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The Effects of Pulmonary Rehabilitation in the National Emphysema Treatment Trial*

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Study objectives: **Pulmonary rehabilitation is an established treatment in patients with chronic lung disease but is not widely utilized. Most trials have been conducted in single centers. The National Emphysema Treatment Trial (NETT) provided an opportunity to evaluate pulmonary rehabilitation in a large cohort of patients who were treated in centers throughout the United States.**

Design: **Prospective observational study of cohort prior to randomization in a multicenter clinical trial.**

Setting: **University-based clinical centers and community-based satellite pulmonary rehabilitation programs.**

Patients and intervention: **A total of 1,218 patients with severe emphysema underwent pulmonary rehabilitation before and after randomization to lung volume reduction surgery (LVRS) or continued medical management. Rehabilitation was conducted at 17 NETT centers supplemented by 539 satellite centers.**

Measurements and results: **Lung function, exercise tolerance, dyspnea, and quality of life were evaluated at regular intervals. Significant ($p < 0.001$) improvements were observed consistently in exercise (cycle ergometry, 3.1 W; 6-min walk test distance, 76 feet), dyspnea (University of California, San Diego Shortness of Breath Questionnaire score, −3.2; Borg breathlessness score: breathing cycle, −0.8; 6-min walk, −0.5) and quality of life (St. George Respiratory Questionnaire score, −3.5; Quality of Well-Being Scale score, +0.035; Medical Outcomes Study 36-item short form score: physical health summary, +1.3; mental health summary, + 2.0). Patients who had not undergone prior rehabilitation improved more than those who had. In multivariate models, only prior rehabilitation status predicted changes after rehabilitation. In 20% of patients, exercise level changed sufficiently after rehabilitation to alter the NETT subgroup predictive of outcome. Overall, changes after rehabilitation did not predict differential mortality or improvement in exercise (primary outcomes) by treatment group.**

Conclusions: **The NETT experience demonstrates the effectiveness of pulmonary rehabilitation in patients with severe emphysema who were treated in a national cross-section of programs. Pulmonary rehabilitation plays an important role in preparing and selecting patients for surgical interventions such as LVRS.** ***(CHEST 2005; 128:3799–3809)***

Key words: COPD; pulmonary exercise; pulmonary rehabilitation

Abbreviations: LVRS = lung volume reduction surgery; NETT = National Emphysema Treatment Trial; QWB = quality of well-being; RV = residual volume; SF-36 = Medical Outcomes Study 36-item short form; TLC = total lung capacity; UCSD = University of California San Diego

Pulmonary rehabilitation enhances standard therapy for patients with emphysema by helping to control and alleviate symptoms, to optimize functional capacity, and to reduce the medical and economic burdens of disabling lung disease.[1–9] Most clinical trials have been conducted in individual research-based centers, whereas the majority of pulmonary rehabilitation services are provided in clinical, community-based programs. The National Emphysema Treatment Trial (NETT), a multicenter trial evaluating lung volume reduction surgery (LVRS) in patients with advanced emphysema, provides a unique opportunity to examine the effectiveness of pulmonary rehabilitation administered in a variety of centers throughout the United States.[10,11] In the NETT, all subjects who were eligible after the

initial evaluation completed 6 to 10 weeks of standardized pulmonary rehabilitation prior to randomization. The rehabilitation program was directly supervised by the NETT center where the patient had enrolled, although portions of the program for some patients were carried out at a satellite facility certified by the supervising center.[10] Although NETT

For editorial comment see page 3783

was not specifically designed to evaluate pulmonary rehabilitation, it does allow a descriptive analysis of changes in health outcomes after pulmonary rehabilitation in a large cohort of patients who are widely distributed across the United States. The purpose of this report was to describe these analyses.

Materials and Methods

Study Design, Subjects, and Assessments

The overall design of the NETT and its preliminary results have been reported previously.[10–13] The 17 participating NETT centers randomly assigned 1,218 patients with emphysema (mean FEV_1, 26.9% predicted) to either undergo LVRS with medical therapy or to receive continued medical management alone.[11] All patients gave written informed consent on forms that had been approved by the human subjects committee at each center.

After an initial evaluation to establish preliminary eligibility and before randomization, all subjects were required to complete a comprehensive program of pulmonary rehabilitation regardless of whether they had undergone pulmonary rehabilitation at any time previously. Assessments were performed before and after this initial phase of rehabilitation. Only after successfully completing rehabilitation were subjects eligible to enter the randomized portion of the trial.

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†A complete list of participants and centers in the NETT is located in the Appendix.

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NETT Pulmonary Rehabilitation Program

The NETT rehabilitation program was designed to optimize physical and psychosocial function and to improve each patient's understanding of lung disease and his/her ability to manage it. Secondary goals included the provision of detailed information to the patient about the complex NETT protocol to ensure, as follows: (1) truly informed consent; (2) bonding with the NETT center to optimize continued participation in this difficult, long-term trial; and (3) adherence to recommendations for optimal medical management. The basic principle of the rehabilitation program was a study-directed daily care program with specified center-based supervised sessions to ensure that all patients received standardized educational and psychosocial treatment and appropriate adjustment of exercise training. All patients were expected to continue their rehabilitation care plans daily at home throughout the study.

The NETT pulmonary rehabilitation program was divided into the following three phases: prerandomization; postrandomization; and long-term maintenance. The prerandomization phase included a total of 16 to 20 supervised sessions that were completed over a period of 6 to 10 weeks. The comprehensive program included components of exercise training (*ie*, lower extremity, upper extremity, flexibility, and strength), education, psychosocial assessment and treatment, and nutritional assessment and treatment. Individual goals were established during an initial rehabilitation evaluation during screening for the trial. The first four rehabilitation sessions were provided at a NETT center. The remaining 12 to 16 sessions were provided either at the same NETT center or at a satellite facility nearer to the patient's home that had been certified by the NETT center that remained responsible for patient management. Individual satellite centers could be certified by more than one NETT center. The certifying NETT center was responsible for ensuring that satellite center staff members were trained in NETT procedures and for overseeing the patient's rehabilitation program through regular communication including weekly progress reports and exercise session logs.

Each required session included supervised exercise training and either an education or psychosocial session. The exercise-training program incorporated lower extremity endurance exercise that was accomplished either by walking or by riding on a bicycle (five times per week), supported or unsupported upper extremity exercise (three times per week), flexibility exercises (five times per week), and strength training with latex resistive bands and tubing, free weights, or circuit training (three times per week). Each NETT center was responsible for developing a specific exercise-training program consistent with the NETT protocol and for ensuring compliance in its certified satellite centers. The education program was tailored to the individual patient, and covered both disease-specific and study-related topics. Psychosocial assessment was performed by rehabilitation staff during the initial evaluation, and was supplemented by the Beck Depression Inventory,[14,15] the Self-Evaluation Questionnaire of state and trait anxiety,[16] and the Trail Making Test to assess divided attention and psychomotor functioning.[17] Psychosocial counseling was provided by an appropriate mental health professional. Patients with serious psychological problems were referred to a psychologist or psychiatrist. After completing prerandomization pulmonary rehabilitation, each patient was reevaluated at the NETT center and was allowed to proceed to randomization only after completing this evaluation.

The postrandomization phase included an additional 8 to 9 weeks of supervised rehabilitation. LVRS patients began rehabilitation activities in the hospital as soon as was practical after surgery. At the time of hospital discharge, they received a minimum of two rehabilitation sessions at the NETT center

followed by supervised sessions at least once weekly over 8 weeks at either the NETT center or a satellite center. Similar to the prerandomization phase, supervised sessions included reinforcement education, and exercise, psychosocial, and nutrition components. For medical patients, this phase began immediately after randomization. A minimum of two psychosocial sessions was required to assist the patient in overcoming any disappointment concerning the assigned treatment arm.

The long-term maintenance phase continued for the duration of follow-up in the NETT. Each NETT center maintained contact through scheduled in-person visits that were supplemented with regular telephone contact to assess adherence to the rehabilitation treatment plan. When necessary, additional supervised rehabilitation sessions could be prescribed.

Statistical Analysis

Measures of physiologic and psychosocial function before and after rehabilitation were evaluated with descriptive statistics and paired *t* tests. In addition to the analysis for all patients, stratified analyses by prior rehabilitation experience and rehabilitation location were performed. All p values were based on two-sided tests and were not corrected for multiple comparisons. A p value of < 0.05 was considered to be significant. Multivariate analyses of determinants of change after rehabilitation were performed by forward stepwise linear regression. The dependent variables analyzed included maximum cycle ergometry workload, measured in watts (a primary outcome measure in the NETT),[10,11] total St. George Respiratory Questionnaire score,[18] and the University of California, San Diego (UCSD) Shortness of Breath Questionnaire score.[19] The following candidate-independent variables were selected for univariate analysis: FEV_1; inspiratory capacity; residual volume (RV)/total lung capacity (TLC)ratio; diffusing capacity of the lung for carbon monoxide; cutaneous oxygen saturation on the oxygen titration walk; maximum workload and perceived symptoms of breathlessness and muscle fatigue on the cycle ergometry test; St. George Respiratory Questionnaire total and subscale scores; quality of well-being (QWB) score; Medical Outcomes Study 36-item short form (SF-36) subscale and physical and mental component scores; UCSD Shortness of Breath score; prior rehabilitation experience (yes/no); rehabilitation location (NETT center or satellite); and income level. For the multivariate models, candidate-independent variables for all analyses included age, gender, NETT center, and prerandomization value for the dependent variable in addition to any of the other independent variables for which the univariate model p value was < 0.15. Independent variables for the final multivariate model were then selected as predictive if the p value from stepwise forward selection was < 0.05.

In the primary report of the NETT results,[11] key subgroups were identified because of important findings of differential outcome by treatment group. Maximum exercise capacity after rehabilitation and the distribution of emphysema proved to be important characteristics in defining these subgroups. Therefore, we examined the impact of pulmonary rehabilitation on subgroup assignment. Patients were categorized into high and low exercise capacity groups based on the 40th percentile gender-specific values that previously had been identified in the NETT (women, 25 W; men, 40 W) both before and after pulmonary rehabilitation.[11] The McNemar test was used to test for the statistical significance of change in subgroup assignment from prerehabilitation to postrehabilitation. A separate analysis was performed for patients with and without prior pulmonary rehabilitation.

Additional multivariate analyses were performed to evaluate the potential effects of changes after pulmonary rehabilitation on predicting differential mortality and a 10-W change in maximum cycle work (primary outcome measures in NETT) by treatment. Mortality was analyzed using Cox regression. Improvement, as defined by a change in the maximum cycle work of ≥ 10 W, was analyzed using logistic regression. For these analyses, the independent variables selected for analysis included changes after prerandomization pulmonary rehabilitation in maximum workload, 6-min walk distance, St. George total score, QWB score, and UCSD Shortness of Breath Questionnaire score. The model for predicting differential outcome included the independent variable, the treatment group assignment, and the interaction between them. All analyses were performed using a statistical software package (SAS, version 8.0; SAS Institute; Cary, NC).

Results

Study Patients

A total of 3,777 patients underwent comprehensive evaluation at 1 of the 17 participating centers. Of these patients, 1,796 met the preliminary eligibility criteria and began the prerandomization pulmonary rehabilitation program. Over the next 10 weeks, 578 of these patients did not proceed to randomization for a variety of reasons including the following: not completing the rehabilitation program or postprogram assessment; doing well in rehabilitation and becoming unwilling to risk surgery; decline in function during rehabilitation and being declared ineligible either by choice or by study investigators; making an informed choice not to continue after further discussions during rehabilitation; illness or other complication rendering patients ineligible for surgery; or exclusion by the surgeon. It should be noted that surgeons had the option to exclude any patient they were unwilling to operate on at the time of the preoperative evaluation that was required prior to randomization. Additional data were not available about these patients who were excluded from the study and further follow-up. The analyses presented in this article were based on complete prerandomization and postrandomization data that were collected on all patients in the final cohort who successfully completed pulmonary rehabilitation and proceeded to randomization.

Effects of Prerandomization Pulmonary Rehabilitation

The characteristics of the 1,218 patients at initial evaluation prior to rehabilitation are presented in Table 1. Of note, 777 patients (64%) had received prior pulmonary rehabilitation, and 786 patients (65%) had utilized one of the satellite rehabilitation centers. As expected, on average, these patients had severe airflow obstruction and marked impairment in exercise capacity, symptoms of dyspnea, and reduction in health-related quality of life. On the oxygen titration test, 58% required supplemental oxygen to maintain saturation levels of $> 90\%$ by cutaneous oximetry.

Table 1—*Characteristics of the Patients Prior to Pulmonary Rehabilitation (n = 1,218)

Characteristics	Values
Age at randomization, yr	67.1 ± 6.1
Race or ethnic group	
Non-Hispanic white	1156 (95)
Non-Hispanic black	42 (3)
Other	20 (2)
Sex	
Female	472 (39)
Male	746 (61)
Education	
Less than high-school	247 (20)
High school	385 (32)
More than high-school	403 (33)
College	183 (15)
Prior rehabilitation	777 (64)
Satellite or other NETT clinic used for rehabilitation	786 (65)
FEV_1 after BD	26.9 ± 7.1
% predicted	
L	0.77 ± 0.24
RV/TLC ratio after BD, %	65.2 ± 8.1
IC after BD, L	1.71 ± 0.6
DLCO, % predicted	28.5 ± 9.8
Maximum work, W	35.9 ± 21.1
Borg scale†	
Muscle fatigue (at maximum workload)	5.2 ± 2.5
Breathlessness (at maximum workload)	5.8 ± 2.3
Distance walked in 6 min, feet	1,142.0 ± 312.4
Borg scale	
Muscle fatigue	3.4 ± 2.3
Breathlessness	5.0 ± 2.1
Oxygen flow rate (during 6-min walk, based on O_2 titration walk), L/min	
0	512 (42)
1–2	366 (30)
≥ 3	338 (28)
Quality of life	
St. George Respiratory Questionnaire†	
Total score	56.5 ± 13.0
Activity score	81.9 ± 12.7
Impacts score	41.4 ± 16.7
Symptoms score	58.3 ± 19.3
UCSD Shortness-of-Breath Questionnaire score‡	65.7 ± 19.0
QWB average daily score§	0.537 ± 0.122
SF 36‖	
Physical health summary score	28.3 ± 7.4
Mental health summary score	53.2 ± 10.9
Physical functioning score	22.1 ± 16.8
Role limit (physical health problems) score	20.9 ± 30.8
Role limit (personal/emotional problems) score	68.5 ± 41.0
Energy/fatigue score	43.8 ± 19.6
Emotional well-being score	74.6 ± 17.5
Social functioning score	61.8 ± 27.7
Bodily pain score	75.8 ± 23.7
General health perceptions	37.6 ± 20.2

*Values are given as the mean ± SD or No. (%). BD = bronchodilator; IC = inspiratory capacity; DLCO = diffusion capacity of the lung for carbon monoxide. The Borg scale is a 10-point categoric perceived symptom scale in which the patient rates symptoms of breathlessness and muscle fatigue at the end of the exercise tests; higher scores indicate worse symptoms.

†The St. George Respiratory Questionnaire is a 51-item respiratory disease-specific, health-related, quality-of-life questionnaire that is completed by the patient. The total score ranges from 0 to 100, with lower scores indicating better health-related quality of life.

‡The UCSD Shortness-of-Breath Questionnaire is a 24-item questionnaire about dyspnea with activities of daily living that is completed by the patient. The total score ranges from 0 to 120, with lower scores indicating less shortness of breath.

§The QWB scale is a 77-item questionnaire that is completed by the patient with regard to general quality of life. The average daily total score ranges from 0 to 1, where higher scores indicate better quality of life.

‖SF 36 is a 36-item questionnaire completed by the patient with regard to general quality of life; scores on the eight subscales range from 0 to 100, where higher scores indicate better quality of life. Scores on the physical and mental health summary scores are standardized to the normal US population with a mean of 50 and an SD of 10, where higher scores indicate better quality of life.

Changes after pulmonary rehabilitation are presented in Table 2 for (1) all patients (n = 1218), (2) patients with prior pulmonary rehabilitation (n = 777) and without prior pulmonary rehabilitation (n = 441), and (3) patients who completed pulmonary rehabilitation using a satellite center (n = 786) or solely a NETT center (n = 432). Overall, there were highly statistically significant changes in all measures of exercise capacity, dyspnea, and quality of life except for the SF-36 pain score. With the exception of slightly less hyperinflation (*ie*, a decrease in the RV/TLC ratio of 0.6%), as expected, there were no significant changes in lung function. Improvements were significantly greater in patients without prior rehabilitation experience than for those with prior rehabilitation for measures of maximum work; 6-min walk distance; St. George total, activity, and impacts scores; UCSD Shortness of Breath score; and SF-36 scores of physical health summary, and components of physical functioning, emotional well-being, and general health perceptions. There were no significant differences in changes for patients who completed the prerandomization rehabilitation program at satellite centers vs NETT centers.

Box plots for changes in maximum cycle workload, St. George Respiratory Questionnaire total score, and UCSD Shortness of Breath Questionnaire score for all patients, as well as for those with and without prior pulmonary rehabilitation experience, are presented in Figure 1. These demonstrate greater im-

Table 2—*Response to Rehabilitation: Changes from Prerehabilitation to Postrehabilitation for All Patients and by Prior Rehabilitation Experience**

Characteristics	Changes (Post-Pre)				
		Prior Rehabilitation		Rehabilitation Performed at	
	All Patients (n = 1,218)	Yes (n = 777)	No (n = 441)	Satellite (n = 786)	NETT Center (n = 432)
FEV_1 after BD					
% predicted	− 0.13 ± 3.67	− 0.13 ± 3.57	− 0.12 ± 3.85	− 0.18 ± 3.64	− 0.02 ± 3.73
L	− 0.01 ± 0.11	− 0.01 ± 0.11	0.00 ± 0.11	− 0.01 ± 0.12	0.00 ± 0.10
RV/TLC ratio after BD, %	− 0.6 ± 5.1†	− 0.5 ± 5.1	− 0.7 ± 5.1	− 0.5 ± 5.1	− 0.8 ± 4.9
IC after BD use, L	− 0.00 ± 0.36	− 0.02 ± 0.34	0.03 ± 0.39	− 0.02 ± 0.36	0.03 ± 0.35
Maximum work, W	3.1 ± 11.1†	2.4 ± 10.4	4.3 ± 12.0‡	2.7 ± 11.1	3.9 ± 11.0
Borg scale					
Muscle fatigue	− 0.9 ± 2.3†	− 0.8 ± 2.3	− 1.0 ± 2.3	− 0.8 ± 2.3	− 1.0 ± 2.4
Breathlessness	− 0.8 ± 2.2†	− 0.7 ± 2.1	− 1.0 ± 2.4	− 0.8 ± 2.3	− 0.8 ± 2.2
Distance walked in 6 min, feet	75.5 ± 176.3†	60.7 ± 184.6	101.7 ± 157.3‡	70.7 ± 180.4	84.2 ± 168.4
Borg scale					
Muscle fatigue	− 0.3 ± 2.1†	− 0.2 ± 2.0	− 0.5 ± 2.2	− 0.3 ± 2.0	− 0.5 ± 2.2
Breathlessness	− 0.5 ± 1.9†	− 0.4 ± 1.9	− 0.6 ± 2.0	− 0.5 ± 1.9	− 0.5 ± 2.0
Quality of life					
St. George Respiratory Questionnaire					
Total score	− 3.5 ± 9.8†	− 2.6 ± 9.6	− 5.1 ± 10.1‡	− 3.6 ± 9.7	− 3.2 ± 10.0
Activity score	− 2.4 ± 10.7†	− 1.3 ± 10.2	− 4.4 ± 11.4‡	− 2.3 ± 10.6	− 2.8 ± 11.0
Impacts score	− 4.4 ± 13.3†	− 3.5 ± 13.2	− 6.1 ± 13.5‡	− 4.7 ± 13.2	− 3.8 ± 13.6
Symptoms score	− 2.4 ± 16.1†	− 2.0 ± 16.1	− 3.0 ± 16.3	− 2.6 ± 16.2	− 1.9 ± 16.1
UCSD Shortness-of-Breath Questionnaire	− 3.2 ± 13.4†	− 2.3 ± 13.5	− 4.8 ± 13.0‡	− 3.1 ± 13.5	− 3.4 ± 13.1
QWB average daily score	0.035 ± 0.117†	0.034 ± 0.113	0.036 ± 0.125	0.032 ± 0.114	0.040 ± 0.122
SF 36					
Physical health summary score	1.3 ± 7.1†	0.9 ± 7.2	2.2 ± 6.8‡	1.4 ± 6.9	1.3 ± 7.4
Mental health summary score	2.0 ± 9.6†	1.8 ± 9.8	2.3 ± 9.2	1.9 ± 9.5	2.2 ± 9.9
Physical functioning score	3.6 ± 14.9†	2.6 ± 14.9	5.5 ± 14.8‡	3.4 ± 14.3	4.1 ± 16.0
Role limit score					
Physical health problems	7.9 ± 37.9†	6.7 ± 38.2	10.1 ± 37.5	8.7 ± 37.6	6.4 ± 38.5
Personal/emotional problems	6.1 ± 46.0†	6.0 ± 47.2	6.2 ± 44.0	4.6 ± 45.0	8.8 ± 47.7
Energy/fatigue score	4.9 ± 17.4†	4.3 ± 17.3	6.0 ± 17.5	5.1 ± 17.1	4.6 ± 18.0
Emotional well-being score	3.2 ± 14.3†	2.3 ± 14.1	4.7 ± 14.7‡	3.0 ± 14.1	3.6 ± 14.8
Social functioning score	4.9 ± 25.3†	4.2 ± 25.0	6.0 ± 26.0	5.9 ± 25.2	3.1 ± 25.4
Bodily pain score	1.2 ± 22.9	0.3 ± 22.9	2.7 ± 22.9	0.4 ± 22.3	2.6 ± 24.0
General health perceptions	2.9 ± 16.6†	1.8 ± 16.4	4.7 ± 17.0‡	2.6 ± 16.1	3.4 ± 17.6

*Values are given as the mean ± SD. See Table 1 for abbreviations and explanations not given in the text.

†$p < 0.001$ from the paired *t* test or signed rank test when nonnormal.

‡$p < 0.01$ from the two-sample *t* test comparing patients with prior rehabilitation and those without prior rehabilitation. No differences were observed comparing rehabilitation at NETT centers only vs that at NETT plus satellite centers.

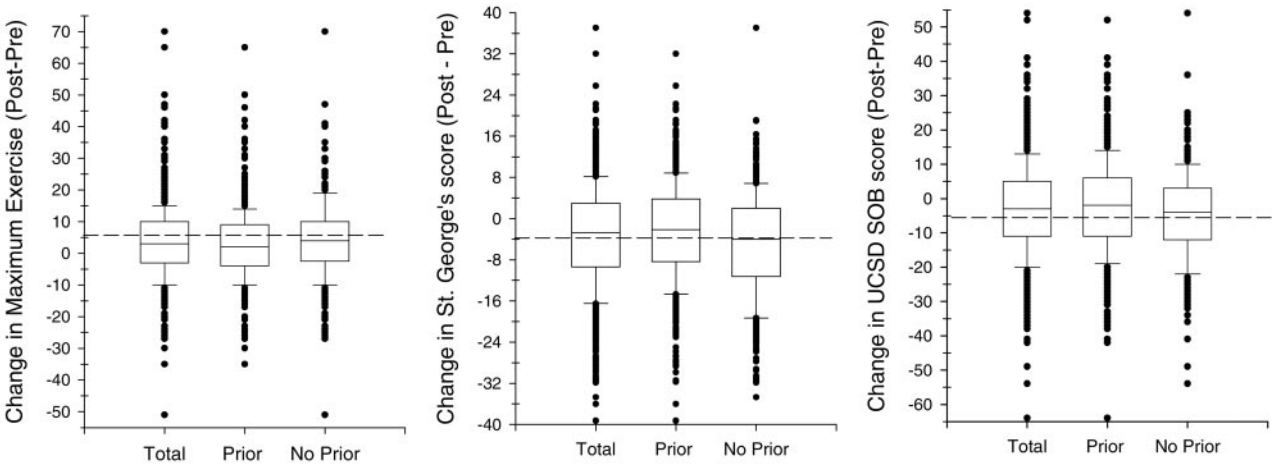

FIGURE 1. Box plots of changes from prerandomization pulmonary rehabilitation program in exercise capacity (maximum workload), health-related quality of life (St. George Respiratory Questionnaire total score), and dyspnea (UCSD Shortness of Breath [SOB] Questionnaire score) for all 1,218 patients, as well as for subgroups with and without prior pulmonary rehabilitation experience. Dashed lines represent the following estimated minimal clinically important differences: 5-W increase for maximum workload; 4-U decrease for the St. George Respiratory Questionnaire total score; and 5-U decrease for the UCSD Shortness of Breath Questionnaire score.

provements in patients without prior rehabilitation. Approximately half of the NETT patients demonstrated clinically important improvements for each of these measures based on investigator estimates of minimal clinically important differences, as follows: cycle workload, 5 W; St. George Respiratory Questionnaire total score, 4 U[20]; and UCSD Shortness of Breath Questionnaire score, 5 U.[21]

Changes in the eight subscales of the SF-36 health profile are presented in Figure 2. After pulmonary rehabilitation, seven of the eight subscales showed significant improvement. Only the bodily pain score, which had been nearly normal at baseline, failed to improve.

Predictors of Improvement in Pulmonary Rehabilitation

The results of the multivariate analyses of determinants of changes after pulmonary rehabilitation are presented in Table 3. In general, the amount of variability explained by the independent variables was very small, suggesting that the changes after pulmonary rehabilitation cannot be explained using prerehabilitation measures. Because of significant differences between NETT centers with respect to changes in maximum workload and St. George Respiratory Questionnaire total score, the estimates for these dependent variables were adjusted by NETT clinic. There were no significant differences between centers for the UCSD Shortness of Breath Questionnaire score.

Effect of Pulmonary Rehabilitation on NETT Subgroups

Prerandomization pulmonary rehabilitation had a significant effect on NETT subgroup assignment

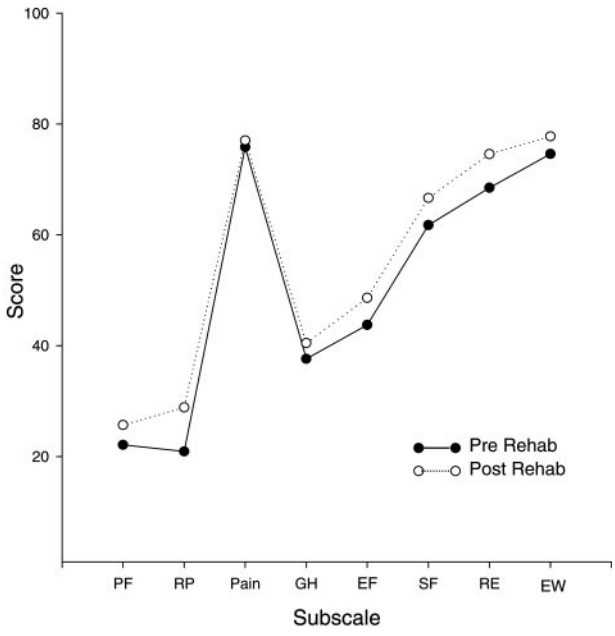

FIGURE 2. Changes in the subscales of the SF-36. PF = physical functioning; RP = role limit (physical health problems); Pain = bodily pain; GH = general health perceptions; EF = energy/fatigue; SF = social functioning; RE = role limit (personal/emotional problems); EW = emotional well-being (higher values indicate better quality of life); Pre Rehab = prerehabilitation; Post Rehab = postrehabilitation.

Table 3—*Multivariate Regression Model Estimates and 95% Confidence Limits for Change in Function or Quality of Life Before and After Rehabilitation

Outcome Covariate	Coefficients		p Value
	Estimate†	95% CI	
Change in maximum exercise capacity ($R^2 = 0.11$)			
Age, yr	− 0.17	− 0.27, − 0.07	0.001
Gender (female vs male)	− 4.09	− 5.44, − 2.74	< 0.001
Prior participation in rehabilitation (no vs yes)	1.59	0.30, 2.89	0.02
Change in St. George Respiratory Questionnaire score ($R^2 = 0.25$)			
Prior participation in rehabilitation (no vs yes)	− 1.68	− 2.74, − 0.62	0.002
IC in 0.1 L	− 0.10	− 0.19, − 0.01	0.03
SF-36 physical summary score	− 0.16	− 0.25, − 0.08	< 0.001
SF-36 mental summary score	− 0.08	− 0.14, − 0.03	0.004
UCSD SOB score	0.09	0.05, 0.13	< 0.001
Change in UCSD SOB score ($R^2 = 0.23$)			
Prior participation in rehabilitation (no vs yes)	− 2.70	− 4.10, − 1.31	< 0.001
IC in 0.1 L	− 0.30	− 0.42, − 0.18	< 0.001
FEV_1 % predicted	− 0.18	− 0.27, − 0.08	< 0.001
SF-36 physical summary score	− 0.22	− 0.33, − 0.11	< 0.001
St. George Respiratory Questionnaire score	0.16	0.09, 0.23	< 0.001

*SOB = shortness of breath. See Table 1 for other abbreviations not used in the text. Covariates included in the regression analyses were treatment group, age, gender, center identification, prerehabilitation value for the dependent variable, plus candidate variables with p values < 0.15 in the univariate analysis, as indicated in the text. Variables identified in the final model were selected if the p values from forward selection were > 0.05.

†Estimated increase or decrease in the change in functional outcome or quality-of-life outcome per unit increase in a continuous variable or comparing two groups for binary variables after adjusting for the baseline value. The estimates for the change in maximum exercise capacity and St. George Respiratory Questionnaire score were also adjusted for clinic because there were some differences by clinic.

based on maximum exercise capacity for all non-high-risk patients[11,12] as well as for subgroups with and without prior rehabilitation experience (Table 4). Overall, 20% of patients changed subgroup after rehabilitation, 13.5% from the low exercise subgroup to the high exercise subgroup and 6.5% from the high exercise subgroup to the low exercise subgroups. The effect of rehabilitation on subgroup assignment was greater for patients without prior rehabilitation in whom 16.5% changed from the low exercise subgroup to the high exercise subgroup and 6.2% from the high exercise subgroup to the low exercise subgroup.

Table 4—*Classification of Patients Into High and Low Exercise NETT Subgroups Before and After Pulmonary Rehabilitation for All Non-High-Risk Patients as well as Those Patients With and Without Prior Experience of Pulmonary Rehabilitation*

Patients	Before		p Value*
	Low	High	
All non-high-risk patients (n = 1,078)			
After			≤ 0.001
Low	369	70	
High	145	494	
All non-high risk patients with prior rehabilitation (n = 672)			
After			0.003
Low	233	45	
High	78	316	
All non-high risk patients with no prior rehabilitation (n = 406)			
After			≤ 0.001
Low	136	25	
High	67	178	

*From McNemar test.

Effects of Pulmonary Rehabilitation on Primary NETT Outcome Measures

In multivariate analyses, changes in exercise, dyspnea, and quality of life after pulmonary rehabilitation were not significant predictors of differential mortality and change in maximum cycle work (the primary outcomes of NETT) by treatment group (data not shown).

Discussion

The NETT study provides a remarkable demonstration of the effectiveness of pulmonary rehabilitation in a large cohort of patients with advanced emphysema who had been treated in a cross-section of programs in the United States. The study was not designed specifically to evaluate pulmonary rehabilitation, and there was no comparison group without rehabilitation. Nevertheless, significant improve-

ments in exercise capacity, dyspnea, and health-related quality of life were observed consistently across many of the NETT centers (17) and satellite centers (539). The only variable that consistently demonstrated an effect on rehabilitation outcomes was whether the patient had rehabilitation experience prior to enrolling in the NETT. As expected, those patients without prior rehabilitation experience demonstrated the greatest gains.

These results confirm and extend those previously published from single, specialized centers as well as other multicenter outcome studies[9,22] and provide strong evidence that the benefits from pulmonary rehabilitation as currently practiced are generalizable to community-based centers. In the overall analyses, the magnitude of improvement in most variables was less than that typically observed in single-center studies and less than the accepted thresholds for clinically important differences. However, patients in NETT were recruited regardless of prior pulmonary rehabilitation experience, although all were required to complete the NETT pulmonary rehabilitation program before randomization. Because prior rehabilitation experience appears to have blunted the response to pulmonary rehabilitation, the results in patients without prior rehabilitation (Table 2) may be a truer indication of the expected response in this patient group. In these patients, the average changes after rehabilitation did reach the levels generally considered to represent clinically important differences for the measures of exercise capacity, dyspnea, and health-related quality of life.

It should also be noted that patients enrolled in the NETT had more severe obstructive lung disease than that typically found in pulmonary rehabilitation programs. The mean FEV_1 in the NETT (26.9% predicted) was lower than that reported in any study in one evidence-based review (range, 35 to 80% predicted; median, 43% predicted).[1]

We attempted to standardize the NETT rehabilitation protocol by training all rehabilitation staff and certifying satellite centers. Even among the 17 NETT centers, there were some significant center-specific differences in the magnitude of change in maximum exercise capacity and the St. George Respiratory Questionnaire score. There were no significant center differences noted in the UCSD Shortness of Breath Questionnaire score, indicating that improvements in dyspnea were quite consistent.

Although measured changes in the rehabilitation program were not predictors of a differential effect on the primary outcome measures in NETT by treatment (survival or maximum exercise capacity), our experience suggests that pulmonary rehabilitation did play an important role in evaluating and preparing patients for surgery and in maintaining patients in the study. In designing the NETT protocol, we were quite concerned about the difficulties in maintaining subject compliance with the challenging study requirements. It was thought that close contact with the pulmonary rehabilitation staff during the prerandomization and immediate postrandomization phases would be important in ensuring that patients fully understood the study requirements and were committed to returning for follow-up, regardless of their treatment assignment. Although there are no data that are specific to the effect of rehabilitation, the impression of many centers was that this was a critical element in the extraordinary adherence to treatment achieved in the NETT.

Besides optimizing preoperative physical and emotional function, an important function of pulmonary rehabilitation was to help select appropriate patients for surgery and to ensure that patients made a truly informed choice about treatment options. Although we cannot quantify it precisely, the experience in the NETT was that many patients (perhaps 10%) who came to the study eager for surgery experienced such positive effects from pulmonary rehabilitation that they were subsequently unwilling to proceed to randomization and accept the surgical risks. Other patients, who might have initially seemed appropriate for surgery, were subsequently found during pulmonary rehabilitation to be too ill or fragile for surgery.

In extrapolating NETT results to clinical practice, the subgroups identified on the basis of postrehabilitation exercise capacity proved to be important. These results demonstrated that 20% of patients changed their subgroup designation after rehabilitation. Although most of these changes (67%) were from the low exercise subgroup to the high exercise subgroup, some patients (33%) changed from the high (33%) to the low exercise subgroup. This occurred slightly more commonly in patients with prior rehabilitation experience (37% vs 27% of subgroup changes, respectively) who may have already achieved maximum benefit from rehabilitation. However, this was also due to patients experiencing exacerbations during rehabilitation that impeded their progress but were not severe enough to prevent them from completing the program and qualifying for randomization.

Despite the extensive requirements of NETT and the out-of-pocket expenses, many patients traveled long distances and made a considerable effort to participate. In designing the pulmonary rehabilitation program for the NETT, we were concerned about the variability in services that might be provided in so many satellite centers, but wanted to make the protocol as available as possible to patients throughout the country. The fact that 65% of ran-

domized patients utilized satellite centers indicates the strong motivation of many patients and justifies the inclusion of geographically dispersed centers. In retrospect, the relative consistency of improvements from pulmonary rehabilitation observed across centers in the NETT relieves these concerns.

Although these analyses focus on the prerandomization phase of pulmonary rehabilitation, it should be remembered that the NETT rehabilitation program was designed to be a daily home-care program that was continued throughout the study. Patients were required to return for additional supervised visits after randomization and were monitored for adherence through regular telephone and in-person contacts. Also, NETT centers had the option of prescribing additional supervised rehabilitation sessions if they were deemed necessary. This is distinctly different from the usual practice of pulmonary rehabilitation that is often restricted to one treatment period of a few months duration and without allowance for continued follow-up, reassessment, or retreatment.

Overall, pulmonary rehabilitation in the NETT produced significant benefits for these patients with advanced emphysema and played an important role in the selection of appropriate patients for possible LVRS. The consistency of the results, both in the NETT centers and at the satellite centers, demonstrates the effectiveness of pulmonary rehabilitation in the management of patients with chronic lung diseases.

Appendix: NETT Credit Roster

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