

Update on Lung Volume Reduction

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INTRODUCTION

Lung-volume reduction surgery was a forgotten chapter in the history of thoracic surgery until it was reincarnated in a new form in 1994. The first report of 20 patients presented startlingly good results with minimal morbidity and mortality and interest in the procedure rapidly disseminated among the thoracic surgical community [1]. Within 2 years over a dozen additional articles appeared from other institutions describing small patient series, all of which corroborated the original report describing benefit from the procedure. Lung-volume reduction surgery (LVRS) appeared to be the answer to the prayers of patients with end-stage emphysema who heretofore had little to look forward to other than a slow inexorable decline toward increased breathlessness and death. Not surprisingly, patients in the hundreds flocked to hospitals seeking this surgical redress. Unfortunately, not all clinical results were as beneficial as those that had been published. Most of the published series had low mortalities and significant clinical improvement, but they had short-term follow-up that was often somewhat incomplete. The only early study of significant size in which there was complete mortality data was the Medicare series of 722 patients operated on between October 1995 and January 1996. The 3-, 12-, and 18-month mortalities were 14, 23, and 28%, respectively [2]. Not only did these exceed the previously reported mortality, the report also noted that the number of hospitalizations actually increased rather than decreased following the LVRS procedures. Within the Health Care Finance Administration (HCFA) there was a significant concern regarding these results and the potential morbidity from LVRS on a nationwide basis. These factors as well as questions regarding the durability of

clinical improvement led to a moratorium for Medicare coverage of LVRS in December 1995.

It was at this point that most of the individuals involved in lung-volume reduction surgery realized that a nationwide prospective randomized trial would be required prior to reinstitution of public funding for this procedure. The National Heart, Lung, and Blood Institute partnered with the Health Care Finance Administration to sponsor a national LVRS randomized trial and thus the National Emphysema Treatment Trial (NETT) was born.

The major criticisms of prior single institution case series reports included:

1. Size and criteria—most early reports were of very limited size ranging from 20 to 60 patients. The patient selection criteria were often poorly defined or varied from series to series.
2. Aggregate data—most results were presented as mean results and on occasion standard deviations were missing. It was impossible to determine what proportion of patients experienced improvement instead of decline.
3. Controls—none of the early series included randomized controls. Each report assumed the gradual inexorable decline of physiological function for emphysema patients. However, they failed to account for the fact that these surgical case series selected only the best, most functional patients from the emphysema population and thus such patients did not accurately represent emphysema patients as a whole and their natural history might differ.
4. Incomplete follow-up—early reports rarely provided follow-up beyond 3 to 6 months. Those that did provide follow-up often included data on only a fraction of patients operated on.
5. Survivorship bias—because of the above phenomenon, reported results necessarily were limited to those patients still alive and, in most cases, well enough to travel and undergo testing. This provided an artifactu-

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ally optimistic picture of lung-volume reduction patients as a whole and ignored the results of those who had either died or were too sick to be tested.

The National Emphysema Treatment Trial was designed to overcome these shortcomings and provide a full and accurate picture regarding the true value of lung-volume reduction surgery in the end-stage emphysema patient population.

There are several questions that require answers prior to determining the value of lung-volume reduction surgery. With regard to benefit, what is the effect of lung-volume reduction surgery on spirometry, exercise capacity, quality of life, and survival? How long does the benefit last? What is the cost of lung-volume reduction surgery, not only with regard to the economic aspects, but also the human costs in terms of morbidity and mortality? Last, the question of optimal patient selection is critical. Which emphysema patient should consider undergoing lung-volume reduction surgery? For each of these issues there is much to be learned, both from the single institution reports as well as from the NETT.

SPIROMETRIC RESULTS

In his initial report Cooper [1] documented an 82% improvement in FEV₁ but his subsequent work and that of other investigators have demonstrated that this is an unrealistic expectation. More commonly, improvements in the range of 25–35% have been reported for unilateral LVRS [3, 4] and 30 to 60% for bilateral LVRS [5, 6] in the majority of publications. Cooper's original article reported a decline of 39% with regard to residual volume; however, most subsequent reports note changes in the 15–30% range [3–6]. Different surgical techniques have been demonstrated to produce varying improvements in pulmonary function. McKenna *et al.* noted that bilateral lung-volume reduction patients enjoyed significantly improved spirometric results in comparison to those patients undergoing unilateral lung-volume reduction surgery [7]. Lowdermilk presented a multicenter prospective but nonrandomized study of thoracoscopic LVRS in which he confirmed this differential benefit [8]. Unfortunately, no prospective randomized trial exists to definitively confirm the superiority of the bilateral approach.

Comparisons have also been made regarding the operative approach. Bilateral lung-volume reduction performed using either video-assisted thoracic surgery techniques (VATS) or median sternotomy have been examined. Kottloff demonstrated no difference in short-term results [9]. The work of Wisser [10] and Hazelrigg [11] corroborated the similarity of results when LVRS was performed using open and thoracoscopic approaches. Only the work of Ko and Waters suggested that spirometric improvement varied with

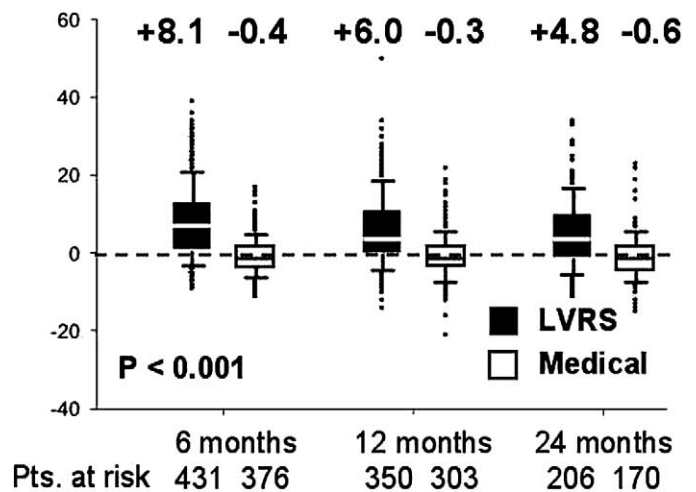


FIG. 1. “Box and whisker” plot for NETT data in which the value change of FEV₁ (as percent predicted) for all patients within the cohort are represented. The box defines the central upper and lower quartiles. Error bars depict the standard deviation and the dots represent all values outside the standard deviation. The transverse line within the box and the numbers at the top depict the mean value in each group at each time point.

the technique used; they found that VATS LVRS provided a significantly greater improvement in FEV₁ [12].

The most definitive data regarding changes in pulmonary function come from the recently published National Emphysema Treatment Trial [13]. This randomized trial included over 1200 patients and demonstrated significant increases in FEV₁ in those patients undergoing LVRS (Fig. 1). Importantly, however, it also demonstrates that even as early as at 6 months, 35% of patients undergoing surgery either had no improvement whatsoever or had failed to return for follow-up due to expiration or some unknown reason. While this is markedly better than the experience in the medically randomized group (73% failed to improve or were not tested), it is still important to realize that over one-third of the patients in the NETT had no improvement from lung-volume reduction surgery. It is, however, important to note that the NETT was designed to be a broadly inclusive trial that used much looser entry criteria than had been the practice. Still, one must understand that not everyone undergoing lung-volume reduction surgery, even in the most highly selected case series, will enjoy spirometric benefit following the procedure. Those that do improve will vary greatly with regard to the extent of their improvement. It is not an all or none effect.

Fig. 1 depicts the spirometric results from the NETT. Patients undergoing LVRS had, in the aggregate, significant improvement in FEV₁, whereas the medical cohort did not improve. Throughout the 24 months of follow-up, the relative advantage in FEV₁ of the surgical group *versus* the medical group was maintained.

EXERCISE CAPACITY

While improvements in spirometric and volumetric parameters are encouraging, their presence alone without concomitant changes in other parameters such as exercise capacity and quality of life would be meaningless. From the onset, exercise capacity has been one of the most important measures reported by investigators in the field. The most common test reported is the 6-min walk. Ciccone reported the 5-year results of the 250 patients in the Washington University experience [14]. Patients enjoyed on average an 18% increase in their 6-min walk distance from 1142 to 1345 feet, an increment that was statistically significant. This improvement remained unchanged through the 1 year mark and gradually declined to approximately baseline levels at 5 years. Similar improvements have been noted by many other investigators [3, 8, 15]. One early randomized trial by Pompeo also documented improved exercise capacity [16], but two others did not. Criner and colleagues prospectively compared bilateral stapled LVRS to medical therapy in a randomized fashion [17]. Although they observed significant improvements in FEV₁, residual volumes, and pCO₂ levels, there was no significant difference in 6-min walk distance or maximal oxygen consumption. However, 13 of the 18 medical patients were eventually allowed to cross over 6 months after randomization and once these patients were added to the surgical arm, the 6-min walk and maximal oxygen consumption improvements became statistically significant. Geddes and his colleagues also performed a prospective randomized trial comparing LVRS to medical therapy [18]. Once again, improvement in FEV₁ and residual volume were noted as well as quality of life improvements. However, there was no improvement in exercise capacity.

The most definitive data on exercise capacity comes from the recently published National Emphysema Treatment Trial [13]. Although 6-min walk values were measured, the NETT used cycle ergometry with maximal workload as the gold standard for exercise capacity. Concerns regarding use of the 6-min walk included the reproducibility given the different personnel, walking paths, and patient learning curves. Within the NETT approximately 1200 patients were randomized to either the LVRS group or the optimal medical therapy group. At 6 months there was a statistically significant improvement of approximately 5.5 W over baseline in the lung-volume reduction group as opposed to a 4.4 W decrease in exercise capacity in the medical group (Fig. 2). This difference in medical and surgical groups of approximately 10 W was maintained throughout the 24-month follow-up, demonstrating that, in the aggregate, the mean exercise capacity was superior in the lung-volume reduction group. However, investigators within the NETT also identified that

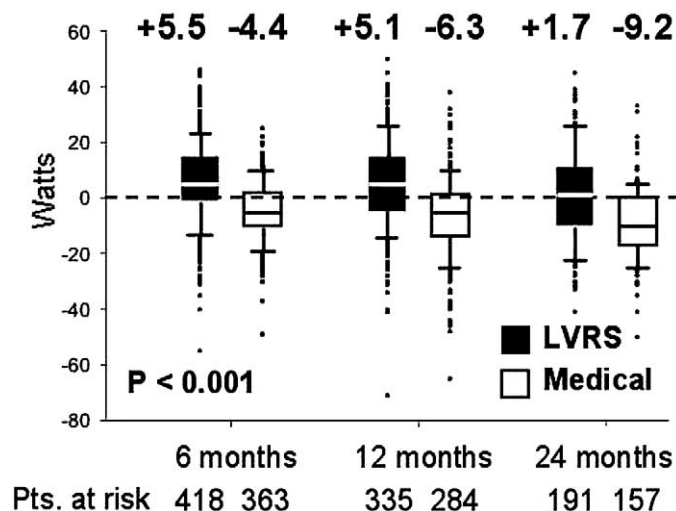


FIG. 2. “Box and whisker” plot for NETT data in which the value change of exercise capacity (in W) for all patients within the cohort are represented. The box defines the central upper and lower quartiles. Error bars depict the standard deviation and the dots represent all values outside the standard deviation. The transverse line within the box and the numbers at the top depict the mean value in each group at each time point.

there was an extremely wide variation in the benefit experienced by patients in the LVRs group and wished to determine what proportion of patients clinically improved. While a 5 W improvement was deemed to be the minimally clinically identifiable difference, it was decided that a 10 W increment would provide a threshold for marked clinical improvement and that threshold was then used to further assess results. Patients in the surgical group had an improved chance of achieving this clinically significant threshold with an odds ratio (OR) of 6.27. Further stratification of the surgical group was undertaken and it became clear that patients with upper-lobe predominant emphysema and relatively low initial exercise capacity had the very best chance of achieving and maintaining this marked clinical benefit at 24 months. None of the patients in the medical group enjoyed this improvement. The results of the 6-min walk test within the NETT study were similar with significant improvements being enjoyed by the LVRs group at 6, 12, and 24 months, while the medical group gradually declined throughout the 2 years of follow-up.

There is now little doubt that lung-volume reduction surgery significantly increases exercise capacity in a meaningful fashion for many patients undergoing the procedure. However, it is important to recognize that there is wide variability among patients and it is difficult to identify who will achieve such benefit.

DYSPNEA AND QUALITY OF LIFE

From the outset, the primary goal for lung-volume reduction was symptom palliation for patients with

TABLE 1
Five-Year Follow-Up After LVRS

	1 yr	2 yr	3 yr	4 yr	5 yr
Respiratory mortality	4%	19%	31%	46%	58%
Patients with improvement in FEV ₁ > 200 ml	73%	46%	35%	27%	8%
Patients with improvement in dyspnea at least one grade	88%	69%	46%	27%	15%

Note. FEV₁ = forced expiratory volume in 1 s; LVRS = lung volume reduction surgery. Table modified from Gelb *et al.* [22].

end-stage emphysema. There have been many analyses of quality of life results in nonrandomized reports but perhaps the largest and most extensive is that of Yusen *et al.* [19]. In a review of 200 patients in the Washington University series, Yusen followed dyspnea using the modified Medical Research Council dyspnea scale (MRC) and quality of life using the SF-36 Medical Outcome Survey Short Form. Patients noted significantly decreased severity of dyspnea at 6 months, 3 years, and 5 years. There was a corresponding improvement in physical functioning as measured by the SF-36 form at those same time intervals. Similar 6-month results were reported by Brenner in 145 patients, who reported decreased dyspnea also using the MRC [20].

Several randomized trials have assessed both dyspnea and quality of life in end-stage emphysema patients. Criner assessed patients in his randomized trial using a tool called the System Impact Profile (SIP) [17]. He was able to assess 11 of 18 surgical patients and 15 of 18 medical patients randomized to these treatments. At 3 months he noticed improved psychosocial and physical scores with an overall improvement in SIP in the LVRS cohort. Goldstein and coinvestigators in Toronto followed 28 LVRS patients and 27 medical patients for 12 months with only those who had expired lost to follow-up [21]. Using the Chronic Respiratory Questionnaire, Goldstein found improvements in dyspnea, fatigue, and emotional function in those patients undergoing LVRS. Similarly, Geddes assessed his patients who were randomized between LVRS and best medical therapy and found that at 12 months there was an improved total score in patients in the LVRS cohort with concomitant worsening in patients undergoing medical therapy [18].

The most comprehensive look at dyspnea and quality of life assessments comes from the NETT [13]. The tools used include the SF-36, the St. George's Respiratory Questionnaire (SGRQ), the Quality of Wellbeing Index (QWB), and the University of California San Diego (UCSD) Shortness of Breath Questionnaire. The mean follow-up was at 29 months in this study but measurements were taken at 6, 12, and 24 months. As occurred with exercise capacity, NETT investigators set a threshold for marked clinical improvement at twice the minimal clinically identifiable differences

(MCID) in health-related quality of life and dyspnea. Patients undergoing LVRS had a markedly higher chance for improvement in the health-related quality of life and in their dyspnea (using the UCSD dyspnea scale) with an OR approaching 5 for both indices. As occurred with exercise capacity, there were independent predictors for improvement in the quality of life parameters. Patients who initially had low exercise capacity were noted to have a several-fold increase with regard to the chance of significant clinical improvement. Such patients with upper-lobe emphysema had an OR of approximately 8.4, while those with non-upper-lobe emphysema and low exercise capacity had an OR of 7.35.

In summary, the results of both single-institution case series and randomized trials strongly support the contention that bilateral lung-volume reduction surgery results in relief of dyspnea and improved quality of life in a significant percentage of patients. As with exercise capacity, the variability of response is quite high, but the chance of improvement far exceeds any found in the medical subgroup.

DURATION OF BENEFIT

The majority of articles dealing with LVRS presented results obtained between 3 and 12 months following the surgical procedure. However, as experience has grown, there have been a few articles dealing with longer term follow-up with regard to spirometric, exercise, and quality of life indices.

Gelb and colleagues reported on 5-year follow-up for 26 patients operated on early in their experience (Table 1) [22]. The patients described underwent bilateral thoracoscopic resection of the apical portion of the lung in the setting of heterogeneous emphysema. These patients started out with an average FEV₁ of 0.7 ± 0.2 L, a figure that represents 29% of the predicted value for the patients. Almost three-quarters of the patients obtained an improvement of 200 ml or greater over their baseline value at the 1-year mark. Over the 5 years of follow-up, this progressively declined to a value of 8%. They noted that improvement in dyspnea (decrease in at least one grade) mirrored the course for FEV₁ changes in that it declined from 88% improvement at 1 year to 15% improvement at 5 years. At the 5-year

follow-up, although 11 of the 26 patients had survived, the investigators felt that only two had continued palliation at that time. All 15 patients who had expired at 5 years had died from respiratory failure.

Flaherty and colleagues collated the long-term results on 89 patients undergoing bilateral stapled LVRS via median sternotomy (Table 2) [23]. These investigators had followed patients for only 36 months and their results suggest that the duration of benefit extends throughout that interval. Nearly three-quarters of the patients had a consistent increase in FEV₁ greater than 200 ml over baseline at the 3-year mark. They did note that the absolute value for FEV₁ begins to decline at approximately 2 years. Interestingly, these investigators found very little correlation between spirometric changes and exercise outcome as measured by a 6-min walk test. Although there was a decline in FEV₁ during the latter portion of this 3-year period, the patients were found to have a marked increase in 6-min walk, an improvement that was sustained by continued cardiopulmonary rehabilitation throughout the 3-year period. It is also interesting to note that the level of dyspnea relief was maintained throughout the 3 years of follow-up.

Ciccone recently reported the long-term results of 250 consecutive patients operated on at Washington University for end-stage emphysema [14]. These are arguably the best results reported thus far for lung-volume reduction surgery. The investigators have been highly selective in their choice of candidates and thorough with follow-up testing. As can be seen in Table 3, LVRS resulted in a marked increase in the spirometric values that had not yet returned to baseline by year 5. Similarly, 6-min walk distances improved by approximately 18% and fell back to baseline by approximately year 5. Parameters measuring dyspnea (Modified Medical Research Council Dyspnea Scale) and quality of life (SF-36 scale) also showed marked improvement early that gradually decreased over the 5 years, but still maintained improvement over baseline.

While these results are outstanding, it is uncertain whether they will be reproducible at other institutions.

TABLE 2
Follow-Up Data for LVRS

	1 yr	2 yr	3 yr
Mean FEV ₁ (L)	0.73	0.79	0.84
Patients with improvement in FEV ₁ > 200 ml	83%	75%	74%
6 MW improvement over baseline	+52%	+57%	+60%

Note. FEV₁ = forced expiratory volume in 1 s; 6 MW = Six-minute walk; LVRS = lung volume reduction surgery. Table modified from Flaherty *et al.* [23].

TABLE 3
Long-Term Results of LVRS

	After cardiopulmonary rehabilitation	1 yr	3 yr	5 yr
FEV ₁ Percent predicted	26%	38%	34%	30%
6-minute walk (ft)	1142	1341	1271	1154
Dyspnea improved	—	79%	60%	42%
QOL improved	—	94%	87%	79%

Note. FEV₁ = forced expiratory volume in 1 s; QOL = quality of life; LVRS = lung volume reduction surgery. Table modified from Ciccone *et al.* [14].

It is also critical to remember that these results suffer from the effect of survivorship bias. That is, only those patients that do well continue to be alive and return for follow-up in the later years. No effort has been made to “correct” these values by taking into account the dead or disabled. The assumption of many investigators is that such a correction is not needed. They seem to believe that medically managed patients never remain stable or improve; rather they inevitably deteriorate and die. Thus any improvement will be better than medical management and a medical control group is unnecessary. However, the recently published National Emphysema Treatment Trial results provide evidence that this perspective is not valid.

The NETT was a randomized trial comparing lung-volume reduction to medical therapy. Of interest, the medical control group in some cases evidenced improvement in spirometric, exercise, and quality of life indices over a 24-month period. Although these improvements occurred sporadically and did not, in the aggregate, reach the same level of benefit as those enjoyed by LVRS, it helps dispel the notion that medical controls are unnecessary because end-stage emphysema is a progressive, unrelenting downward spiral.

Figures 1 through 3 demonstrate the aggregate changes in FEV₁, exercise capacity (by cycle ergometry), and dyspnea (University of California San Diego Dyspnea Scale) over a 24-month follow-up period. There were significant improvements in all these outcomes although the improvements tended to fade over the 24 months. However, it is interesting that the medical group, in the aggregate, declined from baseline throughout this 2-year period of time. Thus, even though the aggregate data would suggest that the surgical patients would return to baseline in these three parameters at 24 months, their clinical status remained superior to that of the medical group as a whole over this 2-year period. Even though the clinical benefit gradually disappears as the values return toward the baseline, such patients appear better off than they

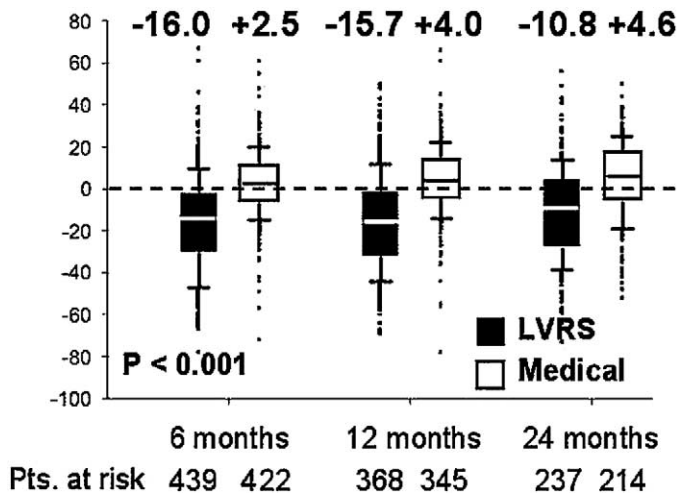


FIG. 3. “Box and whisker” plot for NETT data in which the value change in dyspnea [using the University of California San Diego (UCSD) scale] for all patients within the cohort are represented. The box defines the central upper and lower quartiles. Error bars depict the standard deviation and the dots represent all values outside the standard deviation. The transverse line within the box and the numbers at the top depict the mean value in each group at each time point.

would have been with medical therapy alone due to the persistent deterioration in this latter group.

These results in Figs. 1 through 3 do include the same survivorship bias as noted in prior studies. However, the NETT also was designed to consider those patients who are dead or so disabled as not to be able to return for testing. A special scoring system allowed such patients to be taken into account and thus mitigate the survivorship bias seen in all of the prior uncontrolled studies. This analysis demonstrated that even accounting for the dead and disabled, significant improvements were identified in the LVRS group with regard to exercise capacity, dyspnea relief, and spirometry at all periods of follow-up (6 months, 1 year, 2 years). It should also be noted that the NETT included a broad range of candidates, many of whom would have been excluded from routine LVRS in a majority of institutions. Prior to the NETT inclusion and exclusion criteria were based primarily on Cooper’s initial publication [1]. Although specific contraindications to surgery were accepted and widely disseminated, most were based on very small patient series or anecdotal reports. It was the intention of the NETT investigators to cast a wide net and determine in a rigorous fashion who should and who should not become a candidate for LVRS. Thus, the aggregate results for the NETT include those of both “good” and “bad” candidates as assessed by the pre-NETT standards. However, further analysis did allow for stratification of results among the high-risk and low-risk groups as will be noted in the subsequent section on patient selection.

SURVIVAL

One of the most contentious issues regarding lung-volume reduction has to do with its effect on long-term survival. The prevailing opinion among investigators performing lung-volume reduction was that unoperated patients with end-stage emphysema had little in their future other than a progressive unremitting decline in respiratory capacity with inevitable death from pulmonary failure. While it is true that studies describing the natural history of end-stage emphysema suggested a relatively steep mortality curve with 5-year survivals less than 40%, the populations described therein were not representative of those patients undergoing lung-volume reduction surgery [24, 25]. As previously noted, the majority of programs accept fewer than 30% of patients with end-stage emphysema as appropriate candidates. In effect, the investigators “skim the cream” from the top of the emphysema population, selecting only the best and most hardy patients for consideration of surgery. The true 5-year survival of such a highly selected group is not known and thus impossible to compare to a stand-alone surgery group. This was yet another strong argument supporting the need of a randomized medical cohort.

With time, we now have some better figures regarding long-term follow-up. Brenner and colleagues in 1999 analyzed a cohort of 256 patients who had undergone bilateral thoracoscopic stapled LVRS in patients with heterogeneous emphysema. Twelve of the 256 patients were unavailable for follow-up. Because it has been suggested in the literature that such patients were much more likely to be deceased than alive, Brenner and colleagues depicted survival curves with those patients lost to follow-up both in a standard actuarial fashion and in a manner they called the “worse-case scenario,” in which all patients were assumed dead at the time they were lost to follow-up [20]. Their median follow-up was approximately 20 months. The 3-year follow-up in this group was 72% for the group overall and 67% using the worst-case scenario.

A somewhat better survival rate was reported by Fugimoto and colleagues [26]. With a mean follow-up time of 54 months, they noted that their 86-patient cohort enjoyed a 5-year survival rate of 71%. However, it should be noted that this appears from the demographics to be a relatively younger and healthier group of patients than can be found in most American experiences. The mean age of these patients was only 56 years, thus suggesting it is a relatively healthier group of patients who might understandably have a better 5-year survival. Ciccone recently reported on long-term results in 250 consecutive patients from the Washington University experience [14]. Survival in these patients at 1, 3, and 5 years was 94, 84, and 68%, respectively. The authors note that this is far better than for the natural history of end-stage emphysema patients

but this comparison is not wholly valid as these patients were highly selected, unlike those reported in the natural history articles. Perhaps a better comparison is in the work of Myers *et al.* from that same institution [27]. This was a comparison between patients who had undergone LVRS and those who had been accepted for the LVRS procedure but in whom the operation had been canceled due to cessation of reimbursement by Medicare in 1995. These latter patients were followed with optimal medical care alone. In the original report, there was an initial decline in survival due to perioperative mortality, while the medical group noted a survival curve which dropped more slowly. At the end of 2 years there was no significant difference in the two groups. However, an update on this article depicts 4-year data and demonstrated a significant difference in actual survival with those patients undergoing lung-volume reduction surgery enjoying improved survival as compared to best medical therapy alone (72 versus 41%, $P = 0.02$). The authors do acknowledge that these two groups were not randomized but their demographic and clinical profiles were virtually identical, and this is strong presumptive evidence that lung-volume reduction surgery may be able to prolong long-term survival.

Perhaps the most definitive data come from the recent NETT reports. The first NETT publication in 2001 identified a high-risk group of candidates [FEV_1 percent predicted ≤ 20 with either homogenous disease or diffusing capacity (DLCO) $\leq 20\%$ of predicted] [28]. In this high-risk group, at 6 months one-third of the patients were dead; one-third were unimproved or worse, and the final third had improvement of varied degrees. This high-risk group was subsequently shown to have poor long-term survival.

In the most recent NETT publication, a comparison of the entire surgical group and the medical group showed essentially no effect of LVRS on mortality over time [13]. There was no survival benefit from the operation but, also important, there was no apparent "survival cost" to the operation. In other words, any improvements that occurred did not come at a risk of increased long-term mortality. Five-year actuarial survival in the LVRS group was approximately 65%. Although this number appears at first inferior to other quoted series, it is important to remember that these patients were not as highly selected as with other experiences. It was the intention of the investigators to broaden selection criteria and include in the randomization those patients that might not have been included for LVRS according to the prevailing opinions prior to the trial. This is perhaps best evidenced by the average age of the participants, which was 67 years. These patients were, on average, a decade older than most of the experiences in Europe and 5 years older

than those patients operated upon in most American institutions.

However, perhaps the most interesting survival statistics occurred when the cohort of patients within the NETT was stratified with regard to predictors of mortality. The high-risk group was excluded as it had previously been shown to be a relative surgical contraindication. This left 1048 "non-high-risk" patients as a separate cohort to be analyzed. When the clinical parameters had been analyzed with regard to mortality, there were two predictors of survival identified. These included upper-lobe emphysema and exercise capacity. These two interacted in such a fashion that the combination of the two parameters led to clinically significant stratification with regard to survival (Fig. 4). Those patients with upper-lobe disease and low exercise capacity (corrected for gender) experienced a survival benefit from lung-volume reduction surgery. Such patients had only half the chance of dying as those in the medical control group (relative risk of 0.47). However, on the other end of the spectrum, those patients with non-upper-lobe emphysema who had high exercise capacity were found to have twice the long-term mortality risk (relative risk, 2.08) and thus lung-volume reduction in this patient cohort was contraindicated. In the remaining two stratification groups (upper-lobe emphysema with high exercise capacity, non-upper-lobe emphysema with low exercise capacity) LVRS had no significant effect on survival. Thus, there was no survival "cost" and any improvements that occurred in these groups did so without an increased risk of mortality in those patients undergoing the surgical procedure.

These results from the NETT were the first conclusive data regarding survival and have demonstrated that LVRS can indeed have a significant effect on long-term survival.

PATIENT SELECTION

Advanced age has been suggested to be an increased predictor of mortality in patients undergoing lung-volume reduction surgery by many authors; however, the recently published NET trial did not find advanced age to be an independent risk factor for mortality [11, 23, 29].

Because of the advanced age and smoking history, significant coronary artery disease has been found to coexist in up to 15% of patients with emphysema [30]. Other comorbidities that are relative contraindications include pulmonary hypertension and alpha-1-antitrypsin disease [12, 31].

Physiological parameters have most often been used in an attempt to identify appropriate candidates for lung-volume reduction surgery. Sophisticated pulmonary function testing has been done in many patients and multiple parameters have been suggested as pre-

Subgroup Treatment Effects

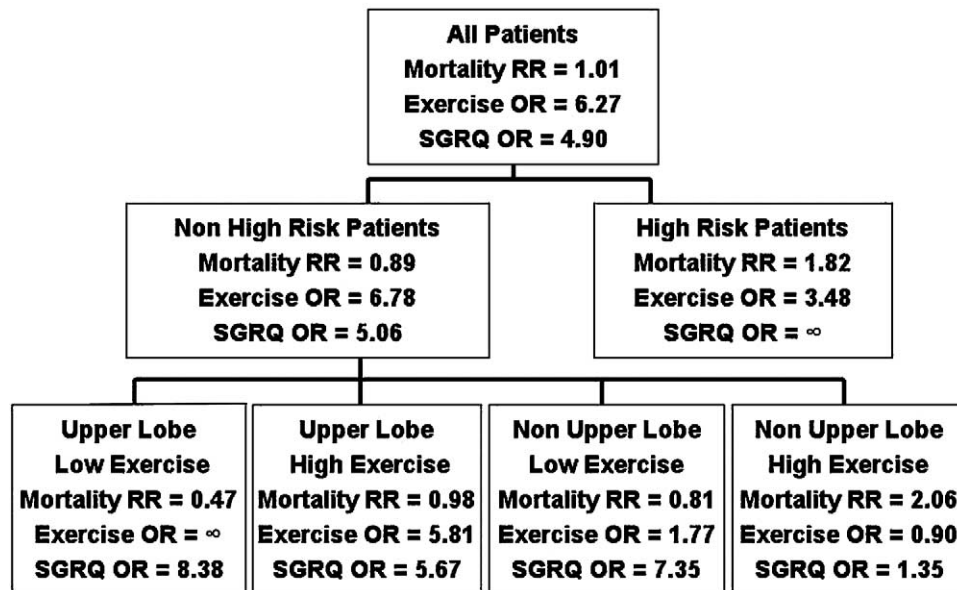


FIG. 4. The illustration depicts the risk stratification subgroups defined in the NETT and the relative risk (RR) and odds ratios (OR) for change in the LVRS cohort as compared to the medical cohort.

dictors of outcome including FEV₁ less than 500 ml [32], inspiratory resistance, PEEP_i, DYN level greater than 5 cm of water [33], elevated total lung capacity (TLC) [34, 35], and residual volume to total lung capacity ratio (RV/TLC) [36]. Importantly, however, the NETT did not identify lung volume as a predictor of mortality or function improvement after bilateral stapled lung-volume reduction surgery (NETT).

Abnormalities in blood gases and diffusion have been suggested to predict a bad outcome. A very low DLCO has been reported to increase the risk [3, 37]. Hypercapnia has been suggested to lead to a higher mortality and worsened income, while other investigators have suggested that is not the case [3, 15, 37, 38]. However, once again the most definitive data available come from the NETT publications [13, 28]. In this, baseline pCO₂ was not associated with impaired outcome and hypercarbia, similarly, did not affect outcomes. However, a high-risk group could be characterized by a specific combination of poor spirometric values and either severely limited diffusion capacity and or specific disease pattern on imaging. Patients with a post-bronchodilator FEV₁ less than or equal to 20% of predicted and either DLCO less than or equal to 20% predicted or homogenous disease (as noted on a CAT scan and perfusion scan) were found to be a high-risk group.

Yet another parameter that has been reported to be helpful in predicting outcomes is the preoperative exercise capacity. A low 6-min walk distance was identified as being associated with a greater likelihood of

poor outcome by multiple investigators [37, 39]. The NETT has confirmed that exercise capacity can play a key role in predicting outcomes from lung-volume reduction surgery. However, in the NETT, exercise capacity was assessed using cycle ergometry in conjunction with the usage of supplemental oxygen. Differential thresholds were identified for males and females as being the breakpoints for low *versus* high exercise capacity (25 W in females and 40 W in males). When these thresholds were used in conjunction with the distribution of emphysema (as assessed by computer tomography) patients could be stratified into four separate categories. The effects on survival, exercise, and dyspnea relief as evidenced by relative risk and odds ratios are depicted in these four categories in Fig. 4. In summary, it appears that the strongest predictors for outcome are the distribution of emphysema (as determined by imaging studies) and the exercise capacity as assessed by using cycle ergometry via the NETT protocol.

SUMMARY

Lung-volume reduction surgery has been demonstrated to be a viable surgical alternative for the treatment of end-stage emphysema. While this had been suspected from the positive results reported by a plethora of nonrandomized trials, it was left to the NETT to prove definitively the value of the operation. Patients undergoing lung-volume reduction were more likely to have improvements in spirometry, quality of life, and

exercise capacity than those patients treated with medical therapy alone. The NETT also demonstrated improved survival in specific subsets of patients. The patient selection analysis of NETT identified subcategories of patients and will in the future allow for appropriate patient selection and counseling.

REFERENCES

- Cooper, J. D., Trulock, E. P., Triantafillou, A. N., *et al.* Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. *J. Thorac. Cardiovasc. Surg.* **109**: 106, 1995.
- Shalala, D. E. Report to Congress. Lung volume reduction surgery and medicare coverage policy: Implications of recently published evidence. Washington, DC: Department of Health and Human Services, 1998.
- Keenan, R. J., Landrenau, R. J., Sciruba, F. C., *et al.* Unilateral thoracoscopic surgical approach for diffuse emphysema. *J. Thorac. Cardiovasc. Surg.* **111**: 308, 1996.
- Naunheim, K. S., Keller, C. A., Krucylak, P. E., *et al.* Unilateral video-assisted thoracic surgical lung reduction. *Ann. Thorac. Surg.* **61**: 1092, 1996.
- Benditt, J. O., Lewis, S., Wood, D. E., *et al.* Lung volume reduction surgery improves maximal O₂ consumption, maximal minute ventilation, O₂ pulse, and dead space-to-tidal volume ratio during leg cycle ergometry. *Am. J. Respir. Crit. Care Med.* **156**: 561, 1997.
- Daniel, T. M., Chan, B. B. K., Bhaskar, V., *et al.* Lung volume reduction surgery. Case selection, operative technique and clinical results. *Ann. Surg.* **223**: 526, 1996.
- McKenna, R. J., Brenner, M., Fischel, R. J., *et al.* Should lung volume reduction for emphysema be unilateral or bilateral? *J. Thorac. Cardiovasc. Surg.* **112**: 1331, 1996.
- Lowdermilk, G. A., Keenan, R. J., Landreneau, R. J., *et al.* Comparison of clinical results for unilateral and bilateral thoracoscopic lung volume reduction. *Ann. Thorac. Surg.* **69**: 1670, 2000.
- Kotloff, R. M., Tino, G., Bavaria, J. E., *et al.* Bilateral lung volume reduction surgery for advanced emphysema. A comparison of median sternotomy and thoracoscopic approaches. *Chest* **110**: 1399, 1996.
- Wisser, W., Tschernko, E., Senbaklavaci, O., *et al.* Functional improvement after volume reduction: Sternotomy versus video-endoscopic approach. *Ann. Thorac. Surg.* **63**: 822, 1997.
- Hazelrigg, S. R., Boley, T. M., Magee, M. J., *et al.* Comparison of staged thoracoscopy and median sternotomy for lung volume reduction surgery. *Ann. Thorac. Surg.* **66**: 1134, 1998.
- Ko, C. Y., and Waters, P. F. Lung volume reduction surgery: A cost and outcomes comparison of sternotomy versus thoracoscopy. *Am. Surg.* **64**: 1009, 1998.
- Fishman, A., Martinez, F., Naunheim, K., *et al.* A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N. Engl. J. Med.* **348**: 2059, 2003.
- Ciccone, A. M., Meyers, B. F., Guthrie, T. J., *et al.* Long-term outcome of bilateral lung volume reduction in 250 consecutive patients with emphysema. *J. Thorac. Cardiovasc. Surg.* **125**: 513, 2003.
- Argenziano, M., Thorashow, B., Jellen, P. A., *et al.* Functional comparison of unilateral versus bilateral lung volume reduction surgery. *Ann. Thorac. Surg.* **64**: 321, 1997.
- Pompeo, E., Marino, M., Nofroni, I., *et al.* Reduction pneumoplasty versus respiratory rehabilitation in severe emphysema: A randomized study. *Ann. Thorac. Surg.* **70**: 948, 2000.
- Criner, G. J., Cordova, G. C., Furukawa, S., *et al.* Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **160**: 2018, 1999.
- Geddes, D., Davies, M., Koyama, H., *et al.* Effect of lung-volume-reduction surgery in patients with severe emphysema. *N. Engl. J. Med.* **343**: 239, 2000.
- Yusen, R. D., Lefrak, S. S., Gierada, D. S., *et al.* A prospective evaluation of lung volume reduction surgery in 200 consecutive patients. *Chest* **123**: 1026, 2003.
- Brenner, M., McKenna, R. J. Jr, Chen, J. C., *et al.* Survival following bilateral staple lung volume reduction surgery for emphysema. *Chest* **115**: 390, 1999.
- Goldstein, R. S., Todd, T. R. J., Guyatt, G., *et al.* Influence of lung volume reduction surgery (LVRS) on health related quality of life in patients with chronic obstructive pulmonary disease. *Thorax* **58**: 405, 2003.
- Gelb, A. F., McKenna, R. J., Brenner, M., *et al.* Lung function 5 yr after lung volume reduction surgery for emphysema. *Am. J. Respir. Crit. Care* **163**: 1562, 2001.
- Flaherty, K. R., Kazerooni, E. A., Curtis, J. L., *et al.* Short-term and long-term outcomes after bilateral lung volume reduction surgery. Prediction by Quantitative CT. *Chest* **119**: 1337, 2001.
- Anthonisen, N. R., Wright, E. C., and Hodgkins, J. E. Prognosis in chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* **133**: 14, 1986.
- Postma, D. S., and Sluiter, H. J. Prognosis of chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* **140**: S95, 1989 (3 Pt. 2).
- Fujimoto, T., Teschler, H., Hillejan, L., *et al.* Long-term results of lung volume reduction surgery. *Eur. J. Cardiothorac. Surg.* **21**: 483, 2002.
- Meyers, B. F., Yusen, R. D., Guthrie, T. J., *et al.* Improved long term survival seen after lung volume reduction surgery compared to continued medical therapy for emphysema. *Ann. Thorac. Surg.* **71**: 2081, 2001.
- National Emphysema Treatment Trial Research Group Patients at high risk of death after lung-volume-reduction surgery. *N. Engl. J. Med.* **345**: 1075, 2001.
- Gierada, D. S., Slone, R. M., Bae, K. T., *et al.* Pulmonary emphysema: Comparison of preoperative quantitative CT and physiologic index values with clinical outcome after lung-volume reduction surgery. *Radiology* **205**: 235, 1997.
- Thurnher, R., Muntwyler, J., Stammberger, U., *et al.* Coronary artery disease in patients undergoing lung volume reduction surgery for emphysema. *Chest* **112**: 122, 1997.
- Cooper, J. D., Patterson, G. A., Sundaresan, R. S., *et al.* Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. *J. Thorac. Cardiovasc. Surg.* **112**: 1319, 1996.
- Eugene, J., Dajee, A., Kayaleh, R., *et al.* Reduction pneumoplasty for patients with a forced expired volume in 1 second of 500 milliliters or less. *Ann. Thorac. Surg.* **63**: 186, 1997.
- Ingenito, E. P., Evans, R. B., Loring, S. H., *et al.* Relation between preoperative inspiratory lung resistance and the outcome of lung-volume-reduction surgery for emphysema. *N. Engl. J. Med.* **338**: 1181, 1998.
- Tschernko, E. M., Kritzing, M., Gruber, E. M., *et al.* Lung volume reduction surgery: Preoperative functional predictors for postoperative outcome. *Anesth. Analg.* **88**: 28, 1999.

35. Lefrak, S. S., Yusen, R. D., Trulock, E. P., *et al.* Recent advances in surgery for emphysema. *Ann. Rev. Med.* **48**: 387, 1997.
36. Fessler, H. E., and Permutt, S. Lung volume reduction surgery and airflow limitation. *Am. J. Respir. Crit. Care Med.* **157**: 715, 1998.
37. Hazelrigg, S., Boley, T., Henkle, J., *et al.* Thoracoscopic laser bullectomy: A prospective study with three-month results. *J. Thorac. Cardiovasc. Surg.* **112**: 319, 1996.
38. O'Brien, G. M., Furukawa, S., Kuzma, A. M., *et al.* Improvements in lung function, exercise, and quality of life in hypercapnic COPD patients after lung volume reduction surgery. *Chest* **115**: 75, 1999.
39. Szekely, L. A., Oelberg, D. A., Wright, C., *et al.* Preoperative predictors of operative morbidity and mortality in COPD patients undergoing bilateral lung volume reduction surgery. *Chest* **111**: 550, 1997.