects. Inhaled furosemide has also been found to suppress the behavioural response to airway occlusion in anesthetized cats without affecting their response to somatic noxious stimuli (11). These experimental findings are also in agreement with several clinical observations of nebulized furosemide being an effective and useful palliative treatment for dyspnea in terminally ill patients. Shimoyama and colleague (12) described 3 terminal cancer patients with severe dyspnea in whom 20 mg of furosemide nebulized and inhaled 4 times a day dramatically improved the dyspnea and controlled the symptom for weeks. Another recent study (13) reported that nebulized furosemide improved dyspnea scores in 12 of 15 patients with terminal cancer whose dyspnea were uncontrollable by standard therapy. Stone and colleagues (14) also reported that inhaled furosemide caused a remarkable improvement of severe dyspnea in a patient with end-stage pulmonary Kaposi's sarcoma. Contrary to their earlier findings, Stone and colleague (15) recently described the initial findings of a double blind placebo-controlled study in patients with cancer that showed no significant difference between the furosemide and saline arms for dyspnea. However, this study only investigated the effectiveness of a single dose of furosemide, rather than the regular dosing as described by Shimoyama and colleague in their case reports. Presently the effectiveness of nebulized furosemide for dyspnea in terminal cancer patients has not been established.

Both incremental and constant-load exercise testing have been used to assess therapeutic responses in patients with COPD. The finding of improved dyspnea sensation after furosemide inhalation during constant-load endurance testing but not at peak exercise during incremental exercise testing requires further elucidation. In a study aimed at testing the reproducibility of Borg dyspnea ratings, inspiratory capacity (to monitor

lung hyperinflation), and endurance time during constant-load symptom-limited cycle exercise in patients with advanced COPD, O'Donnell et al (16) found that Borg ratings of dyspnea measured with this exercise protocol were highly responsive to treatment with ipratropium bromide and highly reproducible when repeated over an 8-wk period. In contrast, the Borg ratings at the symptom-limited peak of exercise following incremental workload testing, although highly reproducible, were poorly responsive to the inhaled anticholinergic agent. Oga et al (17) also compared 3 different exercise tests (progressive cycle ergometry, cycle endurance test and 6-min walking test) and found that the endurance test was the most sensitive in detecting the effects of inhaled oxitropium bromide. Hence dyspnea ratings during incremental exercise testing may not be as sensitive in evaluating symptom responses to therapy as ratings of dyspnea during endurance exercise testing. Another possible explanation for the positive outcome during endurance but not incremental exercise testing in this study is that the furosemide inhalation was repeated before constant-load exercise tests. Repeating the dose of inhaled furosemide before constant-load exercise tests in this study was necessary, as its effect might have diminished over the duration of the trial in each patient otherwise. Nonetheless, this could have led to a greater effectiveness of the drug in reducing dyspnea during the constant-load exercise tests. The duration of action of inhaled furosemide is not known. In the study by Nishino et al (7), dyspneic sensation was measured for only 15 minutes after inhalation of 40 mg of furosemide. None of the previous studies evaluating inhaled furosemide in acute asthma (described below) had monitored symptoms or lung function longer than 60 minutes. With regard to its protective effect on exercise-induced asthma, Novembre et al (18) found that doubling

the dose of inhaled furosemide (30 mg versus 15 mg) has a longer duration of action but no difference in protective effect on exercise-induced asthma in children.

Although furosemide prevents or attenuates bronchospasm caused by many factors, such as hyperpnea, drugs (metabisulphite, bradykinin, AMP), physical agents (hypo- and hypertonic aerosols), and allergen challenge in asthmatic patients (4-6), its acute bronchodilator effect is questionable (19) and its effectiveness in acute exacerbation of asthma is unproven (20). It has also been shown that furosemide has no direct effect on the airway smooth muscle in vitro (21,22). Several randomized, double blind trials (20, 23, 24, 25) investigating the short-term responses of inhaled furosemide in addition to standard treatment in acute asthma exacerbation have been published. These studies suggest that inhaled furosemide has only a limited role in the treatment of asthmatic exacerbations in adults and children when used in addition to standard therapy like albuterol but they do not rule out the possibility that inhaled furosemide, when used singly, may have acute bronchodilator effects compared to placebo. The bronchodilating effect of furosemide is further supported by an earlier study (26) among patients with stable and chronic asthma, showing that high-dose (100 mg) aerosolized furosemide has the same bronchodilator effect as aerosolized 1% salbutamol. To our knowledge, the bronchodilating effect of inhaled furosemide in acute or stable COPD has not been reported previously.

The improvement in FEV₁ after furosemide inhalation may suggest that the overall reduction in dyspneic sensation during endurance testing among the patients in this study might be accounted for by bronchodilation induced by inhaled furosemide. After inhalation of furosemide and exercise, the increase in FVC was proportionally

greater than the increase in FEV₁, leading to a significant decrease in FEV₁/FVC.

Assuming that the total lung capacity remained constant in each patient, the increase in FVC reflects reciprocal decrease in residual volume, i.e., the degree of hyperinflation at rest is reduced. Whether the degree of hyperinflation during exercise is also reduced is not known. As dynamic lung hyperinflation is an important causative factor of exertional dyspnea in COPD (27), future studies should include measurement of the level of lung hyperinflation at rest and during exercise. However, the minute ventilation at SET during incremental and constant work rate exercise testing was not significantly different after furosemide and after placebo in this study. This observation makes a sole explanation for the alleviation of dyspnea by bronchodilation less likely although it does not exclude the possibility that it may be a contributory factor.

Besides bronchodilation, other possible mechanisms for the alleviation of dyspnea during exercise after furosemide inhalation should also be considered. It has been postulated that inhaled furosemide has a primary effect on the airway epithelium and may influence the responsiveness of sensory nerve endings or affect the activation of inflammatory cells by inhibiting mediator release from these cells (4,5,28). Nishino et al (7) hypothesized that the observed alleviation of dyspnea after inhalation of furosemide in healthy subjects was caused by the altered activity of sensory receptors. In particular, inhaled furosemide is considered to cause a decrease in the activity of vagal irritant and C-fiber receptors, stimulation of which increase the intensity of dyspnea and alter its quality while increasing the activity of pulmonary stretch receptors, activation of which relieves the sensation of respiratory distress. The subsequent finding that inhaled furosemide activates pulmonary stretch receptors and inhibits the activity of pulmonary

irritant receptors in anesthetized rats (29) supported this hypothesis. In this study, the observation that the effects of furosemide on reducing dyspneic sensation were mainly evident at higher levels of ventilation during constant load exercise may be an indication of the effects of furosemide on lung receptors. The firing of the pulmonary stretch receptors increases with the degree as well as the rate of lung inflation. In fact, at higher lung volumes, the receptors are known to show more marked sensitivity to changes in flow rate than to changes in lung volume. The irritant receptor fires predominantly during inflation and its firing also depend strongly on the rate of airflow (30). In addition, activation of slowly adapting pulmonary stretch receptors is known to decrease airway cholinergic tone (31) and their stimulation by furosemide may also account for the bronchodilation observed in this study. Other postulations for the reduction of dyspneic sensation by furosemide include effects on ventilatory drive and carbon dioxide (CO₂) chemosensitivity. However, the VT/TI ratio and other breathing pattern parameters during exercise after furosemide or placebo were not significantly different in this study to suggest an effect on the ventilatory drive by furosemide. Minowa et al (32) recently demonstrated that, in healthy subjects, inhaled furosemide improved dyspnea produced by hypercapnic hyperpnea but that the mechanism of the improvement was not associated with the decrease in CO₂ chemosensitivity.

Although there was a reduction in dyspneic sensation at standardized exercise time during endurance exercise testing after furosemide inhalation, no significant improvement in exercise endurance time was observed. In patients with COPD, ventilatory limitation is considered to be the most important reason for stopping exercise (33). As with previous studies that failed to show significant effects of bronchodilators on

exercise capacity (33), a limitation of the present study was that it was unclear whether the patients were actually limited by their ventilatory capacity. Some patients could have stopped exercising due to nonventilatory reasons, such as leg muscle fatigue. In these cases, the extent to which furosemide inhalation alleviates dyspneic sensation during exercise may be irrelevant to the improvement of exercise endurance. Whereas dyspnea is more likely to be the primary limiting symptom in more advanced COPD, leg discomfort has been shown to be the predominant limiting symptom in mild to moderate disease (34). Hence, further studies should be performed on patients with more severe airflow limitation and the ratings for both dyspnea and leg fatigue during exercise should be evaluated to determine their contribution to limiting exercise.

In conclusion, inhalation of furosemide alleviates the sensation of dyspnea during constant-load exercise testing in patients with stable COPD. There is small but statistically significant improvement in mean FEV₁ after inhalation of furosemide compared to placebo in these patients.

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FIGURE LEGENDS

Figure 1. The timing of events and measurements for every experimental visit

Figure 2. VAS scores at standardised exercise time during constant work rate exercise testing after inhalation of furosemide or placebo. Thin lines represent individual patients; the thick line indicates mean values. Two subjects were at 50 after placebo inhalation and 30 after furosemide inhalation.

Figure 3. Mean VAS scores over time during constant work rate exercise testing. Values shown are at rest for the first minute and during unloaded pedalling for the subsequent 3 minutes, followed by constant load exercise till termination.

Table 1. – Anthropometric and pulmonary function data*

Male:Female	19:0	
Age, years	68 ± 6	(50-75)
Height, m	1.65 ± 0.05	(1.52-1.70)
Weight, kg	57.9 ± 11.3	(38.0-86.3)
Body Mass Index	21.3 ± 4.0	(14.5-30.2)
FEV ₁ , L	1.02 ± 0.40	(0.47-1.74)
FEV ₁ , % predicted	42.1 ± 16.3	(19.0-69.0)
Postbronchodilator FEV ₁ , % predicted	44.5 ± 16.8	(20.0-74.0)
FVC, L	2.21 ± 0.53	(1.20-3.02)
FVC, % predicted	75.1 ± 15.5	(40.0-97.0)
FEV ₁ /FVC, %	46.7 ± 13.5	(22.0-65.0)

*Values are means ± SD with range in parentheses except Male:Female ratio

Table 2. – Spirometry during control and test trials*

	Before Placebo	After Placebo and Exercise	Before Furosemide	After Furosemide and Exercise
FEV ₁ , L	1.07 ± 0.37	1.06 ± 0.36	1.05 ± 0.39	1.10 ± 0.42 [†]
FEV ₁ , % predicted	43.95 ± 14.78	43.53 ± 14.53	42.89 ± 15.30	45.37 ± 16.66 [‡]
FVC, L	2.19 ± 0.60	2.22 ± 0.58	2.14 ± 0.62	2.34 ± 0.63 [‡]
FVC, % predicted	71.37 ± 18.63	72.37 ± 17.65	69.68 ± 18.71	75.95 ± 18.69 [‡]
FEV ₁ /FVC, %	49.56 ± 13.66	48.18 ± 13.11	49.38 ± 11.21	46.96 ± 11.87 [‡]
PEFR, L/min	3.35 ± 1.16	3.17 ± 1.10 [§]	3.26 ± 1.36	3.27 ± 1.41
PEFR, % predicted	45.8 ± 16.1	43.3 ± 15.4 [§]	44.4 ± 18.6	44.5 ± 19.0

* Values are means ± SD

[†]p < 0.05, compared with values before furosemide and after placebo

[‡]p < 0.05, compared to values before furosemide

[§]p < 0.05, compared to values before placebo

Table 3. – Selected parameters at peak exercise during incremental CPET*

	Placebo	Furosemide
WR, watts	48.9 ± 22.3	48.2 ± 23.2
$\dot{V}O_2$, mL/minute	777.1 ± 412.2	765.4 ± 437.8
VAS score	42.9 ± 25.1	40.3 ± 25.0
$\dot{V}E$, L/minute	31.5 ± 11.3	32.4 ± 13.2
V_T , L	0.98 ± 0.28	1.00 ± 0.31
f, breaths/minute	33 ± 10	34 ± 10
T_I/T_{tot}	0.40 ± 0.07	0.41 ± 0.05
V_T/T_I , L/second	1.19 ± 0.37	1.23 ± 0.44
HR, beats/minute	139 ± 24	132 ± 23
BP, mmHg	182/81 ± 31/13	183/88 ± 35/11
RER	0.88 ± 0.14	0.90 ± 0.15
SaO ₂ , %	93.0 ± 3.6	93.1 ± 4.4

* Values are means ± SD

Definition of abbreviations: WR = work rate; $\dot{V}O_2$ = oxygen uptake; VAS = visual analogue scale; $\dot{V}E$ = minute ventilation; V_T = tidal volume; f = breathing frequency; T_I/T_{tot} = duty cycle; HR = heart rate; BP = blood pressure; RER = respiratory exchange ratio; SaO₂ = oxygen saturation

Table 4. – Respiratory variables at standardized exercise time during incremental exercise testing*

	Placebo	Furosemide	p value
WR, watts	46.4 ± 22.4	46.4 ± 22.4	-
VAS score	35.8 ± 22.1	35.5 ± 23.7	0.921
$\dot{V}E$, L/minute	28.5 ± 10.4	29.3 ± 10.5	0.428
V_T , L	0.93 ± 0.30	0.99 ± 0.33	0.229
f, breaths/minute	31 ± 8	31 ± 8	0.875
T_I/T_{tot}	0.42 ± 0.11	0.41 ± 0.06	0.692
V_T/T_I , L/second	1.16 ± 0.39	1.18 ± 0.39	0.685
SaO ₂ , %	93.3 ± 3.6	93.0 ± 4.2	0.567

*Values are means ± SD

Definition of abbreviations: see Table 3

Table 5. – Respiratory variables at standardized exercise time during constant work rate exercise testing*

Variable	Placebo	Furosemide	p value
WR, watts	34.3 ± 16.0	34.3 ± 16.0	-
Duration of exercise, seconds	482 ± 370	482 ± 370	-
VAS score	42.4 ± 24.0	33.7 ± 25.2	0.014
$\dot{V}E$, L/min	26.4 ± 9.4	24.1 ± 10.3	0.159
V_T , L	0.90 ± 0.28	0.86 ± 0.31	0.398
f, breaths/minutes	31 ± 10	30 ± 12	0.576
T_I/T_{tot}	0.42 ± 0.07	0.43 ± 0.11	0.328
V_T/T_I , L/seconds	1.07 ± 0.36	0.98 ± 0.44	0.206
SaO ₂ , %	92.8 ± 4.0	92.5 ± 4.8	0.731

*Values are means ± SD

Definition of abbreviations: see Table 3

Figure 1

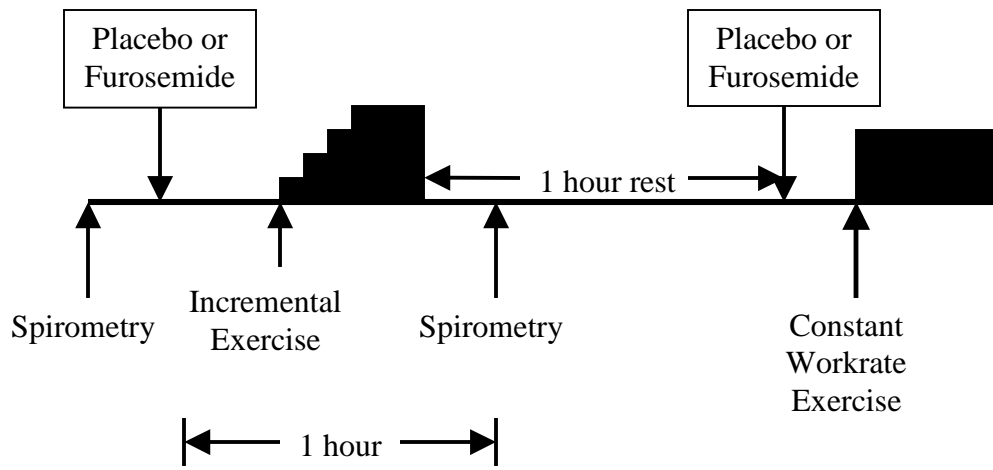


Figure 2

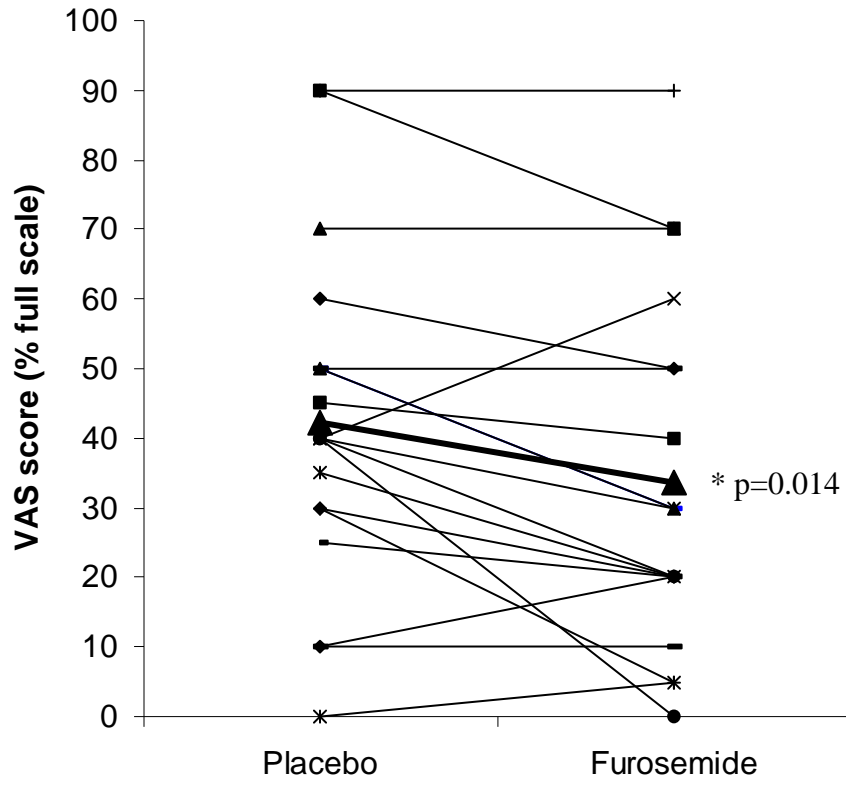
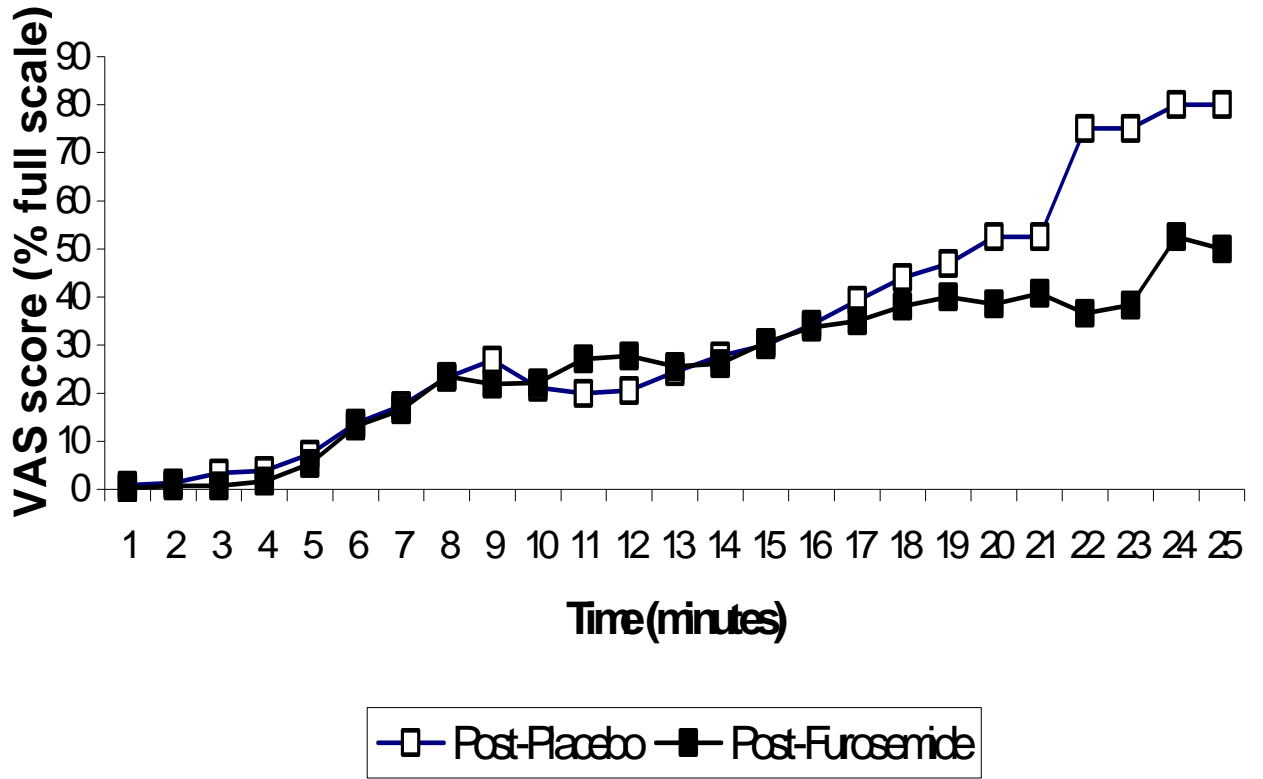


Figure 3



TITLE: Effects of inhaled furosemide on exertional dyspnea in
Chronic Obstructive Pulmonary Disease

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Earnest, Yee-Tang Wang

ONLINE DATA SUPPLEMENT

METHODS

Subjects

Subjects included patients with stable COPD who satisfied the following criteria: (1) moderate to severe COPD ($FEV_1 < 70\%$ predicted) with a clinical course consistent with chronic bronchitis and/or emphysema and a long history of cigarette smoking; (2) moderate to severe chronic breathlessness (Medical Research Council Dyspnea Scale grade 4 and 5) (E1); (3) age 50 yr or older; and (4) clinically stable as defined by no exacerbations or hospital admissions in the preceding six weeks. Use of medications remained stable throughout the study period for each patient. Exclusion criteria were as follows: an increase in $FEV_1 \geq 10\%$ following inhaled bronchodilator, known adverse effects to furosemide, contraindications to exercise testing as stipulated by the American College of Sports Medicine (E2), a history of asthma or atopy, a history of other active lung disease or significant disease that could contribute to dyspnea or exercise limitation, and oxygen desaturation to less than 80% during exercise on room air. All the patients had completed a pulmonary rehabilitation program at our hospital in the preceding year. As part of this program, all the subjects had undergone evaluation of lung function and exercise testing before and after completion of the program. They were familiar with the procedure and requirements of these tests as well as the visual analogue scale (VAS) for evaluating their symptoms of breathlessness at rest and during exercise as they had undergone similar exercise tests on at least 2 previous occasions.

Study design

The study was conducted on two days (not more than 2 weeks apart) in a double-blind, randomized, crossover design. The order of study visits was randomized for each

subject. Computer software was used to generate a set of random numbers. Eligible subjects were assigned to the order of study visits (placebo-frusemide or frusemide-placebo) using simple randomization. On each of the 2 days, baseline spirometry was performed before the patient was asked to inhale furosemide or placebo.

Incremental cardiopulmonary exercise testing (CPET) was performed immediately after completion of nebulization. After recovery from exercise and at one hour after nebulization of placebo or furosemide, the patients performed another spirometry. After this, the patients rested and one hour after termination of the incremental exercise test, they received another nebulization of furosemide or placebo (the same agent as that received earlier in the day) followed immediately by constant workload exercise testing. Figure E1 shows the timing of events and measurements during experimental visits.

Four millilitres of furosemide (Lasix; Hoechst, Tokyo, Japan) as a 10 mg/ml solution containing NaCL 7.0 mg plus NaOH at pH 9 and water to make up 1 ml, and 4 ml of placebo (0.9% saline solution) were administered by means of a jet nebulizer (Inspiron, CR Bard International Ltd, Sunderland, UK) driven by compressed air at 8L/minute (output, 0.4ml/minute; mass median diameter, 4.5 μ l) and nebulized to dryness with the subjects breathing tidally over 15 minutes.

The study was approved by the institutional Ethics Committee and each patient gave informed consent to the methodology of the study.

Pulmonary function tests

Before each visit, patients discontinued use of inhaled short-acting β_2 -agonists, anti-cholinergics, long-acting β_2 -agonists and theophyllines at least 6, 12, and 24 hours, respectively before testing. Each subject's height (cm) and weight (kg) were measured in

exercise attire (excluding shoes), using a standard physician's scale. Weight was measured to the nearest 0.1 kg and height was assessed to the nearest 0.5 cm. Age was recorded as at the last birthday. Spirometry was performed in accordance with recommended standards (E3). All lung function tests were performed with the subject seated. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) were measured with a clinical spirometer (SensorMedics 6200, Yorba Linda, CA). Predicted values for FEV₁ and FVC were determined using the prediction equations from Chia et al (E4).

Exercise testing

The instructions given to the subjects were similar to the routine instructions sent to patients coming to the laboratory for clinical exercise testing (E5). Symptom-limited CPET was performed using an electronically braked cycle ergometer (Ergometrics 800S, SensorMedics, Yorba Linda, CA). CPET was performed under the supervision of a physician with defined criteria for stopping, such as serious cardiac arrhythmias, hypotension and electrocardiographic changes and severe oxygen desaturation. An incremental exercise protocol was used in which the work rate was increased by 5 watts every minute after an initial 3 minutes of unloaded pedalling. Standard 12-lead electrocardiograms were obtained at rest, every 3 minutes during exercise, at peak exercise and for 5 minutes into the recovery phase while blood pressures were measured using a standard cuff sphygmomanometer at similar intervals. Subjects wore a tight-fitting facemask (Rudolph Face Mask for Exercise Testing; Hans Rudolph Inc., Kansas City, MO) connected to a pneumotachograph. Measurements of mixed expired oxygen, mixed expired carbon dioxide and expired volume were determined at rest and for each

breath throughout exercise using a metabolic cart (Vmax 229, SensorMedics, Yorba Linda, CA). The gas analyzer was calibrated for both accuracy and linearity prior to each test. Oxygen uptake ($\dot{V}O_2$ in ml/minute, standard temperature and pressure, dry), carbon dioxide production ($\dot{V}CO_2$, in ml/minute), gas exchange ratio, minute ventilation ($\dot{V}E$, in L/minute, BTPS), respiratory rate (f), tidal volume (VT), and the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$) was determined and averaged every 30 seconds. The peak $\dot{V}O_2$, $\dot{V}E$ and heart rate (HR) were selected as the highest values obtained from any 30-seconds measurement period. Maximum work rate (WR) was defined as the highest work level that was reached. Oxygen saturation (SaO₂) via pulse oximetry and heart rate by electrocardiography were recorded continuously throughout exercise and during recovery. At the end of exercise, the reason/s for termination were obtained from the subjects. Constant work rate (CWR) exercise testing was performed at 70% of the peak work rate achieved in the initial incremental exercise test, again after an initial 3 minutes of unloaded pedalling, with similar recording of ventilatory and gas exchange measurements as during incremental CPET. Patients were instructed to cycle on the ergometer for as long as possible and the total exercise time at the target level was recorded.

At the beginning of every minute during exercise testing, each patient was asked to rate the intensity of sensation of dyspnea using a VAS (E6). The analogue scale consisted of a vertical straight line, 100-mm in length with 10 equally spaced markers. It was labelled 100 at the top and 0 at the bottom. Patients were instructed to point to a spot on the line indicating the sensation of respiratory effort at that point in time. The numerical value of zero indicated no sensation at all and 100 indicated a sensation that

was intolerable. Dyspnea was defined as an unpleasant urge to breathe with no further clarification or definition given.

Statistical Analysis

Sample size calculation was based on a two-period, two-treatment crossover study design. The calculation was done for the primary efficacy variable, which was the dyspneic VAS score. The paired t test was used to compare the mean VAS score between placebo and furosemide. For a two-sided, 0.05 level of significance test with at least 80% power, a sample of 20 subjects would be adequately powered to detect a statistically significant result. This was based on a minimum clinical difference of 6 units in VAS scores between the placebo and furosemide treatment groups and a common standard deviation of 8.9 units.

We analyzed the data obtained during exercise testing after placebo inhalation and after furosemide inhalation using two-tailed paired t tests. The primary outcome measures were dyspneic VAS scores during incremental and CWR exercise testing after inhalation of placebo or furosemide. We compared the exercise responses at standardised exercise time (SET) during incremental and during CWR exercise testing for each patient. SET was equal to the time of the highest equivalent amount of work (isoworkrate) or time (isotime) completed in the incremental or endurance exercise tests for each patient, that is, the time of the shorter of the 2 incremental or endurance tests for each patient.

Spirometry results at baseline, after placebo inhalation and after furosemide inhalation were also analyzed using two-tailed paired t tests. Results were reported as means \pm SD. The conventional level of statistical significance of 0.05 was used for all

analyses. Data was entered into SPSS for Windows Version 9 (SPSS, Inc., Chicago, IL) for analysis.

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FIGURE LEGENDS

Figure E1. The timing of events and measurements for every experimental visit

Figure E1

