Predictors of operative mortality and cardiopulmonary morbidity in the National Emphysema Treatment Trial

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The National Emphysema Treatment Trial is supported by the National Heart, Lung, and Blood Institute (contracts N01HR76101, N01HR76102, N01HR76103, N01HR76104, N01HR76105, N01HR76106, N01HR76107, N01HR76108, N01HR76109, N01HR76110, N01HR76111, N01HR76112, N01HR76113, N01HR76114, N01HR76115, N01HR76116, N01HR76118, and N01HR76119); the Centers for Medicare and Medicaid Services; and the Agency for Healthcare Research and Quality.

Read at the Eighty-fifth Annual Meeting of The American Association for Thoracic Surgery, San Francisco, Calif, April 10-13, 2005.

Received for publication April 12, 2005; revisions received Sept 4, 2005; accepted for publication Sept 9, 2005.

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J Thorac Cardiovasc Surg 2006;131:43-53
0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2005.09.006

Objective: We sought to identify predictors of operative mortality, pulmonary morbidity, and cardiovascular morbidity after lung volume reduction surgery.

Methods: Univariate and multivariate logistic regression analyses were performed. Candidate predictors included demographic characteristics, physical condition characteristics, pulmonary function measures, measures of the distribution of emphysema as determined by radiologists and by means of computerized analysis of chest computed tomographic scans, and measures of exercise capacity, dyspnea, and quality of life. End points analyzed were operative mortality (death within 90 days of the operation), major pulmonary morbidities (tracheostomy, failure to wean, reintubation, pneumonia, and ventilator for ≥ 3 days), and cardiovascular morbidities (infarction, pulmonary embolus, or arrhythmia requiring treatment).

Results: Five hundred eleven patients in the non-high-risk group of the National Emphysema Treatment Trial underwent lung volume reduction. The incidence of operative mortality was 5.5%, major pulmonary morbidity occurred in 29.8% of patients, and cardiovascular morbidity occurred in 20.0% of patients. Predictors for these end points are as follows:

		Relative odds	P value
Operative mortality	Non-upper-lobe predominance (radiologist)	2.99	.009
Pulmonary morbidity	Age in years	1.05	.02
	FEV ₁ % predicted	0.97	.05
	DLCO % predicted	0.97	.01
Cardiovascular morbidity	Age in years	1.07	.004
	Oral steroid use	1.72	.04
	Non-upper-lobe predominance (QIA α measure)	2.67	<.001

FEV₁, Forced expiratory volume in 1 second; DLCO, diffusion capacity; QIA, quantitative image analysis.

Conclusions: Although lung volume reduction can be performed in selected patients with acceptable mortality, the incidence of major cardiopulmonary morbidity remains high. The lone predictor for operative mortality of lung volume reduction was the presence of non-upper-lobe-predominant emphysema, as assessed by the radiologist. Pulmonary morbidity can be expected in elderly patients who have a low diffusing capacity for carbon monoxide and forced expiratory volume in 1 second. When assessing morbidity, the computer-assisted chest computed tomographic analysis proved useful only in predicting cardiovascular complications.

Abbreviations and Acronyms

CT	= computed tomography
DLCO	= diffusing capacity for carbon monoxide
FEV ₁	= forced expiratory volume in 1 second
HU	= Hounsfield unit
LVRs	= lung volume reduction surgery
NETT	= National Emphysema Treatment Trial
QIA	= quantitative image analysis
RO	= relative odds
UCSD	= University of California San Diego

Lung volume reduction surgery (LVRs) has been demonstrated to be beneficial in selected patients with severe emphysema.¹ However, because of the fragile nature of patients with severe emphysema, surgical morbidity and mortality remain higher than for most other elective thoracic surgical procedures. Reported operative mortalities have ranged from 4% to as high as 14%, whereas the incidence of pulmonary complications, such as pneumonia, reintubation, and ventilator dependence, are also reported to be higher than that observed for most other commonly performed thoracic procedures.^{2,3}

Previous studies have proposed several demographic, pulmonary, and cardiovascular physiologic and/or radiographic features predictive of excessive morbidity in patients undergoing LVRs.⁴⁻⁹ It was hoped that identification of factors that portend high morbidity might lead to the exclusion of patients from consideration for LVRs, or alternatively, practitioners might be alerted to specific risks and take steps to avoid predicted complications. However, these studies yield conflicting results about which factors are predictive of morbidity, and uncertainty still remains regarding the validity of their predictions. Unfortunately, virtually all of these studies have serious limitations, including small patient numbers, selection bias, institutional bias, and incomplete or suboptimal data collection.

The National Emphysema Treatment Trial (NETT), a large, prospective, randomized, multicenter, long-term trial comparing optimum medical therapy with optimum therapy plus LVRs was conceived and designed to provide more definitive answers regarding not only the value of LVRs but also optimal patient selection. A prior NETT publication sought to establish the efficacy of LVRs and to identify factors predictive of midterm to long-term survival, as well as functional outcome.¹ The purpose of this article is to extend the findings of these prior reports and specifically identify predictors of short-term mortality and morbidity after LVRs in the NETT population, including operative mortality and major cardiopulmonary complications.

Materials and Methods**Study Design**

The designs and methods of the NETT have been fully described in a prior publication but will be reviewed briefly.¹⁰ Patients with severe emphysema underwent thorough medical evaluation to confirm the presence of severe emphysema and overall fitness for potential LVRs candidacy. These evaluations were undertaken at 17 NETT clinical centers throughout the country that had been selected by the National Heart, Lung, and Blood Institute. Baseline measurements included collection of demographic data, postbronchodilator spirometry, lung volume plethysmographic assessment, chest computed tomography (CT), split ventilation-perfusion nuclear imaging, standard anteroposterior and lateral chest radiography, cardiovascular assessment (routine dobutamine stress tests and echocardiography), and exercise capacity, as measured both by means of a standardized 6-minute walk and formal maximum symptom-limited cycle ergometry with graded exercise loading and oxygen supplementation. In addition, patients underwent assessment of their subjective well-being by using questionnaires regarding dyspnea (University of California San Diego [UCSD] Shortness of Breath Questionnaire and St George's Respiratory Questionnaire) and quality of life (Quality of Well Being scale and SF-36 short form questionnaire).

Diagnostic Imaging Studies

The distribution of emphysema was determined by using several methodologies. Initially, it was classified as heterogeneous or homogeneous on the basis of the high-resolution CT scan by using a visual scoring system in which the radiologist had been trained and certified. The radiologist also classified the craniocaudal distribution of emphysema as affecting predominantly the upper lobes (upper-lobe-predominant disease), or it was reported as mainly involving the lower lobes, the superior segment of the lower lobes, or the lungs. These latter 3 classifications were grouped together under the heading of non-upper-lobe emphysema. A complete description of this evaluation technique has been previously published.¹⁰

Additionally, a measure of emphysema distribution was obtained by using quantitative image analysis (QIA) of digitized spiral CT scans. Patients screened between October 1997 and July 2002 were imaged by using various single-slice spiral CT scanners. Patients were instructed to hold their breath at full inspiration (at or near-total lung capacity). A volumetric image data set was reconstructed, with slice thickness ranging between 5 and 10 mm (the majority of studies had a slice thickness of 7-8 mm) and slice spacing set to half of the slice thickness. Image data were reconstructed by using the appropriate scanner equivalent of a normal reconstruction kernel. A software package developed by the University of Iowa (Pulmonary Analysis Software Suite) was used to identify the lungs, divide the lungs into the left and right lungs, and then divide each lung into the upper, middle, and lower thirds on the basis of the apex-to-base distance. The software also provided a set of metrics that characterized the distribution of Hounsfield unit (HU) levels for the voxels comprising each lung region, including the number of voxels with density of less than -950 HU, a level generally accepted as corresponding to severe emphysema. This count was used with the total number of voxels comprising a region to obtain the proportion of emphysema for the region expressed as

a percentage. The difference between the upper lung and the lower lung in the percentage of emphysema at the -950 HU threshold was used to categorize the disease. Those whose percentage of emphysema was greater in the upper than in the lower cuts were classified as upper lobe predominant emphysema and all others were non-upper-lobe-predominant emphysema.

A second distribution metric was calculated by the software on the basis of the number and size of holes in the lung, as demonstrated in the digitized CT scans. This was designated as the α measure and is based on the work of Mishima and colleagues.¹¹ They hypothesized that if the initial onset of emphysema was a random process whereby small holes appeared randomly throughout a lung region, the log-log plot of the percentage of holes in that region versus hole size would prove to be linear. Then if the progression of the disease is based on the small holes destabilizing a region whereby small holes join to form large holes, the slope of the log-log plot of percentage holes (y-axis) versus hole size (x-axis) will decrease as larger holes increasingly dominate over small holes and provides a measure of emphysema severity. In our analysis a hole in the lung is defined as voxels of less than -950 HU. The slope from the log-log relationship of hole size plotted against the number of "holes" determines the alpha value. The difference between the upper lung and the lower lung in alpha at the -950 HU threshold determines site of predominance. When alpha is less than 0 it is upper lobe predominant versus non-upper lobe predominant when it is 0 or higher.

Finally, a measurement of the distribution was obtained from nuclear imaging scans. The regional distribution was quantified, and the ratio of upper-lobe perfusion to lower-lobe perfusion was obtained.

All patients eligible for randomization were required to complete a 6- to 10-week course of formal outpatient pulmonary rehabilitation supervised by the clinical centers. After pulmonary rehabilitation, repeat physiologic testing and patient assessment was conducted before randomization to continued medical therapy with maintenance rehabilitation or LVRS, followed by continued medical treatment and maintenance rehabilitation.

Patients randomized to LVRS underwent a bilateral stapled wedge resection with the goal of resecting 20% to 35% of each lung. The resections were targeted by using the imaging modalities of both CT scans and nuclear images of the lung. Eight centers performed the operation by means of median sternotomy, 3 centers by means of video-assisted thoracic surgery, and 6 centers by means of median sternotomy or video-assisted thoracic surgery selected randomly.

Definition of Outcome

Because of the prolonged duration of hospitalization in many patients undergoing LVRS and the frequently observed discharge from the acute-care hospital to a chronic-care facility, neither 30-day mortality nor hospital discharge mortality were believed to be representative of the true risk of mortality. Thus the 90-day mortality from all causes (measured from the day of LVRS) was chosen as the best surrogate for overall operative mortality. Vital status was determined by using routine reports from the clinical centers, as well as from a review of the 2004 Death

Master File from the Social Security Administration. Major pulmonary morbidity was defined as the need within 30 days of the operation for tracheostomy, reintubation, or ventilator support for 3 or more days; pneumonia within 30 days of the operation; or ventilator dependency for more than 30 days after LVRS. Major cardiovascular morbidity was defined as intraoperative arrhythmia requiring pharmaceutical or electrophysiologic treatment or myocardial infarction, pulmonary embolus, or arrhythmia requiring treatment within 30 days after LVRS.

Statistical Analysis

Predictors for each of the 3 outcomes were investigated by using univariate and multivariate logistic regression. The relative odds (RO) obtained from the logistic regression expresses either the risk of the outcome for patients with the specified factor compared with the risk for patients without the factor (binary factor) or the incremental risk per each unit change in the factor (continuous factor). Candidate predictors were 23 clinical variables describing demographics (age, sex, and race-ethnicity), physical condition (body mass index; oxygen use at rest, with exercise, and during sleep; prescription of oral steroids at the postrehabilitation, prerandomization visit; and serum creatinine level), pulmonary function measures (forced expiratory volume in 1 second [FEV₁] percent predicted, residual volume percent predicted, ratio of residual volume to total lung capacity ratio, the diffusing capacity for carbon monoxide [DLCO], PacO₂, and the ratio of expired volume to the volume of CO₂), exercise capacity (6-minute walk distance and maximum exercise capacity by means of bicycle ergometry [categorized as low or high]), dyspnea (UCSD Shortness of Breath Questionnaire and St George's Respiratory Questionnaire scores) and quality of life (Quality of Well-Being Scale), and imaging measures (perfusion ratio and assessments by the study radiologists of heterogeneity, upper-lobe distribution, and hyperinflation), as well as by means of computerized analysis of CT scans performed at the imaging center.

The NETT was approved by the institutional review boards at each of the 17 clinical centers, and informed consent was obtained from all participants.

Results

Between January 1998 and July 2002, 3777 patients were considered for entry into the NETT, and 1218 progressed through screening evaluation, formal pulmonary rehabilitation, repeat physiologic and radiologic testing, and randomization to treatment. There were 610 patients assigned to medical therapy and 608 to surgical therapy. Of the 608 patients randomized to surgical therapy, 580 (95.4%) eventually underwent LVRS either by using a median sternotomy approach (406 patients) or by means of video-assisted surgery (174 patients). Twenty-one patients randomized to LVRS declined surgical intervention, and 7 patients were deemed unsuitable for surgical intervention by the surgeon or anesthesiologist at some point after randomization. Sixty-nine of the 580 patients who underwent LVRS were in the subgroup identified by

TABLE 1. Characteristics of patients at baseline* (n = 511)

Characteristic	Mean $\pm$ SD or n (%)
Age at surgical intervention, y	67.0 $\pm$ 6.2
Sex	
Female	219 (42.9)
Male	292 (57.1)
Emphysema distribution on CT	
Predominant upper lobe	332 (65.0)
Predominant non-upper lobe	179 (35.0)
Heterogeneous (%)†	295 (57.7)
Homogeneous (%)‡	216 (42.3)
FEV ₁ after BD use, % predicted	28.1 $\pm$ 6.8
TLC after BD use, % predicted	127.3 $\pm$ 15.1
RV after BD use, % predicted	214.4 $\pm$ 45.6
DLCO, % predicted	29.2 $\pm$ 9.3
Pao ₂ , mm Hg	65.2 $\pm$ 10.6
Paco ₂ , mm Hg	42.8 $\pm$ 5.6
Saint George's Respiratory Questionnaire total score‡	52.2 $\pm$ 12.8
UCSD Shortness of Breath Questionnaire total score§	61.0 $\pm$ 18.4
Quality of Well-Being Scale average daily score	0.58 $\pm$ 0.12

SD, Standard deviation; CT, computed tomography; FEV₁, forced expiratory volume in 1 second; BD, bronchodilator; TLC, total lung capacity; RV, residual volume; DLCO, diffusion capacity; Pao₂, partial pressure of arterial oxygen; Paco₂, partial pressure of arterial carbon dioxide; UCSD, University of California at San Diego. *Baseline measurements are obtained after rehabilitation and before randomization, except for the diffusion capacity of carbon dioxide, which is obtained before rehabilitation and before randomization. †Emphysema distribution is based on scores assigned subjectively to each of 3 lung zones in each lung. ‡The Saint George's Respiratory Questionnaire is a 51-item questionnaire completed by the patient with regard to respiratory symptoms, where the total score ranges from 0 to 100, and lower scores indicate fewer respiratory symptoms. §The UCSD Shortness of Breath Questionnaire is a 24-item questionnaire completed by the patient with regard to shortness of breath, where the total score ranges from 0 to 120, and lower scores indicate less shortness of breath. ||The Quality of Well-Being Scale is a 77-item questionnaire completed by the patient with regard to quality of life. The average daily total score ranges from 0 to 1, where higher scores indicate better quality of life.

the Data and Safety Monitoring Board as being at high risk of mortality after LVRS with little chance of functional benefit; enrollment of this patient subgroup in the NETT was terminated in May 2001. This high-risk patient subgroup has already been described in a previous publication, and they are excluded from this analysis.¹² The remaining 511 non-high-risk patients who underwent LVRS are the subject of this report.

Patient Characteristics

Table 1 depicts baseline clinical characteristics. The majority of patients were men, and the average age at the time of the operation was 67 years. The distribution of

TABLE 2. Complications and mortality (n = 511)

Intraoperative	
None	91.0%
Hypotension	0.4%
Arrhythmia	1.2%
Arrhythmia requiring treatment	1.0%
Hypoxemia	2.2%
Cardiac arrest	0.4%
Uncontrolled air leak	1.0%
Postoperative (within 30 d of operation)	
None	41.3%
Arrhythmia	23.5%
Arrhythmia requiring treatment	18.6%
Myocardial infarction	1.0%
Failure of early extubation	3.9%
Tracheostomy	8.2%
Failure to wean	5.1%
Reoperation for air leak	3.3%
Pulmonary embolus	0.8%
Readmission to ICU	11.7%
Mediastinitis	0.6%
Sternal debridement	0.6%
Pneumonia	18.2%
Urinary retention	3.5%
Epidural catheter complications	0.8%
Sepsis	2.5%
Readmission within 72 h after discharge	2.5%
Ventilated more than 2 d	13.6%
At least 1 reintubation	21.8%
Major pulmonary morbidity*	29.8%
Major cardiac morbidity†	20.0%
Dead within 90 d of operation	5.5%

ICU, Intensive care unit. *Major pulmonary morbidity is defined as incidence of 1 or more of the following in the 30 days after lung volume reduction surgery: tracheostomy, failure to wean, pneumonia, at least 1 postoperative intubation, or ventilator use for 3 or more days. †Major cardiac morbidity is defined as incidence of 1 or more of the following: intraoperative or postoperative (in the 30 days after lung volume reduction surgery) arrhythmia requiring treatment or myocardial infarction or pulmonary embolus in the 30 days after lung volume reduction surgery.

emphysema was upper-lobe predominant in approximately two thirds of patients and judged as heterogeneous in 58% of patients. Mean FEV₁ percent predicted was 28%, and mean residual volume was 215% of predicted value. At baseline rest, patients were neither hypoxemic nor severely hypercapneic but did demonstrate a severe degree of dyspnea, as shown by the St George's Respiratory Questionnaire and the UCSD Shortness of Breath Questionnaire scores.

Operative Morbidity

Table 2 outlines the intraoperative and postoperative morbidity. More than 90% of patients had no intraoperative complications; however, more than 50% of patients had

TABLE 3. Factors related to death 90 or fewer days after lung volume reduction surgery

Risk factor	% with risk factor or mean	Logistic regression relative odds of death within 90 days*			
		Unadjusted		Final model after backward selection	
		RO	P value†	RO	P value‡
No. of patients	511			425§	
Demographics					
Age at operation, y (per y of age)	67.0	1.07	.06	—	—
Minority (yes vs no)	4.7%	0.74	.77	—	—
Male sex (yes vs no)	57.1%	1.62	.24	—	—
Treatment and physical condition					
Body mass index, kg/m ² (per unit change)	24.7	0.94	.25	—	—
Using oxygen constantly (yes vs no)	49.1%	1.41	.38	—	—
Prescribed oral steroids at baseline (yes vs no)	31.9%	0.85	.70	—	—
Abnormal creatinine level at baseline (yes vs no)	10.6%	1.02	.98	—	—
Radiologic measures					
Nonheterogeneous (radiologist evaluation; yes vs no)	42.3%	1.20	.65	—	—
Non-upper lobe (radiologist evaluation; yes vs no)	35.0%	3.06	.005	2.99	.009
Hyperinflation on chest radiograph (any vs none)	96.6%	0.94	.95	—	—
Perfusion ratio (per unit change)	0.30	2.31	.23	—	—
Non-upper lobe, QIA α measure (n = 458; yes vs no)	47.4%	2.63	.03	—	—
Non-upper lobe, QIA % emphysema measure (n = 458; yes vs no)	22.1%	1.32	.54	—	—
Pulmonary function measures					
FEV ₁ percent predicted (per unit change)	28.1	1.00	.90	—	—
RV percent predicted (per unit change)	214.4	1.00	.74	—	—
RV/TLC (per unit change)	0.64	0.04	.19	—	—
DLco percent predicted (per unit change)	29.2	0.97	.21	—	—
Paco ₂ (per mm Hg)	42.8	0.97	.46	—	—
Exercise measures					
Low exercise (yes vs no)	40.9%	0.93	.86	—	—
Ve/Vco ₂ at max work (per unit change)	0.37	6.79	.33	—	—
Six-min walk distance (per ft)	1246	1.00	.53	—	—
QOL measures					
UCSD SOB total score (per unit change)	61.0	1.00	.79	—	—
QWB average daily score (per unit change)	0.58	2.71	.55	—	—

RO, Relative odds; QIA, quantitative image analysis; FEV₁, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; DLco, diffusion capacity; Paco₂, partial pressure of arterial carbon dioxide; Ve/Vco₂, ratio of expired volume to the volume of carbon dioxide; QOL, quality of life; UCSD SOB, University of California at San Diego Shortness of Breath Questionnaire; QWB, Quality of Well-Being Scale. *Relative odds is defined as the ratio of the odds for those with versus the odds for those without the factor (yes vs no) or incremental odds for each specified change in the factor (continuous). †Wald χ^2 test for logistic regression with response variable of death within 90 days of lung volume reduction surgery and regressor of risk factor. ‡P value for stepwise logistic regression (forward selection) with response variable of death within 90 days of lung volume reduction surgery (yes vs no) and candidate regressors of all factors listed in the table. §n = 511 because of missing data and ability to estimate.

significant postoperative complications. As noted in Table 2, the most frequent complication was the need for reintubation (22%), followed by postoperative arrhythmia requiring therapy (19%), pneumonia (18%), mechanical ventilation for 3 or more days (14%), and the need for a tracheostomy (8%). Of note, almost 12% of patients required readmission to the intensive care unit at some time during the initial hospitalization. The incidence of major pulmonary morbidity was almost 30%, and the incidence of major cardiac morbidity was 20%.

Operative (90-day) Mortality

The 90-day mortality after LVRS was 5.5% (28 patients, Table 2) among the 511 non-high-risk patients. The stated cause of death was respiratory (pneumonia, acute respiratory distress syndrome, aspiration, and progressive respiratory failure) in 12 (43%) patients, cardiovascular (infarction, arrhythmia, and pulmonary embolism) in 5 (18%) patients, multiorgan failure in 2 (7%) patients, cerebrovascular accident and sepsis in 1 (4%) patient each, and unclassified in 7 (25%) patients. As noted in Table 3, univar-

TABLE 4. Factors related to major pulmonary morbidity in the 30 days after lung volume reduction surgery*

Risk factor	% with risk factor or mean	Logistic regression relative odds of pulmonary morbidity in 30 d†			
		Unadjusted		Final model after backward selection	
		RO	P value‡	RO	P value§
No. of patients	511			440	
Demographics					
Age at operation, y (per y of age)	67.0	1.03	.08	1.05	.02
Minority (yes vs no)	4.7%	0.78	.60	—	—
Male sex (yes vs no)	57.1%	1.22	.32	—	—
Treatment and physical condition					
Body mass index, kg/m ² (per unit change)	24.7	0.97	.32	—	—
Using oxygen constantly (yes vs no)	49.1	1.48	.05	—	—
Prescribed oral steroids at baseline (yes vs no)	31.9%	0.94	.76	—	—
Abnormal creatinine level at baseline (yes vs no)	10.6%	1.21	.54	—	—
Radiologic measures					
Nonheterogeneous (radiologist evaluation; yes vs no)	42.3%	0.95	.81	—	—
Non-upper lobe (radiologist evaluation; yes vs no)	35.0%	1.12	.58	—	—
Hyperinflation on chest radiograph (any vs none)	96.6%	1.02	.97	—	—
Perfusion ratio (per unit change)	0.30	1.05	.91	—	—
Non-upper lobe, QIA α measure (n = 458; yes vs no)	47.4%	1.09	.68	—	—
Non-upper lobe, QIA % emphysema measure (n = 458; yes vs no)	22.1%	0.92	.74	—	—
Pulmonary function measures					
FEV ₁ percent predicted (per unit change)	28.1	0.97	.03	0.97	.05
RV percent predicted (per unit change)	214.4	1.00	.55	—	—
RV/TLC (per unit change)	0.64	2.49	.45	—	—
DLco percent predicted (per unit change)	29.2	0.97	.003	0.97	.01
Paco ₂ (per mm Hg)	42.8	1.00	.79	—	—
Exercise measures					
Low exercise (yes vs no)	40.9%	1.57	.02	—	—
Ve/Vco ₂ (per unit change)	0.37	2.40	.042	—	—
Six-min walk distance (per ft)	1246	1.00	.10	—	—
QOL measures					
UCSD SOB total score (per unit change)	61.0	1.01	.22	—	—
QWB average daily score (per unit change)	0.58	0.36	.23	—	—

RO, Relative odds; QIA, quantitative image analysis; FEV₁, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; DLco, diffusion capacity; Paco₂, partial pressure of arterial carbon dioxide; Ve/Vco₂, ratio of expired volume to the volume of carbon dioxide; QOL, quality of life; UCSD SOB, University of California at San Diego Shortness of Breath Questionnaire; QWB, Quality of Well-Being Scale. *Major pulmonary morbidity is defined as incidence of 1 or more of the following in the 30 days after lung volume reduction surgery: tracheostomy, failure to wean, pneumonia, at least 1 postoperative intubation, or ventilator use for 3 or more days. †Relative odds is defined as the ratio of the odds for those with versus the odds for those without the factor (yes vs no) or incremental odds for each specified change in the factor (continuous). ‡Wald χ^2 test for logistic regression with response variable of major pulmonary morbidity in the 30 days after lung volume reduction surgery (yes vs no) and regressor of risk factor. §P value for stepwise logistic regression (forward selection) with response variable of major pulmonary morbidity in the 30 days after lung volume reduction surgery and candidate regressors of all factors listed in the table. ||n = 511 because of missing data.

iate analysis suggested several factors potentially predictive for operative mortality, including age at the time of the operation ($P = .06$), non-upper-lobe-predominant emphysema determined by the radiologist ($P = .005$), and non-upper-lobe emphysema determined by using the α measure with quantitative CT image analysis ($P = .03$). The logistic regression model with backward selection determined that a single factor, non-upper-lobe-predominant emphysema determined by the radiologist, was predictive of 90-day mortality (RO, 2.99; $P = .009$).

Major Pulmonary Morbidity

The univariate analysis suggested several factors potentially predictive for major pulmonary morbidity in the first 30 days after LVRS (Table 4). These included age at the time of the operation ($P = .08$), continuous oxygen use ($P = .05$), FEV₁ percent predicted ($P = .03$), DLco percent predicted ($P = .003$), and low exercise capacity, as measured by means of symptom-limited maximum cycle ergometry ($P = .02$). However, the logistic regression model determined that only 3 of these factors were in-

TABLE 5. Factors related to major cardiac morbidity in the 30 days after lung volume reduction surgery*

Risk factor	% with risk factor or mean	Logistic regression relative odds of cardiac morbidity in 30 days†			
		Unadjusted		Final model after backward selection	
		RO	P value‡	RO	P value§
No. of patients	511			440	
Demographics					
Age at operation, y (per y of age)	67.0	1.07	.001	1.07	.004
Minority (yes vs no)	4.7%	0.56	.36	—	—
Male sex (yes vs no)	57.1%	1.84	.01	—	—
Treatment and physical condition					
Body mass index, kg/m ² (per unit change)	24.7	0.99	.82	—	—
Using oxygen constantly (yes vs no)	49.1	1.27	.28	—	—
Prescribed oral steroids at baseline (yes vs no)	31.9%	1.35	.20	1.72	.04
Abnormal creatinine level at baseline (yes vs no)	10.6%	1.64	.13	—	—
Radiologic measures					
Nonheterogeneous (radiologist evaluation; yes vs no)	42.3%	1.21	.39	—	—
Non-upper lobe (radiologist evaluation; yes vs no)	35.0%	1.32	.22	—	—
Hyperinflation on chest radiograph (any vs none)	96.6%	0.44	.12	—	—
Perfusion ratio (per unit change)	0.30	2.21	.09	—	—
Non-upper lobe, QIA α measure (n = 458; yes vs no)	47.4%	2.65	<.001	2.67	<.001
Non-upper lobe, QIA % emphysema measure (n = 458; yes vs no)	22.1%	1.53	.11	—	—
Pulmonary function measures					
FEV ₁ percent predicted (per unit change)	28.1	0.99	.53	—	—
RV percent predicted (per unit change)	214.4	1.00	.84	—	—
RV/TLC	0.64	0.73	.82	—	—
DLco percent predicted (per unit change)	29.2	1.00	.84	—	—
Paco ₂ (per mm Hg)	42.8	1.03	.09	—	—
Exercise measures					
Low exercise (yes vs no)	40.9%	1.59	.04	—	—
Ve/Vco ₂ (per unit change)	0.37	1.51	.74	—	—
Six-min walk distance (per ft)	1246	1.00	.12	—	—
QOL measures					
UCSD SOB total score (per unit change)	61.0	0.99	.22	—	—
QWB average daily score (per unit change)	0.58	1.19	.86	—	—

RO, Relative odds; QIA, quantitative image analysis; FEV₁, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity; DLco, diffusion capacity; Paco₂, partial pressure of arterial carbon dioxide; Ve/Vco₂, ratio of expired volume to the volume of carbon dioxide; QOL, quality of life; UCSD SOB, UCSD Shortness of Breath Questionnaire; QWB, Quality of Well-Being Scale. *Major cardiac morbidity is defined as incidence of 1 or more of the following: intraoperative or postoperative (in the 30 days after lung volume reduction surgery) arrhythmia requiring treatment or myocardial infarction or pulmonary embolus in the 30 days after lung volume reduction surgery. †Relative odds is defined as the ratio of the odds for those with versus the odds for those without the factor (yes vs no) or incremental odds for each specified change in the factor (continuous). ‡Wald χ^2 test for logistic regression with response variable of major cardiac morbidity in the 30 days after lung volume reduction surgery (yes vs no) and regressor of risk factor. §P value for stepwise logistic regression (forward selection) with response variable of major cardiac morbidity in the 30 days after lung volume reduction surgery and candidate regressors of all factors listed in the table. ||n = 511 because of missing data.

deed independent predictors for pulmonary morbidity. These included age (RO, 1.05; $P = .02$), FEV₁ percent predicted (RO, 0.97; $P = .05$), and DLco percent predicted (RO, 0.97; $P = .01$).

Major Cardiac Morbidity

Table 5 shows the analysis for predictors of major cardiac morbidity. The univariate analysis suggests that as many as 6 factors might be predictive for major cardiac morbidity. These include age at the time of the operation ($P = .001$),

male sex ($P = .01$), perfusion ratio ($P = .09$), non-upper-lobe-predominant emphysema determined from the α measure from the quantitative CT image analysis ($P < .001$), Paco₂ ($P = .09$), and low exercise capacity ($P = .04$). However, the multivariate logistic regression determined only 3 factors proved to be independent predictors, and these included age at the time of the operation (RO, 1.07; $P = .004$), oral steroid use at the time of the operation (RO, 1.72; $P = .04$), and non-upper-lobe-predominant emphy-

TABLE 6. Predictors of mortality in prior publications

Age	Naunheim and coworkers ⁶ Glaspole and coworkers ⁸
Male sex	Naunheim and coworkers ⁶ Ciccone and coworkers ¹³
Exercise tolerance	Szekely and coworkers ⁴ Naunheim and coworkers ⁶ Geddes and coworkers ⁷ Ciccone and coworkers ¹³
Paco ₂	Szekely and coworkers ⁴ O'Brien and coworkers ¹⁴ Keenan and coworkers ⁵
FEV ₁	NETT ¹⁰ Ciccone and coworkers ¹³
DLCO	Geddes and coworkers ⁷ Keenan and coworkers ⁵ NETT ¹⁰
Imaging studies	Slone and coworkers ¹⁶ Wisser and coworkers ¹⁵ NETT ¹⁰ Weder and coworkers ¹⁷

Paco₂, Partial pressure of arterial carbon dioxide; FEV₁, forced expiratory volume in 1 second; NETT, National Emphysema Treatment Trial; DLCO, diffusion capacity.

sema determined by the α measure by using quantitative image analysis (RO, 2.67; $P < .001$).

Discussion

Reported predictors of short-term mortality, operative mortality, or both after LVRS have included many factors describing patient demographic profile, spirometry, lung volume, gas exchange, exercise tolerance, and imaging studies (Table 6).^{4-8,10,13-17} Unfortunately, the predictive risk factors vary widely from article to article, and their validity is questionable. In several reports age is described as a strong predictor of morbidity^{6,8} yet is reported to be insignificant in others.^{4,5,13} Similarly, Paco₂ was noted as a significant risk factor by some investigators^{4,14,16} but not by others.^{6,13,15} Likely some of this uncertainty is due to the very nature of the studies cited. They were, in general, single-institution, nonrandomized, uncontrolled trials that involved small numbers of patients with variable measures and time points for evaluation, as well as a lack of consistency in the manner in which testing was conducted. Selection criteria varied from institution to institution, and the operative techniques varied widely as well.

The lack of consistency between these reports made risk assessment quite problematic for physicians counseling patients regarding the risks and benefits of LVRS. However, many of the above shortcomings were addressed with the institution of the NETT, a prospective, multi-institutional, randomized controlled trial that eventually enrolled more than 1200 patients. One of the major secondary end points

in the NETT was to provide clinical insight to allow for optimal patient selection, both with regard to risk and outcome. The NETT protocol was carefully designed to comprehensively characterize patients' preoperative pulmonary, cardiac, and functional status to diminish the effect of underlying significant diseases that would adversely affect patient outcome. Therefore the complications that we report in this study are ones that occurred in the setting of patients who had no overt signs of existing cardiopulmonary disease before LVRS other than their emphysema.

The first clinical publication of the NETT fulfilled this goal partially when it identified a subgroup of patients at exceedingly high risk for operative mortality and poor outcome measured at 6 months.¹¹ Those patients with an FEV₁ of less than 20% of predicted value and either a DLCO of less than 20% of predicted value or homogeneous distribution of emphysema as assessed by the radiologist were found to have a high 30-day mortality (16%) without substantially improved functional outcome in survivors compared with that seen in the medically treated control group at 6 months after randomization to treatment. Once this high-risk subgroup was identified, such patients were excluded from further entry into the trial; however, accrual of non-high-risk patients continued. A subsequent NETT publication has identified predictors of outcome and survival after an average of 29 months of follow-up; however, an analysis regarding early surgical mortality and morbidity has been lacking up to the present time.¹

Significant cardiac morbidity has been rarely reported with LVRS, with the exception of the development of arrhythmias, including atrial fibrillation, supraventricular tachycardia, and some ventricular arrhythmias. The only independent predictors for cardiac morbidity were increasing age, oral steroid use, and non-upper-lobe-predominant emphysema identified by the α measure on QIA. It is doubtful whether preoperative identification of these factors would likely be of great benefit in avoiding cardiac morbidity. The QIA model is not widely available, and the effect of increasing age, although significant, is so small it is unlikely to be of great clinical value. Perhaps clinically, the most practical suggestion would be to consider prophylactic pharmacologic prevention, as is currently undertaken in many cardiac surgery practices. Indeed, the incidence of these arrhythmias approaches that found after routine coronary artery bypass surgery, and prophylaxis might prove to be the best strategy. However, because this strategy was not studied, its value is purely speculative.

Pulmonary morbidity is perhaps the most daunting aspect of perioperative care for patients undergoing LVRS. Approximately 5% of patients fall into the failure to wean category, 18% had pneumonia, and 8% eventually proceed to tracheostomy, whereas more than 7% of patients will spend more than 2 weeks on the ventilator. Once again,

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looking to the independent predictors for help in avoiding significant pulmonary morbidity will likely prove futile. Although age, FEV₁ percent predicted, and DLCO are all statistically predictive of increased pulmonary morbidity, the changes in the RO ratio are not great, and it is highly unlikely any specific threshold could be identified that would represent a valid cutoff for patients or physicians. Perhaps patients with 2 or more risk factors (age >70 years and either FEV₁ or DLCO approaching 20% of predicted value) should be seen as approaching the previously published high-risk cohort and could be reasonably counseled against LVRS.

Perhaps the only area in which this risk analysis model is likely to be helpful clinically is in the arena of operative mortality. non-upper-lobe-predominant emphysema determined by the radiologist had an RO ratio of 2.99 ($P = .009$), suggesting that even in this non-high-risk group, patients with non-upper-lobe-predominant emphysema carry a significantly increased risk of dying within the first 90 days after LVRS. This factor has already been shown to be predictive of both poor physiologic outcome and worse operative mortality in a cohort of patients with preserved exercise capacity.^{1,12} The current findings emphasize the point that the distribution of emphysema identified on the chest CT might be useful in guiding the physician in counseling the patient regarding the advisability of this procedure. A practitioner considering LVRS must think long and hard before suggesting this surgical intervention for patients who have been demonstrated as having non-upper-lobe-predominant emphysema, even if all other factors appear encouraging. Although it is impossible to predict results in any individual patient, the combination of relatively increased operative mortality coupled with the inferior outcomes already described makes the decision for surgical intervention in this particular patient subgroup highly suspect.

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Discussion

Dr Joel D. Cooper (*St Louis, Mo*). Thank you for the opportunity, and thank you, Dr. Naunheim, for an excellent presentation and a chance to review the article. It is widely overlooked that the National Emphysema Treatment Trial (NETT) trial did have in advance a written hypothesis. The hypothesis stated "that patients who improve will have preoperative heterogeneously distributed emphysema involving the upper lobes predominantly." One of the disappointments of the NETT trial was the unwillingness to prospectively stratify patients according to that hypothesis to allow prospective analysis, and one of the major criticisms has been that most analyses now have had to be post hoc subgroup analyses, which detracts from the strength of the conclusions. To date, none of the NETT publications, including the presentation today, have stratified the patients according to the hypothesis of the trial, and therefore one question I have is this: When will the database be available so that the analysis of the group who are hypothesized to be lowest risk and greatest benefit will be available?

Our own single-institution population of about 300 patients is clearly a different set of patients: they have only heterogeneous distribution, with 92% of them having upper-lobe-predominant emphysema. I believe that is the reason why there is a disparity between the results we and others have obtained and those reported by the NETT, specifically reintubation in our series of 7% versus 22%, tracheostomy in our series of 4% versus 8%, and overall pulmonary morbidity of 14% instead of 30%. I think this has nothing to do with the skill or the care of the patients. I think it has

only to do with the selection of the patients. And therefore the second question is that I would like to ask your opinion of that.

I have always been a bit confused by the difference between homogenous distribution of emphysema and non–upper-lobe-predominant emphysema. In the figures that you presented, 67% of patients were classified as having the upper-lobe-predominant pattern, but only 58% of all the patients were described as having a heterogeneous pattern. This means that many of the patients classified as having upper-lobe-predominant emphysema were also classified as homogenous rather than heterogeneous, and I wonder if you could help me understand that.

Your mortality risk showed that, by far, the greatest factor was non–upper-lobe-predominant emphysema (an odds ratio of 3). Have you any idea why this predictor did not hold up for your major pulmonary morbidity? Pulmonary morbidity was the major cause of death. You showed that mortality was related to it but not morbidity in terms of the distribution of the emphysema pattern.

Finally, previous NETT publications have identified exercise capacity as an important prognostic indicator to the point that some Medicare patients are now denied the operation on the basis of that discriminator. Do you have any idea why that discriminator, exercise capacity, did not fall out as a major predictor of morbidity and mortality in your analysis?

Thank you very much for the privilege.

Dr Naunheim. Thank you, Joel. The answer to your first question is that the database will be available to the public in the spring of 2006.

The premise of the NETT trial was to do a prospective randomized trial comparing medical versus surgical therapy for a wide variety of patients and not just those with upper-lobe heterogeneous disease. There is no doubt that the inclusion criteria within the NETT trial were broader and intentionally so than those used by Dr Cooper and some other investigators. The idea was not just to determine whether the procedure was going to be effective but also in what group of patients it would be effective or ineffective and contraindicated. Thus it is true that our patient population is more diverse than that of Dr Cooper and his colleagues and than those of other investigators in the field.

The disparity between results with regard to the incidence of tracheostomy, reintubation, pneumonia, and the like is indeed due

to this difference in patient selection. First of all, our patients, because of the Medicare funding, were on average 5 years older than in other series, and as you know, in this ill patient subset 5 years is an eternity. Therefore our patients were indeed older, more ill, and more fragile and did have more homogenous disease.

The question of upper-lobe versus heterogeneous disease is one we have also asked. You said that 67% of the patients were classified as having upper-lobe-predominant emphysema and only 58% as heterogeneous, and that really has to do with the subjective radiologist's evaluation of the heterogeneity and of the predominance. This was purely subjective. We are hoping that eventually the computerized analysis will give us a better and more objective feel for who has upper-lobe predominance versus lower-lobe predominance and who has homogenous versus heterogeneous, but that full analysis has not been done yet.

The fourth question was why upper-lobe emphysema did not hold up for pulmonary morbidity, and that I honestly cannot answer. I would have thought that it would have because it seemed to be so consistent in both our first and second major publications, in which homogeneity proved to be critical. Therefore the fact that the distribution of emphysema was not significant as a predictor for pulmonary morbidity also is a nettlesome question for us. I do not have the answer for that.

Finally, why didn't exercise capacity hold up as a predictor? If you remember, the exercise capacity was reported in the midterm survival and functional outcome results in the primary NETT outcome trial paper. And the reason that exercise capacity appeared to be a significant predictor was not because the surgical patients mattered with regard to high or low exercise but more of the fact that the medical patients who had low exercise capacity—as you remember, that was the indicator for “good outcome”—those who had low exercise capacity in the medical group deteriorated and died so quickly that it made the surgical group look better by comparison. It had nothing to do with the surgical group itself in regard to exercise capacity but rather with the very fragile condition of the medical group who had poor exercise capacity, and that group deteriorated very rapidly and died at an increased rate. Therefore we did see exercise capacity as a predictor of outcome and survival but only in the long term and not in the short term.

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