Concise Clinical Review

The National Emphysema Treatment Trial (NETT)

Part I: Lessons Learned about Emphysema

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The National Emphysema Treatment Trial (NETT) was a multicenter prospective randomized controlled trial that compared optimal medical treatment, including pulmonary rehabilitation, with optimal medical treatment plus lung volume reduction surgery (LVRS). It was the largest and most complete collection of patient demographic, clinical, physiological, 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 airway disease have on survival. NETT emphasized the importance of addressing nonpulmonary issues such as nutrition, cardiac disease, anxiety, and depression in emphysema. NETT demonstrated that physiological, genomic, and radiographic phenotype can predict patient survival as well as response to treatment. Because the major purpose of NETT was to compare bilateral LVRS with 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 to 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.

Keywords: emphysema; COPD; lung reduction surgery

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 airway disease. New attention was directed toward the anesthetic and operative care of patients with advanced emphysema. Optimization of medical therapy before LVRS enhanced our knowledge of oxygen and rehabilitation therapy.

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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, with optimal medical treatment plus LVRS (1). NETT randomized 1,218 patients and demonstrated an overall survival advantage for LVRS, with a 5-year risk ratio 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 on the basis of their performance on postrehabilitation exercise testing and the pattern of emphysema on chest computed tomography (CT) imaging. Patients with upper lobe-predominant emphysema 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 that it 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, physiological, and radiographic data ever compiled in severe emphysema (3). NETT provided much information regarding medical care in severe emphysema; specifically how physiological 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 nonpulmonary 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. Last, NETT highlighted the complexities of performing long-term trials in patients with severe emphysema 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 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. Because the major purpose of NETT was to compare bilateral LVRS with 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 (FEV_1 between 15 and 45% predicted, total lung capacity [TLC] > 105% predicted, and residual volume [RV] > 150% predicted) and to avoid poor surgical candidates (significant cardiac abnormalities, bronchiectasis and significant sputum production, nonpulmonary disorders that would adversely affect surgical outcomes, prior lung resectional surgery or median sternotomy, lack of bilateral emphysema, poor surgical candidate by the surgeon's 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 comorbidities. At baseline, NETT patients had bilateral emphysema on chest CT and demonstrated severe airflow obstruction (mean FEV_1, 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 COPD. These features of the NETT patient population offer distinct advantages (well-characterized predominant emphysematous phenotype) and disadvantages (lack of comorbidities 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 to correlate the pathological changes with various clinical COPD phenotypes. Whereas the different pathological characterizations of emphysema are well known, the contribution of small airway disease and attendant mucus hypersecretion to the morbidity and mortality is only beginning to be elucidated. Moreover, the role of innate and adaptive immunity in perpetuating chronic inflammation and disease progression of COPD has also come to light.

Even in patients with advanced emphysema, small airway disease remains an important component of the disease and dictates the clinical course of the patient. In a seminal study reported by Hogg and coworkers, surgically resected lung tissue from 159 patients with COPD undergoing LVRS or other types of lung biopsies showed that COPD progression was strongly associated with small airway wall thickening (<2 mm), 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). In addition, 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 pathological changes were believed to occur as a result of tissue remodeling after 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 Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 and GOLD stage 4 disease who underwent LVRS, the quartile of patients with the greatest mucoid luminal occlusion had higher mortality compared with 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 airway mucoid occlusion is unclear and may be due to increased susceptibility to infection due to retained secretions. Future drug development should target the pathological changes that occur in the small airways.

GENETICS OF COPD

To date, severe α_1-antitrypsin deficiency is the only proven genetic determinant of COPD. However, this genetic defect is present only in 1% of patients with COPD. 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], α_1-antichymotrypsin [SERPINA3], surfactant protein B [SFTPB], tumor necrosis factor-α [TNF], 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 (7). Polymorphisms in two 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 two genes were found to be predictive of a change in BODE (Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity) Index score 6 months after LVRS (8). These

two xenobiotic-metabolizing enzymes are thought to be important in decreasing lung oxidative stress due to reactive oxygen species and free radicals after cigarette smoke exposure. Specifically, glutathione *S*-transferases are expressed in the lung and serve as antioxidants and hydroperoxidases. Of the two common polymorphic variants, Ile105Val and Ala114Val, the Ile105Val variant was associated with upper lobe–predominant emphysema. The variant at position 105 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 the 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 (Tyr113His) 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 maximal work output, low exercise capacity, 6-minute walk distance, FEV_1, diffusion capacity, University of California at San Diego Shortness of Breath Questionnaire (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-β_1 (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 maximal work capacity, diffusion capacity, and UCSD SOBQ score. Variants in the two genes in the TGF-β pathway, TGFB1 and LTBP4, were associated with maximal 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. Serpin-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-year study period. Genetic variation in the SFTPB promoter region, rs3024791, was associated with COPD susceptibility and exacerbation frequency.

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 SNPs were genotyped in 389 NETT patients and 472 smoking control subjects 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 a biomarker.

Research suggests that COPD is a disease due in part to accelerated aging. One line of evidence supporting the senescence hypothesis of COPD pathogenesis is the accelerated attrition of telomere length found in patients with emphysema. A genome-wide association study was performed in 2,380 patients with COPD from 3 independent white cohorts (Bergen Norway, NETT, and ECLIPSE) (19). Genome-wide association studies showed an association of SNPs in the 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 biological 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 concerning 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. Information indicates that hyperinflation not only impairs respiratory mechanics but may have important negative consequences for cardiac performance as well.

A study conducted outside of NETT in 138 patients with mild to severe COPD (GOLD stages 1–4) illustrates the importance of hyperinflation in cardiac function and clinical performance (20). These authors demonstrated stronger inverse relationships with cardiac chamber size measured by echocardiography and static lung hyperinflation measurements (inspiratory capacity/total lung capacity [IC/TLC]), functional residual capacity, and residual volume) compared with measurements of airway obstruction or diffusion capacity. IC/TLC correlated the strongest with cardiac chamber size; patients with an IC/TLC not exceeding 0.25 had impaired left ventricular (LV) filling and an impaired Tei Index compared with patients with IC/TLC greater than 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 patients with emphysema (residual volume, 272% predicted), intrathoracic blood volume, LV end-diastolic volume index, right ventricular

end-diastolic index, cardiac index, and stroke volume index as assessed by magnetic resonance imaging (MRI) are reduced compared with control subjects (21). Even in severe COPD, a condition in which the right ventricle hypertrophies, MRI data during systole show that the interventricular septum flattens, which could explain why the LV ejection fraction remains relatively normal (22).

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 LVRS on pulmonary hemodynamics (25). A total of 110 of the 163 patients evaluated for the cardiovascular 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 6 months postrandomization. End-expiratory right heart catheterization pressures (pulmonary artery diastolic; pulmonary artery, mean; right atrial; right ventricular diastolic; right ventricular systolic; pulmonary artery systolic) in LVRS patients tended to be slightly lower at 6 months postrandomization than those of patients who were medically treated, compared with 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 with 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 with a medically treated group, signify a decrease in juxtacardiac intrathoracic pressures.

LVRS has been shown by other investigators to increase LV end-diastolic dimensions and filling and to significantly increase the cardiac index (26). In aggregate, these data suggest that some of the beneficial effects of LVRS in severely hyperinflated patients with emphysema, that is, 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 high-resolution chest CT (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) because 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, HRCT, and radionuclide angiography to comprehensively characterize pulmonary hemodynamics and ventricular function in 120 patients with severe emphysema, hyperinflation, and gas trapping (mean FEV_1, 27% predicted; RV, 225% predicted; diffusion capacity for carbon monoxide [D_{LCO}], 27% predicted) (27). Of the patients, 85.5% had a pulmonary artery systolic pressure greater than 20 mm Hg but not exceeding 35 mm Hg, for 5% it was greater than 35 mm Hg, and for 9.2% it was 20 mm Hg or less. In 61.4% of subjects, end-expiratory wedge pressure (PAWP) was greater than 12 mm Hg. The cardiac index was normal. Mean pulmonary artery pressure correlated inversely with Pa_{O_2} and severity of emphysema on HRCT and directly with PAWP. No correlation was found between the severity of emphysema and pulmonary artery 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 extraalveolar vessels. In 67 NETT subjects who underwent right heart catheterization (RHC), lung elastic recoil was measured at TLC (coefficient of retraction, CR) and at functional reserve capacity (CRfrc) (28). No correlation was found between CR and PVR, pulmonary artery systolic pressure, or mean pulmonary artery pressure. Similarly, no correlation was found between CRfrc 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 challenging (29). In 163 NETT patients who underwent 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 World Health Organization 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 less than 5 mm^2 ($CSA_{<5}$) and 5–10 mm^2 ($CSA_{5–10}$) and the percentage of total CSA for the lung area (%$CSA_{<5}$ and %$CSA_{5–10}$, respectively) was calculated. The %$CSA_{<5}$ and %$CSA_{5–10}$ were correlated with mean pulmonary artery pressure (Ppa) determined by RHC. The %$CSA_{<5}$ value significantly correlated with mean Ppa ($P < 0.0001$), but the correlation between %$CSA_{5–10}$ and mean Ppa did not reach significance ($P = 0.083$). The %$CSA_{<5}$ and D_{LCO} independently predicted mean Ppa ($r^2 = 0.541$). These data show that %$CSA_{<5}$ 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_1 and FVC between test sessions in patients with a range of COPD severity, whether the severity of COPD affects the intersession variability of FVC and FEV_1 measurements, and whether criteria for significant changes in FEV_1 or FVC should be defined using absolute or percent predicted values, or both (31). A total of 5,886 subjects in LHS and 1,215 in NETT who had performed postbronchodilator spirometry during the two baseline sessions were studied. Mean ± SD FEV_1 for the initial session was 2.64 ± 0.60 L (75.1 ± 8.8% predicted) for LHS and 0.68 ± 0.22 L (23.7 ± 6.5% predicted) for 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, the intersession percent difference in FEV_1 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_1 difference less than 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_1 rather than percent 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). Five hundred and forty-four NETT subjects randomized to the medical arm underwent multiple measurements of bronchoreversibility at a mean of 4 sessions over 1.91 years. Mean baseline FEV_1 was 24%; 22.2% of subjects demonstrated bronchoreversibility on one or more sessions according to American Thoracic Society/European Respiratory Society criteria. Few subjects (0.37%) had bronchoreversibility on all tests. A large change in FEV_1 (≥400 ml), occurring at least once, occurred infrequently (1.8%) and no patient met that criterion at all testing sessions. Those subjects who exhibited bronchoreversibility in FEV_1 were more likely to be male and to have better lung function and less emphysema. Large changes in FVC (≥400 ml) were found in 64% of the subjects, signifying that patients with COPD 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 D_{LCO} to predict the need for supplemental oxygen during rest and exercise was also assessed in 1,071 NETT subjects (33). Mean D_{LCO} was 8.0 ± 3.1 ml/minute/mm Hg (28 ± 10% predicted) and mean resting Pa_{O_2} was 64 ± 10 mm Hg. A positive correlation existed between D_{LCO} and both resting Pa_{O_2} and the requirement for oxygen to maintain arterial oxygen saturation (Sa_{O2}) at more than 90% for 3 minutes during a walk test at 1 mile per hour (mph). The odds of requiring oxygen during a 1-mph walk was nine times greater in subjects with a D_{LCO} not exceeding 20% predicted than in those with a D_{LCO} greater than 35% of predicted. Eighty-four percent of subjects with a D_{LCO} not greater than 20% predicted required supplemental oxygen with low levels of exercise compared with 38% of subjects with a D_{LCO} greater than 35%. On the basis of these data, D_{LCO} is a useful tool to indicate whether supplemental oxygen is required during exercise.

Quantitative (computer-based threshold scoring) and semiquantitative (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 percent predicted ($P = 0.004$) and RV/TLC ($P = 0.0001$) values. No method of HRCT analysis (different Hounsfield unit [HU] thresholds to detect emphysema, radiologist semiquantitative 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 with 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 –950 HU and both AWT and SRWA. AWT weakly correlated with postbronchodilator FEV_1 percent predicted ($P = 0.02$). Multivariate analyses showed correlations with AWT or SRWA and percent emphysema at –950 HU with postbronchodilator FEV_1 percent predicted. Male subjects had thicker airway walls compared with 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. In addition, these data show that patients with an airway wall phenotype are influenced by sex and that some HRCT findings may be associated with physiologically determined variables of lung function.

Exercise testing via either the 6-Minute Walk Test (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 subjects with emphysema enrolled into NETT. In this group with an average FEV_1% predicted of 26.9 ± 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 the 6-MWT (27.6 ± 16.8 vs. 67.9 ± 18.9% predicted). Both tests similarly correlated with quality of life measures, but maximal exercise capacity correlated better with lung function measurements than the 6-MWT. The 6-MWT had a greater association with SGRQ score than cardiopulmonary exercise. These data suggested that the 6-MWT may be a better test of functional capacity; however, maximal cardiopulmonary testing may be a better measure of impaired lung function.

DIFFERENCES IN THE PRESENTATIONS OF EMPHYSEMA IN AFRICAN-AMERICAN VERSUS WHITE PATIENTS

Of the 1,218 patients enrolled into NETT, 42 (3.4%) were African American and 1,156 (95%) were white. African Americans were younger (63 ± 7 vs. 67 ± 6 yr age; $P = 0.01$) and smoked less (26 ± 14 vs. 32 ± 14 cigarettes/d; $P = 0.01$) (37). Despite similar FEV_1, Pa_{O_2}, exercise watts, and quality of life measures, radiographic analysis revealed significantly less and different distribution of emphysema in African Americans compared with white subjects.

Thirty-four African-American patients were matched with white 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 with white patients, and white patients had a greater core–peel emphysema difference in the lung apices compared with 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 use, hemoglobin, smoking history, quantitative emphysema markers on CT, a modification of the BODE Index (body mass index, degree of airflow obstruction measured by FEV_1 percent predicted, dyspnea measured by the UCSD SOBQ, and exercise capacity as measured by 6-min walk distance). High mortality (292 deaths; median follow-up, 3.9 yr) was seen in the cohort; the overall death rate was 12.7 deaths per 100 person-years. In multivariate analyses, older age, oxygen use, lower TLC percent predicted, higher RV percent predicted, lower cardiopulmonary exercise test workload, greater proportion of emphysema in the lower versus upper lung zone, lower upper to lower lung perfusion, and modified BODE Index were predictive of mortality. FEV_1 was a significant predictor of mortality in univariate but not multivariate analysis. The predictive value of a longitudinal change in modified BODE (mBODE) Index was also assessed (39). The mBODE was calculated at baseline and then at 6, 12, and 24 months in follow-up. Patients were classified as having decreased, increased, stable, or missing BODE on the basis of 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 components.

MEDICAL THERAPY IN EMPHYSEMA

Rehabilitation

Pulmonary rehabilitation has been shown to alleviate symptoms and improve functional capacity and quality of life in patients with COPD. In NETT, all subjects completed 6 to 10 weeks of standardized pulmonary rehabilitation before 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 four rehabilitation sessions at the NETT center. The postrandomization phase of rehabilitation included an additional 8 to 9 weeks of supervised sessions. The long-term maintenance phase continued for the duration of follow-up in 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 used one of the satellite rehabilitation centers. After pulmonary rehabilitation, significant improvement occurred in exercise capacity, dyspnea, and quality of life measures except for the Short Form (SF)-36 Health Survey pain score. In patients who were rehabilitation naive, significantly greater improvement in measures of maximal work, 6-minute walk distance, SGRQ, UCSD SOBQ 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 (SGRQ total score, 4; and UCSD SOBQ score, 5 U).

Of note, prerandomization pulmonary rehabilitation had a significant effect on NETT subgroup assignment, based on maximal 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 control subjects 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 traveled 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 and 35% (43). The causes of undernutrition in patients with COPD are multifactorial, in part caused by 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 the body mass index (BMI) has been incorporated in calculation of the BODE score, a multidimensional predictor of death among patients with COPD (45).

In the NETT substudy, the metabolic profile of 79 patients with COPD was compared with 20 age-matched healthy subjects (46). There were no significant differences in age, body mass index, and body composition between the two groups. Patients with COPD 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 two groups. The BMI was the strongest predictor of resting oxygen consumption ($R\dot{V}O_2$/kg) in the COPD group, and patients with lower BMI showed the greatest difference in $R\dot{V}O_2$/kg compared with control subjects. There were no correlations between $R\dot{V}O_2$/kg and $R\dot{V}O_2$/FFM with the different indices of airflow obstruction (FEV_1) or hyperinflation (TLC). Overall, these data suggest that even in stable patients with emphysema, 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 patients with COPD is currently actively investigated.

Oxygen Use in Nonhypoxemic Patients with Emphysema

NETT reported on the clinical characteristics and survival of nonhypoxemic patients with emphysema who used continuous oxygen therapy (47). At enrollment into NETT, 260 patients (33.8% of NETT enrollees) reported continuous oxygen use. When compared with 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, and FEV_1 percent predicted, the presence of exercise desaturation accounted for the higher mortality within the nonhypoxemic patients who reported using continuous oxygen. These data suggested that the presence of oxygen desaturation may increase a 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 National Heart, Lung, and Blood Institute 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 before randomization and then continued to perform detailed long-term follow-up in the medical group postrandomization. As a result these data provide novel information regarding the clinical phenotypic characterization of emphysema and the impact of medical treatment on short-term 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, physiological, and radiographic features may predict mortality and that a modified BODE Index provides additional prognostic information in severe emphysema. NETT demonstrated that small airway mucoid occlusion increases mortality in emphysema. NETT data also suggest 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. Last, 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.

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