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David Stav and Meir Raz

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CHEST

Original Research

COPD

Effect of N-Acetylcysteine on Air Trapping in COPD

A Randomized Placebo-Controlled Study

David Stav, MD; and Meir Raz, MD

Background: **FEV_1 is used for the classification of disease severity and is a good predictor of COPD mortality. However, it is a poor predictor of clinical symptoms, exercise tolerance, and response to bronchodilators in COPD. Progressive reduction in inspiratory capacity (IC) during exercise reflects dynamic hyperinflation and is a good predictor of decreased exercise ability as well as increased exertional dyspnea. In animal models of COPD, N-acetylcysteine (NAC), an antioxidant/mucous modifier, has been shown to modify small airways, which mainly causes lung hyperinflation.**

Objective: **Our goal was to examine the effect of 1,200 mg/d of NAC on lung hyperinflation at rest and after exercise in patients with moderate-to-severe COPD.**

Methods: **This was a randomized, double-blind, cross-over study that included 24 eligible patients > 40 years of age with a diagnosis of COPD, a FEV_1 < 70% of predicted, FEV_1/FVC ratio < 0.70, and a functional residual capacity > 120% of predicted normal. Patients were randomized to placebo treatment or NAC treatment twice daily for 6 weeks. This was followed by a 2-week washout period, and then patients were crossed over to alternate therapy for an additional 6 weeks. Evaluation was performed after each 6 weeks of each treatment.**

Results: **IC and FVC were higher especially after exercise after NAC treatment compared with placebo treatment. In addition, the relationship of residual volume to total lung capacity was reduced in a similar pattern. Furthermore, endurance time was longer after NAC treatment compared with placebo treatment.**

Conclusions: **NAC treatment of patients with stable, moderate-to-severe COPD has a beneficial effect on physical performance, probably due to a reduction in air trapping.**

Trial registration: **Clinicaltrials.gov Identifier: NCT00476736** ***(CHEST 2009; 136:381–386)***

Abbreviations: DH = dynamic hyperinflation; IC = inspiratory capacity; NAC = N-acetylcysteine; PFT = pulmonary function test; RV = residual volume; TLC = total lung capacity

COPD is characterized by a chronic airflow limitation that is usually progressive. Since the mid-1990s, mortality from COPD has increased, and COPD is expected to become the third-greatest cause of mortality in Western countries by the year 2020. The majority of the patients are current or former smokers.[1]

Although FEV_1 is used for disease severity classification and is a good predictor of COPD mortality, it is a poor predictor of clinical symptoms, exercise tolerance, and response to bronchodilators in COPD. Therefore, additional measures have been sought.[2] Exercise testing using constant or incremental cycle ergometry with repeated measurements of inspiratory capacity (IC) has been used to detect dynamic hyperinflation (DH) and evaluate the response to bronchodilators. Previously, it was reported that dyspneic score ratings and measurements of IC and endurance time during submaximal cycle exercise

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Affiliations: From the Pulmonary Institute (Dr. Stav), Assaf Harofeh Medical Center, Zerifin, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; and Maccabi Health Care Services (Dr. Raz), Tel Aviv, Israel.

Correspondence to: David Stav, MD, Pulmonary Institute, Assaf Harofeh Medical Center, Zerifin 70300 Israel; e-mail: dstav@post.tau.ac.il

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Table 1—*Baseline Characteristics of Patients With COPD*

Characteristics	Mean	SD
Age, yr	66 (range, 59–73)	6.5
Current smoker	None	
FEV_1, % predicted	58	7
IC, L	2.2	0.5
RV/TLC, %	137	18

testing are highly reproducible and responsive to changes in severe COPD.[3] A progressive reduction in IC during exercise reflects DH and is a good predictor of decreased exercise ability as well as increased exertional dyspnea.[4]

Treatment of patients with COPD depends on the stage of the disease. At the outset, it is strongly recommended that such patients quit smoking. Bronchodilators drugs are then administered. In a more advanced stage, inhaled corticosteroids and pulmonary rehabilitation are added. In hypoxemic patients, long-term supplemental oxygen is advised.[1]

N-acetylcysteine (NAC) provides cysteine for enhanced production of the antioxidant glutathione and has antioxidant effects *in vitro* and *in vivo*. There were equivocal results regarding the benefits of the administration of antioxidant/mucous modifier drugs in patients with COPD, in contrast to animal studies.[5] However, it should be stressed that the daily dose used did not exceed 600 mg. In all the studies, FEV_1 was used to demonstrate the beneficial effect of the drug despite the fact that the disease changes are at the level of small airways, which is not usually expressed by the measurement of FEV_1. IC, however, is a lung volume measure that has been found to correlate well with patient dyspnea and exercise tolerance. Our aim was to demonstrate that 1,200 mg/d of NAC may reduce resting and postexercise hyperinflation in patients in addition to increasing exercise endurance time in patients with stable moderate-to-severe COPD.

Materials and Methods

Patients

We enrolled 24 patients who had a smoking history of 27 pack-years (range, 20 to 40 pack-years) but were not active smokers. They were followed up for not less than 1 year in our clinic, and were known to have COPD for >5 years. Their COPD grade was defined as moderate to severe (stage II and III; Global Initiative for Chronic Obstructive Lung Disease), but they were clinically stable for at least 8 weeks prior to the present study and were not receiving oxygen. All visits were conducted at the same time of day for each subject. Subjects remained on their usual medication between visits (inhaled long-acting β-agonists and inhaled steroids).

Patients were excluded if they had a history of physician-diagnosed asthma, non-COPD respiratory disorders, lung volume reduction surgery or transplantation, or long-term oxygen therapy requirements. Finally, subjects were asked to avoid caffeine, dark chocolate, cola beverages, heavy meals, alcohol, and major physical exertion prior to visits because these factors could influence exercise performance.

Written informed consent was obtained from all patients participating in the study. The protocol was approved by the institutional review boards.

Materials

Twelve patients received 1,200 mg of NAC, and 12 patients received a placebo orally for 6 consecutive weeks, followed by a 2-week interval. Subsequently, the groups switched treatment for an additional 6 weeks (Fig 1). The investigators and patients were blinded with regard to treatment.

Physiologic Measures

Resting pulmonary function tests (PFTs) were performed, followed by bicycle ergometry for 6 min with an exercise workload of 50 W. After 2 min of rest, PFTs were performed. PFTs included lung volumes (total lung capacity [TLC], thoracic gas volume, residual volume [RV]/TLC, and IC) and spirometry (FVC and FEV_1). The endurance time test was performed as follows: the patients paddled without resistance for 2 min after which the workload was increased to 75 W, and was stopped when symptoms occurred.[6]

Statistical Analysis

Statistical software (VassarStats; http://faculty.vassar.edu/lowry/VassarStats.htm) was used for basic linear correlation and regression, and the *t* test was used to compare between the two groups.

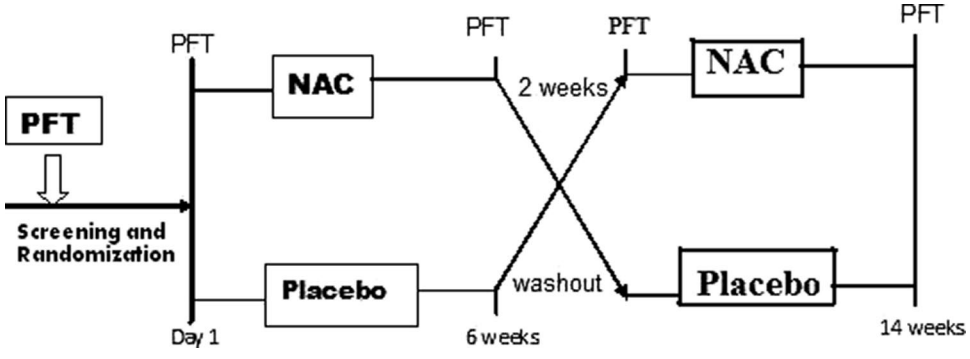

Figure 1. Schematic presentation of study protocol.

Results

A total of 24 patients were randomized. Two dropouts occurred during the study: one due to cardiac hospitalization, and the other for personal reasons. All patients recruited received NAC, and all served as controls. Demographic data, smoking history, and dyspnea, lung function, and exercise values at screening are shown in Table 1.

There was a significant statistical improvement in FVC during rest and after NAC treatment ($p < 0.048$), while the changes in p values of TLC and RV/TLC were 0.058 and 0.055, respectively, in favor of NAC treatment. Although no significant difference was observed in IC at rest, results after exercise showed that IC measured after exercise was higher in patients receiving NAC compared with patients receiving placebo ($p < 0.0033$) [Fig 2]. A similar pattern was observed in FVC after exercise in patients who received NAC compared with patients who received a placebo ($p < 0.0029$) [Fig 3]. In this case, FVC served as an additional parameter for the measurement of small airway narrowing.[7]

There was also a significant difference in RV/TLC after exercise. It was significantly lower after exercise in the NAC group ($p < 0.001$) [Fig 4]. These results showed that the parameters expressing air trapping at rest tended to decrease, and this became much more pronounced after exercise in NAC-treated patients with COPD. No significant exacerbation was documented.

Exercise Endurance Time

NAC significantly increased exercise time compared with placebo, with treatment differences of 22 s, which was highly significant (Fig 5). The majority of subjects (80%) discontinued exercise due to respiratory symptom limitations. The remaining subjects discontinued due to leg discomfort (20%).

Correlates of Exercise Endurance Time

With NAC treatment, postdose improvement in exercise time at week 6 was significantly correlated with the increase in FVC at rest ($R = 0.45$, $p < 0.001$) but not with FEV_1 ($R = 0.23$, $p < 0.08$).

We also measured the magnitude of the effects, which take into account the effect of size. All reported results that were significantly different meant that the magnitude of effects was high, except for endurance time, for which the significance was high but the effect low.

Adverse Events

Apart from mild epigastric discomfort that was reported by a few patients in the treated group, no other complaints or findings were recorded.

Discussion

The results of this study demonstrated that treatment of patients with COPD with NAC, 1,200

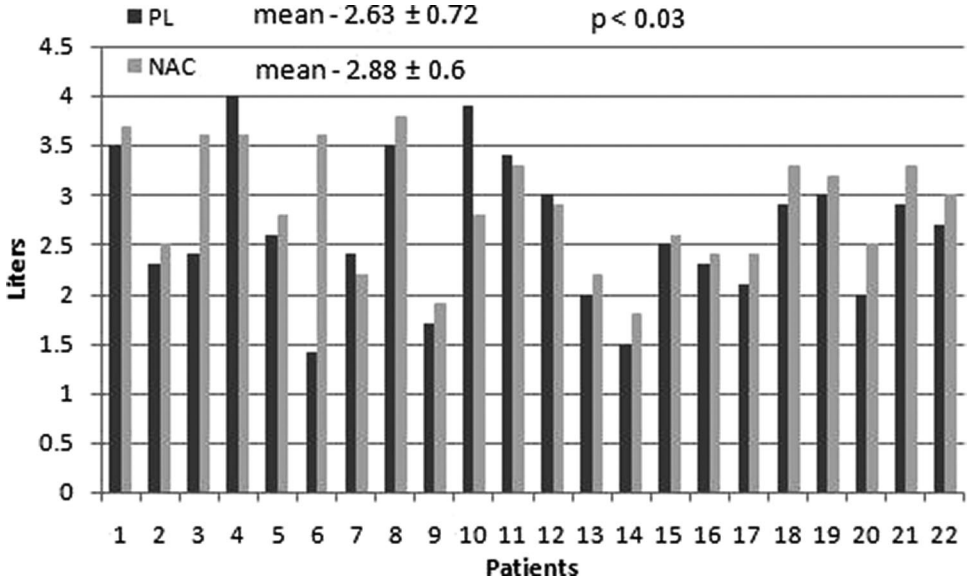

Figure 2. Postexercise measurements of IC. PL = placebo.

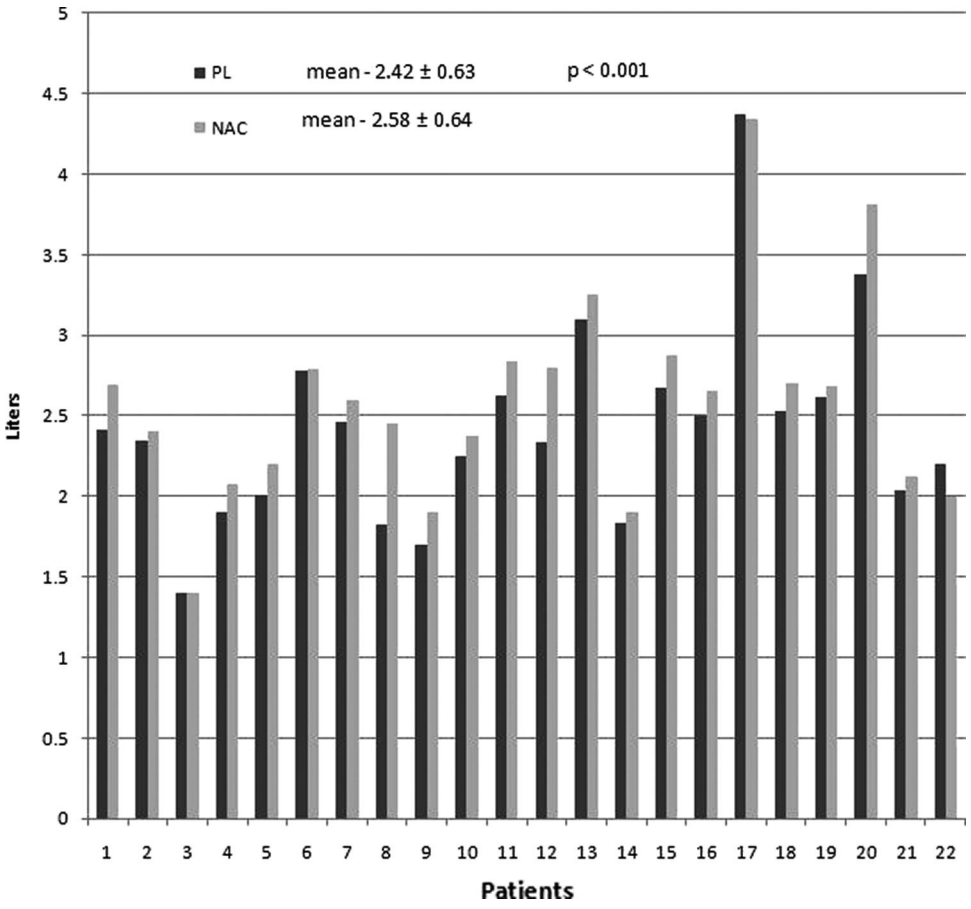

FIGURE 3. Postexercise measurements of FVC. See Figure 2 for abbreviation not used in the text.

mg/dbid for 6 weeks, significantly reduced the air trapping that occurred due to DH after exercise. There was also a significant improvement in exercise endurance time after treatment with NAC, compared with treatment with placebo. While the major difference in the treatment was observed after exercise, a similar, less pronounced pattern was observed at rest. It should be stressed that one of the impor-

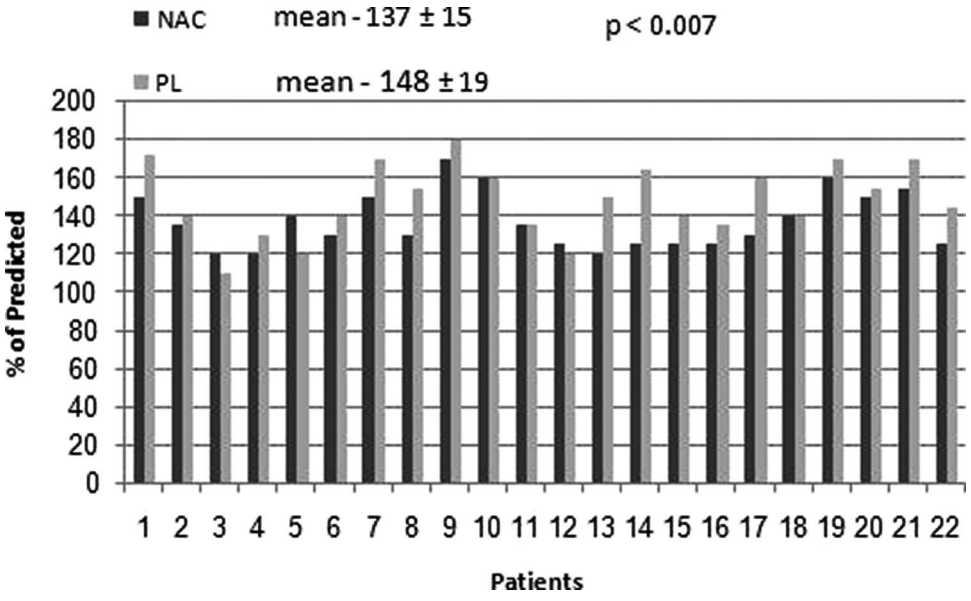

FIGURE 4. Postexercise measurements of RV/TLC. See Figure 2 for abbreviation not used in the text

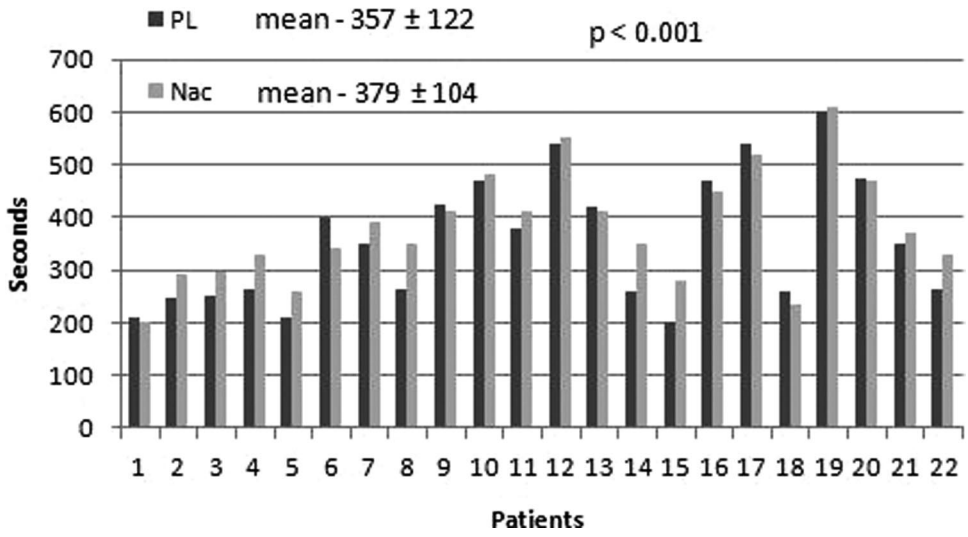

FIGURE 5. Comparison of endurance time. See Figure 2 for abbreviation not used in the text.

tant limitations experienced by patients with COPD occurs during effort. Therefore, such an improvement may have an important impact on their quality of life.

In a study of great magnitude that included 50 centers, 523 patients with COPD examined the effect of 600 mg/d of NAC compared with placebo, during 3 years of follow-up on the yearly rate of FEV_1 decline. This resulted in no advantage of NAC over placebo in this regard. Furthermore, the number of exacerbations per year did not differ between the groups.[8] We believe that the following were the two main problems in the study design: (1) Patients received only 600 mg of NAC. Even the authors in their discussion speculated that a dose $>$ 600 mg might have produced a clearer effect on pulmonary function; (2) They chose FEV_1 as a primary outcome parameter for physiologic improvement despite the fact that FEV_1 barely represents small airways, which are greatly involved in COPD. They also found a decrease in functional residual capacity in patients treated with NAC compared with patients treated with a placebo, and this may be an indication of small airway improvement. Regarding the dosage chosen, in a series of articles[9–11] that investigated the effect of 1,200 mg/d of NAC, they observed a reduction of oxidant markers such as H_2O_2 in exhaled air in a dose-dependent manner, and a reduction in inflammatory markers. An additional advantage of NAC was a reduction of COPD exacerbations, which was summarized in a systematic review[11] of studies. Furthermore, in a recent investigation[12,13] using a similar drug with a large number of subjects and a 1-year follow-up period, a reduction in exacerbations and an improvement in quality of life were shown. Previous results, which support our improved exercise endurance time, showed that NAC pretreatment in humans improves the performance of limb and respiratory muscles during fatigue protocols and extends time to task failure during volitional exercise.[14–16]

Our study has two limitations. First, 6 weeks is probably too short for such a chronic disease, although long-term studies produce many methodologic problem such as seen in the Towards a Revolution in COPD Health (or TORCH) and Understanding Potential Long-Term Impacts on Function with Tiotropium (or UPLIFT) studies.[17,18] Secondly, the number of participants was only 24. However, since this was a crossover study, the number of participants was equivalent to 48 persons examined in a randomized double-blind investigation.

In conclusion, the treatment of patients with COPD with NAC was effective in terms of reducing the air trapping due to DH. This was achieved by a relatively short period of treatment. Therefore, it is worthwhile conducting a similar study for a longer period of time and with more patients.

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