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Sequential Cognitive Skills in Emphysema Patients Following Lung Volume Reduction Surgery: A Two Year Longitudinal Study

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Abstract

PURPOSE—This study compared visuomotor speed and cognitive flexibility in emphysema patients treated either with standard multidisciplinary medical therapy (MT) or lung volume reduction surgery (LVRS), followed over a 2-year period.

METHODS—MT patients (n=544) and 542 LVRS patients completed the Trail Making Test (TMT) Parts A and B prior to randomization (baseline). Testing was repeated at 1 and 2 years.

RESULTS—There were no differences on scores for TMT Part A and B between the LVRS and MT groups at baseline or at years 1 and 2. No significant difference between MT and LVRS was noted in terms of overall change in TMT Part A and B over 2 years. The MT group had a significant improvement on TMT-Part A at each followup time compared to baseline ($P<.03$) but the LVRS group did not. Both the MT and LVRS groups had a significant decline in performance (increase in time to completion) on TMT-Part B when comparing year 1 to baseline ($P<.0001$).

CONCLUSION—Emphysema patients who received LVRS or MT as treatment performed similarly on measures of visuomotor speed and flexibility at baseline and 1 and 2 year followup. Both groups showed improvement on visuomotor speed during the first year yet overall cognitive flexibility declined. By the second year neither group had any significant change from baseline. These findings suggest that improvement on visuomotor speed and flexibility, observed in a previous 6-month study of LVRS subjects, was not sustained at 1 and 2 year followup.

Keywords

Lung volume reduction surgery; Medical therapy; Sequential skills

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Emphysema is a chronic progressive pulmonary disease with significant physical, cognitive and psychological sequelae. Patients with moderate to severe emphysema exhibit cognitive deficits across a variety of domains.¹⁻⁶ Emphysema represents a subset of patients with chronic obstructive pulmonary disease (COPD), and data on patients with COPD are relevant to understanding cognitive impairment in emphysema. In COPD patients with moderate to severe hypoxemia, deficits have been reported in psychomotor speed, perceptual-motor integration, abstract reasoning, attention to auditory stimuli, learning and memory, and language skills.^{2,3,5-7} Several studies have found that psychomotor speed and aspects of executive functioning are the cognitive areas most consistently affected by COPD.⁸⁻¹⁰

The Trail Making Test (TMT) is a common measure of visuomotor speed and executive functioning.¹¹ It has 2 parts, which measure visuomotor processing speed (TMT-Part A) and set shifting and maintenance of effort (TMT-Part B). Impaired executive functioning has been associated with poorer instrumental daily activities in older adults.¹² For example, 1 study of 7717 elderly women demonstrated that impaired executive functioning, measured using the TMT-Part B, was more strongly associated with decline in activities of daily living over 6 years than global cognitive function.¹³ These findings suggest that impairments in executive functioning, including visuomotor speed and sequential ability, have important practical implications for older adults.

Patients with COPD perform worse on the TMT than age matched controls.^{5,9,10} In “end-stage” COPD patients, Crew et al⁸ found that more patients did poorly on TMT-Part B than TMT-Part A. The authors concluded that patients had greater difficulties with set shifting skills and maintenance of response strategies than pure slowing of processing speed. Another study found impairments in both Trail Making Test Part A and B.¹⁰

There is evidence that oxygen therapy, pulmonary rehabilitation and exercise interventions improve cognitive functions in emphysema and COPD.^{4,14-17} The mechanisms associated with improved processing speed and sequencing include enhanced exercise capacity and cerebral oxygenation.¹⁸ Lung volume reduction surgery (LVRS) is a procedure performed on COPD patients that affects both exercise capacity and oxygenation.¹⁹ Previous studies from our group compared the neuropsychological profile of 19 patients following lung volume reduction surgery (LVRS) and 20 patients following standard medical therapy (MT) using data collected at 2 of the 17 sites participating in the National Emphysema Treatment Trial (NETT).²⁰ Participants completed a comprehensive neuropsychological battery including TMT at baseline, prerandomization (6-10 weeks following rehabilitation), and 6 months after randomization. Initial findings suggested that 6 months after randomization to LVRS or MT, LVRS patients had significantly improved performance on several cognitive tests, including the TMT Parts A and B.²¹ Subjects in the main NETT study completed TMT at baseline, prerandomization (following 6-10 weeks multidisciplinary rehabilitation), 12 months, and yearly for up to 5 years.

In the current study we sought to extend the scope and length of followup in our previous cognitive studies to determine whether the cognitive improvement observed at 6 months in a subsample of NETT participants would be evident in the larger sample at 2-year followup. The current study examined changes in the psychomotor speed and sequencing skills of emphysema patients randomized to either LVRS or to MT with data collected at 15 clinic sites (excluding the 2 sites previously examined at 6 months²⁰). We hypothesized that at 2-year followup patients randomized to LVRS would exhibit better performance on psychomotor speed and sequencing skills on the TMT Parts A and B than patients randomized to MT.

METHODS

All MT and LVRS participants were enrolled in the NETT protocol under the specified guidelines.²⁰ All participants from 15 sites with complete TMT A and B data at any time point were selected for analysis. Data from 2 sites (Ohio State University and National Jewish Health) were excluded due to multiple additional cognitive testing time points at those sites which may influence test scores, ie, practice effects. All NETT participants had a diagnosis of severe emphysema with no significant comorbid physical or mental conditions that could interfere with completion of tests, therapy, or followup. Participants had a history and physical exam consistent with COPD, a CT scan with evidence of moderate to severe emphysema, hyperinflation and airflow limitation (post bronchodilator total lung capacity (TLC) >110% predicted, residual volume (RV) >150% predicted, forced expired volume in 1 second (FEV₁) <45% predicted).

Procedures

All NETT patients were randomized after completion of a 6 to 10 week pulmonary rehabilitation program. This program included 1-3 physician visits, 20 exercise training sessions (strength, flexibility, upper and lower extremity endurance), 14 educational sessions, and 5 psychosocial sessions. NETT patients were randomized to 1 of 2 procedures: LVRS or MT. LVRS is a procedure to remove emphysematous lung tissue. The surgical technique was conducted either via median sternotomy (MS) or video assisted thoracoscopy (VATS). Subsequent to randomization, all patients completed followup visits with the NETT physician and received medical management including use of bronchodilators, and other medications, counseling and exercise training.

For the entire NETT study across 17 sites, 1218 emphysema patients were randomized to LVRS or MT. Of these participants, 1086 were available for the TMT analysis (with 2 sites removed): 542 in the LVRS group and 544 in the MT group. There were no group differences in age, education, or ethnicity between those randomized to LVRS versus MT (Table 1). As noted in Table 2, there also were no group differences on measures of lung function (ie, FEV₁, partial pressure of oxygen in arterial blood (PaO₂), partial pressure of carbon dioxide in arterial blood (PaCO₂) or exercise abilities, (ie, 6 minute walk test (6MWT) and workload at pre rehabilitation baseline). For this analysis, TMT Part A and B were analyzed at pre randomization (baseline), and at 2 subsequent annual assessments.

Measures

Both TMT Part A and B consist of 25 circles that are distributed over a sheet of paper.¹¹ In Part A, the circles are numbered from 1-25 and the subjects are asked to draw lines that connect the numbers in ascending order. In part B, circles include both numbers (1-13) and letters (A-L) and are distributed across a sheet of paper. Subjects are asked to draw lines to connect the circles in an ascending sequence alternating between numbers and letters (ie, 1-A-2-B-3-C, etc). Subjects are instructed to work as quickly as they can, and the number of seconds to complete the task is the final score for each part.

Statistical Analysis

All statistical analyses were conducted with the SAS statistical analysis package (version 9.2; SAS Institute Inc., Cary, NC). TMT Part A and B were not normally distributed so a natural logarithm transformation was performed on both variables. Baseline demographic and health characteristics were compared between MT and LVRS groups using a Student *t*-test (for continuous variables) or χ^2 (for categorical variables). Baseline demographic and health characteristics, and TMT Part A and B were also compared between participants who did and did not have follow-up at years 1 and 2 using a Student *t*-test, χ^2 or Fisher's exact

test based on the nature of the data. Percent change in raw score for TMT A and B time to completion was calculated for each patient. Percent change scores were analyzed using a paired *t*-test comparing each follow-up visit against baseline. The mean percent change between the 2 groups was analyzed using a two sample *t*-test. We also compared the change over time, between the MT and LVRS groups, on both TMT-A and TMT-B using a mixed effects linear regression model. Due to baseline differences in walking distance, workload, education, and prednisone use, these variables were included as covariates in all analyses of cognitive function. Two-tailed tests were used for all analyses and *P* values <.05 were designated to be statistically significant.

RESULTS

As noted in Table 3, 44% of the MT patients and 36% for LVRS who had baseline TMT data did not have data at year 1. Of the randomized patients who participated in this subanalysis, 52 assigned to the LVRS (9.6%) and 28 assigned to MT (5.1%) died before the 1-year followup. Additionally, 57% of the MT patients and 46% of the LVRS patients with baseline TMT data did not have year 2 data (12 assigned to LVRS (2.2%) and 32 assigned to MT (5.9%) died between the 1 year and 2-year followup). Due to a change in the protocol (where patients no longer had onsite appointments at year 1 starting in year 2003), 39 patients in the MT group (7.2%) and 40 patients in the LVRS group (7.4%) did not complete TMT data at year 1. Overall completion rates across groups were significantly different at year 1 and year 2 with higher followup data available on the LVRS participants (*P*=.006 and *P*=.0002, respectively).

In order to evaluate potential bias related to subjects who were not followed in year 1 and 2, we compared baseline demographic and health characteristics of participants who had results at one year to those who did not. From baseline to year 1, LVRS participants whose TMT data were not available at year 1 had lower exercise capacity (distance on 6MWT) at baseline compared to LVRS participants whose TMT data were available at year 1 (*P*=.004). MT participants not available at year 1 walked less at baseline and had lower workload (*P*<.001 respectively) compared to those MT participants who completed the 1 year visit. From baseline to year 2, LVRS participants who were not available at 2 years had shorter walk distance and lower workload at baseline (*P*≤.001 respectively). MT participants who were not available at year 2 had both lower walk distance and lower workload at baseline (*P*<.001). For MT patients only, participants who did not complete followup were less educated, and were taking more prednisone at year 1 (*P*=.015) and year 2 (*P*=.013 and *P*=.013 respectively).

Analysis of Trails A and B

As shown in Table 3, no significant difference was found when comparing the log-transformed TMT-A and TMT-B data between the 2 groups at any time point. Using a mixed effects linear regression model for both TMT Part A and B (with log TMT Part A and B as the outcome variable and year in the study as the predictor variable stratifying by treatment group), slopes of both the regression lines were not significantly different from zero for both TMT-Part A (*P*=.79) and TMT-Part B (*P*=.78). In addition, there was no significant difference between the MT and LVRS groups in term of TMT-Part A (*P*=.82) and TMT-Part B (*P*=.77) over time after adjusting for education at baseline and possible confounders changes over time (FEV₁, workload, and prednisone use).

Using percent change in performance over time within groups, the MT group had a significant improvement on TMT-Part A when comparing all followup time points to the baseline (Figure 1) but the LVRS group did not (Table 4, Figure 1). With regard to TMT Part B, there was a decline in performance (increase in time to completion) when comparing

year 1 to baseline for both the LVRS and MT group (Table 4, Figure 2). Neither group showed a significant change when comparing year 2 to baseline on Part B (Figure 2). Finally, there was no significant difference between the LVRS and MT groups in terms of the mean percent change from baseline to follow-up times for TMT Part A and B, respectively (Table 4).

DISCUSSION

Emphysema patients randomized to LVRS or MT showed no difference in visuomotor speed (TMT-Part A) or cognitive flexibility (TMT-Part B) over 2 years. Within the MT group, improvement on visuomotor speed was noted yet it was no greater than change within the LVRS group. Both groups showed a decline in mental flexibility during the first year but this did not decline over the next yearly interval. In our prior study, we found improved sequential visuomotor functions in LVRS compared to MT patients at 6 months post treatment at 2 of the NETT sites not included in this new analysis.²² Thus, with a larger sample size and testing over a longer time interval, there does not appear to be a treatment advantage from LVRS in terms of visuomotor speed or flexibility over time.

Although the test battery is limited, our results indicate that there is no significant decline by year 2 in visuomotor speed and flexibility. Prior research has suggested that COPD patients who do not continue to exercise show a downward trajectory of cognitive function.²³ Our current sample was biased towards patients with greater exercise capacity, and might provide further evidence that cognitive decline is preventable in some COPD patients.

The longer term 2-year findings in this paper differ from our first study that followed patients for 6 months. Several methodological issues may contribute to these discrepant results. First, the prior study included a much smaller sample size compared to this national study (n=56 vs. n=1086) and although procedures (control group and controlling for practice effects in statistical modeling) were utilized in the early study, the findings may not be generalized to the entire study population. Secondly, the national study had a relatively large completion rate over the 2 years that may have influenced the overall findings. As noted in our results, there were some deaths in our group (approximately 7.3% between baseline and year 1 and 4% between year 1 and year 2), and approximately 7% of the subjects in each group that were not scheduled to return at year 1. Our analyses further indicated that dropouts had lower physical function at baseline possibly related to more COPD, or comorbidities. However, we have no additional data indicating specific reasons for missing TMT data at follow-up. Thus, results identified within and between our treatment groups are highly specific to the more physically fit COPD patients limiting the generalizability of our findings. Finally, the multisite NETT study did not include comprehensive cognitive testing and possible improvement in other domains may have occurred without detection. There may have been other influences on TMT performance other than exercise, such as the extension beyond the traditional duration of pulmonary rehabilitation programs.

In conclusion, despite some of our methodological restrictions, we have a relatively large database of patients with emphysema randomized to MT and LVRS who did not show significant changes in performance on visuomotor speed or visuospatial sequencing ability over a 2-year follow-up interval. This suggests that neither treatment group had a long term advantage, or disadvantage, in visuomotor speed or cognitive flexibility.

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Figure 1.

Raw Score Performance on TMT-Part A for MT and LVRS Over 2 Years

Abbreviations: TMT, Trail Making Test; MT, medical treatment group; LVRS, lung volume reduction surgery group

Figure 2. Raw Score Performance on TMT-Part B for MT and LVRS Over 2 Years

Abbreviations: TMT, Trail Making Test; MT, medical treatment group; LVRS, lung volume reduction surgery group

Table 1

Comparison of Demographics Across Groups at Baseline

Variable	Level	MT		LVRS		P-value
		n		n		
Age, y, M(SD)		544	66.6(5.9)	542	66.3(6.4)	.464
Gender	Male	334	61.4%	314	57.9%	.245
	Female	210	38.6%	228	42.1%	
Education	Less than high school	111	20.4%	106	19.6%	.078
	Graduated high school	150	27.6%	184	33.9%	
	Some college or post	185	34.0%	177	32.7%	
	Bachelor's degree or higher	98	18.0%	75	13.8%	

Abbreviations: MT, medical treatment group; LVRS, lung volume reduction surgery group

Table 2

Health Characteristics Across Groups at Pre-Rehabilitation Baseline

Characteristics	MT		LVRS			P-value
	n	Mean	SD	n	Mean	SD
Pre-BD FEV1, % predicted	543	23.99	6.52	542	23.66	6.32
PaO2, mmHg	544	65.19	10.05	541	65.20	9.82
PaCO2, mmHG	544	42.69	5.25	541	42.80	5.26
Walk distance, m	534	342.94	94.67	528	345.23	93.64
Workload, W	532	35.35	20.80	525	35.94	21.55

Abbreviations: MT, medical treatment group; LVRS, lung volume reduction surgery group; Pre-BD FEV1, prebronchodilator forced expired volume in 1 second

Table 3

Comparison of TMT Part A and B Within and Across Groups at Baseline, Year 1 and Year 2

Variable	Year	MT Group			LVRS Group			P value from <i>t</i> -test for comparison of groups
		n	Mean (raw score in seconds)	Standard Deviation	n	Mean (raw score in seconds)	Standard Deviation	
Trail Making Test A (seconds)	baseline	544	43.47	15.73	542	43.04	15.94	.657
	1	304	40.53	15.85	347	40.02	16.35	.688
	2	233	38.94	14.19	294	40.39	18.20	.306
Trail Making Test B (seconds)	baseline	544	98.70	41.58	542	99.22	39.70	.835
	1	301	103.20	40.81	344	103.26	37.65	.986
	2	231	93.03	39.54	290	95.11	40.65	.557

Abbreviations: TMT, Trail Making Test; MT, medical treatment group; LVRS, lung volume reduction surgery group

Table 4

Comparison of % Change in TMT Part A and B Across Groups

Time Interval	MT		LVRS			P value for comparison between groups
	n	Mean % Change in Seconds	P-value for Within Group % Change	n	Mean % Change in Seconds	P-value for Within Group % Change
Trail Making Test –A						
Year 1 vs. baseline	304	–1.06	.025	347	–0.91	.084
Year 2 vs. baseline	233	–1.40	.019	294	–0.96	.117
Trail Making Test –B						
Year 1 vs. baseline	301	1.65	<.001	344	1.98	<.001
Year 2 vs. baseline	231	–0.35	.449	290	–0.59	.292
						.544
						.737

Abbreviations: TMT, Trail Making Test; MT, medical treatment group; LVRS, lung volume reduction surgery group