Critical Analysis of the National Emphysema Treatment Trial Results for Lung-Volume-Reduction Surgery

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KEYWORDS

• Emphysema • Lung-volume-reduction surgery • NETT • COPD • Thoracoscopy

KEY POINTS

- The National Emphysema Treatment Trial directly compared lung-volume-reduction surgery with maximal medical therapy for severe chronic obstructive pulmonary disease in a prospective randomized controlled fashion.
- The combination of a forced expiratory volume in 1 second (FEV_1) less than or equal to 20% of predicted with either homogeneous emphysema or diffusing capacity of the lungs for carbon monoxide (DLCO) less than or equal to 20% of predicted encompasses a group too high risk for surgery.
- In appropriately selected patients, surgery has a lower long-term mortality and improved exercise capacity compared with medical therapy, particularly in patients with upper-lobe emphysema and low pretreatment exercise capacity.
- Major pulmonary and cardiac morbidity occurs in 29.8% and 20.0% of patients, respectively with a 90-day mortality of 5.5%. Low FEV_1 and DLCO, non–upper-lobe emphysema, oral steroid use, and increased age are correlated to these complications.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality in the United States. In 2015 there were 15.5 million adults diagnosed with the lower respiratory disease with 335,000 Medicare hospitalizations and 150,350 associated deaths.[1] Medical treatment consists of a combination of inhaled corticosteroids, bronchodilators, oxygen, and pulmonary rehabilitation. Despite treatment, mortality remains minimally changed over the past 30 years at approximately 40 deaths per 100,000 US population.[2] As early as 1950, surgical lung resection of diseased lung was proposed as potentially beneficial COPD treatment. However, prohibitively high morbidity and mortality caused the procedure to fall out of favor.[3] Lung-volume-reduction surgery (LVRS) was reborn in 2003 when Joel Cooper and colleagues[4] demonstrated the ability to significantly improve outcomes of targeted lung resection by taking advantage of 40 years worth of advances in technology, technique, anesthesia, critical care, and rehabilitation.

The overall goal of LVRS is removal of emphysematous lung in order to enhance overall pulmonary function. Multiple mechanisms have been credited with this beneficial enhancement, including improvements in pulmonary elastic recoil, diaphragmatic function, left ventricular filling, endothelial health, as well as decreased functional residual

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capacity and intrathoracic pressure.[5–8] Single-institution studies initially published demonstrated significant variation in operative mortality (2.5%–19%) with 1-year mortality as high as 23%.[9,10] Uncertainty around the operative morbidity, mortality, magnitude of benefit, duration of improvement, and prognostic predictors of LVRS led to the creation of the National Emphysema Treatment Trial (NETT). This federally funded, multicenter study was created to directly compare LVRS with maximal medical therapy for severe emphysema in a randomized controlled fashion.[11] Much of our current treatment of COPD is still based on this trial.

NATIONAL EMPHYSEMA TREATMENT TRIAL

The NETT was initiated in 1998 in order to clarify the benefit of LVRS. Previously published studies on the efficacy of LVRS were relatively small and included patient cohorts with differing clinical characteristics operated on using various surgical techniques. Almost all studies lacked long-term follow-up and did not comprehensively assess benefit, risk, or cost. NETT sought to reduce the variability in patient characteristics, surgical technique, patient care, and follow-up with the creation of a multiinstitution randomized study. Given the lack of clarity surrounding both the risk and the benefit of surgical intervention, both were evaluated as the study's primary outcome measures. Survival was chosen as a primary outcome, given its ease and accuracy of measurement as well as its clinical significance in a population with emphysema and a resultant high baseline mortality. The other primary outcome measurement was exercise capacity as determined by cycle ergometry. This was chosen over other modalities due to its reproducibility, standardization, and administration. In addition, exercise capacity was favored over pulmonary function testing (PFT), as the latter had not demonstrated a consistent relationship with functional status. A 10-W change in exercise performance and an 8-point change in St. George Respiratory Questionnaire were deemed meaningful clinical changes in exercise capacity. The trial also looked at several secondary outcomes including quality of life (Medical Outcomes Study 36-Item Short Form and Quality of Well-Being Scale), cost, complications, PFTs, radiologic volumetric analysis, 6-minute walk distance, cardiovascular measures, and psychomotor function.

The study was designed as a randomized controlled non-crossover comparison of maximal medical therapy with medical therapy plus LVRS in patients with severe. Patients were randomized in a 1:1 fashion between treatment groups and then within the surgery group were randomized further between median sternotomy and video-assisted thoracoscopic surgery (VATS) in those institutions capable of performing both. Seventeen centers participated in the trial in total, with 8 performing sternotomies only, 3 performing VATS only, and 6 randomizing between the two. Regardless of the approach, the goal was to resect 20% to 35% of bilateral lungs, targeting the most diseased portions.[12] Patients were required to have severe COPD with a forced expiratory volume in 1 second (FEV_1) less than or equal to 45%, a total lung capacity greater than or equal to 100%, a residual volume (RV) greater than or equal to 150%, and $Paco_2$ less than or equal to 60 mm Hg. They were additionally expected to have quit smoking for more than 4 months and to have attended pulmonary rehabilitation for at least 6 to 10 weeks before intervention. Exclusion criteria included prior major lung surgery and/or infection, significant cardiac disease, severe obesity, recent malignancy, 6-minute walk less than 140 m after rehabilitation, or another significant comorbidity.[13]

Before treatment, patient demographics, pulmonary function, imaging, functional status, exercise capacity, and quality of life were measured. Full assessment was repeated at 6 months, 12 months, and then yearly.[11] As a safety measure, at the onset of the study, the monitoring board was providing stopping guidelines to be used to identify those that were clearly benefited and those that were clearly harmed by LVRS. An 8% 30-day mortality was used as the cutoff of unacceptable risk. Initially those predicted to benefit most from surgical intervention were those younger than 70 years with FEV_1 between 15% and 35% of predicted, $Paco_2$ less than 50 mm Hg, RV greater than 200% of predicted, and with a heterogeneous pattern of emphysema with minimal perfusion. These variables were monitored by the board as well as diffusing capacity of the lungs for carbon monoxide (DLCO), work capacity, quality of life, race, and sex. In addition to the regular assessments discussed earlier, these variables were reviewed every 3 months for signs of clear patient benefit or risk. In April of 2001 low FEV_1, homogeneous emphysema, a high perfusion ratio, and low DLCO demonstrated an increased risk of mortality. Additional analyses were performed to define if these parameters met the unacceptable risk criteria. They found that the combination of an FEV_1 less than or equal to 20% of predicted with either homogeneous emphysema or DLCO less than or equal to 20% of predicted led to an 18% 30-day surgical mortality compared with zero deaths in the medical arm of the study. These

groups were labeled as "high risk" and subsequently excluded from the trial.[13]

NETT continued to accrue until 2002, and by 2003 the first complete analysis was performed. In total 1218 patient were randomized out of 3777 evaluated, with 608 in the surgery arm and 610 in the medical arm. One hundred forty of these patients were in the preexclusion high-risk group with 42 and 30 in the surgical and medical arms, respectively. Baseline characteristics were similar between both treatment arms except that there was a higher proportion of men in the medical-therapy arm.[11] Initial, analysis looked at the primary outcomes over the 4-year trial period and with a mean patient follow-up of 2.4 years. Over the following years, subsequent analyses looked at NETT's secondary outcomes and were eventually followed by an updated publication of the primary outcomes. This latter long-term analysis published in 2006 had a median patient follow-up of 4.3 years with 40% more 2-year-postrandomization data than the initial report.[14]

PRIMARY OUTCOMES

Mortality

On initial analysis, 90-day mortality was revealed to be 7.9% (95% confidence interval, 5.9–10.3) in the surgery group, significantly higher than the 1.3% (95% confidence interval, 0.6–2.6) of the medical group ($P<.001$). This was however considered expected, given the immediate trauma of surgery and overall mortality was not significantly different between groups with a total morality of 0.11 deaths per person-year in both treatment arms. When the previously discussed high-risk group was removed from the analysis, 90-day mortality was 5.2% in the surgical arm compared with 1.5% in the medical arm, whereas overall mortality was 0.09 and 0.10 deaths per person-year, respectively ($P = .31$) (**Table 1**).[11] Interestingly, despite increased early mortality in the LVRS arm, long-term analysis in 2006 demonstrated that total mortality was 0.11 deaths per person-year in the surgery group versus 0.13 in the medical group, a statistically significant difference ($P = .02$). This benefit of surgery remained with removal of the high-risk group from analysis with 0.10 and 0.12 deaths per person-year, respectively. In subgroup analysis, mortality was reviewed in relation to the distribution of emphysema as well as exercise capacity. The 2003 initial analysis found that surgery most benefited patients with upper-lobe–predominant emphysema and low pretreatment exercise capacity. In this group, 90-day mortality was no different between the LVRS and medical arms (2.9% vs 3.3%, $P = 1.0$), and total mortality was significantly better after undergoing surgery (0.07 vs 0.15 death per person-year, $P = .005$). This benefit continued in the long-term follow-up (**Fig. 1**). In patients with non–upper-lobe emphysema, 90-day mortality was significantly higher in the surgery group regardless of exercise capacity, and total mortality was significantly higher for those with a high exercise capacity.[15]

Exercise Capacity

Exercise capacity was measured by ergometer and a change of 10 W after treatment was considered clinically significant. At 6, 12, and 24 months of follow-up the surgery group improved in exercise capacity by more than 10 W in 28%, 22%, and 15% of patients, respectively. This is compared with 4%, 5%, and 3% in the medicine group. Although the LVRS group demonstrated an initial improvement in function after the immediate postoperative period, outcome measures showed a progressive decline in capacity over time, as the medical therapy group. Long-term analysis evidenced that trend with the surgery group displaying an over-10 W improvement in 23%, 15%, and 9% compared with 5%, 3%, and 1% in medicine group at 1, 2, and 3 years. In both time frames, the values were statistically significant between treatment arms (**Table 2**). In addition, although not a primary outcome measurement, analyses analyzed St. George's Respiratory Questionnaire (SGRQ) results in addition to ergometry to assess exercise capacity. Clinically significant improvement was determined to be an over-8-unit decrease on the questionnaire. In the LVRS group, said improvement was noted in 40%, 32%, 20%, 10%, and 13% at 1, 2, 3, 4, and 5 years after randomization compared with 9%, 8%, 8%, 4%, and 7% in the medical group at similar intervals; these differences were significant through the first 4 years ($P<.001$, years 1–3; $P = .005$, year 4). In subgroup analysis by emphysema distribution and exercise capacity, those with upper-lobe disease and low pretreatment exercise capacity had the highest likelihood of greater than 10 W capacity improvement and the most benefit at 24 months compared with the medical group (30% vs 0%, $P<.001$). Those with upper-lobe disease and high pretreatment capacity also had statistically significant improvement compared with the medical group but less so (15% vs 3% >10 W change, $P = .001$). Improvement of exercise capacity was similar between treatment arms in those with non–upper-lobe disease (**Fig. 2**). Long-term analysis continued to support these findings and additionally

Table 1
Ninety-day and total mortality among all patients and non–high-risk subgroups at 3 years

	90-Day Mortality			Total Mortality					
	Surgery Group	Medical-Therapy Group		Surgery Group		Medical-Therapy Group			
Patients	No. of Deaths/Total no. (% [95% CI])		*P* Value	No. of Deaths/ Total no.	No. Of Deaths/ Person-Year	No. of Deaths/ Total no.	No. of Deaths/ Person-Year	Risk Ratio	*P* Value
All patients	48/608 (7.9 [5.9–10.3])	8/610 (1.3 [0.6–2.6])	<.001	157/608	0.11	160/610	0.11	1.01	0.90
High-risk[†]	20/70 (28.6 [18.4–40.6])	0/70 (0 [0–5.1])	<.001	42/70	0.33	30/70	0.18	1.82	0.06
Other	28/538 (5.2(3.5–7.4])	8/540 (1.5 [0.6–2.9])	.001	115/538	0.09	130/540	0.10	0.89	0.31
Subgroups[‡]									
Patients with predominantly upper-lobe emphysema									
Low exercise capacity	4/139 (2.9 [0.8–7.2])	5/151 (3.3 [1.1–7.6])	1.00	26/139	0.07	51/151	0.15	0.47	0.005
High exercise capacity	6/206 (2.9 [1.1–6.2])	2/213 (0.9 [0.1–3.4])	.17	34/206	0.07	39/213	0.07	0.98	0.70
Patients with predominantly non–upper-lobe emphysema									
Low exercise capacity	7/84 (8.3 [3.4–16.4])	0/65 (0 [0–5.5])	.02	28/84	0.15	26/65	0.18	0.81	0.49
High exercise capacity	11/109 (10.1 [5.1–17.3])	1/111 (0.9 [0.02–4.9])	.003	27/109	0.10	14/111	0.05	2.06	0.02

Mean patient follow-up of 29.2 months.

[†] High-risk patients were defined as those with a forced expiratory volume in one second (FEV1) that was 20 percent or less of the predicted value and either homogeneous emphysema on computed tomography or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value.

[‡] High-risk patients were excluded from the subgroup analyses. For total mortality, P for interaction=0.004; this P value was derived from binary logistic-regression models with terms for treatment, subgroup, and the interaction between the two, with the use of an exact-score test with three degrees of freedom. Other factors that were considered as potential variables for the definition of subgroups included the base-line FEV1, carbon monoxide diffusing capacity, partial pressure of arterial carbon dioxide, residual volume, ratio of residual volume to total lung capacity, ratio of expired ventilation in one minute to carbon dioxide excretion in one minute, distribution of emphysema (heterogeneous vs. homogeneous), perfusion ratio, score for health-related quality of life, and Quality of Well-Being score; age; race or ethnic group; and sex.

From National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059–2073; with permission.

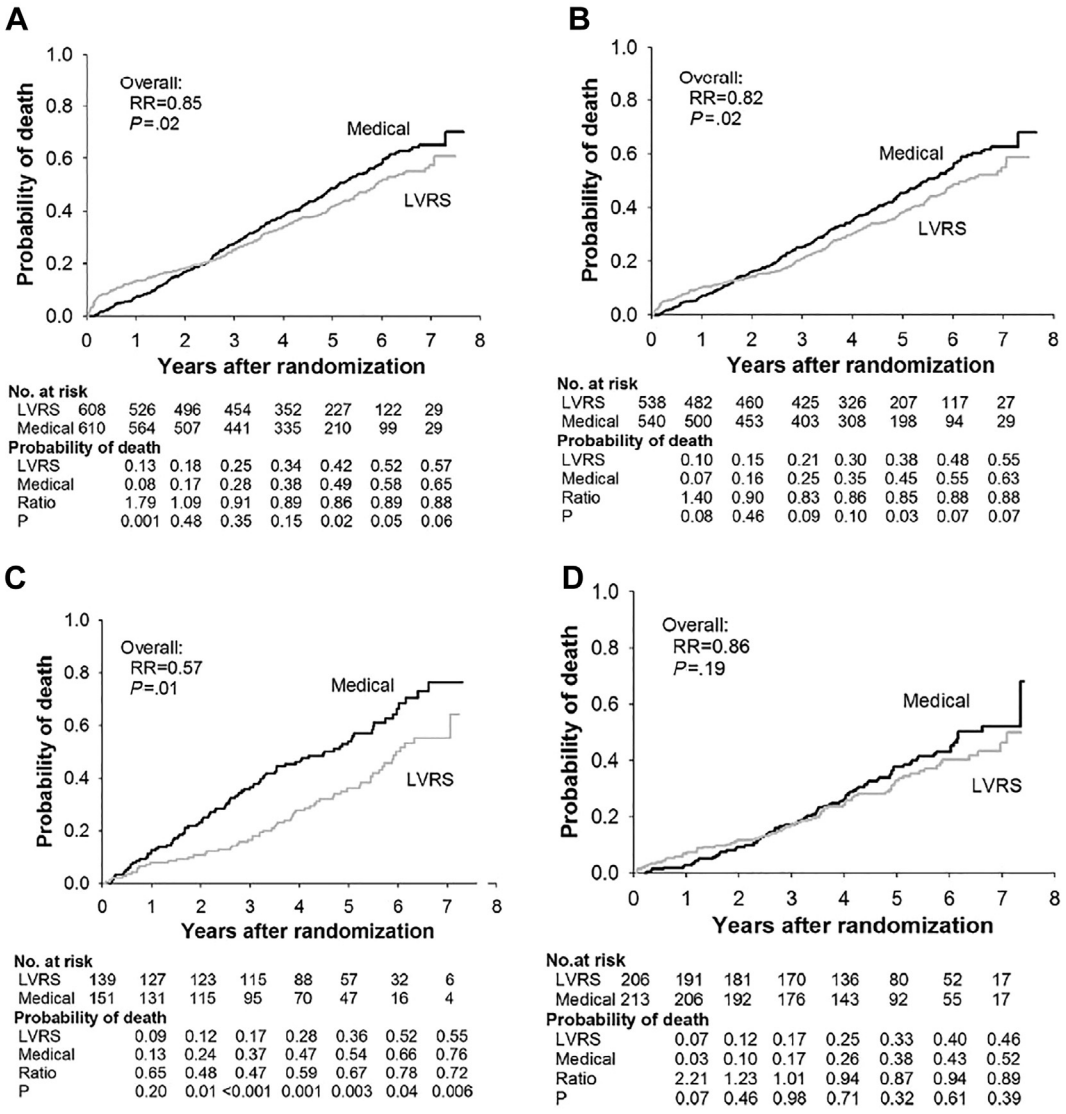

Fig. 1. Kaplan-Meier curves representing the cumulative probability of death after randomization of LVRS and medical treatment groups. (*A*) All patients. (*B*) Non–high-risk patients. (*C*) Upper-lobe–predominant, low exercise capacity. (*D*) Upper-lobe–predominant, high exercise capacity. (*From* Naunheim KS, Wood DE, Mohsenifar Z, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the national emphysema treatment trial research group. Ann Thorac Surg 2006;82:431-443; with permission.)

demonstrated significant improvements in SGRQ score with surgery compared with medical treatment. Statistical significance was maintained through 5 years in patients with upper-lobe, low exercise capacity, 4 years in patients with upper-lobe high exercise capacity, and 3 years in patients with non–upper-lobe low exercise capacity. Patients with non–upper-lobe high exercise capacity were similarly unlikely to have improvement in SGRQ regardless of treatment.[11,15]

SECONDARY OUTCOMES

Six-Minute Walk Distance Reproducibility

Exercise capacity as measured by ergometry was used as a primary respiratory outcome measure in NETT but 6-minute walk distance was also analyzed as a secondary outcome. This test is commonly used in practice to measure functional and exercise capacity. Although it has been somewhat standardized, there is lack of consensus on the importance of course length, shape, or the

Table 2
Improvement in exercise capacity and health-related quality of life as measured by the St. George's Respiratory Questionnaire in all patients and non–high-risk subgroups at 24 months postrandomization

	Improvement in Exercise Capacity				Improvement in Health-Related Quality of Life			
	Surgery Group	Medical- Therapy Group			Surgery Group	Medical- Therapy Group		
Patients	no./Total no. (%)		Odds Ratio	*P* Value	no./Total no. (%)		Odds Ratio	*P* Value
All patients	54/371 (15)	10/378 (3)	6.27	<.001	121/371 (33)	34/378 (9)	4.90	<.001
High-risk[†]	4/58 (7)	1/48 (2)	3.48	.37	6/58 (10)	0/48	—	.03
Other	50/313 (16)	9/330 (3)	6.78	<.001	115/313 (37)	34/330 (10)	5.06	<.001
Subgroups[‡]								
Predominantly upper-lobe emphysema								
Low exercise capacity	25/84 (30)	0/92	—	<.001	40/84 (48)	9/92 (10)	8.38	<.001
High exercise capacity	17/115 (15)	4/138 (3)	5.81	.001	47/115 (41)	15/138 (11)	5.67	<.001
Predominantly non–upper-lobe emphysema								
Low exercise capacity	6/49 (12)	3/41 (7)	1.77	.50	18/49 (37)	3/41 (7)	7.35	.001
High exercise capacity	2/65 (3)	2/59 (3)	0.90	1.00	10/65 (15)	7/59 (12)	1.35	.61

Improvement in exercise capacity defined as an increase on ergometry of greater than 10 W or a decrease on the questionnaire of greater than 8 units from pretreatment baselines.

[†] High-risk patients were defined as those with a forced expiratory volume in one second (FEV1) that was 20 percent or less of the predicted value and either homogeneous emphysema on computed tomography or a carbon monoxide diffusing capacity that was 20 percent or less of the predicted value.

[‡] High-risk patients were excluded from the subgroup analyses. For improvement in exercise capacity, P for interaction=0.005; for improvement in health-related quality of life, P for interaction=0.03. These P values were derived from binary logistic-regression models with terms for treatment, subgroup, and the interaction between the two, with the use of an exact-score test with three degrees of freedom. Other factors that were considered as potential variables for the definition of subgroups included the base-line FEV1, carbon monoxide diffusing capacity, partial pressure of arterial carbon dioxide, residual volume, ratio of residual volume to total lung capacity, ratio of expired ventilation in one minute to carbon dioxide excretion in one minute, distribution of emphysema (heterogeneous vs. homogeneous), perfusion ratio, score for healthrelated quality of life, and Quality of Well-Being score; age; race or ethnic group; and sex.

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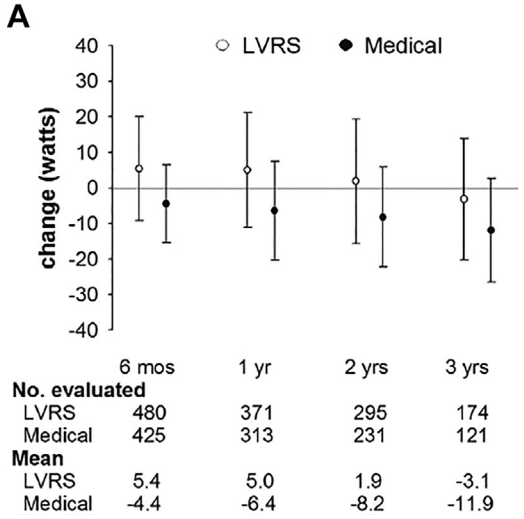
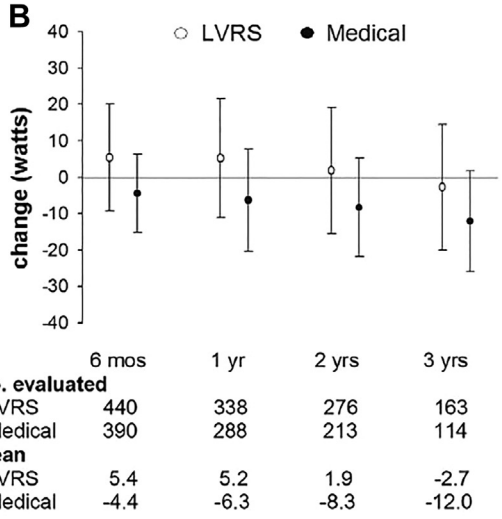
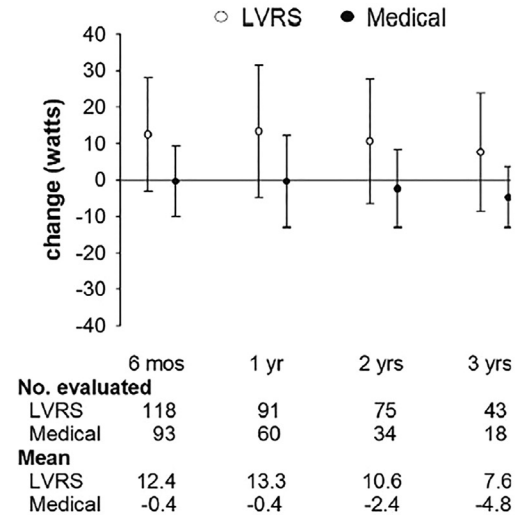


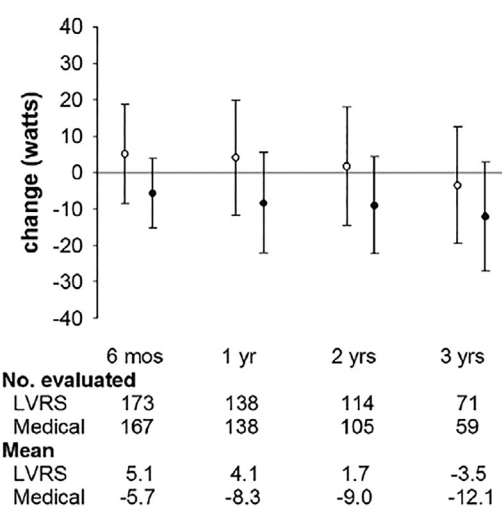
	6 mos	1 yr	2 yrs	3 yrs
No. evaluated				
LVRS	480	371	295	174
Medical	425	313	231	121
Mean				
LVRS	5.4	5.0	1.9	-3.1
Medical	-4.4	-6.4	-8.2	-11.9



	6 mos	1 yr	2 yrs	3 yrs
No. evaluated				
LVRS	440	338	276	163
Medical	390	288	213	114
Mean				
LVRS	5.4	5.2	1.9	-2.7
Medical	-4.4	-6.3	-8.3	-12.0



	6 mos	1 yr	2 yrs	3 yrs
No. evaluated				
LVRS	118	91	75	43
Medical	93	60	34	18
Mean				
LVRS	12.4	13.3	10.6	7.6
Medical	-0.4	-0.4	-2.4	-4.8



	6 mos	1 yr	2 yrs	3 yrs
No. evaluated				
LVRS	173	138	114	71
Medical	167	138	105	59
Mean				
LVRS	5.1	4.1	1.7	-3.5
Medical	-5.7	-8.3	-9.0	-12.1

Fig. 2. Mean change in exercise capacity from pretreatment baseline as measured at 6 months, 1 year, 2 years, and 3 years between LVRS and medical treatment groups. Numbers reflect number of patients evaluated and mean change. Error bars represent the standard deviation of change. (*A*) All patients. (*B*) Non–high-risk patients. (*C*) Upper-lobe–predominant, low exercise capacity. (*D*) Upper-lobe–predominant, high exercise capacity. (*From* Naunheim KS, Wood DE, Mohsenifar Z, et al. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the national emphysema treatment trial research group. Ann Thorac Surg 2006;82:431-443; with permission.)

role of practice/second walk. Four hundred seventy of the NETT participants at 17 institutions were asked to undergo a 6-minute walk test as well as a second test the following day. The test was reproducible on subsequent days but with a clear learning effect. Walked distance was greater on the second day by an average of 66.1 feet ($P<.0001$) or 7%. Seventy percent of people improved the on second day with the greatest improvements generally accomplished by those with greater first-day distances. Track length did not seem to influence walking distance; however, participants who used a continuous looped track performed better than those on a straight track (1156 feet vs 1266 feet, $P = .003$).[16]

Air Leak

Unlike with traditional anatomic lung resection, air leak after LVRS can be difficult to control due to the degree of lung emphysema and the long parenchymal staple lines. As such, LVRS was

often performed with buttressed or reinforced staple lines even though true effectiveness in reducing air leak was unclear. Five hundred fifty-two of the NETT LVRS patients had detailed 30-day postoperative air leak data analyzed with attention paid to operative technique, leak prevalence and duration, and medical consequences. Of the patients evaluated, 90% experienced an air leak at some time during their 30-day postoperative course with a slightly increased risk in those with low DLCO and a decreased risk with a lower lobe staple line. The mean duration of air leak was 7 days, but 66 of the 493 affected patients had an air leak for at least 30 days. Leaks lasted significantly longer in Caucasians, those with low DLCO or FEV_1, those with pleural adhesions, those using inhaled steroids, or those who primarily underwent upper-lobe resection. The use of staple line buttress or the type of buttress did not seem to influence the presence or duration of an air leak. Thirty-day mortality was similar between those that did and did not experience an air leak (4% vs 0%, $P = .11$), but 4.4% of patients with a leak required reoperation and the postoperative complication rate was significantly higher in those who experienced an air leak after propensity matching (57% vs 30%, $P = .004$). Pneumonia and intensive care unit (ICU) readmission were the most severe complications in this group. Lastly, the length of stay in 30-day survivors was longer for those who experienced an air leak (11.8 ± 6.5 days vs 7.6 ± 4.4 days, $P = .0005$).[17]

Pulmonary Rehabilitation

As part of the inclusion criteria for NETT, all patients were required to undergo pretreatment pulmonary rehabilitation. This allowed for patient optimization but also for evaluation of the effectiveness of rehabilitation and analysis of its benefit. Of the 1218 studied patients, 777 (64%) had received pulmonary rehabilitation before the trial and 58% required supplemental oxygen to maintain saturation over 90%. Pulmonary rehabilitation consistently led to significant improvements in exercise capacity, dyspnea, and quality of life measures with more benefit noted in those that had not undergone prior rehabilitation. Approximately half of patients met what was considered clinically important improvements with pulmonary rehabilitation (cycle workload of 5 W, SGRQ score of 4 units, UCSD Shortness of Breath Questionnaire score of 5 units). Overall, 20% of non–high-risk patients changed exercise capacity subgroup after pulmonary rehabilitation, with 13.5% changing from low- to high-capacity subgroups. The effect was even higher for patients without prior rehabilitation experience, with 16.5% changing from the low exercise capacity subgroup to the high exercise capacity subgroup. Functional improvements with pulmonary rehabilitation did not significantly correlate with primary NETT outcome measurements nor objective functional lung improvements; however, it was thought that the pulmonary rehabilitation experience optimized preoperative physical and emotional function as well as helped to exclude those too unhealthy for randomization.[18]

Surgical Approach

After pulmonary rehabilitation, patients were randomized in a 1:1 fashion either into the medical treatment group or into the LVRS group. Within the surgical group, 8 clinical centers performed surgery only by median sternotomy, 3 only by VATS, and at the remaining 6 centers, patients were again randomized 1:1 to either sternotomy or VATS. In total, of the 608 surgically randomized patients, 511 remained after exclusions and removal of the high-risk group, of which 359 patients underwent resection by median sternotomy and 152 by VATS. Patient characteristics were similar between groups other than slightly more heterogeneous emphysema in the sternotomy group (61% vs 51%, $P = .04$). Surgeons estimated larger resections with sternotomy but that was not supported by specimen weight nor was there a difference when analysis was limited to the randomization centers. Mortality was no different between techniques, with 90-day mortality of 5.9% for sternotomy and 4.6% for VATS ($P = .67$) and total mortality of 0.08 and 0.10 deaths per person-year, respectively ($P = .42$). When looking at all centers, VATS cases were 20% longer ($P<.001$), had a higher likelihood of intraoperative hypoxemia ($P = .004$), had a higher rate of postoperative air leak ($P = .05$), and required fewer ICU days ($P<.001$). However, none of these factors were statistically significant when comparison was restricted to the 6 centers that randomized surgical technique. Median length of stay was 1 day longer for sternotomy ($P = .01$), and 30-day independent living was higher in the VATS group. This latter measurement, however, became nonsignificant by 4 months postoperatively. There were no differences in exercise capacity or lung function by approach. Interestingly, both initial hospital costs and 6-month costs were significantly lower for the VATS groups by almost 20% (hospital: \$38557 vs \$30350, $P = .03$; 6 month: \$61481 vs \$51053, $P = .005$).[19]

Cost

Cost is always a difficult measure to analyze in terms of treatment, particularly over the course of time. The NETT group conducted a cost-effectiveness analysis to determine the cost per

quality-adjusted life-year gained in the non–high-risk group. They estimated the "cost" of medical goods and services (Medicare charges), transportation, time spent by family and friends caring for the patient, and time spent by the patient undergoing treatment. These costs were correlated to quality-adjusted life-years through use of the Quality of Well-Being questionnaire. After several exclusions, 531 surgical and 535 medical patients were analyzed with near identical pretreatment Quality of Well-Being scores of 0.58 and 0.57, respectively. Expectedly, over the first-year postrandomization, the surgery group had significantly more hospital days (24.9 vs 4.9), ambulatory care days (10.3 vs 8.6), and nursing home admissions (0.1 vs 0.0) than the medical group ($P \leq .005$). Over the next year however, hospital days were lower in the LVRS group (3.2 vs 6.1, $P = .005$) as were emergency-room visits (0.5 vs 0.7, $P = .04$). No differences in health care utilization were noted in the final year of follow-up. Both direct medical costs and total health care–related costs were significantly higher in the surgery group over the first year of follow-up, with the latter being $71,515 versus $23,371 in the medical group ($P<.001$). Again, this relationship inverts between 13 and 24 months postrandomization, with the medical group incurring nearly twice the total costs of the surgical group in the second year. There was no statistical difference in costs between 25 and 36 months postrandomization. Finally, despite initially higher costs and medical utilization, quality-adjusted life-years gained were significantly higher in the surgical group (1.46 vs 1.27, $P<.001$). This was further evaluated through subgroup (disease location and exercise capacity) analysis. The subgroup with non–upper-lobe emphysema and high pretreatment exercise capacity had significantly higher mortality, costs, and reduced quality-adjusted survival after LVRS. In the other 3 subgroups, however, although total costs were significantly higher in the surgical arms ($P<.001$), quality-adjusted life-years gained were consistently higher after LVRS. As in the other analyses, the subgroup with upper-lobe disease and low exercise capacity faired best with the least cost difference compared with the medical group ($98,952 vs $62,560) as well as the biggest improvement in quality-adjusted survival in years (1.54 vs 1.04, $P<.001$) (**Table 3**).[20]

Operative Morbidity and Mortality Prediction

Even with appropriate patient selection, the risk and complication rate of LVRS is high. The NETT group analyzed 511 non–high-risk patients from the surgery arm of the trial in an attempt to identify predictors of operative morbidity and mortality. Intraoperative complications were rare, with hypoxia being the most common at 2.2%. Thirty-day morbidity on the other hand was high at almost 60%, composed mostly of arrhythmia and respiratory failure, the latter including need for reintubation, prolonged ventilation, ICU readmission, and tracheostomy. Overall, major pulmonary and cardiac morbidity occurred in 29.8% and 20.0% of patients respectively with a 90-day mortality of 5.5%. These data were correlated with patient characteristics followed by logistic regression with backward selection analysis. Ninety-day mortality was only found to be significantly associated with non–upper-lobe emphysematous disease as read by a radiologist ($P = .009$). Thirty-day postoperative pulmonary morbidity was significantly related to age ($P = .02$), FEV_1 percent predicted ($P = .05$), and DLCO percent predicted ($P = .01$). Cardiac morbidity over the same time course was significantly associated with steroid use ($P = .04$), non–upper-lobe disease by software analysis ($P<.001$), and age ($P = .004$). These predictors of morbidity and mortality correlate well with other subgroups analyses of LVRS risk and benefit.[21]

The National Emphysema Treatment Trial Success

The NETT was the first large prospective randomized investigation into the effectiveness and benefit of LVRS. Its initial and subsequent analyses added significant understanding and guidance to our treatment of severe emphysematous lung disease. NETT defined the ideal LVRS-patient population and, as such, demonstrated how preoperative lung function, exercise capacity, and emphysema distribution affect patient outcomes. Further, the large multiinstitutional nature of the trial allowed analyses of several important secondary outcomes that would not have been possible otherwise; some of these have broad implications outside of LVRS. Lastly, although initial studies showed a high mortality with LVRS, after refined patient selection, surgery led not only to significantly greater survival compared with nonoperative management but also to both improvements in functional status and quality of life. The NETT, with its rigorous study design and data collection, serves as the backbone for current and future investigation into the interventional treatment of advanced emphysema.

The National Emphysema Treatment Trial Failure

Despite these demonstrated benefits however, the biggest criticism of NETT was its inability to translate statistical data into clinical practice and

Table 3
Total health care–related costs, quality-adjusted life-years gained, and estimated cost-effectiveness of LVRS and medical treatment in all patients and non–high-risk subgroups at 3 years

	Surgery Group		Medical-Therapy Group			
Variable	No. of Patients	Mean (95% CI)	No. of Patients	Mean (95% CI)	*P* Value	Incremental Cost-Effectiveness Ratio for Surgery ($)
All patients	531		535		<0.001	190,000
Total costs ($)		98,952 (91,694–106,210)		62,560 (56,572–68,547)		
Quality-adjusted life-years gained		1.46 (1.46–1.47)		1.27 (1.27–1.28)	<0.001	
Patients with predominantly upper-lobe emphysema and low exercise capacity	137		148			98,000
Total costs ($)		110,815 (93,404–128,226)		61,804 (50,248–73,359)	<0.001	
Quality-adjusted life-years gained		1.54 (1.53–1.55)		1.04 (1.03–1.05)	<0.001	
Patients with predominantly upper-lobe emphysema and high exercise capacity	204		212			240,000
Total costs ($)		84,331 (73,699–94,962)		55,858 (47,161–64,555)	<0.001	
Quality-adjusted life-years gained		1.54 (1.54–1.55)		1.42 (1.42–1.43)	<0.001	
Patients with non–upper-lobe emphysema and low exercise capacity	82		65			330,000
Total costs ($)		111,986 (93,944–130,027)		65,655 (52,075–79,236)	<0.001	
Quality-adjusted life-years gained		1.25 (1.23–1.26)		1.10 (1.09–1.12)	<0.001	

From National Emphysema Treatment Trial Research Group. Cost effectiveness of lung-volume-reduction surgery for patients with severe emphysema. N Engl J Med 2003;348(21):2092-2102; with permission.

convince both surgeons and referring physicians of the possible role of LVRS. The number of people undergoing LVRS continues to be low and is likely decreasing. Reasons for this trend are not entirely clear but have been attributed to several factors. Firstly, the initial publications out of the trial noted a high overall mortality. NETT included a population of patients who were known to be high risk even before the study and therefore whose outcomes tainted the trial's results somewhat, but more importantly, left a negative connotation of LVRS among the nonsurgical community. Even though further analyses emphasized improved survival with appropriate patient selection, the high-risk nature of LVRS was hard for many to overlook. Given the pretrial suspicion, this high-risk population likely should have never been part of the study. Secondly, although NETT publications throughout the years have helped to define the ideal LVRS patient, what constitutes an appropriate surgical candidate is not clear to the medical community as a whole.[14] This is furthered by the fact that current LVRS is not always adherent to NETT inclusion criteria and as such demonstrates variable risk and benefit.[22] Lastly, restricting LVRS to certain approved centers (NETT, lung transplant, or Joint Commission on Accreditation of Healthcare Organizations–accredited centers), with the requirement for availability-limited pulmonary rehabilitation, makes surgical referral time-consuming, overly complicated, and detrimental to patient access.

CLINICS CARE POINTS

- Lung volume reduction surgery reduces mortality and improves exercise capacity in appropriately selected emphysematous patients compared to medical therapy alone.
- LVRS is most beneficial to those with heterogeneous localized emphysema and a decreased pre-operative exercise capacity.
- Surgery is not recommended for those with either FEV1 or DLCO less than or equal to 20% of predicted.

DISCLOSURE

The authors have no commercial, financial, or other conflicts of interest to disclose.

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