Predictors of Mortality in Patients with Emphysema and Severe Airflow Obstruction

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Online Data Supplement

Methods

Patient selection

The study group of 609 patients includes all patients randomized to medical therapy at 17 clinics as part of the NETT (E1) except for one patient who received LVRS outside of NETT for whom the surgery date was unknown. Thirty-five of the 609 patients received LVRS outside of NETT and an additional 18 of the 609 patients received a lung transplant during NETT; their data are censored as of the date of surgery or transplant. The design and methods of the trial have been previously detailed (E1, E2). Major enrollment criteria included bilateral emphysema evaluated by computed chest tomography and determined to be suitable for lung volume reduction, a $FEV_1 \leq 45\%$ predicted, a total lung capacity $\geq 100\%$ predicted, a residual volume $\geq$ 150% predicted, a PaO2 $\geq$ 45 mm Hg (30 mm Hg in Denver) and a $PaCO_2 \leq 60$ mm Hg (55 mm Hg in Denver). All patients had to be validated nonsmokers for at least four months prior to screening and throughout the screening period and be free of any important comorbidity. All patients provided written informed consent, and the study was approved by the institutional review board at each clinic. Baseline measurements were completed after pulmonary rehabilitation but before randomization.

Clinical assessment

Demographic data and medical history were collected by patient interview using standardized instruments. General health status was assessed using the Quality of Well-Being Scale (QWB) and the Medical Outcomes Study 36-Item Health Survey (SF-36). Disease specific quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ) (E3).

Dyspnea was quantified using the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) (E4). Oxygen utilization was obtained by patient report and characterized as positive if patient was using oxygen at rest or during sleep or exercise.

Physiologic testing

Patients underwent spirometry and plethysmographic lung volume measurement after the administration of albuterol; diffusing capacity, respiratory pressures, and arterial blood gases were also measured. The protocol used for six-minute walk testing (6MWT) has been described in detail and provided the maximal distance walked (E5). Maximal exercise capacity was measured on a cycle ergometer with an increment of 5 or 10 W per minute after three minutes of unloaded pedaling with the patient breathing 30 percent oxygen.

Diagnostic imaging studies

The severity and distribution of emphysema were determined from chest CT scans obtained during full inspiration. Spiral CT scans were acquired with a collimation ranging from 3-10 mm, with the majority of participating centers using a slice collimation of 5 mm or less. Data were evaluated using the standard reconstruction kernel, but were not complete for all patients. Image analysis was done using a custom built software program, the Pulmonary Analysis Software Suite (PASS), after segmenting and dividing the lung according to previously described protocols defining upper, middle, and lower, core and peel regions of the lung (E6). After segmentation, the image voxels within each field were labeled as being emphysema-like based upon their reconstructed image gray scale representing x-ray attenuation coefficient or Hounsfield Unit (HU). The distribution of the number of voxels at each HU within lung fields,

the density histogram, was plotted with HU values less than -950 corresponding to severe emphysema. HU values of -910 and -850 have been roughly corresponded to moderate or mild emphysema regions, respectively. Percent emphysema for the whole lung was calculated, as was the difference between the upper and lower lung regions in percent emphysema. The alpha value (the negative of the slope from the log-log relationship of hole size versus number of holes, with hole membership defined as voxels at -950) also was calculated for the whole lung as was the difference between the upper and lower lung regions in alpha. Lungs with greater proportions of small lesions have a steep slope and a large alpha, while lungs with larger lesions have a smaller alpha (E7).

BODE

The BODE (Body mass index, airflow Obstruction, Dyspnea, Exercise capacity) index is an 11 point composite score (0 through 10) in which higher scores indicate poorer emphysema outcomes. Details of the BODE are reported elsewhere (E8). We modified the original BODE by using the UCSD SOBQ as the dyspnea measure since the Medical Research Council dyspnea scale was not used in NETT. The contribution of dyspnea to the BODE was based on quartile distribution of the UCSD SOBQ in our 609 person sample. A UCSD SOBQ score of less than or equal to 52 contributed 0 points toward the BODE, while a score from 53 through 63 contributed 1 point, a score of 64 through 77 contributed 2 points, and a score of 78 or higher contributed 3 points.

Statistical analysis

Means and standard deviations are reported for baseline characteristics of the sample. The overall mortality rate from all causes was calculated as number of deaths per 100 person years of follow-up. Univariate comparisons of mortality rates by risk factors were performed using Cox proportional hazards regression analysis. For continuous risk factor variables with no obvious clinical cut off point for defining healthy versus unhealthy groups, a least healthy group was identified as the poorest performing quintile on that measure. The reference group for these variables was then defined as the remaining 80% of the distribution. This method was used for hemoglobin, QWB, SGRQ, UCSD SOBQ, FEV_1, total lung capacity, residual volume, IC/TLC, DL_{CO}, PImax, PEmax, PaO_2, $PaCO_2$, six minute walk, percent emphysema, difference in percent emphysema between upper lobe and lower lobe, alpha, difference in alpha between the upper lobe and lower lobe, pack years of cigarette smoking, duration since cessation of cigarette smoking, and BODE. For maximal exercise capacity the thresholds predictive of differential mortality after LVRS were utilized (E1). Both a high and low BMI could be indicative of poor health, so both of these quintiles were used, while the middle 60% of the BMI distribution was used as the reference. Kaplan-Meier mortality curves were created to display differences in mortality by selected risk factors. Differences between mortality curves were assessed using the log rank test.

Two multivariate Cox proportional hazards models were used to identify the variables that predicted mortality after adjusting for all other variables. In the first model, all variables tested with univariate analysis (see Table 2) except the modified BODE index were included in the model. The second model was the same as the first except that the modified BODE index replaced BMI, FEV_1, dyspnea, and six minute walk distance.

Results

Table E1 enumerates the detailed inclusion and exclusion criteria for the NETT (E2). It is noteable that numerous cardiovascular comorbidities were excluded through specific cardiovascular testing. Similar exclusions were noted for comorbid pulmonary conditions.

Table E2 enumerates the cause of death in the subset of the cohort (43%) for whom death certificate date were available. It is evident that the majority of deaths were attributed to respiratory decompensation. This was followed by cardiovascular or cerebrovascular disease.

Figure E1 illustrates the mortality curves for patients using oxygen or not (Panel A), by hemoglobin level (Panel B), by RV (Panel C), by emphysema distribution (Panel D), and by maximal workload achieved during oxygen supplemented maximal cycle ergometry (Panel E).

References:

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Figure Legend

Figure E1. Kaplan-Meier estimates of the probability of death as a function of number of months after randomization for medically treated patients segregated by oxygen utilization at rest, on exercise, or while sleeping (Panel A); hemoglobin (Panel B); RV (Panel C); the difference in emphysema percent between the upper and lower lung zones (Panel D); and cardiopulmonary exercise capacity (Panel E). Low exercise is defined as a maximal workload at or below the sex-specific 40th percentile (25 W for females and 40 W for males; high exercise is defined as a workload above this threshold). The P-values were derived by the log rank test for the comparison between subgroups over a median follow-up period of 3.9 years.

Table E1. Detailed inclusion and exclusion criteria for the NETT.

Inclusion criteria	Exclusion criteria
History and Physical examination	Previous surgery
Consistent with emphysema	Lung transplant
BMI < 31.1 kg/m2 (♂) or < 32.3 kg/m2 (♀)	Lung volume reduction surgery
No steroid use of stable prednisone dose (< 20 mg/day)	Median sternotomy or lobectomy
Radiographic	Cardiovascular
Bilateral emphysema	Dysrhythmia precluding exercise
Physiologic	Resting bradycardia (< 50 beats/min)
FEV_1 < 45% pred (> 15% pred if age > 70 years)	Frequent multifocal PVCs, complex ventricular arrhythmia or sustained SVT
TLC > 100% pred	Exercise related syncope
RV > 150% pred	Myocardial infarction within 6 months and LVEF < 45%
$PaCO_2$ < 60 mm Hg (< 55 mm Hg in Denver)	CHF within 6 months and LVEF < 45%
	Uncontrolled hypertension (SBP > 200 mm Hg

PaO_2 > 45 mm Hg (> 30 mm Hg in Denver) Post-rehabilitation 6MWT distance > 140 meters and able to complete 3 minutes of unloaded cycle ergometry Cardiac assessment Approval by cardiologist if LVEF < 45% or dobutamine-radionuclide scan suggests coronary artery disease or ventricular dysfunction Surgical assessment Approval by thoracic surgeon, pulmonologist and anesthesiologist Smoking Plasma cotinine < 13.7 ng/mL or arterial carboxyhemoglobin < 2.5% if using nicotine replacement	or DBP > 110 mm Hg) Pulmonary Recurrent infections with clinically significant sputum production Pleural or interstitial disease precluding surgery Clinically significant bronchiectasis Pulmonary nodule requiring surgery Giant bulla Pulmonary hypertension (peak systolic PPA > 45 mm Hg (> 50 mm Hg in Denver) mean PPA > 35 mm Hg (> 38 mm Hg in Denver) Requiring > 6 L O_2 to keep saturation > 90% with exercise Radiographic Diffuse emphysema on CT unsuitable for LVRS General criteria

Rehabilitation Completion of rehabilitation program	Unplanned weight loss > 10% usual weight in previous 90 days Systemic disease or neoplasia compromising 5 year survival 6MWT distance < 140 meters after rehabilitation Inability to complete follow-up visits Unwillingness/inability to complete screening

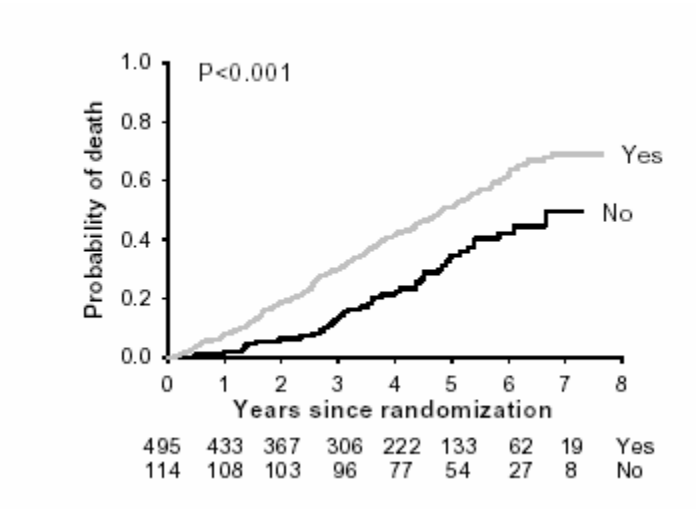
BMI – body mass index; FEV_1 – forced expiratory volume in 1 second; TLC – total lung capacity; RV – residual volume; $PaCO_2$ - partial pressure of carbon dioxide in mm Hg; PaO_2 - partial pressure of oxygen in mm Hg; 6MWT – six minute walk test; LVEF – left ventricular ejection fraction; PVCs – premature ventricular contractions; CHF – congestive heart failure; SBP – systolic blood pressure; DBP – diastolic blood pressure; PPA – pulmonary artery pressure; CT – computed tomograph; LVRS – lung volume reduction surgery

Table E2. Cause of death in sample of patients with severe COPD and emphysema who died during period of observation (n=127)

Respiratory causes	78%
Cardiovascular disease	10%
Cerebrovascular disease	2%
Miscellaneous	10%

Figure E1

Panel A



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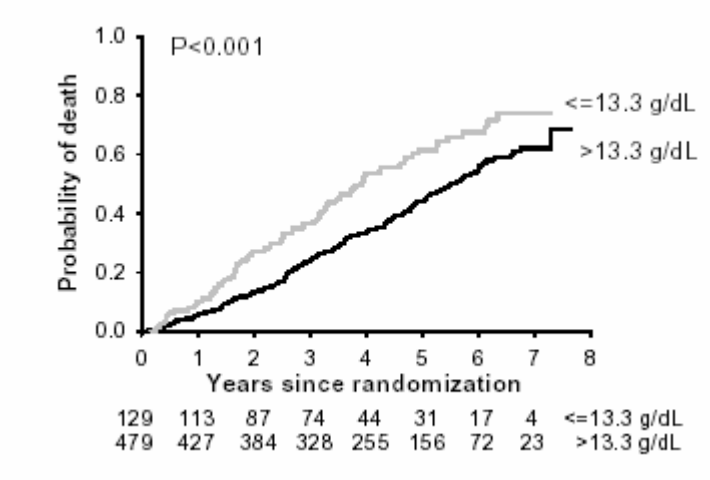

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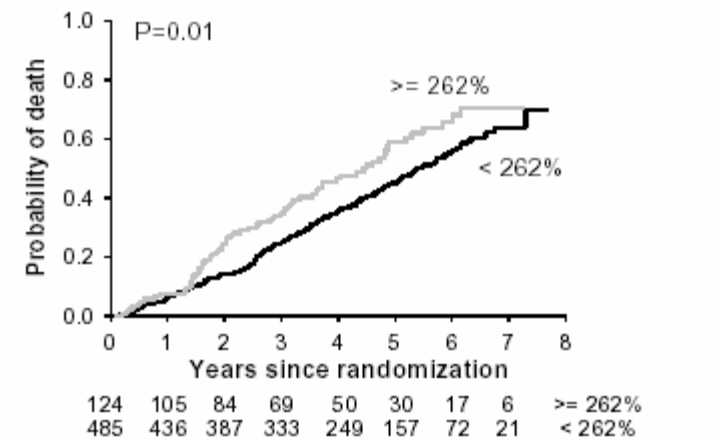

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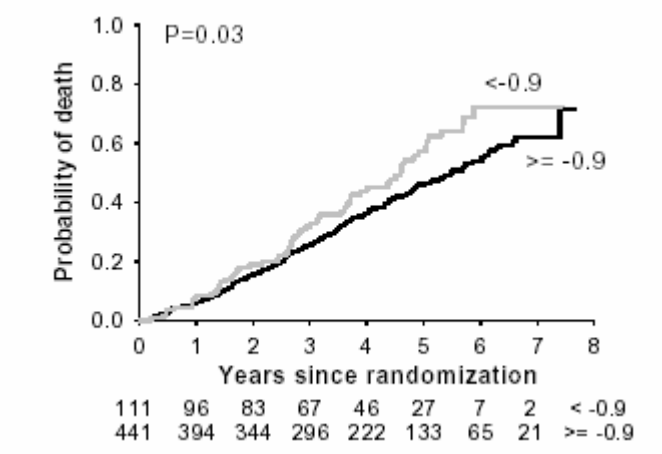

Panel E