The NETT: Part I - Lessons Learned about Emphysema
Gerard J. Criner, M.D., Francis Cordova, M.D., Alice L. Sternberg, Sc.M., and Fernando J. Martinez, M.D.

1 Division of Pulmonary and Critical Care Medicine, Temple University, Philadelphia, PA;
2 Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; and
3 Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, Michigan

Correspondence:
Gerard J. Criner, M.D.
Director, Pulmonary and Critical Care Medicine
And Temple Lung Center
Temple University School of Medicine
745 Parkinson Pavilion
3401 North Broad Street
Philadelphia, Pa 19140
Phone: 215-707-8113
Fax: 215-707-6867
Email: crinerg@tuhs.temple.edu

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Abstract:

NETT was a multicenter prospective randomized controlled trial that compared optimal medical treatment, including pulmonary rehabilitation, to optimal medical treatment plus Lung volume Reduction Surgery (LVRS). It was the largest and most complete collection of patient demographic, clinical, physiologic and radiographic data ever compiled in severe emphysema. NETT investigated the effects of optimal medical management and LVRS on short and long-term survival, as well as lung function, exercise performance and quality of life. NETT also provided much information regarding the evaluation and prognosis of severe emphysema; specifically the important negative influences that hyperinflation and small airways disease have on survival. NETT emphasized the importance of addressing non-pulmonary issues such as nutrition, cardiac disease, anxiety and depression in emphysema. NETT demonstrated that physiologic, genomic and radiographic phenotype can predict patient survival as well as response to treatment. Since the major purpose of NETT was to compare bilateral LVRS vs. optimal medical treatment in emphysema, patients enrolled into NETT were comprehensively characterized and selected to have a specific window of airflow obstruction and hyperinflation and lack significant comorbidities. The NETT patient population’s restrictive features offer distinct advantages (well characterized predominant emphysematous phenotype) and disadvantages (lack of comorbidities and significant chronic bronchitis) that must be considered when interpreting the implications of these results. Herein, we provide a summary of the major NETT findings that provide insight into the evaluation and medical treatment of emphysema.
Introduction

A vast amount of new information regarding the pathogenesis, clinical expression and treatment of chronic obstructive pulmonary disease (COPD) has emerged over the past two decades. The investigation and implementation of lung volume reduction surgery (LVRS) as a therapeutic modality for severe emphysema contributed much to this accumulation of information. LVRS prompted intensive study into the radiological characterization of distinct COPD phenotypes, and the pathological examination of lung tissues resected during LVRS provided insights into the pathogenesis and prognosis of airways disease. New attention was directed towards the anesthetic and operative care of patients with advanced emphysema. Optimization of medical therapy prior to LVRS enhanced our knowledge of oxygen and rehabilitation therapy.

Much of the information regarding LVRS and medical care in severe emphysema emanated from the National Emphysema Treatment Trial (NETT). NETT was a multicenter prospective randomized controlled trial that compared optimal medical treatment, including pulmonary rehabilitation, to optimal medical treatment plus LVRS. (1) NETT randomized 1218 patients and demonstrated an overall survival advantage for LVRS, with a 5-year risk ratio (RR) for death of 0.86 (p = 0.02). (2) The LVRS group was more likely to have improved maximal exercise through 3 years and health-related quality of life (measured by the St. George’s Respiratory Questionnaire [SGRQ]) through 4 years. In post hoc analyses, four subgroups were identified based on their performance on post rehabilitation exercise testing and the pattern of emphysema on chest CT imaging. Upper-lobe patients with low exercise capacity demonstrated improved survival (p = 0.003), exercise throughout 3 years (p < 0.001), and symptoms (SGRQ) through 5 years (p < 0.001 years 1 to 3, p = 0.01 year 5). Upper-lobe-predominant and high-exercise-capacity LVRS patients experienced no survival
advantage but were likely to improve exercise capacity (p < 0.01 years 1 to 3) and SGRQ (p < 0.01 years 1 to 4). NETT demonstrated that the effects of LVRS are durable, and is strongly recommended in upper-lobe-predominant emphysema with low exercise capacity and should be considered for palliation in patients with upper-lobe emphysema and high exercise capacity.

NETT was the largest and most complete collection of patient demographic, clinical, physiologic and radiographic data ever compiled in severe emphysema. (3) NETT provided much information regarding medical care in severe emphysema; specifically how physiologic and radiographic phenotype can predict patient survival as well as response to treatment and that static and dynamic hyperinflation has devastating consequences on patient symptoms, exercise performance, quality of life and survival. NETT was the first large scale study to associate different clinical phenotypes with genomic characterization and responses to medical and surgical therapy. In addition, NETT emphasized the need to address non-pulmonary issues such as nutrition, cardiac disease and anxiety and depression. Ancillary studies on NETT patients provided substantial information on genomic characterization and its influence on clinical expression in emphysema and on the effects of LVRS on cognition. Finally, NETT highlighted the complexities of performing long-term trials in severe emphysema patients in whom multiple comorbidities, frequent COPD exacerbations, and the severity of the underlying disease complicate subject participation and data collection.

As a result of the broad and comprehensive structure of NETT, multiple peer-reviewed scientific manuscripts (>75 to date) detailing the short- and long-term outcomes of LVRS and optimal medical treatment in severe emphysema have been published across many specialties and journals (4). In fact, NETT investigators continue
to analyze and publish the rich database of baseline and longitudinal data collected during NETT. The volume and dispersion of NETT results across multiple journals and specialties may have escaped the awareness of the active clinician.

In this review, we summarize what we currently know about the pathogenesis and treatment of severe emphysema as a result of insights gained from NETT. In addition to providing valuable insights into the nature of emphysema, the primary intent of NETT was to investigate the role of Lung Volume Reduction Surgery (LVRS), which will be the subject of Part II.

**NETT Patient Population**

The NETT patient population had several unique features that should be considered when interpreting the results of the studies reviewed below. Since the major purpose of NETT was to compare bilateral LVRS vs. optimal medical treatment in emphysema, patients enrolled into NETT were comprehensively characterized and selected to have a specific window of airflow obstruction, hyperinflation and air trapping (FEV₁ between 15-45% predicted, TLC > 105% predicted and RV > 150% predicted) and to avoid poor surgical candidates (significant cardiac abnormalities, bronchiectasis and significant sputum production, non-pulmonary disorders that would adversely affect surgical outcomes, prior lung resectional surgery or median sternotomy, lack of bilateral emphysema, poor surgical candidate by the surgeons judgment). As a result, 3,777 patients were screened and only 1,218 patients were enrolled into NETT signifying a select patient group that met the enrollment windows of lung physiological and radiographic requirements and no significant co-morbidities. At baseline, NETT patients had bilateral emphysema on chest CT and demonstrated severe airflow obstruction ((mean FEV₁ 26% of predicted), hyperinflation (mean TLC 128% of predicted) and air
trapping (mean RV 220% predicted) on pulmonary function testing therefore signifying a
group that had emphysema and Chronic Obstructive Pulmonary Disease (COPD).
These features of the NETT patient population offer distinct advantages (well
characterized predominant emphysematous phenotype) and disadvantages (lack of co-
morbidities and significant chronic bronchitis) that must be considered when interpreting
these results.

**Pathobiology of COPD**

LVRS offered an unprecedented opportunity to study the resected lung tissue
from patients with moderate to advanced emphysema and correlate the pathologic
changes with different clinical COPD phenotypes. While the different pathologic
characterizations of emphysema are well known, the contribution of small airways
disease and attendant mucus hypersecretion on the morbidity and mortality are only
beginning to be elucidated. Moreover, the role of innate and adaptive immunity in
perpetuating chronic inflammation and disease progression of COPD has also recently
come to light.

Even in patients with advanced emphysema, small airways disease remains an
important component of the disease and dictates the clinical course of the patient. In a
seminal study reported by Hogg and co-workers surgically resected lung tissue from
159 COPD patients undergoing LVRS or other types of lung biopsies showed that
COPD progression was strongly associated with small airway wall thickening (<2mm),
and an increase in infiltration of the airway walls with innate and adaptive inflammatory
immune cells (e.g., polymorphonuclear neutrophils, macrophages, CD4 cells, CD8 cells,
B cells). (5) Additionally, COPD progression was also associated with increased
lymphoid follicles around airways, the absolute volume of CD8 and B cells, airway
occlusion due to accumulation of an inflammatory mucous exudate, and thickness of the
airway wall. On multivariate analysis, airway wall thickness had the strongest association with COPD disease progression. The increase in airway wall thickness was found in several airway compartments including the epithelium, lamina propria, muscle, and adventitia. The small airway pathologic changes were believed to occur as a result of tissue remodeling following injury and disturbed mucociliary clearance causing mucus retention. Increases in airway related lymphoid follicles were attributed to a heightened adaptive immune response due to bacterial colonization or chronic infection. Persistent heightened innate and adaptive immune responses in COPD may precipitate an accelerated decline in lung function even after the patient has stopped smoking.

In a subsequent study that included 101 NETT patients with GOLD-3 and GOLD 4 disease who underwent LVRS, the quartile of patients with the greatest mucoid luminal occlusion had higher mortality compared to patients with the least mucoid small airway occlusion. (6) This association persisted even after correcting for the degree of airway obstruction, severity of symptoms and type of LVRS procedure. Treatment with corticosteroids appeared to be beneficial in decreasing the number of lymphoid follicles but had no effect on airway wall thickening or mucoid luminal occlusion. The etiology of the increase in mortality in patients with significant small airways mucoid occlusion is unclear and may be due to increase susceptibility to infection due to retained secretions. Future drug development should target the pathologic changes that occur in the small airways.

**Genetics of COPD**

To date, severe α1 antitrypsin deficiency is the only proven genetic determinant of COPD. However, this genetic defect is present only in 1% of COPD patients. Several clinical observations including marked variability in the development of COPD among cigarette smokers, and familial clustering of COPD among the first-degree relatives of
patients with COPD support the notion that genetic factors may increase the susceptibility to develop COPD. NETT provided substantial data outlining the importance of genetic factors in the presentation, progression and response to treatment in COPD.

In the NETT genetic ancillary study, several candidate genes [glutathione S-transferase P1 (GSTP1), glutathione S-transferase M1 (GSTM1), α1-antichymotrypsin (SERPINA3), surfactant protein B (SFTPB), tumor necrosis factor α (TNFα), microsomal epoxide hydrolase (EPHX1), and latent transforming growth factor β binding protein-4 (LTBP4)] were associated with various COPD phenotypes that predicted the responses to lung volume reduction surgery (radiographic distribution of emphysema, functional capacity, pulmonary function test, and gas exchange) presence of respiratory symptoms and frequency of acute exacerbations.

In the NETT genetic substudy, 282 patients were evaluated to determine whether apical predominant emphysema is in part driven by genetic susceptibility. Polymorphisms in 2 candidate genes, glutathione s-transferase P1 (GSTP1), and microsomal epoxide hydrolase (EPHX1) were strongly associated with apical predominant emphysema when analyzed by both the densitometric and visual scoring techniques. Interestingly, the same 2 genes were found to be predictive of a change in BODE score 6 months after LVRS. These 2 xenobiotic metabolizing enzymes are thought to be important in decreasing lung oxidative stress due to reactive oxygen species and free radicals following cigarette smoke exposure. Specifically, glutathione S-transferases are expressed in the lung and serve as antioxidants and hydroperoxidases. Of the 2 common polymorphic variants, Ile105 Val and Ala114Val, the Ile105 Val variant was associated with upper lobe predominant emphysema. The variant at the 105 position is thought to alter GSTP1 enzymatic activity to enable more efficient metabolism of aromatic epoxides. It is theorized that polymorphism in GSTP1 at
this functional site may influence regional detoxification of xenobiotic and oxidant 
stressors. This variant has also been associated with COPD in Japanese cohorts (9) 
and lung function decline in individuals with a family history of COPD in the Lung Health 
Study. (10)

Microsomal epoxide hydrolase has high affinity in the lung and is involved in the 
initial metabolism of reactive epoxide intermediates that are found in cigarette smoke. A 
coding variant, known as fast variant (His139Arg) because of its effect on enzyme 
activity, has been shown to be protective against upper lobe emphysema.(11) The slow 
variant allele (Tyr113HHis) has been associated with COPD in case control studies 
(12)(13), and a rapid decline in lung function in the Lung Health Study.(14).

In another NETT genetic study exploring the association of genetic 
polymorphism and clinical phenotypes including maximum work output, low exercise 
capacity, 6 minute walk distance, FEV\textsubscript{1}, diffusion capacity, UCSD SOBQ score, and 
BODE score, polymorphisms in four genes, microsomal epoxide hydrolase (EPHX1), 
latent transforming growth factor β binding protein-4 (LTBP4), surfactant protein B 
(SFTPB), and transforming growth factor-β1(TGFB1) were found to be significantly 
associated with measures of functional capacity, pulmonary function tests and 
respiratory symptoms(15). Single nucleotide polymorphisms in EPHX1 were associated 
with maximum work capacity, diffusion capacity and UCSD SOBQ score. Variants in the 
2 genes in the TGF-β pathway, TGFB1 and LTBP4, were associated with maximum 
work output and UCSD SOBQ score. Gene variants in LTBP4 and SFTPB were 
associated with 6 minute walk distance.

Several of the same candidate genes were also found to be important in 
determining the degree of hypoxemia, hypercarbia and the presence of secondary 
pulmonary hypertension in NETT patients with advanced emphysema. Single nucleotide 
polymorphisms in EPHX1 and serpin peptidase inhibitor, clade E, member 2
(SERPINE2) were found to be associated with the presence of hypoxemia. One single nucleotide polymorphism (SNP) within surfactant protein B (SFTPB) was associated with pulmonary hypertension (16). These findings were replicated in the Boston Early-onset COPD study which showed that SNPs in EPHX1 and SERPINE2 were associated with the need for supplemental oxygen. SERPINE2 has been reported as a COPD-susceptibility gene in pedigree–based association and in case-control replication analysis. Serpine 2 is an inhibitor of thrombin, urokinase, and plasmin. It has been shown to hinder neuron apoptosis and injury-mediated cell death. Its exact role in acute COPD exacerbation remains to be elucidated.

To test for the presence of genetic determinants in COPD exacerbation, 88 SNPs in the same 5 candidate genes were genotyped in the same cohort of NETT patients (17). Acute exacerbation was defined as emergency room visits or hospitalization identified from the Center for Medicare and Medicaid Services claims records. One or more exacerbations were experienced by 216 (56%) subjects during the 8 years study period. Genetic variation in the SFTPB promoter region, rs3024791, was associated with COPD susceptibility and exacerbation frequency.

Recently, single nucleotide polymorphisms in surfactant protein D (SFTPD) were associated with susceptibility to develop COPD (18). Pulmonary surfactant decreases alveolar surface tension and promotes alveolar stabilization and mucociliary clearance. SFTPD is immunomodulatory and plays an important role in the lung’s innate immunity through bacterial agglutination, opsonization and neutralization of viruses. Six single-nucleotide polymorphisms (SNPs) were genotyped in 389 NETT patients and 472 smoking controls from the Normative Aging Study. Case-control association analyses were performed and significant associations were attempted to be replicated in the Boston-Early-Onset COPD Study, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (Eclipse) Study and the Bergen Cohort. Multiple
polymorphisms in SFTPD were found to correlate with serum protein concentrations of surfactant protein D providing additional support for the role of surfactant protein D in the pathogenesis of COPD and its usefulness as biomarker.

Recent research suggests that COPD is a disease in part due to accelerated aging. One line of evidence supporting the senescence hypothesis of COPD pathogenesis is the accelerated attrition of telomere length found in emphysema patients. A genome-wide association study was performed in 2,380 COPD patients from 3 independent white cohorts (Bergen Norway, NETT and ECLIPSE) cohorts. (19) Genome-wide association studies showed an association of SNP in BICD1 gene with the presence of emphysema on CT chest imaging. Variants in BICD1 associated with telomere length support the role of aging in the pathogenesis of COPD.

The genes that have shown significant association with various COPD phenotypes have varied biologic functions that involve xenobiotic metabolism, maintenance of extracellular matrix properties and surfactant integrity, host defense control of inflammation and signaling pathways, and regulation of telomere length. Overall the NETT genetic ancillary study provided valuable insights in the gene-environment interaction and the pathogenesis of emphysema. Many of these factors may play an important role in COPD pathogenesis.

**Importance of Hyperinflation in COPD**

Lung hyperinflation in COPD impairs chest wall and respiratory muscle mechanics, increases breathlessness, impairs weaning from mechanical ventilation, decreases exercise performance and increases mortality. Recent information indicates that hyperinflation not only impairs respiratory mechanics but may have important negative consequences for cardiac performance as well.
A recent study conducted outside of NETT in 138 mild to severe COPD (GOLD I-IV) patients illustrates the importance of hyperinflation on cardiac function and clinical performance. (20). These authors demonstrated stronger inverse relationships with cardiac chamber size measured by echocardiography and static lung hyperinflation measurements (IC/TLC, functional residual capacity and residual volume) compared to measurements of airways obstruction or diffusion capacity. IC/TLC correlated the strongest with cardiac chamber size; patients with an IC/TLC ≤ 0.25 had impaired LV filling and an impaired Tei-index compared to patients with IC/TLC > 0.25. A reduction in LV filling was independently associated with a reduced 6-minute walk distance.

Hyperinflation increases intrathoracic pressures and thereby decreases venous return and right and left ventricular volumes and consequently LV stroke volume. In hyperinflated emphysema patients (residual volume 272% predicted), intrathoracic blood volume, LV end-diastolic volume index, RV end-diastolic index, cardiac index and stroke volume index as assessed by MRI are reduced compared to controls(21). Even in severe COPD, a condition in which the right ventricle hypertrophies, MRI data during systole shows that the interventricular septum flattens, which could explain why LV ejection fraction remains relatively normal (22).

Lung volume reduction surgery (LVRS) provides indirect corroboration that reducing hyperinflation improves cardiac function. LVRS has been shown to reduce hyperinflation and improve spirometry, breathlessness, exercise performance and quality of life (23, 24). In a cardiac substudy, NETT examined the effect of medical treatment versus lung volume reduction surgery (LVRS) on pulmonary hemodynamics. (25) A total of 110 of the 163 patients evaluated for the CV substudy were randomized in NETT (53 were ineligible), 54 to medical treatment and 56 to LVRS. Fifty-five of these patients had both baseline and repeat right heart catheterization at six months post randomization. End-expiratory right heart catheterization pressures (pulmonary artery diastolic;
pulmonary artery mean; right atrial; right ventricular diastolic; right ventricular systolic; pulmonary artery systolic pressures) in LVRS patients tended to be slightly lower compared with patients who were medically treated at 6 months post randomization compared to baseline values, but none of the differences achieved statistical significance. However, a small but significant reduction in pulmonary capillary wedge pressure at end-expiration post-LVRS was noted compared to medical treatment (−1.8 vs. 3.5 mm Hg, p = 0.04). These data showing that LVRS reduced end-expiratory pulmonary artery wedge pressure compared to a medically treated group, signifies a decrease in juxtacardiac intrathoracic pressures.

LVRS has been shown by other investigators to increase LV end-diastolic dimensions and filling and significantly increase cardiac index (26). In aggregate, these data suggest that some of the beneficial effects of LVRS in severely hyperinflated emphysema patients, specifically improved exercise performance and even reduced mortality, may be mediated via improvements in pulmonary vascular and cardiac function, in addition to respiratory mechanics.

**Pulmonary Hemodynamics in Severe Emphysema**

NETT provided insight into the prevalence and magnitude of pulmonary hypertension in severe emphysema and the value of noninvasive tests including echocardiography and HRCT in assessing the degree of pulmonary hypertension. It should be noted, however, that NETT patients were purposely excluded from randomization if they were found to have abnormal LV function, significant arrhythmias, coronary artery disease, and pulmonary hypertension (systolic pulmonary artery pressure> 45 mm HG) since patients were being evaluated for potential bilateral lung resectional therapy. The lack of underlying coronary artery disease, cardiomyopathy
and significant pulmonary hypertension in the NETT cohort should be considered when interpreting the following results.

NETT combined data from pulmonary function testing, right heart catheterization, high resolution chest CT (HRCT), and radionuclide angiography to comprehensively characterize pulmonary hemodynamics and ventricular function in 120 patients with severe emphysema, hyperinflation, and gas trapping (mean FEV₁ 27% predicted, RV 225% predicted, DLco 27% predicted) (27). 85.5% of patients had Pa systolic pressure > 20 and < 35 mm Hg, 5% > 35 mmHg, and 9.2% < 20 mmHg. In 61.4% of subjects, end-expiratory wedge pressure (PAWP) was > 12 mmHg. Cardiac index was normal. Mean pulmonary artery pressure correlated inversely with PaO₂ and severity of emphysema on HRCT and directly with PAWP. No correlation was found between the severity of emphysema and PA pressures. Diastolic ventricular pressures were increased, but no evidence of systolic dysfunction was detected by radionuclide angiocardiography. These data demonstrated that elevations in pulmonary artery pressures were common in severe emphysema and that elevated cardiac diastolic pressures were found without systolic dysfunction, indicating that elevated intracardiac pressures reflect mechanical heart-lung interactions due to elevations in lung volume rather than intrinsic myocardial disease.

Proposed mechanisms of secondary pulmonary hypertension in emphysema include chronic hypoxia with subsequent vascular remodeling, destruction of the pulmonary vascular bed and compression of the vasculature due to hyperinflation. A physiological feature of emphysema is a loss of lung elastic recoil which precipitates the development of static and dynamic hyperinflation, dynamic airway collapse and airway obstruction. Reduced lung recoil has also been proposed as an additional mechanism that causes pulmonary hypertension in emphysema by the lack of a tethering effect on the extra-alveolar vessels. In 67 NETT subjects who underwent RHC, lung elastic recoil
was measured at TLC (coefficient of retraction, CR) and at FRC (CR\text{\textsubscript{FRC}}).(28) No correlation was found between CR and PVR, PA systolic pressure, or mean PA pressure. Similarly no correlation was found between CR\text{\textsubscript{FRC}} and any pulmonary artery pressure. These data suggest that elastic lung recoil is not an important determinant of pulmonary artery pressure in severe emphysema and that the other proposed mechanisms (hypoxia and vascular remodeling, destruction of the pulmonary vascular bed and compression of the vasculature due to hyperinflation) are more prominent causes of pulmonary hypertension in this patient group.

Noninvasive detection of pulmonary hypertension in severe emphysema can be very challenging.(29) In 163 NETT patients who underwent right heart catheterization (RHC) and Doppler echocardiography, the accuracy of echocardiography to determine pulmonary artery pressures was examined. In 74 paired RHCs and echocardiograms in 63 patients, mean values of pulmonary artery systolic and estimated right ventricular pressures were similar. Using WHO definitions of pulmonary hypertension, echocardiographic measurement of pulmonary artery pressures weakly correlated with RHC and the sensitivity and specificity of the echocardiography to detect pulmonary artery hypertension were poor (sensitivity 60%, specificity 74%, positive predictive value 68%, negative predictive value 67%) compared with RHC. In this patient group, echocardiography performed poorly in assessing the presence of pulmonary artery hypertension.

NETT also explored the in vivo relationship between pulmonary hypertension and structural alteration of the small pulmonary vessels in severe emphysema as assessed by HRCT analysis.(30) In 79 NETT patients, total cross-sectional area (CSA) was measured in vessels < 5 mm\textsuperscript{2} (CSA\textsubscript{<5}) and 5-10 mm\textsuperscript{2} (CSA\textsubscript{5-10}) and the % of total CSA for the lung area (%CSA\textsubscript{<5} and %CSA\textsubscript{5-10}, respectively) was calculated. %CSA\textsubscript{<5} and %CSA\textsubscript{5-10} were correlated with mean pulmonary artery pressure (Ppa) determined by
RHC. %CSA<sub>&lt;5</sub> significantly correlated with mean Ppa (p<0.0001), but the correlation between %CSA<sub>5-10</sub> and mean Ppa did not reach significance (p=0.083). %CSA<sub>&lt;5</sub> and DLco independently predicted mean Ppa (r<sup>2</sup>=0.541). These data show that %CSA<sub>&lt;5</sub> measured on HRCT may be useful in estimating the degree of pulmonary hypertension in severe emphysema.

**Physiological measurements of lung function in severe emphysema**

Data from NETT and the Lung Health Study (LHS) were used to determine the short-term variability of FEV<sub>1</sub> and FVC between test sessions in patients with a range of COPD severity, whether severity of COPD affects the intersession variability of FVC and FEV<sub>1</sub> measurements, and whether criteria for significant changes in FEV<sub>1</sub> or FVC be defined using absolute or % predicted values, or both.(31) A total of 5,886 subjects in LHS and 1,215 in NETT who had performed post-bronchodilator spirometry during the two baseline sessions were studied. Mean ± SD FEV<sub>1</sub> for the initial session was 2.64 ± 0.60 L (75.1 ± 8.8 % predicted) for the LHS and 0.68 ± 0.22 L (23.7 ± 6.5 % predicted) for the NETT. The number of days between testing sessions was 24.8 ± 17.1 for LHS and 85.7 ± 21.7 for NETT. As the degree of obstruction increased, intersession % difference of FEV<sub>1</sub> increased. However, the absolute difference between the test sessions remained similar despite the severity of airflow obstruction (0.106±0.10 L). Greater than 90% of subjects had an intersession FEV<sub>1</sub> difference < 225 ml regardless of the degree of airflow obstruction. These data obtained across broad based populations of subjects with mild to very severe airflow obstruction demonstrate that absolute changes in FEV<sub>1</sub> rather than % change should be used to determine whether lung function has improved or worsened between test sessions.

NETT also examined the prevalence and clinical correlates of bronchoreversibility during pulmonary function testing in severe emphysema.(32) 544
NETT subjects randomized to the medical arm underwent multiple measurements of bronchoreversibility on mean of 4 sessions over 1.91 years. Mean baseline FEV\textsubscript{1} was 24%; 22.2% of subjects demonstrated bronchoreversibility on one or more sessions according to ATS/ERS criteria. Few subjects (0.37%) had bronchoreversibility on all tests. Large changes in FEV\textsubscript{1} (\geq 400ml) at least once was observed infrequently (1.8%) and no patient met that criteria at all testing sessions. Those subjects who exhibited bronchoreversibility in FEV\textsubscript{1} were more likely to be male, have better lung function and less emphysema. Large changes in FVC (\geq 400ml) were found in 64% of the subjects signifying that COPD patients suffering from severe airflow obstruction and air trapping with a predominant emphysematous phenotype respond to bronchodilator therapy with an exhalation of increased expiratory volume rather than flow.

The ability of single breath diffusing capacity (DLco) to predict the need for supplemental oxygen during rest and exercise was also assessed in 1,071 NETT subjects. Mean DLco was 8.0±3.1 mL/min/mmHg (28±10% predicted) and mean resting PaO\textsubscript{2} was 64±10 mmHg. A positive correlation existed between DLco and both resting PaO\textsubscript{2} and the requirement for oxygen to maintain SaO\textsubscript{2} > 90% for 3 minutes during a walk test at 1 mph. The odds of requiring O\textsubscript{2} at a 1 mph walk was 9 times greater in subjects with a DLco \leq 20% predicted than those with a DLco > 35% of predicted. 84% of subjects with a DLco \leq 20% predicted required supplemental O\textsubscript{2} with low levels of exercise compared to 38% of subjects with a DLco > 35%. Based on these data, DLco is a useful tool to indicate whether supplemental oxygen is required during exercise.

Quantitative (computer based threshold scoring) and semi-quantitative (radiologist interpretation using a visual score) measurements of the magnitude of emphysema were compared in 1,094 NETT subjects for their ability to predict lung
mechanics (spirometry, lung volumes, diffusion capacity and in a subset, measurements of lung static recoil). (34)

Univariate analyses showed weak correlations between the radiologist HRCT emphysema score and FEV$_1$ % predicted (p=0.004) and RV/TLC ( p=0.0001). No method of HRCT analysis (different HU thresholds to detect emphysema, radiologist semi-quantitative analyses, and computer based quantitation) clearly outperformed the other. These data illustrate that quantitation of the emphysema burden on HRCT is a poor predictor of physiological lung function.

In a subsequent analysis, association of HRCT measures of emphysema and airway disease with lung function was assessed in 338 NETT subjects.(35) Densitometric measures of emphysema were made using a -950 HU threshold; airway wall thickness (AWT) and the square root of airway wall area (SRWA) of a 10 mm luminal perimeter airway were calculated. Using univariate analysis, negative correlations were found between the extent of emphysema at -950HU and both AWT and SRWA. AWT weakly correlated with post-bronchodilator FEV$_1$ % predicted (p=0.02). Multivariate analyses showed correlations with AWT or SRWA and % emphysema at -950 HU with post-bronchodilator FEV$_1$ % predicted. Male subjects had thicker airway walls compared to females (p= 0.007 for AWT and p=0.0006 for SRWA). These data demonstrate that the HRCT may have value in structurally characterizing patients with advanced COPD. Additionally these data show that patients with an airway wall phenotype are influenced by gender and that some HRCT findings may be associated with physiologically determined variables of lung function.

Exercise testing via either the 6 MWT or the cardiopulmonary exercise test is commonly used to evaluate impairment in emphysema.(36) The correlation of these two tests in the assessment of exercise tolerance and their relationship to physiological parameters were studied in 1,218 emphysema subjects enrolled into NETT. In this group
with an average FEV$_1$% predicted of $26.9 \pm 7.1$, the two forms of exercise testing correlated with each other (r=0.57, p<0.0001). The impairment of performance on cardiopulmonary exercise testing was greater than on 6 MWT ($27.6 \pm 16.8$ vs. $67.9 \pm 18.9$ % predicted). Both tests similarly correlated with quality of life measures, but maximum exercise capacity correlated better with lung function measurements than 6 MWT. 6 MWT had a greater association with SGRQ score than cardiopulmonary exercise. These data suggested that 6 MWT may be a better test of functional capacity; however, maximum cardiopulmonary testing may be a better measure of impaired lung function.

**Differences in the presentations of emphysema in African American vs. Caucasian Patients.**

Of the 1218 patients enrolled into NETT, 42 (3.4%) were African-American and 1,156 (95%) were Caucasians. African-Americans were younger ($63 \pm 7$ vs. $67 \pm 6$ years age, p=0.01) and smoked less ($26 \pm 14$ vs. $32 \pm 14$ cigarettes per day, p=0.01). Despite similar FEV$_1$, PaO$_2$, exercise watts, and quality of Life measures, radiographic analysis revealed significantly less and different distribution of emphysema in African-Americans compared to Caucasians.

34 African American patients were matched to Caucasian patients who had complete CT data that permitted quantitative analysis. Taking -950 HU as the cutoff point, African American patients had less severe emphysema compared to Caucasians, and Caucasians had a greater core-peel emphysema difference in the lung apices compared to African Americans. These data suggest that there may be race based differences in the response of the lungs to smoke exposure.

**Risk for mortality in emphysema.**
NETT provided a unique opportunity to assess the risk factors for mortality in patients afflicted predominantly with emphysema. (38) A total of 609 patients randomized to the medical arm of NETT were studied to investigate risk factors for all cause mortality, including demographics, body mass index, oxygen utilization, hemoglobin, smoking history, quantitative emphysema markers on CT and a modification of the BODE index (body mass index, degree of airflow obstruction measured by FEV1 % of predicted, dyspnea measured by the University of California at San Diego Shortness of Breath Questionnaire (UCSD-SOBQ) and exercise capacity as measured by 6 minute walk distance). High mortality (292 deaths; median follow-up 3.9 years) was seen in the cohort; the overall death rate was 12.7 deaths per 100 person-years. In multivariate analyses, older age, oxygen utilization, lower total lung capacity % predicted, higher residual volume % predicted, lower cardiopulmonary exercise test workload, greater proportion of emphysema in the lower vs. upper lung zone, lower upper to lower lung perfusion and modified BODE were predictive of mortality. FEV1 was a significant predictor of mortality in univariate but not multivariate analysis. The predictive value of a longitudinal change in modified BODE index was also assessed. (39) The mBODE was calculated at baseline and then 6, 12 and 24 months in follow-up. Patients were classified as having decreased, increased, stable, or missing BODE based on their absolute changes from baseline. An increase in mBODE of more than 1 point from baseline to 6, 12, or 24 months was associated with increased mortality whether receiving LVRS or medical treatment. A change in mBODE predicted survival better than any of the mBODE’s components.

Medical therapy in emphysema

Rehabilitation
Pulmonary rehabilitation has been shown to alleviate symptoms, improve functional capacity, and quality of life in COPD patients. In NETT, all subjects completed 6 to 10 weeks of standardized pulmonary rehabilitation prior to randomization regardless of whether they had previously undergone pulmonary rehabilitation.(40) In addition, the NETT rehabilitation program was continued after randomization with a long-term maintenance program. The active stage of the rehabilitative program consisted of 16 to 20 supervised sessions and included exercise training, education, psychosocial and nutritional evaluation and treatment. The rehabilitation program was supervised by the NETT centers but subjects could complete the program in a certified satellite facility after completing the first 4 rehabilitation sessions at the NETT center. The post randomization phase of rehabilitation included an additional 8 to 9 weeks of supervised sessions. The long-term maintenance phase continued for the duration of the follow-up in the NETT and consisted of scheduled in-person visits that were supplemented with regular telephone contact to assess adherence to the rehabilitation treatment plan.

Of the 1,218 patients who were enrolled in NETT, 777 patients (64%) had prior pulmonary rehabilitation and 786 patients (65%) had utilized one of the satellite rehabilitation centers. After pulmonary rehabilitation, significant improvement in exercise capacity, dyspnea, and quality of life measures except for the SF-36 pain score. In patients who were rehabilitation naïve, significantly greater improvement in measures of maximum work, 6 min walk distance, St George Respiratory Questionnaire, UCSD shortness of breath score, and SF-36 scores of physical health summary, and components of physical conditioning, emotional well-being, and general health perception were observed. Patients who completed the rehabilitation program at satellite centers had comparable improvement in post-rehabilitation parameters. Approximately half of the patients demonstrated clinically meaningful improvement in
exercise capacity (cycle workload, 5 W), quality of life (St. George Respiratory Questionnaire total score, 4, and UCSD shortness of breath questionnaire score, 5 U.

Of note, pre-randomization pulmonary rehabilitation had a significant effect on NETT subgroup assignment based on maximum exercise capacity for all non-high risk patients. Overall, 20% of patients changed subgroup assignment after rehabilitation, 13.5% moved from the low exercise to high exercise subgroup, and 6.5% moved from the high exercise to the low exercise subgroup. The effect of rehabilitation on subgroup assignment was greater for patients without prior rehabilitation in whom 16.5% changed from the low to high exercise subgroup, and 6.2% changed from the high exercise to low exercise subgroup.

These NETT results confirmed prior reports on the benefit of pulmonary rehabilitation in COPD. More importantly, it provided strong evidence that the benefits derived from pulmonary rehabilitation can be achieved in community-based programs. Moreover, a NETT ancillary study involving 56 patients and 54 matched healthy controls showed that pulmonary rehabilitation also led to improvement in global cognitive function, in measures of visuomotor sequential skills and visual memory as well as significant reductions in measures of depression and anxiety. (41) Several factors such as lower educational background, presence of depressive or anxiety symptoms, and distance travelled to the rehabilitation facility were determinants of poor adherence to the rehabilitation program. (42)

**Nutrition**

Undernutrition is common in patients with underlying chronic pulmonary disease especially when they develop acute respiratory failure. In clinically stable patients, the incidence of undernutrition has been reported to be between 20 to 35%. (43) The causes of undernutrition in COPD patients are multifactorial in part due to poor oral
intake due to early satiety, increased work of breathing, and the presence of chronic systemic inflammation. Undernutrition is an independent risk factor for mortality in COPD. (44) Recognizing this fact, nutritional status via BMI has been incorporated in the calculation of the BODE score, a multidimensional predictor of death among patients with COPD. (45)

In the NETT substudy, the metabolic profile of 79 COPD patients was compared to 20 age-matched healthy subjects. (46) There were no significant differences in age, body mass index, and body composition between the 2 groups. COPD patients had higher resting oxygen consumption normalized to body weight (p<0.001) fat-free mass (FFM) (p<0.001) and higher circulating soluble tumor necrosis factor receptors (sTNF-Rs, p=0.02). There was no difference in serum leptin levels between the 2 groups. The BMI was the strongest predictor of RV0/kg in the COPD group, and patients with lower BMI showed the greatest difference in RV0/kg compared to controls. There were no correlations between RV0/kg and RV0/FFM with the different indices of airflow obstruction (FEV1) or hyperinflation (TLC). Overall these data suggest that even in stable emphysema patients, markers of energy consumption and chronic systemic inflammation are both increased. A decrease in caloric intake can easily lead to weight loss. Nutritional support should be an integral part of comprehensive COPD management. Treatment intervention designed to decrease chronic systemic inflammation in COPD patients is currently actively investigated.

**Oxygen use in non-hypoxemic emphysema patients**

NETT reported on the clinical characteristics and survival of non hypoxemic emphysema patients who used continuous oxygen therapy. (47) At enrollment into NETT, 260 patients (33.8% of NETT enrollees) reported continuous oxygen use. When compared to a similar cohort in NETT not using oxygen, those using
oxygen had worse dyspnea and quality of life, more frequent oxygen desaturation during exercise and a higher mortality rate. After adjusting for age, body mass index, FEV\textsubscript{1} % predicted, the presence of exercise desaturation accounted for the higher mortality within the non-hypoxemic patients that reported using continuous oxygen. These data suggested that the presence of oxygen desaturation may increase patient’s mortality, but the beneficial or potential detrimental effects of oxygen could not be assessed. The effects of continuous oxygen therapy in this patient population are currently unknown and are now the focus of the ongoing NHLBI Long Term Oxygen Treatment Trial (LOTT).(48) (49)

Summary

NETT was unique in its design because it comprehensively characterized both the medical and LVRS groups before and after pulmonary rehabilitation prior to randomization and then continued to perform detailed long-term follow-up in the medical group post randomization. As a result these data provide novel information regarding the clinical phenotypic characterization of emphysema and the impact of medical treatment on short as well as long-term outcomes. Although NETT was an expensive undertaking, it provides much more information than just the effect of LVRS by examining the overall pathogenesis of emphysema and its response to medical therapy. These features of NETT should be considered when designing future clinical trials that examine important clinical therapeutic questions to maximize the knowledge that can be gleaned about the pathogenesis of the underlying disease.

NETT provides substantial evidence that demographic, physiologic and radiographic features may predict mortality and that a modified BODE index provides additional prognostic information in severe emphysema. NETT demonstrated that small airways mucoid occlusion increases mortality in emphysema. NETT data also suggests
that genetic and radiological characterization in emphysema can define distinct clinical
phenotypes that have different physiological characteristics and may respond differently
to treatment. NETT also demonstrated the importance that hyperinflation has on
dyspnea, functional performance and survival and that mild-moderate pulmonary
hypertension is common but challenging to diagnose in severe emphysema. Finally
NETT data firmly established the pivotal role that pulmonary rehabilitation has in
improving outcomes even in severe emphysema and the potential negative
consequences that undernutrition and oxygen desaturation may present for this patient
population.
References


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