

## Effectiveness and Safety of Hypertonic Saline Inhalation Combined With Exercise Training in Patients With Chronic Obstructive Pulmonary Disease: A Randomized Trial

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**BACKGROUND:** Inhaled hypertonic saline is used for bronchial challenge and sputum induction in patients with chronic obstructive pulmonary disease (COPD). We studied the effects of saline aerosol inhalation before each exercise session in an 8-week pulmonary rehabilitation program. **METHODS:** This was a double-blind randomized parallel controlled trial, conducted at an outpatient clinic. Sixty-eight subjects with COPD (mean age  $67 \pm 6.5$  y, percent of predicted FEV<sub>1</sub>  $47 \pm 21$ ) were randomized to inhale either 3% hypertonic saline (34 subjects) or normal saline (34 subjects) before each exercise session in an 8-week exercise program that had 3 sessions per week. We measured 6-min walk distance, dyspnea, and quality of life (with the Medical Outcomes Study 36-item short-form health survey). **RESULTS:** After the 8-week exercise program, both groups' mean 6-min walk distance had significantly increased: from  $195 \pm 92$  m to  $251 \pm 97$  m ( $P < .001$ ) in the hypertonic-saline group, and from  $237 \pm 93$  m to  $441 \pm 121$  m in the normal-saline group ( $P < .001$ ). The normal-saline group had greater improvement than the hypertonic-saline group ( $P < .001$ ). Dyspnea score improved from  $3.1 \pm 0.9$  to  $2.3 \pm 0.8$  ( $P < .01$ ) in the hypertonic-saline group, and from  $3.5 \pm 0.2$  to  $2.3 \pm 1.0$  ( $P < .01$ ) in the normal-saline group. Quality of life also significantly improved, except for the physical-functioning and social aspect domains in the hypertonic-saline group. Adverse effects (cough or bronchospasm) occurred in 4 patients (12%) in the hypertonic-saline group. **CONCLUSIONS:** The improvement in 6-min walk distance was greater with normal saline than with hypertonic saline. Hypertonic saline was associated with adverse effects. It is unclear whether the only predictor of improved functional exercise capacity was exercise training. (ClinicalTrials.gov number, NCT00639236.) *Key words:* chronic obstructive pulmonary disease, COPD, hypertonic, saline, exercises, dyspnea. [Respir Care 2009;54(3):327–333. © 2009 Daedalus Enterprises]

### Introduction

Patients with chronic obstructive pulmonary disease (COPD) can have airway mucus hypersecretion<sup>1,2</sup> and gob-

let cell hypertrophy.<sup>3</sup> Mucus hypersecretion leads to airway obstruction, increased airway resistance, flow limitation, gas trapping, and increased residual volume, which decrease the efficiency of the diaphragm and reduce functional exercise capacity. Poorly ventilated lung regions cause ventilation-perfusion mismatch and hypoxemia.<sup>4,5</sup>

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The authors declare no conflicts of interest.

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Inadequate secretion clearance may promote bacterial colonization, repeated chest infections, and exacerbations of chronic conditions, particularly of COPD.<sup>6</sup> Chronic mucus hypersecretion in subjects with COPD is associated with deterioration of clinical variables, including lung function, risk of hospitalization, and risk of death.<sup>6</sup>

The general term for medications that modify the properties of mucus and promote secretion clearance is “mucoactive.” These medications include expectorants, mucolytics, mucoregulatory, mucospissic, and mucokinetic drugs.<sup>7</sup> A Cochrane review analyzed the effects of mucolytics in patients with chronic bronchitis or COPD, on number of exacerbations, number of days of disability, lung function, adverse effects, 6-min walk distance, and quality of life. The review concluded that mucolytics are associated with a small reduction in exacerbations and fewer days of disability.<sup>8</sup>

Inhaled hypertonic saline is an expectorant that promotes osmosis from the airway epithelium, which increases the water content of the airway mucus.<sup>9</sup> The hydrated airway mucus may then be more easily removed by mucociliary clearance and cough.<sup>9</sup> Hypertonic saline is also easy and inexpensive to produce.<sup>10</sup>

Inhaled hypertonic saline has been extensively studied in healthy subjects and patients with asthma, bronchiectasis, cystic fibrosis, and COPD as a method for inducing sputum;<sup>2,11-13</sup> increasing the effectiveness of chest physiotherapy;<sup>14-16</sup> and improving mucus clearance,<sup>17,18</sup> lung function,<sup>13,18-21</sup> quality of life,<sup>22</sup> and airway inflammation.<sup>23</sup> However, Rubin<sup>24</sup> concluded that changes in functional exercise capacity are related to adequate ventilation, gas exchange, blood circulation, oxygen transport, muscle mass, patient effort, and patient training. Hence, such changes are probably a more sensitive indicator of mucus clearance than are the usual pulmonary function measurements. This suggests that studies of other variables, such as those mentioned by Rubin, are required.

There is strong (level A) evidence that pulmonary rehabilitation with muscle-training methods improves functional exercise capacity, dyspnea, and health-related quality of life in patients with COPD.<sup>25</sup> However, it remains unclear whether the addition of hypertonic saline or normal saline to exercise training improves clinical outcomes. In subjects with COPD undergoing exercise training we compared the effects of hypertonic saline versus normal saline on functional exercise capacity, dyspnea, and quality of life, and analyzed any adverse effects.

## Methods

### Study Design

After we obtained protocol approval from our institutional ethics committee, we conducted a double-blind randomized parallel controlled trial in our out-patient clinic, between 2004 and 2006.

### Subjects

Subjects age 40–75 y, referred by a physician to the pulmonary rehabilitation program, and who had a clinical

Table 1. Modified Medical Research Council Dyspnea Scale

Score	Dyspnea Level	Description
0	None	No dyspnea except with strenuous exercise
1	Slight	Shortness of breath when hurrying on the level or walking up a slight hill
2	Moderate	Breathlessness causes slower on-the-level walking than people of the same age
3	Severe	Stops for breath after walking about 100 m or after a few minutes on the level
4	Very severe	Too breathless to leave the house, or breathless when dressing or undressing

and spirometric diagnosis of moderate or severe COPD (according to the Global Initiative for Chronic Obstructive Lung Disease criteria)<sup>26</sup> were screened for the study. During the study period we recommended to the subjects that they continue their current dose schedule of bronchodilators and inhaled corticosteroids. The subjects needed to have been stable for at least a year, to be former smokers (more than 6 months without smoking), and to be free from any severe and/or unstable heart disease or any other pathology that could impair their physical activities.

Patients with unstable lung disease (defined as more than 2 acute-care hospitalizations for COPD over the last year)<sup>13</sup> or asthma were excluded. All subjects gave informed consent prior to participation.

All subjects underwent a clinical examination to obtain clinical and personal data, including anthropometric data, medications, pulmonary function tests, and measurement of blood oxygen saturation.

### Outcomes

The primary outcome was functional exercise capacity, as measured by the 6-min walk test,<sup>27</sup> which provides a good, reproducible measurement of overall functional capacity in patients with COPD.<sup>28-30</sup> At baseline (before starting the exercise program) and after the 8-week exercise program, we measured blood pressure, heart rate, oxygen saturation via pulse oximetry ( $S_{pO_2}$ ), dyspnea (with the modified Medical Research Council scale [Table 1]),<sup>31</sup> and fatigue (with the Borg scale).<sup>32</sup>

General health status was measured with the Medical Outcomes Study 36-item short-form health survey (SF-36),<sup>33</sup> which has 8 domains: physical functioning, physical aspects, pain, general health, vitality, social aspects, emotional aspects, and mental health. The total score range is 0–100, and a higher score indicates a better quality of life. We used the Portuguese-language version<sup>34</sup> of the SF-36, which is reliable<sup>35</sup> and responsive for evaluating COPD.<sup>36-39</sup> The subjects were assessed with the SF-36 at baseline and after completing the 8 weeks of exercise treatment.

Table 2. Baseline Values ( $n = 68$ )

	Hypertonic Saline Group ( $n = 34$ )	Normal Saline Group ( $n = 34$ )	<i>P</i>
Age (mean $\pm$ SD y)	68 $\pm$ 6.5	67 $\pm$ 6.5	.53
Female/male	13/21	14/20	.80
BMI (mean $\pm$ SD kg/m <sup>2</sup> )	25.7 $\pm$ 4.8	26.9 $\pm$ 4.6	.19
FEV <sub>1</sub>			.76
L (mean $\pm$ SD)	1.27 $\pm$ 0.63	1.31 $\pm$ 0.65	
% of predicted (mean $\pm$ SD)	45 $\pm$ 20	49 $\pm$ 21	
FVC			.70
L (mean $\pm$ SD)	2.32 $\pm$ 0.87	2.18 $\pm$ 0.86	
% of predicted (mean $\pm$ SD)	67 $\pm$ 26	65 $\pm$ 24	
FEV <sub>1</sub> /FVC (mean $\pm$ % of predicted)	67 $\pm$ 22	76 $\pm$ 23	.12
S <sub>p</sub> O <sub>2</sub> (mean $\pm$ SD %)	91 $\pm$ 3	91 $\pm$ 3	.41
6-min walk distance (mean $\pm$ SD m)	195 $\pm$ 92	237 $\pm$ 93	.14
MRC dyspnea score (mean $\pm$ SD)	3.1 $\pm$ 0.9	3.5 $\pm$ 0.2	.13
Concomitant therapies ( <i>n</i> , %)			
Bronchodilators	34 (100)	33 (97)	< .001
Corticosteroids	34 (100)	33 (97)	< .001

BMI = body mass index  
FEV<sub>1</sub> = forced expiratory volume in the first second  
FVC = forced vital capacity  
S<sub>p</sub>O<sub>2</sub> = oxygen saturation measured via pulse oximetry  
MRC = Medical Research Council

We observed for adverse effects after each inhalation of saline aerosol. The subjects were free to ask that the procedure be discontinued if they experienced undesired symptoms (eg, coughing or a sensation of needing effort to breathe).<sup>40</sup> The presence of bronchospasm was measured in accordance with a sputum-induction protocol.<sup>13</sup> If peak expiratory flow fell by  $\geq 20\%$  from the baseline, we measured the forced expiratory volume in the first second (FEV<sub>1</sub>). If FEV<sub>1</sub> fell by  $\geq 20\%$  from the baseline, the inhalation was terminated.

All the data were collected by the same evaluator, who was blinded to the treatment, as were the subjects.

### Randomization

We used a standard random numbers table to allocate the boxes of hypertonic and normal saline ampoules. Each box contained 24 ampoules of saline solution, and we used a rigorously predetermined dose schedule and sequence. Once opened, the box number was recorded along with demographic information by a person not involved in the study.

### Study Protocol

The subjects were randomized to inhale either hypertonic saline (5 mL of a 3% solution) or normal saline (5 mL of a 0.9% solution). All the subjects kept their

regular medication regimens and followed their usual diets during the study.

### Exercise Training Program

The exercise training program comprised three 90-min sessions per week, for 8 weeks. Before each exercise session, 200  $\mu$ g of albuterol was administered from a metered-dose inhaler.<sup>13</sup> Ten minutes later the saline aerosol was administered with an ultrasonic nebulizer (Respiramax, NS Products, São Paulo, Brasil), which has an output of 1 mL/min and particles of 0.5  $\mu$ m. The subjects remained seated and held the oral mask close to the mouth. They were instructed to breathe through the mouth for 15 min. Each session included a warm-up period, followed by mobility training, dynamic strength training of the upper and lower limbs, whole-body endurance training (20 min on the treadmill), and stretching exercises.<sup>41</sup> The training intensity was individualized to 80% of the maximum heart rate reached in the lower-limb incremental test, following the Harbor protocol.<sup>42</sup>

### Statistical Analysis

We calculated that a sample of 68 subjects would provide a power of 80% ( $\alpha = 0.05$ ,  $\beta = 0.20$ ), to detect a 20% change in functional exercise capacity from the treatment, between the 2 groups.<sup>43</sup>

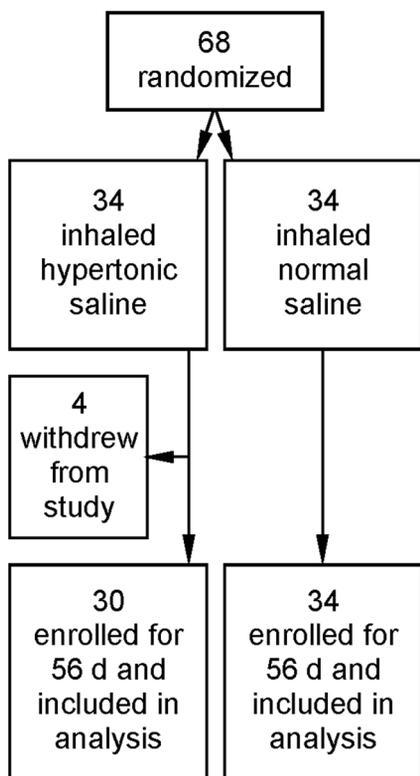


Fig. 1. Screening, exclusion, and inclusion of study subjects.

We analyzed the data with statistics software (Statistica 7, StatSoft, Tulsa, Oklahoma). All the data were tested for normality with the Kolmogorov-Smirnov test. The results are presented as mean ± SD. Differences between the 2 groups at baseline were analyzed with the *t* test for independent samples. The chi-square test was used to analyze the differences in dyspnea scores. Differences in 6-min walk distance were analyzed with the *t* test for dependent samples. Differences in dyspnea scores were analyzed with the Wilcoxon matched-pairs test.<sup>44</sup> We assumed that *P* < .05 represented a statistically significant difference.

**Results**

Table 2 shows the baseline anthropometry and mean ± SD values for pulmonary function, S<sub>pO<sub>2</sub></sub>, 6-min walk distance, dyspnea score, and concomitant bronchodilators and corticosteroids. None of the subjects were using antibiotics.

Of the 68 subjects randomized to receive either hypertonic saline (*n* = 34) or normal saline (*n* = 34), 64 (hypertonic saline = 30, normal saline = 34) completed at least 56 days of treatment (Fig. 1). Four subjects in the hypertonic-saline group dropped out of the study because of adverse effects.

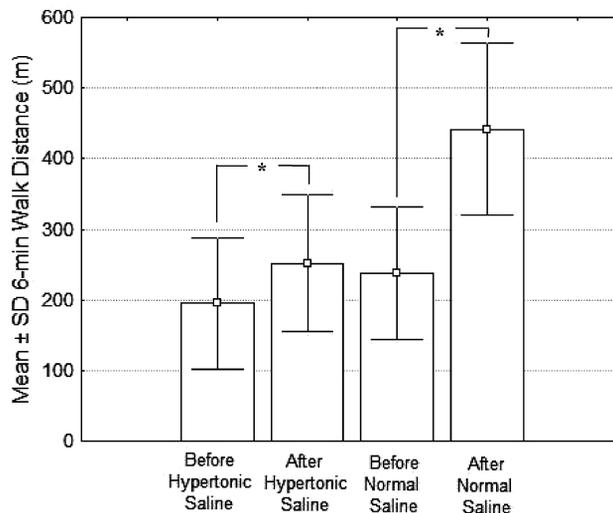


Fig. 2. Mean ± SD 6-min walk distance before and after an 8-week exercise training program with inhaled hypertonic saline or inhaled normal saline. \* *P* < .01.

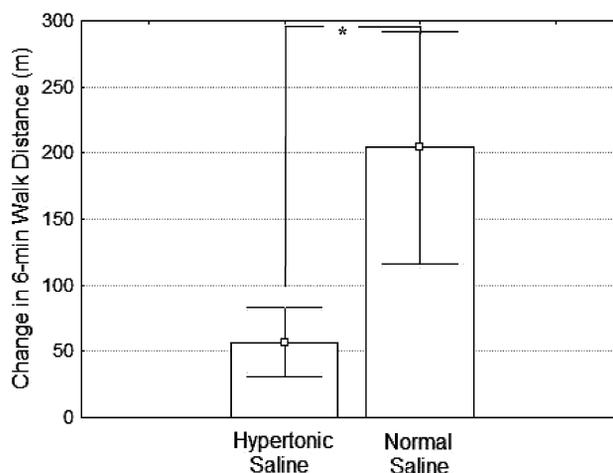


Fig. 3. Mean ± SD change in 6-min walk distance before and after an 8-week exercise training program with inhaled hypertonic saline or inhaled normal saline. \* *P* < .001.

**6-Min Walk Distance**

After the 8-week exercise program, both groups had significant improvement in 6-min walk distance: from 195 ± 92 m to 251 ± 97 m (*P* < .001) in the hypertonic-saline group, and from 237 ± 93 m to 441 ± 121 m (*P* < .001) in the normal-saline group (Fig. 2). The normal-saline group had greater improvement than the hypertonic-saline group (*P* < .001) (Fig. 3).

**Dyspnea**

Dyspnea score improved significantly in both groups: from 3.1 ± 0.9 to 2.3 ± 0.8 (*P* < .01) in the hypertonic-

Table 3. SF-36 Domain Scores

SF-36 Domain	Before Hypertonic Saline (mean $\pm$ SD)	After Hypertonic Saline (mean $\pm$ SD)	<i>P</i> (before vs after hypertonic saline)	Before Normal Saline (mean $\pm$ SD)	After Normal Saline (mean $\pm$ SD)	<i>P</i> (before vs after normal saline)	<i>P</i> (hypertonic vs normal saline)
Functional-functioning	29 $\pm$ 19	54 $\pm$ 23	.16	34 $\pm$ 24	59 $\pm$ 23	<.001	.93
Physical aspect	26 $\pm$ 30	46 $\pm$ 42	< .001	28 $\pm$ 34	55 $\pm$ 40	<.001	.85
Pain	53 $\pm$ 27	63 $\pm$ 27	.001	50 $\pm$ 28	64 $\pm$ 24	<.001	.85
General state of health	50 $\pm$ 23	57 $\pm$ 19	.001	48 $\pm$ 23	57 $\pm$ 20	<.001	.70
Vitality	43 $\pm$ 21	55 $\pm$ 20	.001	40 $\pm$ 26	60 $\pm$ 18	<.001	.57
Social aspect	59 $\pm$ 33	71 $\pm$ 26	.32	56 $\pm$ 33	71 $\pm$ 33	<.001	.58
Emotional aspect	40 $\pm$ 41	60 $\pm$ 43	.002	48 $\pm$ 43	72 $\pm$ 41	<.001	.62
Mental health	60 $\pm$ 28	69 $\pm$ 23	.006	56 $\pm$ 41	70 $\pm$ 21	<.001	.60

SF-36 = Medical Outcomes Study 36-item short-form health survey

saline group, and from  $3.5 \pm 0.2$  to  $2.3 \pm 1.0$  ( $P < .01$ ) in the normal-saline group. There was no significant difference in dyspnea-improvement between the groups ( $P = .08$ ).

### Quality of Life

There was significant improvement in overall quality of life in both groups, except for the physical functioning and social aspects domains in the hypertonic-saline group. There were no significant differences between the groups in the other SF-36 domains (Table 3).

### Adverse Effects

There were adverse effects in 4 subjects (12%) in the hypertonic-saline group: 3 subjects reported increased coughing, and one had bronchospasm.

### Discussion

After the 8-week exercise program, both groups had improved 6-min walk distance, dyspnea score, or quality of life, except for the physical functioning and social aspect SF-36 domains in the hypertonic-saline group. Hypertonic saline was associated with cough and bronchospasm (a 20% decrease in FEV<sub>1</sub>). The 2 groups had similar baseline anthropometry, pulmonary function, S<sub>pO<sub>2</sub></sub>, 6-min walk distance (hypertonic saline 204 m vs normal saline 237 m), dyspnea, and bronchodilator and corticosteroid use. There were more men in both groups.<sup>45-46</sup> The subjects had moderate to severe COPD,<sup>26</sup> and all but one were using bronchodilators and corticosteroids.

In both groups, 6-min walk distance significantly improved (defined by a minimum clinically important difference of 54 m),<sup>29</sup> but the normal-saline group had greater improvement. The lesser improvement in the hypertonic-

saline group might be explained by inflammatory response, which, according to some studies, changes lung function,<sup>13</sup> reduces inspiratory capacity, and increases intrathoracic gas volume and residual volume,<sup>47</sup> which compromises ventilation and decreases oxygen delivery to the peripheral musculature.

Both groups' dyspnea improved (the minimal clinically important difference was defined as a one-unit change in dyspnea score<sup>48</sup>), but there was no difference in dyspnea-improvement between the groups. These results disagree with those of Makris et al,<sup>40</sup> who concluded that in patients with advanced COPD, hypertonic saline increased dyspnea and oxygen desaturation. In patients with moderate to severe COPD, Taube et al<sup>47</sup> found that hypertonic (3%) saline and normal saline increased dyspnea and decreased forced inspiratory and expiratory capacity.

Despite the fact that our subjects were pretreated with albuterol, 4 subjects had cough and bronchospasm after hypertonic-saline inhalation. In a study by Postma and Kerstjens,<sup>49</sup> two thirds of the subjects with COPD reported adverse effects after inhaling hypertonic saline. Carpagano et al<sup>23</sup> suggested that hypertonic saline causes low-level airway inflammation that would be identifiable from inflammatory markers such as interleukin-6 or tumor necrosis factor alpha.

The SF-36 scores indicated significant improvement in quality of life in both groups, except for the physical functioning and social aspects domains in the hypertonic-saline group. The normal-saline group had larger means and smaller standard deviations in all the SF-36 domains, which can be explained by the fact that both groups were undergoing physical training. One study found that exercise increases the production of  $\beta$  endorphins and biogenic amines, which reduce anxiety and produce a sense of well-being.<sup>50</sup>

Snoeck-Stroband et al<sup>22</sup> concluded that the worse health status among patients with COPD was associated with

higher inflammatory cell counts in induced sputum. In subjects with COPD, Pellegrini et al<sup>51</sup> found that steam inhalation improved quality of life, as measured by the activity and impact domains of the St George's respiratory questionnaire.

The strength of the present study lies in the fact that we compared different outcomes (such as mucociliary clearance, pulmonary function, number of exacerbations, and sputum induction), rather than just testing inhaled hypertonic saline combined with exercise training, as was done in previous studies.

One of the limitations of this study was the sample size. However, the results are consistent with previous findings and can be extrapolated to clinical practice.

It remains unclear whether the functional-exercise-capacity response to inhaled hypertonic saline was associated with deterioration of lung function, and whether the only predictor of improvement in functional exercise capacity was exercise training. Clearly, further study is required, with comparison of no inhaled saline versus hypertonic saline and normal saline.

### Conclusions

Both the hypertonic-saline and normal-saline groups had significantly improved 6-min walk distance, dyspnea score, and quality of life (except for the physical functioning and social aspects domains in the subjects who inhaled hypertonic saline). The normal-saline group had greater improvement in 6-min walk distance. Hypertonic saline caused cough and bronchospasm in 4 subjects.

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