# Alternatives to Lung Transplantation: Lung Volume Reduction for COPD

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- Lung volume reduction surgery
- National Emphysema Treatment Trial • COPD
- Bronchoscopic lung volume reduction

Emphysema is a progressive and debilitating disease that is recalcitrant to medical interventions. Hyperinflation is the sentinel complication of emphysema that decreases exercise performance and quality of life, impairs respiratory muscle and chest wall mechanics, increases breathlessness, prolongs respiratory failure requiring mechanical ventilation, and increases mortality[1–4] Recent evidence suggests that hyperinflation has implications that go far beyond the respiratory system and may also exert its negative effects on exercise performance and mortality by reducing cardiac chamber size and impairing right and left ventricular function.[5–7] It may also heighten systemic inflammation.[8]

Lung volume reduction surgery (LVRS) was devised with the intent of mitigating the degree and impact of hyperinflation. Before the National Emphysema Treatment Trial (NETT), data regarding LVRS consisted mainly of uncontrolled, single-center studies that were characterized by small patient numbers, substantial variability in patient selection criteria and surgical approach, duration of follow-up, and definitions of complications and outcomes.[9–17] NETT was a randomized, controlled, prospective, multicenter, long-term trial designed to provide definitive answers regarding the independent effects of LVRS in comparison with medical therapy on survival as well as exercise performance, lung function, patient symptoms, and quality of life.[18] NETT demonstrated a 5.2% 90-day postoperative mortality compared with 1.5% with optimal medical therapy. This risk is acceptable to many severely impaired patients with emphysema, but other patients remain apprehensive and forego LVRS and await less invasive therapeutic options.[19,20] In May 2003, soon after the publication of NETT results, interest grew in nonsurgical bronchoscopic approaches to lung volume reduction (BLVR).[21–29]

Herein I review the effects of LVRS in comparison with medical therapy, characterize the optimum candidate for LVRS, and provide an up-to-date review of the various experimental bronchoscopic lung reduction techniques that are currently undergoing investigation.

## LUNG VOLUME REDUCTION SURGERY

In 2003, the results of the NETT were published, detailing the effects of LVRS on survival and maximum exercise capacity in 1218 patients with emphysema who were randomized to LVRS or medical treatment between January 1998 and July 2002 and followed for a mean of 2.4 years.[30] NETT also reported the effects of LVRS on pulmonary function, oxygen requirement, 6-minute walk distance (6MWD), quality of life, respiratory

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symptoms, and health care use. In 2006, the NETT Research Group published updated analyses of survival and functional measures data with a median follow-up of 4.3 years.[31] These analyses included 40% more patients with functional measures at 2 years after randomization compared with the original 2003 outcomes report. Subsequent NETT publications reported on the prevalence and duration of air leaks,[32] optimum surgical approach to perform LVRS,[33] and cost effectiveness of the procedure.[34,35] The major findings of these reports are summarized as follows.

### *Major Outcomes in NETT: All Patients*

Between January 1998 and July 2002, 3777 patients were screened for NETT and 1218 underwent randomization: 608 to LVRS and 610 to medical treatment. Baseline characteristics (**Table 1**) were similar between groups. Of 608 patients assigned to LVRS, 580 (95.4%) underwent LVRS (406 [70%] by median sternotomy, 174 [30%] by video-assisted thoracoscopic surgery), 21 (3.5%) declined LVRS, and 7 (1.2%) were considered unsuitable by the surgeon for LVRS.

Ninety-day mortality rate was 7.9% (95% confidence interval [CI], 5.9%–10.3%) in the LVRS group compared with 1.3% in the medical group (95% CI, 0.6%–2.6%, $P<.001$). At a mean follow-up of 29.2 months after randomization, 160 patients assigned to medical treatment died compared with 157 patients assigned to LVRS. There was no difference in mortality rates at this time point between groups, although a higher initial mortality rate was identified in the LVRS group soon after the operation (**Fig. 1**A).

Exercise capacity improved 10 W or more in 28%, 22%, and 15% of LVRS patients after 6, 12, and 24 months, respectively compared with 4%, 5%, and 3% of medical control patients ($P<.001$ at each time point, **Fig. 2**, **Table 2**). Additionally, patients who underwent LVRS were more likely to demonstrate improvements in 6MWD, % predicted forced expiratory volume in 1 second ($FEV_1$), severity of dyspnea, and general as well as disease-specific quality of life assessments compared with the control group (see **Fig. 2**; **Table 2**).

### *Identifying a Patient Subgroup at High Risk of Death Following LVRS*

Before NETT commenced, a 30-day surgical mortality greater than 8% in either treatment group was defined as a stopping end point. In May 2001, a subgroup defined by $FEV_1$ of less than or equal to 20% predicted and either a diffusing capacity for carbon monoxide ($DL_{CO}$) of less than or equal to 20% predicted or homogeneous emphysema met the prespecified stopping criteria because of excessive mortality with LVRS.[36] The 30-day mortality in those who received LVRS was 16% (95% CI, 8.2%–26.7%, $P<.001$) compared with no deaths in the medical group. For those "high-risk profile" LVRS-treated patients who survived 6 months after randomization, there was little or no difference in functional and quality-of-life outcomes compared with the medically treated group: exercise capacity increased by 4.5 $\pm$ 13.0 W versus a decrease of 4.4 $\pm$ 14.8 W ($P = .06$), 6MWD increased by 14.9 $\pm$ 63.7 m versus a decrease of 21.6 $\pm$ 56.7 m ($P = .03$), and $FEV_1$ increased by 5.5% $\pm$ 6.9% predicted versus a decrease of 0.4% $\pm$ 1.9% predicted ($P<.001$). At 6 months, the Quality of Well-Being score showed a similar decrease (0.01 units) for both groups.

As described by the previous data, patients with severe emphysema characterized by an $FEV_1$ of less than or equal to 20% predicted and either a homogeneous pattern of emphysema on chest CT or a $DL_{CO}$ of less than or equal to 20% predicted have high postoperative LVRS mortality and little chance of clinically meaningful improvements in lung function, exercise tolerance, or quality of life. As a result, these types of patients are not approved for LVRS by the Centers for Medicare and Medicaid Services (CMS) or by the Joint Commission for the Accreditation of Healthcare Organization (JCAHO) guidelines.

### *Results of NETT: Outcomes in Non–High-Risk Patients*

Among 1078 NETT patients who were not high risk, the 30-day mortality after LVRS was 2.2% and 0.2% after medical treatment ($P<.001$). Ninety-day mortality rate was 5.2% with LVRS and 1.5% with medical therapy ($P = .001$; **Table 3**). At a mean 29.2 months follow-up after randomization into NETT, LVRS provided no survival benefit over medical treatment, even with exclusion of the high risk for death subgroup. Patients who underwent LVRS more likely had improvements in 6MWD, maximum exercise capacity, $FEV_1$% predicted, and quality of life (disease specific and general) compared with continued medical treatment ($P<.001$ for each comparison; see **Fig. 2**).

### *Preoperative Predictors of LVRS Outcomes in Non–High-Risk NETT Patients*

The baseline factors associated with differences in mortality, functional outcomes, and quality-of-life