The Effect of Lung Volume Reduction Surgery on Chronic Obstructive Pulmonary Disease Exacerbations

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Rationale: **Lung volume reduction surgery (LVRS) has been demonstrated to provide a functional and mortality benefit to a select group of subjects with chronic obstructive pulmonary disease (COPD). The effect of LVRS on COPD exacerbations has not been as extensively studied, and whether improvement in postoperative lung function alters the risk of disease exacerbations is not known.**

Objectives: **To examine the effect, and mechanism of potential benefit, of LVRS on COPD exacerbations by comparing the medical and surgical cohorts of the National Emphysema Treatment Trial (NETT).**

Methods: **A COPD exacerbation was defined using Centers for Medicare and Medicaid Services data and *International Classification of Diseases, Ninth Revision,* discharge diagnosis.**

Measurements and Main Results: **There was no difference in exacerbation rate or time to first exacerbation between the medical and surgical cohorts during the year before study randomization (P = 0.58 and 0.85, respectively). Postrandomization, the surgical cohort experienced an approximate 30% reduction in exacerbation frequency (P = 0.0005). This effect was greatest in those subjects with the largest postoperative improvement in FEV_1 (P = 0.04) when controlling for changes in other spirometric measures of lung function, lung capacities, and room air arterial blood gas tensions. Finally, LVRS increased the time to first exacerbation in both those subjects with and those without a prior history of exacerbations (P = 0.0002 and $P < 0.0001$, respectively).**

Conclusions: **LVRS reduces the frequency of COPD exacerbations and increases the time to first exacerbation. One explanation for this benefit may be the postoperative improvement in lung function.**

Clinical trial registered with www.clinicaltrials.gov (NCT 00000606).

Keywords: COPD; LVRS; exacerbation

Chronic obstructive pulmonary disease (COPD) is responsible for an estimated 176 million hospital bed days per year in the United States and an annual loss of almost 60 million workdays (1). A significant portion of the health care costs incurred by COPD is due to acute exacerbations. Although the mainstays of medical treatment and prevention include inhaled long-acting bronchodilators and corticosteroids, their efficacy in this regard is debated (2–4). The basis for their presumed beneficial effect is a combination of their bronchodilating and antiinflammatory properties, effects that may offset the increased risk of exacerbations found with declining lung function (5–12). Given this, mechanical interventions that improve function, such as lung volume reduction surgery (LVRS), may reduce the frequency of acute exacerbations.

Results from the National Emphysema Treatment Trial (NETT) suggest that there is a subset of subjects with COPD who obtain functional, quality-of-life, and mortality benefits from LVRS (13). Although still statistically significant at 3 years postrandomization, these postsurgical improvements in lung function for LVRS patients had attenuated and were approaching measurements made in the medical cohort. The effect of LVRS on the rate of acute exacerbations, and the durability of any effects on exacerbations as the postrandomization lung function of the medical and surgical cohorts converge, is unstudied. Here we present a retrospective investigation of the effect of LVRS on the frequency of acute exacerbations as defined by emergency department and hospitalization records collected during the NETT. Some of the results of these studies have been previously reported in the form of an abstract (14).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Lung volume reduction surgery (LVRS) offers morbidity and mortality benefits to a subset of people with chronic obstructive pulmonary disease (COPD). Its effect on acute exacerbations is unknown. Improving lung function with LVRS may prevent COPD exacerbations.

What This Study Adds to the Field

LVRS reduces the frequency of COPD exacerbations and increases the time to first exacerbation. LVRS may decrease the risk of an acute exacerbation through its beneficial effect on lung function.

METHODS

The methods, design, and outcomes of the NETT have been described in detail previously (13, 15, 16). Briefly, 1,218 subjects were enrolled

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between January 1998 and July 2002 into a randomized trial investigating the efficacy, safety, and cost-effectiveness of LVRS versus optimal medical therapy for severe COPD. Enrollment criteria included an $FEV_1 \leq 45\%$ predicted and bilateral emphysema on computed tomographic imaging of the chest.

The primary parallel outcomes of the trial were overall mortality and exercise capacity. In addition, the cost-effectiveness of LVRS was evaluated versus medical therapy. This last outcome was assessed using Medicare claims provided by the Centers for Medicare and Medicaid Services (CMS). Claims data were collected for the year before enrollment and at least 3 years after study randomization or until subject death.

Definition of COPD Exacerbation

A COPD exacerbation was defined with CMS data consisting of a COPD-related emergency room (ER) visit or hospitalization using *International Classification of Diseases*, *Ninth Revision* (ICD-9), discharge diagnosis codes as previously described by Fan and colleagues (17). Prior investigation has found that discharge diagnosis codes ICD-9-CM (*Clinical Modification*) 491, 492, 493, and 496 accurately identify subjects with COPD compared with review of chart diagnosis (18). An event was defined as a COPD exacerbation if either an ER visit or hospitalization occurred that was associated with one of these codes. Outpatient management of exacerbations and visits to a subject's physician for an exacerbation were not captured by this method of analysis. An exacerbation defined by an ICD-9 diagnosis code corresponding to an ER visit or hospitalization occurring within 30 days of a prior exacerbation was not considered a new event.

Medical Comorbidities

Baseline health care utilization and identification of medical comorbidities were determined using the CMS data collected during the year before randomization. Patient comorbidity before randomization was expressed as a modified Charlson comorbidity index (19, 20).

Study Interval

The year preceding study enrollment was defined as the 365 days before the time of subject randomization to either LVRS or medical therapy. The 3-year or 1,095-day follow-up interval was defined as starting at study randomization in both the medical and surgical groups. Subjects were monitored until death or the 3-year interval endpoint.

Statistical Analysis

Analysis was based on the intention-to-treat principle and included the 140 subjects identified as being at high risk for death postoperatively (21). Fourteen subjects were excluded from this analysis (seven medical and seven surgical) because they were not enrolled in Medicare, had additional insurance plans, or had missing claims data (16). Of the remaining 601 subjects randomized to LVRS, 28 subjects did not undergo surgery either by choice or due to medical contraindications. An additional six subjects underwent lung transplantation after having LVRS. Similarly, 43 of the remaining 603 subjects randomized to medical therapy underwent LVRS and an additional 19 received lung transplantation. These 96 subjects were included in the primary analysis to which they were originally randomized. Analysis was also performed excluding the subjects that crossed randomization and those that were identified as being at high risk of death from LVRS (21).

Baseline characteristics of the study cohorts and postrandomization changes in measures of lung function are presented as means ± SD and were compared using unpaired *t* tests for continuous data and χ^2 tests for dichotomous data. The time to first exacerbation was analyzed using a log-rank test, censoring patients at their time of death. The event rate of exacerbations (total number of exacerbations divided by the total person-years of follow-up) was analyzed using a Poisson regression model with the time in the study as an offset variable and the confidence intervals adjusted for overdispersion. (3). It was assumed that exacerbations were random independent events within the study cohort (Poisson distribution of events). Within this model, however, the pooled exacerbation rate could be significantly influenced by a small number of subjects experiencing frequent exacerbations. Adjustments in the *P* value and confidence intervals were therefore performed by including a metric of this intersubject variability in exacerbation rates (adjustment for overdispersion). In the surgical cohort, Cox regression analysis was used to evaluate the effect of 6-month postoperative changes in lung function, lung volumes, arterial blood gases, and exercise capacity on the time to first exacerbation. This regression analysis was restricted to those subjects who survived to the 6-month time point and were well enough to return for such data collection. Reported *P* values are two-sided and a *P* value of less than 0.05 is considered statistically significant. Data analysis was performed using SAS version 8.0 (SAS Institute, Cary, NC).

RESULTS

A total of 1,204 subjects with complete Medicare claims data were monitored pre- and postrandomization, 601 randomized to surgery and 603 to medical therapy. Demographic and baseline characteristics at the time of study enrollment are reported in Table 1. Differences in the distribution of age, sex, and measures of lung function from those originally reported (13) are due to the exclusion of subjects with missing Medicare claims data. There were no significant differences in the groups except for more males in the medical cohort and a greater percentage of the surgical cohort receiving oral corticosteroids ($P = 0.04$ and 0.01, respectively).

In the year before randomization, 156 subjects (26%) of the surgical cohort and 154 subjects (26%) of the medical cohort experienced one or more COPD exacerbations, with a mean rate of 0.36 and 0.34 exacerbations per person-year, respectively (Table 1; $P = 0.58$). There was no difference between the groups in time to event analysis for the year before randomization (Figure 1; $P = 0.85$).

From randomization through the subsequent 3-year period of data collection, there were 148 deaths in the surgical cohort and 157 deaths in the medical cohort, with a mean follow-up time of 2.54 ± 0.9 and 2.64 ± 0.7 years, respectively. The mean exacerbation rate was 0.27 per person-year in the surgical cohort and 0.37 per person-year in the medical cohort, or a 30% (95% confidence interval [CI], 13–48%; $P = 0.0005$) lower exacerbation rate in the surgical group. Inspection of the time to event analysis in Figure 2A reveals that the beneficial effect of LVRS on time to first COPD exacerbation does not become apparent until after approximately Day 150 at which point a significant difference persists until the end of the observation

TABLE 1. BASELINE CHARACTERISTICS OF THE 1,204 SUBJECTS INCLUDED IN THE ANALYSIS

	Surgical Cohort (*n = 601*)	Medical Cohort (*n = 603*)	*P* Value
Age, yr	66.8 ± 6.4	66.9 ± 5.9	$P = 0.69$
Male sex, n (%)	351 (58)	388 (64)	$P = 0.04$
FEV_1, L/s	0.76 ± 0.24	0.78 ± 0.24	$P = 0.21$
FEV_1,% predicted	27 ± 7	27 ± 7	$P = 0.8$
Charlson score*	0.75 ± 1.25	0.73 ± 1.22	$P = 0.72$
Oral steroids†	35%	28%	$P = 0.01$
Inhaled steroids	68%	71%	$P = 0.21$
Long-acting sympathomimetics‡	45%	45%	$P = 0.91$
Resting oxygen supplementation	50%	51%	$P = 0.69$
Nocturnal oxygen supplementation	65%	66%	$P = 0.9$
Individuals having an exacerbation	156	154	
Exacerbation rate, per person-year	0.36	0.34	$P = 0.58$
Range, per person	0–6	0–5	

* n = 600 for the surgical cohort and n = 602 for the medical cohort.

† Subjects were required to be on a stable dose of ≤20mg of prednisone or its equivalent per the original screening criteria.

‡ β-Agonists such as salmeterol.

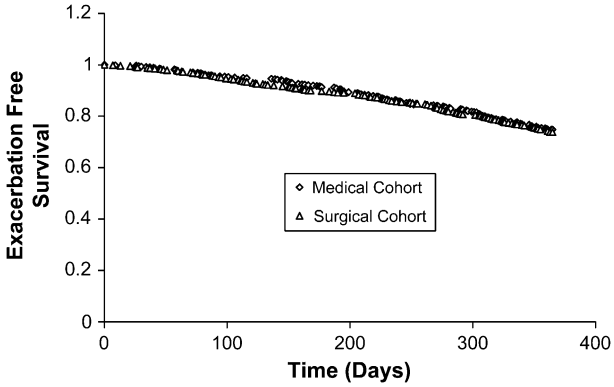

Figure 1. Time to first exacerbation analysis performed during the year before enrollment in the National Emphysema Treatment Trial, where Day 365 corresponds to the day of study randomization ($P = 0.85$).

period ($P < 0.0001$). There was no difference in the time to event analysis in these cohorts for all non–COPD-related hospitalizations or ER visits (Figure 2B; $P = 0.31$). After excluding the 96 subjects who crossed from their original study randomization group, those subjects undergoing LVRS exhibited a 35% reduction in their exacerbation rate (CI, 18–53%; $P = 0.0001$), and when excluding instead those subjects deemed to be at high risk of death from LVRS, the remaining cohort undergoing surgery experienced a 29% reduction in their exacerbation rate (95% CI, 11–48%; $P = 0.0019$).

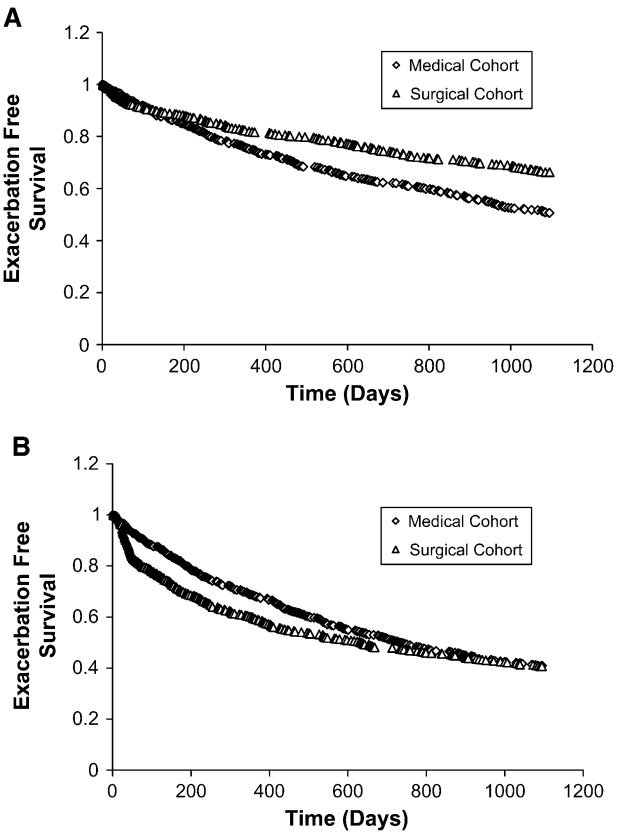

Figure 2. (*A*) Time to exacerbation analysis in the 3 years after enrollment in the National Emphysema Treatment Trial. The surgical cohort experienced a statistically significant increase in the time to first exacerbation ($P < 0.0001$). (*B*) The same time to event analysis using all other ICD-9 discharge codes (nonexacerbation codes) ($P = 0.31$).

The difference in the change of the FEV_1 between the medical and surgical cohorts during the time of data collection is reported in Table 2. LVRS conferred a statistically significant increase in the mean FEV_1 at all time points over the course of the 3 years after randomization. This effect peaked at almost 200 ml at 6 months and then declined to approximately 70 ml by 3 years.

Table 3 provides the list of covariates included in the Cox regression model to determine whether changes in physiologic variables were associated with exacerbations among patients in the surgical group. This analysis included the change in FEV_1, slow VC, maximal expiratory pressure, and FRC, the change in maximum workload achieved on cycle ergometry exercise testing, and the change in arterial blood partial pressures of oxygen and carbon dioxide, all measured at 6 months postrandomization compared with enrollment values. In those subjects alive and able to perform such testing, only the postsurgical change in FEV_1 measured at 6 months, when adjusted for the other covariates listed in Table 3, was a statistically significant predictor of the time to first exacerbation.

Secondary Analyses

To further examine the effect of postoperative change of lung function on COPD exacerbations, the surgical cohort was stratified on the basis of an improvement in FEV_1 of 200 ml or greater (the group mean postoperative improvement in FEV_1 at 6 mo was 0.200 ± 0.244 L). This resulted in 230 subjects with a mean improvement at 6 months of 0.401 L, defined as the surgical responders, compared with 260 subjects with a mean improvement of only 0.021 L, defined as surgical nonresponders (111 of the 601 subjects [18%] had data missing at that time point, counting 58 deaths, and were not included in this analysis). At the same 6-month time point for the medical cohort, the mean change in FEV_1 was –0.019 ± 0.123 L (166 subjects of the medical cohort were not included, counting 20 deaths, due to missing data). Surgical patients with an improvement in FEV_1 greater than 200 ml had a significantly extended time to first exacerbation compared with surgical nonresponders (Figure 3; $P = 0.002$). A similar comparison between the surgical nonresponders and the medical cohort also demonstrated a significant extension in the time to first exacerbation analysis (Figure 3; $P = 0.003$).

Finally, to examine the influence of LVRS on those subjects with a history of COPD exacerbations in the year before randomization, the medical and surgical cohorts were stratified into the subjects with at least one exacerbation in the year before randomization (154 and 156 subjects for the medical and surgical cohorts, respectively) and those without a documented exacerbation in that same time period. In both groups, those with and those without a prior exacerbation history, LVRS significantly extended the time to first exacerbation over optimal medical therapy alone ($P = 0.0002$ and $P < 0.0001$, respectively).

TABLE 2. BASELINE AND POSTRANDOMIZATION COMPARISON OF FEV_1 AT PRERANDOMIZATION AND 6, 12, 24, AND 36 MONTHS POSTRANDOMIZATION

Time from Randomization, Mean FEV_1 (*L*)	Surgical Cohort	Medical Cohort	Difference (*L*)	*P* Value
Prerandomization	0.76 (n = 601)	0.78 (n = 603)	−0.014	0.32
6 Months	0.97 (n = 490)	0.78 (n = 437)	0.19	<0.001
12 Months	0.92 (n = 420)	0.79 (n = 364)	0.13	<0.001
24 Months	0.88 (n = 353)	0.80 (n = 290)	0.08	<0.001
36 Months	0.84 (n = 222)	0.77 (n = 169)	0.07	0.04

TABLE 3. RESULTS OF MULTIVARIATE COX REGRESSION ANALYSIS TO PREDICT TIME TO FIRST EXACERBATION BASED ON 6-MONTH CHANGE IN PHYSIOLOGIC VARIABLES AMONG SURGICAL PATIENTS

Variable*	Hazard Ratio	*P* Value
ΔFEV_1 (10 ml)	3.2	0.002
Δ Slow VC (10 ml)	1.13	0.28
ΔRV (10 ml)	1.02	0.33
ΔFRC (10 ml)	1.01	0.59
Δ Maximal work (1 W)	1.00	0.40
ΔPa_{O_2} (1 mm Hg)	1.01	0.33
ΔPa_{CO_2} (1 mm Hg)	1.01	0.79
ΔMEP (1 cm H_2O)	1.00	0.73

Definition of abbreviation: MEP = maximal expiratory pressure.

Increments of each covariate used for calculation of the hazard Ratio are provided in parentheses after the named covariate in the first column.

* Each of the covariates was calculated at the absolute change in value between the 6-month postoperative measurement and baseline, prerandomization values (i.e., 6-mo FEV_1 in L – FEV_1 in L measured before randomization).

DISCUSSION

LVRS is believed to improve lung function through resection of the most diseased, hyperinflated regions, thereby increasing the elastic recoil of the remaining lung and improving chest wall mechanics (22). The resultant improvement in lung function increases expiratory gas flow, exercise tolerance, and possibly the clearance of respiratory secretions (22–24). Enhanced removal of these secretions may reduce the burden of airway pathogens, augment pulmonary immune defense mechanisms, and thus reduce the risk for infections, which are responsible for most exacerbations in persons with severe COPD.

To test this hypothesis and to determine if a single measure of improvement in lung function was a best predictor of response to LVRS, a multivariate model was constructed, with the dependent variable being the time to first exacerbation. Included in this model were the 6-month changes in the standard measures of lung function, maximal expiratory pressure, Pa_{O_2}, Pa_{CO_2}, and maximal exercise capacity, where the latter was believed to reflect improvement in general daily exertional capacity and subsequent clearance of respiratory secretions. In those subjects able to perform such testing, when accounting for postoperative changes in all of the variables, an improvement in the FEV_1 at 6 months post-LVRS was significantly associated with an increase in the time to first exacerbation (Table 3).

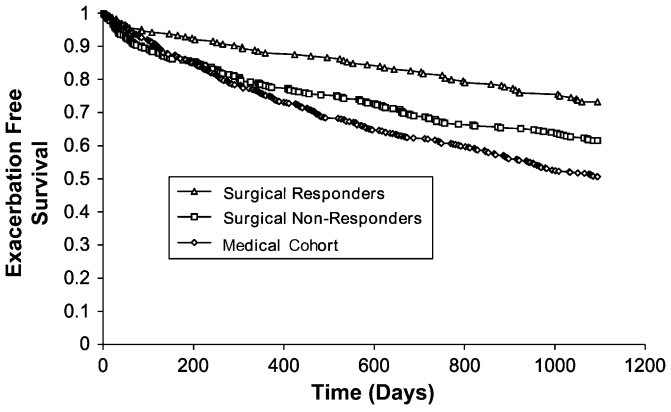

Figure 3. Time to event analysis of surgical responders defined as 6-month improvement in FEV_1 greater than 0.200 L and the surgical nonresponders defined as those with less than a 0.200-L improvement in FEV_1 over the same time period.

Prior publications have reported a beneficial effect of the administration of long-acting inhaled β-receptor agonist and anticholinergic bronchodilators on preventing acute exacerbations of COPD (6, 25). The mean improvement in FEV_1 in these cohorts ranged from approximately 70 ml up to 170 ml when comparing the active drug arm to placebo, values consistent with the postoperative improvements in FEV_1 seen in the NETT surgical cohort even 3 years after randomization. Assuming that the predominant mechanism of action of these inhaled medications is purely bronchodilation, the durability of the post-LVRS benefit on exacerbations may not be surprising.

Recently, Calverley and colleagues reported the results of the TORCH [Towards a Revolution in COPD Health] investigation (4). In this trial, the cohort of subjects randomized to salmeterol therapy was found to have a statistically significant reduction in the frequency of their acute exacerbations as compared with placebo, while on average only experiencing a 20- to 50-ml improvement in their FEV_1 over that same time period. Such a modest functional change in a group that experienced a significant reduction in exacerbation frequency suggests that the beneficial effect of LVRS on the surgical nonresponders may be plausible through similarly modest improvements in lung function.

Although it is possible that even isolated small improvements in FEV_1 may beneficially impact a person's ability to clear respiratory sections, an additional mechanism to explain this surgical effect was investigated. By increasing a subject's maximal expiratory pressure (MEP) and VC, the authors postulated that LVRS could improve secretion clearance through a more efficacious cough. Ultimately, LVRS was not found to have a beneficial effect on a subject's MEP (data not shown) and the postoperative increase in slow VC was not significant in a multivariate model. Such findings do not preclude the presence of a postoperative improvement in a subject's cough but mechanistically make it less likely.

The authors acknowledge limitations to this investigation. Ascertainment of the frequency of acute exacerbations was not a study endpoint of the original NETT and for the present investigation this was determined through the use of medical claims data. Aside from the assumption that ICD-9 medical coding accurately correlates with the clinical diagnosis of an acute exacerbation, this method does not capture urgent clinic visits or illnesses managed on an outpatient basis. The differential effect of excluding such episodes in the two treatment arms is difficult to predict. In theory, exclusion of such data should be equally distributed between the two cohorts. One of the outcomes of LVRS is, however, an improvement in symptoms of dyspnea and quality of living. It is possible that subjects in the surgical cohort experiencing an acute exacerbation may be less symptomatic than their counterparts randomized to medical therapy. In such a case, the surgical cohort would then be less likely to seek or be referred for inpatient care for acute exacerbations. Therefore, the observed reduction in the number of ER visits or hospitalizations might be offset by a proportional increase in exacerbations treated on an outpatient basis. If this is true, LVRS may not reduce the frequency of COPD exacerbations but may alleviate some of the symptoms related to these events. Given that the clinical symptoms associated with an exacerbation are a major factor for deciding on inpatient or outpatient care, LVRS could be responsible for our findings in this manner.

Another potential bias may be that Medicare claims for exacerbations were coded differently for patients post-LVRS compared with those in the medical arm. Such a bias might be introduced if post-LVRS subjects suffering from a COPD exacerbation were systematically diagnosed using ICD-9 codes other than those used in this investigation to define an exacerbation. If this was the case, one would expect to see an increase

in non–COPD-related ER visits and hospital admissions proportional to the observed decrease in COPD-related events, an effect not found in this data analysis.

Finally, there is a differential pattern of withdrawal in the two cohorts, with a greater percentage of subjects in the surgical cohort presenting for data collection at subsequent study visits. This will lead to a survivor bias in the reported Cox regression analysis in the surgical cohort. These results suggest that the postoperative improvement in FEV_1 is largely responsible for the observed delay in time to first exacerbation. As reported, only those subjects who lived to the 6-month study time point and were well enough to perform lung function testing were included in this analysis. The necessary exclusion of such missing data likely skews the reported results away from the null hypothesis that LVRS does not have a beneficial impact on exacerbation frequency and time to first exacerbation.

The results of this investigation must be kept in the context of the inclusion criteria of NETT. The homogeneous cohort of subjects selected to participate in NETT had severe COPD with evidence of emphysema on their computed tomographic scans and, as such, these results are not immediately generalizable to all subjects with COPD. It is also not the authors' recommendation that LVRS be used as a treatment for the specific therapeutic goal of decreasing exacerbation frequency. This investigation does suggest, however, that a reduction in the rate of acute exacerbations can be achieved through an improvement in lung function independent of the antiinflammatory effects found in most medications used for this purpose.

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References

1. Druss BG, Marcus SC, Olfson M, Pincus HA. The most expensive medical conditions in America. *Health Aff (Millwood)* 2002;21:105–111.
2. Alsaeedi A, Sin DD, McAlister FA. The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. *Am J Med* 2002;113:59–65.
3. Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:842–846.
4. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356:775–789.
5. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl* 2003;41:46s–53s.
6. Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, Cassino C, Kesten S. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med* 2005;143: 317–326.
7. Koyama S, Rennard SI, Robbins RA. Acetylcholine stimulates bronchial epithelial cells to release neutrophil and monocyte chemotactic activity. *Am J Physiol* 1992;262:L466–L471.
8. Nomura J, Hosoi T, Okuma Y, Nomura Y. The presence and functions of muscarinic receptors in human T cells: the involvement in IL-2 and IL-2 receptor system. *Life Sci* 2003;72:2121–2126.
9. Johnson M, Rennard S. Alternative mechanisms for long-acting beta(2)-adrenergic agonists in COPD. *Chest* 2001;120:258–270.
10. Korn SH, Jerre A, Brattsand R. Effects of formoterol and budesonide on GM-CSF and IL-8 secretion by triggered human bronchial epithelial cells. *Eur Respir J* 2001;17:1070–1077.
11. Spoelstra FM, Postma DS, Hovenga H, Noordhoek JA, Kauffman HF. Additive anti-inflammatory effect of formoterol and budesonide on human lung fibroblasts. *Thorax* 2002;57:237–241.
12. Barnes NC, Qiu YS, Pavord ID, Parker D, Davis PA, Zhu J, Johnson M, Thomson NC, Jeffery PK. Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. *Am J Respir Crit Care Med* 2006;173:736–743.
13. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059–2073.
14. Washko G, Fan VS, Ramsey SD, Reilly JJ, for the NETT Research Group. The effect of lung volume reduction surgery on acute exacerbations of chronic obstructive pulmonary disease [abstract]. *Am J Respir Crit Care Med* 2007;175:A812.
15. National Emphysema Treatment Trial Research Group. Rationale and design of the National Emphysema Treatment Trial (NETT): a prospective randomized trial of lung volume reduction surgery. *J Thorac Cardiovasc Surg* 1999;118:518–528.
16. Ramsey SD, Sullivan SD, Kaplan RM, Wood DE, Chiang YP, Wagner JL. Economic analysis of lung volume reduction surgery as part of the National Emphysema Treatment Trial. NETT Research Group. *Ann Thorac Surg* 2001;71:995–1002.
17. Fan VS, Ramsey SD, Make BJ, Martinez FJ. Physiologic variables and functional status independently predict COPD hospitalizations and emergency department visits in patients with severe COPD. *COPD* 2007;4:29–39.
18. Rawson NS, Malcolm E. Validity of the recording of ischaemic heart disease and chronic obstructive pulmonary disease in the Saskatchewan health care datafiles. *Stat Med* 1995;14:2627–2643.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
20. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613–619.
21. National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med* 2001;345:1075–1083.
22. Sciurba FC, Rogers RM, Keenan RJ, Slivka WA, Gorcsan J III, Ferson PF, Holbert JM, Brown ML, Landreneau RJ. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. *N Engl J Med* 1996;334:1095–1099.
23. Brantigan OC, Mueller E, Kress MB. A surgical approach to pulmonary emphysema. *Am Rev Respir Dis* 1959;80:194–206.
24. Rogers RM, DuBois AB, Blakemore WS. Effect of removal of bullae on airway conductance and conductance volume ratios. *J Clin Invest* 1968; 47:2569–2579.
25. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:449–456.