PURPOSE: To evaluate the neuropsychological and psychological functioning of emphysema patients following 10 weeks of multidisciplinary medical therapy (MT).

METHODS: Patients with moderate to severe emphysema (n = 56) enrolled in the National Emphysema Treatment Trial at 2 sites (National Jewish Health and Ohio State University) completed cognitive, psychological, and quality-of-life (QOL) tests at baseline and 6 to 10 weeks following participation in pulmonary rehabilitation. Healthy control subjects (matched on age, sex, race, and education, n = 54) completed the same tests at baseline and 6 to 10 weeks later.

RESULTS: Controlling for practice effects and educational level, emphysema patients in the MT group demonstrated significant improvement compared with controls on a global index of cognition, and in measures of visuomotor sequential skills and visual memory. The MT group showed significant reductions in several measures of depression and anxiety, and the control group showed a significant reduction in total depression, but acute anxiety scores were worse 6 to 10 weeks later. The MT group showed significant improvement on 6 of 9 QOL variables and no change was detected in the control group. Improvement on the cognitive index score in the MT group was related to decline in depression and increased workload.

CONCLUSION: Emphysema patients who received MT demonstrated improvement in specific neuropsychological functions, depression, anxiety, and QOL scores compared with control subjects during the same interval (with no treatment). Mechanisms for these neurobehavioral changes include greater exercise endurance and decreased depression.

Emphysema is associated with significant physical, cognitive, and psychological sequelae. Common medical treatment modalities in emphysema such as oxygen therapy and physical rehabilitation improve neurobehavioral functions. Recently published results from the National Emphysema Treatment Trial (NETT) indicate that non–high-risk patients randomized to surgery had notable improvement in disease-specific quality of life (QOL) and physical function, as well as improvements in mood and aspects of neuropsychological functioning.

Emphysema patients with moderate to severe disease have demonstrated cognitive deficits in simple motor movement, overall strength, perceptual-motor integration, abstract reasoning, attention to auditory stimuli, learning and memory, and language skills. Even with mild disease, emphysema patients have been notably impaired in aspects of reasoning, auditory and visual attention, verbal and nonverbal memory, and visuomotor skills.

In addition, psychological distress is common in chronic obstructive pulmonary disease (COPD).
Wagena et al\textsuperscript{22} evaluated 118 patients with COPD and found that they experienced more psychological distress than the general population but less distress than psychiatric outpatients. No correlation was reported between severity of pulmonary disease and level of psychological distress, but patients with severe or very severe COPD had an increased risk of depression. Using a variety of standardized questionnaires and interviews, depression\textsuperscript{4,17-21,23-25} and anxiety\textsuperscript{16,26-28} appear to be the most common psychological difficulties in emphysema patients. van Manen et al\textsuperscript{29} reported that in patients with severe COPD, the prevalence of depression was 25% compared with 19.6% in patients with mild to moderate COPD. Adjusting for demographic variables and comorbidity, the risk of depression was 2.5 times greater for patients with COPD compared with controls.

Improved cognition and reduced psychological distress in COPD has also been reported following multidisciplinary rehabilitation.\textsuperscript{2,3,29-32} Significant improvement in levels of depression, anxiety, and neuropsychological function (complex attention, visual processing, and motor speed) was reported in 64 COPD patients following a 30-day exercise and rehabilitation program.\textsuperscript{2} In a subsequent study, Emery et al\textsuperscript{3} found decreased anxiety and improvement in verbal fluency among COPD patients participating in a comprehensive 10-week rehabilitation program (exercise, education, and stress reduction) compared with a group receiving education and stress reduction alone. These results demonstrate important cognitive change in COPD patients following rehabilitation.

Kozora et al\textsuperscript{32} found that improved cognitive functioning following 3 weeks of multidisciplinary treatment was associated with decreased depression. Specifically, decreased depression was related to improved visual attention, complex visuomotor attention, and visuospatial skills. No associations were found between increased exercise abilities and cognition following rehabilitation. This suggests that the early improvement in cognition seen in COPD patients is likely associated with psychological improvement not physical endurance, and that treatment aimed at reduced psychological distress may improve cognitive skills.

In a previously published study with NETT, Kozora et al\textsuperscript{33} compared neuropsychological and psychological functioning in emphysema patients following lung volume reduction surgery (LVRS) compared with medical therapy (MT). In this prior study, 21 patients were randomized to MT and 19 patients were randomized to LVRS. Cognitive and psychological testing were obtained at baseline, 6 to 10 weeks following pulmonary rehabilitation, and at 6 months following randomization to MT or LVRS. Results indicated that patients who received LVRS demonstrated greater improvement than MT patients in cognitive functions, depression, anxiety, and QOL. In this previous publication, analyses focused on comparing outcomes of 2 treatment arms with a smaller group of emphysema patients over a 6-month period. This current study and analysis was designed to examine the cognitive and psychological effects of pulmonary rehabilitation on a larger group of emphysema patients.

This study included neuropsychological evaluations at 2 time points for patients enrolled in NETT at baseline and after 6 to 10 weeks of rehabilitation (just prior to randomization). We hypothesized that emphysema patients in MT would experience improvements in cognitive performance over and above those observed in a healthy control group. Second, we expected the MT group to report significant reductions in psychological distress and improved quality of life after rehabilitation. Finally, we hypothesized that increased exercise, improved lung function, and better psychological status would be associated with neuropsychological improvement following rehabilitation among emphysema patients.

**METHODS**

Two groups of subjects completed this NETT ancillary study: 56 MT patients and 54 healthy controls matched by age, education, race, and gender. All MT subjects had moderate to severe emphysema and were enrolled as participants in the NETT protocol.\textsuperscript{5} The NETT subjects participated in a pulmonary rehabilitation program for 6 to 10 weeks. Consistent with the NETT protocol, each subject completed a 2- to 3-hour initial comprehensive rehabilitation evaluation from which an exercise prescription was determined. The standard program consisted of at least 16 sessions, with typical sessions including exercise training plus 1 education, psychosocial, or nutrition encounter. Each exercise session lasted 60 to 90 minutes and included endurance, stretching, and strengthening exercises. The education component included topics such as physiology of COPD, use of supplemental oxygen, proper nutrition, and sexuality. The psychosocial component consisted of individual or group sessions covering topics such as stress management and coping with chronic illness.

Patients in the NETT study at National Jewish Health (NJJ) and Ohio State University (OSU) \((n = 56)\) were recruited into this ancillary study and completed baseline (time 1) and postrehabilitation (time 2) neuropsychological testing. The matched sample of 54 control subjects (with no history of
Measures and Procedures

All patients enrolled in NETT at NJH and OSU sites were invited to participate in this study. Those who agreed to participate signed a consent and continued with the neuropsychological battery described below (time to complete was approximately 1.5 hours), administered by trained neuropsychological personnel. All NETT patients at the NJH and OSU sites completed the Beck Depression Inventory (BDI), State Trait Anxiety Inventory (STAI), and Trail Making Test (TMT) as a part of the initial assessment for the general NETT study. To ensure proper oxygenation throughout the neuropsychological testing, oximetry readings were recorded before and after testing (Datec-Ohmeda 3800 Oximeter).

Neuropsychological tests

The battery was developed to evaluate areas of cognitive dysfunction that have been documented among patients with emphysema, including reasoning, attention, memory, language, and visuospatial functions. Tests included 4 subtests from the Wechsler Adult Intelligence Scale–Revised to estimate IQ; the Logical Memory, Verbal Paired Associates, and Faces subtests from the Wechsler Memory Scales–Third Edition as measures of immediate and delayed recall for verbal and nonverbal information; the WAIS-R Digit Span and Arithmetic subtests as measures of immediate auditory attention; the Digit Vigilance Test as a measure of sustained visual attention; the TMT Form A and B as a measure of efficiency in completing sequential tasks; the Complex Ideational Material subtest from the Boston Diagnostic Aphasia Examination as a measure of verbal comprehension; the Controlled Oral Word Association Test and Animal Naming Test as measures of oral verbal fluency to letter and semantic cues; a 15-item version of the Boston Naming Test as a measure of naming to confrontation (BNT-15); and Clock drawing to command as a measure of visuospatial constructional processes.

Neuromedical interview

At baseline the patients completed a brief (10- to 15-minute) structured interview regarding current and past medical, neurological, and psychiatric history. Any changes in this background information were recorded at the follow-up assessment.

Psychological functioning and QOL measures

The BDI is a 21-item scale with well-established reliability and validity that measures symptoms of depression. Scores for each item can range from 3 (the most severe) to 0 (absence). A total score of 63 is possible, with higher scores indicating greater depressive symptoms. Subscales of cognitive-affective and somatic symptoms were also derived according to BDI procedures. The STAI is a 40-item self-report questionnaire that examines both the state (acute) and trait (chronic) symptoms of anxiety. It has been used in prior clinical studies and reliability and validity are well established. The first 20 items are summed to create a State Anxiety score (range, 20–80) and the latter 20 items form the Trait Anxiety score (range, 20–80). The Medical Outcomes Study Short Form (SF-36) examines functional status and well-being in a self-administered format using Likert-type scales. It provides 8 subscale scores as well as a total score. The subscales include physical functioning, social functioning, role limitations due to physical problems, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions. Reliability and validity are well established, and it is a valid indicator of change in health status.

Exercise measures

Maximal workload measures exercise capacity (the maximal workload that the subject achieves during an incremental cycle exercise test) is a primary outcome measure in NETT. Testing was performed using 30% inspired oxygen in all subjects and included 3 minutes of unloaded pedaling. The 6-minute walk is a measure of exercise capacity and is calculated as the maximum distance walked on a level surface in 6 minutes.

Statistical Analysis

Data are presented as means ± SD for continuous data and as percentages for dichotomous data. To compare demographic and health characteristic variables at baseline among groups, the chi-square or Fisher exact test was used for dichotomous variables and the Student t test was used for continuous variables. A repeated-measures analysis of variance model was used to compare MT and control groups on psychological functioning, neuropsychological measures, and QOL. To correct for practice effects in evaluating neuropsychological tests, a regression approach was employed. Control group data were used to generate formulae for predicting time 2 scores from time 1 scores. To examine potential associations among cognitive improvements and changes in BDI, exercise capacity, and pulmonary function in the MT group, a mixed-effects linear regression model was used with cognitive total score as the outcome variable and health characteristics, psychological
functioning, or QOL as the predictor variable, respectively. All data analyses were conducted using SAS (version 9.1, SAS Institute Inc, Cary, North Carolina), with a 2-tailed \( P < .05 \) indicating statistical significance.

**RESULTS**

No differences were observed across the MT and control groups at baseline on measures of age, gender, ethnicity, or marital status (Table 1). However, the control group had a slightly higher educational level than controls.

**Health Characteristics**

Table 2 lists the health characteristics of the MT group. As noted, the MT group had significantly more years of smoking and lower oxygen saturation before and after testing and had used significantly higher levels of the following medications: immunosuppressants, antidepressants, antihypertensives, gastrointestinal, theophylline, and aerosol inhalers. Seventy percent of the MT (2% controls) were on oxygen at baseline. Across groups, 16.1% of MT and 20.4% of controls had a history of mild neurological disorders, 9.0% of MT and 3% of controls had moderate to severe neurological histories, 26.8% of MT and 5.6% of controls were receiving current psychological treatment, 25.0% of MT and 24.1% of controls had past psychological treatment, and 3.8% MT and 11.8% of controls had a prior history of alcohol abuse.

**Neuropsychological Functioning**

As noted in Tables 3 and 4, 20 individual test scores and a summary cognitive impairment index were derived from the neuropsychological battery. Utilizing statistical methods that control for practice effects and educational level across the 2 time points as described above, the MT group showed significant improvement compared with the controls on global cognitive functioning, and specific improvement on tests of sequential skills (TMT), visuoconstruction (Clock drawing), and delayed visual memory (Wechsler Memory Scale–III Faces II subtest).

**Psychological Functioning and QOL**

As indicated in Table 5, the MT group showed significant improvement on the BDI (total score and cognitive-affective subscores) and in both state and trait anxiety from the STAI. The control group showed a significant improvement in their BDI total scores. Control subjects reported increased state anxiety at time 2.

As shown in Table 5, the SF-36 QOL subscores were significantly improved in the MT group on 6 of the 9 variables including, Physical Functioning, Role-Physical, Social Functioning, Mental Health, Vitality, and Change in Health. No significant change for the control group subjects was observed.

**Pulmonary Function, Oxygenation, and Exercise Capacity**

The MT group showed significant improvement from time 1 to time 2 in workload and 6-minute walk (see Table 6).

**Cognitive Change and Changes in BDI, Exercise Capacity, and Pulmonary Function in MT Group**

Linear regression analyses were performed to examine potential correlations between the cognitive improvement in the MT group and measures identified above. Results indicate a significant association between improved global cognitive functioning and lowered depression (BDI total score) \( (r = 0.193, P = .015) \). Improved global cognitive functioning (a decline over time) was associated with improved exercise ability measured by workload \( (r = -0.234, P = .046) \) and lowered oxygen saturation \( (PaO_2; r = 0.26, P = .018) \). No significant associations were found between improved global cognitive function and change in 6-minute walk.

**DISCUSSION**

The COPD subjects in this study demonstrated a global improvement in cognitive functioning following pulmonary rehabilitation after controlling for practice effects and educational level. The global measure of cognition used in this study incorporates a wide range of mental domains, including attention, learning and memory, reasoning, language skills, fluency, and visuomotor skills. Specific tests that demonstrated improvement were also identified and included measures of psychomotor speed, visuoconstruction, and visual memory. Overall, these findings are consistent...
the COPD subjects had lower total depression scores, as well as reductions in the cognitive-affective and somatic components of depression. Improvement (lowered levels) in state and trait anxiety were also noted. Interestingly, the control subjects also had an improvement in their total depression score but had

with prior studies of improved neuropsychological performance following multidisciplinary treatment in COPD patients.3,29,31,32

Consistent with prior studies in COPD, the current study also showed significant improvement in depression, anxiety, and QOL measures.3,29–32 Specifically, the COPD subjects had lower total depression scores, as well as reductions in the cognitive-affective and somatic components of depression. Improvement (lowered levels) in state and trait anxiety were also noted. Interestingly, the control subjects also had an improvement in their total depression score but had

| Table 2 • Health Characteristics of NETT Groups at Baselinea |

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MT emphysema group (Mean ± SD)</th>
<th>Control group (Mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of diagnosis, y</td>
<td>8.2 ± 6.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial pressure exerted by CO₂</td>
<td>42.0 ± 6.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial pressure of oxygen</td>
<td>59.5 ± 10.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of days exercised</td>
<td>18.7 ± 2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced expiratory volume, % predicted</td>
<td>24.1 ± 7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced expiratory vital capacity, %</td>
<td>61.3 ± 18.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak oxygen uptake, % predicted</td>
<td>56.7 ± 26.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-minute walk distance, ft</td>
<td>1157 ± 291.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workload, % predicted</td>
<td>30.6 ± 13.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workload, W</td>
<td>43.6 ± 21.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of years patient smoked</td>
<td>41.1 ± 7.9</td>
<td>15.0 ± 15.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Oxygen saturation-pulse oximetry before testing</td>
<td>94.5 ± 2.0</td>
<td>96.1 ± 1.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Oxygen saturation-pulse oximetry after testing</td>
<td>94.6 ± 2.3</td>
<td>96.2 ± 1.5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Medications, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid immunosuppressant</td>
<td>37.5</td>
<td>1.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>19.6</td>
<td>5.6</td>
<td>.03</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>28.6</td>
<td>13.0</td>
<td>.04</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>26.8</td>
<td>7.4</td>
<td>.007</td>
</tr>
<tr>
<td>Theophylline inhaler</td>
<td>33.9</td>
<td>1.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Aerosol inhaler</td>
<td>91.1</td>
<td>1.9</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Abbreviation: MT, medical therapy.
aPercentages for dichotomous data.

| Table 3 • Cognitive Tests Scores Across Group at Baseline and Postrehabilitation |

<table>
<thead>
<tr>
<th>Variable</th>
<th>MT emphysema group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span</td>
<td>14.1 ± 2.9</td>
<td>13.9 ± 3.3</td>
<td>.2132</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>11.4 ± 3.4</td>
<td>12.0 ± 3.9</td>
<td>.9661</td>
</tr>
<tr>
<td>Digit vigilance time</td>
<td>435.4 ± 92.6</td>
<td>427.0 ± 100.3</td>
<td>.9214</td>
</tr>
<tr>
<td>Digit vigilance errors</td>
<td>9.6 ± 8.5</td>
<td>8.2 ± 8.1</td>
<td>.3137</td>
</tr>
<tr>
<td>Digit symbol</td>
<td>42.6 ± 8.5</td>
<td>44.9 ± 8.6</td>
<td>.9005</td>
</tr>
<tr>
<td>Trail making A</td>
<td>40.2 ± 15.8</td>
<td>37.2 ± 13.8</td>
<td>.0026</td>
</tr>
<tr>
<td>Trail making B</td>
<td>107.0 ± 49.5</td>
<td>100.3 ± 44.4</td>
<td>.2707</td>
</tr>
<tr>
<td>Similarities</td>
<td>16.8 ± 5.5</td>
<td>18.3 ± 4.2</td>
<td>.9005</td>
</tr>
<tr>
<td>Picture completion</td>
<td>14.5 ± 2.8</td>
<td>15.2 ± 2.3</td>
<td>.0550</td>
</tr>
<tr>
<td>Boston naming</td>
<td>13.6 ± 1.8</td>
<td>13.6 ± 1.8</td>
<td>.1049</td>
</tr>
<tr>
<td>Complex material</td>
<td>11.1 ± 1.1</td>
<td>11.3 ± 0.9</td>
<td>.0929</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>31.6 ± 10.5</td>
<td>34.1 ± 10.8</td>
<td>.4557</td>
</tr>
<tr>
<td>Animal fluency</td>
<td>19.2 ± 4.4</td>
<td>19.7 ± 3.3</td>
<td>.2941</td>
</tr>
<tr>
<td>Clock drawing</td>
<td>13.9 ± 1.6</td>
<td>14.0 ± 1.5</td>
<td>.0439</td>
</tr>
<tr>
<td>Cognitive total</td>
<td>3.4 ± 2.9</td>
<td>2.6 ± 2.2</td>
<td>.0021</td>
</tr>
</tbody>
</table>

Abbreviation: MT, medical therapy.
aP values are for comparisons on times 1 vs 2 for the rehabilitation group adjusting for practice effects and educational level.
higher levels of acute anxiety at the follow-up time point.

The mechanisms underlying neurobehavioral improvements in emphysema subjects after pulmonary rehabilitation include both psychological and pulmonary factors on the basis of our analyses. There were significant associations between improved global functioning in the emphysema MT group and lowered depression. As this rehabilitation program included a psychological intervention and potential change in medications, it is possible that improved cognitive abilities are in some part related to the improvement in psychological status associated with this portion of the program. Improved global cognitive functioning was also associated with improved exercise ability (6-minute walk and workload). It has been suggested that the “exercise” component of pulmonary rehabilitation programs is the most important factor in improved neurobehavioral functions. For example, Norweg et al54 randomized COPD patients to 3 treatment groups and the group with exercise plus activity training had the greatest reduction in fatigue and dyspnea and improved involvement in functional activities.

Multiple human and animal studies indicate that aerobic exercise can improve cognitive functioning55–58 in healthy elderly subjects participating in moderate or high resistance-training experimental groups. Notably, both visual attention and visual memory functions improved in our COPD patients.

### Table 4 - Additional Memory Test Scores Across Group at Baseline and Postrehabilitation

<table>
<thead>
<tr>
<th>Variable</th>
<th>MT emphysema group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 2</td>
</tr>
<tr>
<td>Logical memory I</td>
<td>35.0</td>
<td>8.1</td>
</tr>
<tr>
<td>Logical memory II</td>
<td>18.9</td>
<td>6.5</td>
</tr>
<tr>
<td>Verbal pairs I</td>
<td>15.9</td>
<td>7.3</td>
</tr>
<tr>
<td>Verbal pairs II</td>
<td>5.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Faces I</td>
<td>33.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Faces II</td>
<td>34.4</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Abbreviation: MT, Medical therapy.

*values are for comparisons on times 1 vs 2 for the rehabilitation group adjusting for practice effects and educational level.

### Table 5 - Comparison of Depression, Anxiety, and Quality-of-life Measures Across Groups at Baseline and Postrehabilitation

<table>
<thead>
<tr>
<th>Variable</th>
<th>MT emphysema group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 2</td>
</tr>
<tr>
<td>BDI cognitive-affective score</td>
<td>5.2 ± 4.1</td>
<td>3.4 ± 2.9</td>
</tr>
<tr>
<td>BDI somatic score</td>
<td>6.0 ± 2.8</td>
<td>4.3 ± 2.3</td>
</tr>
<tr>
<td>BDI total score</td>
<td>11.0 ± 6.5</td>
<td>7.5 ± 4.6</td>
</tr>
<tr>
<td>STAI-acute</td>
<td>43.5 ± 9.5</td>
<td>40.3 ± 11.4</td>
</tr>
<tr>
<td>STAI-chronic</td>
<td>43.6 ± 9.9</td>
<td>41.3 ± 10.7</td>
</tr>
<tr>
<td>SF-physical functioning</td>
<td>21.1 ± 14.9</td>
<td>25.5 ± 16.7</td>
</tr>
<tr>
<td>SF-role-physical</td>
<td>14.5 ± 24.9</td>
<td>28.8 ± 33.7</td>
</tr>
<tr>
<td>SF-role-emotional</td>
<td>63.0 ± 44.3</td>
<td>71.7 ± 37.2</td>
</tr>
<tr>
<td>SF-social functioning</td>
<td>60.5 ± 22.6</td>
<td>67.8 ± 23.0</td>
</tr>
<tr>
<td>SF-bodily pain</td>
<td>69.8 ± 20.9</td>
<td>71.7 ± 20.1</td>
</tr>
<tr>
<td>SF-mental health</td>
<td>71.4 ± 19.3</td>
<td>76.5 ± 15.2</td>
</tr>
<tr>
<td>SF-vitality</td>
<td>41.8 ± 17.9</td>
<td>49.8 ± 17.5</td>
</tr>
<tr>
<td>SF-general health</td>
<td>38.9 ± 17.1</td>
<td>40.5 ± 18.0</td>
</tr>
<tr>
<td>SF-change in health</td>
<td>2.8 ± 1.0</td>
<td>3.4 ± 1.1</td>
</tr>
</tbody>
</table>

Abbreviations: BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory; SF, Medical Outcomes Study Quality of Life Short Form.
following 10 weeks of pulmonary rehabilitation. Similarly, O’Dwyer et al. found that exercise training (alone or with cognitive training) showed better cognitive performance following 16 weeks of treatment and at 6-month follow-up compared to a no-training control group in healthy elderly individuals. Bixby et al. further showed that high levels of self-reported physical activity over 3 to 5 years in healthy men and women were associated with better performance on a measure of complex attention. Finally, patients with dementia or mild cognitive impairment in exercise treatment showed cognitive improvement compared to nonexercise group. In combination with our study findings, it appears that rehabilitation with an exercise or aerobic component improves neurobehavioral function.

The physiology of cognitive improvement associated with aerobic/exercise activity has been subject to debate but likely includes vascular and neuronal changes. Timinkul et al. have shown that exercise is associated with increased cerebral blood flow in the prefrontal cortex, a finding that directly links exercise to increased blood flow and brain oxygenation. Prior animal studies have also suggested that fitness training enhances vascularization in the brain, and a recent review of literature suggests that regular exercise may build a vascular reserve. Animal studies have also identified physical activity associated with cell proliferation and neurogenesis in the hippocampus and subsequent improved spatial learning and enhanced long-term potentiation.

Although findings from this study suggest cognitive improvement following rehabilitation in COPD, there are limitations and future directions suggested by our current research. First, improvement was statistically determined across cognitive measures for the MT group compared with controls; however, the magnitude of change when comparing the 2 groups was minimal. The clinical impact and effect on day-to-day functions remain unclear and may require additional studies. Second, we did not have randomized control interventions with which to separate out the potential contributions of exercise, psychological interventions, and psychoeducational lessons. Both psychological and exercise improvements were related to cognitive improvement, and randomized studies or a large sample size able to factor out components is necessary. Finally, our results are based on follow-up data following 6 to 10 weeks of rehabilitation exercises. Because there is growing evidence that ongoing exercise rehabilitation may be necessary to sustain cognitive improvement, future studies that investigate change as well as adherence over time may be useful in understanding long-term benefits.

In conclusion, this study extends accumulating evidence for improved cognitive functions following a pulmonary rehabilitation program in COPD patients. Specifically, global functions as well as aspects of psychomotor speed, visuospatial abilities, and visual memory were improved. This finding is also strengthened by the use of a control group to factor out the effects of practice effects on cognitive tests.

—Acknowledgments—

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