Annals of Nuclear Medicine Vol. 20, No. 2, 99–106, 2006

Brain perfusion abnormalities in chronic obstructive pulmonary disease: comparison with cognitive impairment

Hulya ORTAPAMUK and Seniha NALDOKEN

Department of Nuclear Medicine, Ankara Numune Research and Training Hospital, Ankara, Turkey

Objectives: To clarify cerebral perfusion distribution and cognitive functions in patients with chronic obstructive pulmonary disease (COPD) according to the hypoxia levels and to assess if there is a relationship between cognitive impairment and cerebral perfusion index. ***Patients and Methods:*** Eight patients with stable hypoxemic COPD (HC), 10 patients with stable nonhypoxemic COPD (NHC), and 10 age-matched healthy volunteers participated in the study. All subjects underwent a complete neuropsychological assessment with the mental deterioration battery (MDB), Wechsler memory scale-revised (WMS-R), color trail test (CCT), and grooved pegboard test (GPT). SPECT examination with Tc-99m HMPAO was performed in all patients and controls. Quantitative analysis was performed by a region of interest (ROI)-based method. ***Results:*** The scores of verbal memory, delayed recall and attention were significantly lower in COPD patients ($p < 0.01$). The scores of other subtests were similar in patients and controls. Comparing NHC patients to HC groups showed that verbal memory was impaired in both groups, but delayed recall and attention scores were significantly worse in HC patients than NHC patients. Perfusion indexes on frontal ROIs in NHC patients and frontal and parietal ROIs in HC patients showed significant decreases. Our scintigraphic findings were correlated with the results of neuropsychological tests. ***Conclusions:*** Our results demonstrate that cerebral perfusion is significantly altered in COPD patients. Hypoxemic patients showed more deterioration in cerebral perfusion and cognitive performance than nonhypoxemic patients. The relationship between decreased perfusion and cognitive impairment and the clinical significance of these results require further studies in larger populations.

Key words: chronic obstructive pulmonary disease, cognitive impairment, Tc-99m HMPAO SPECT

INTRODUCTION

ALTHOUGH AIRFLOW OBSTRUCTION is the most obvious manifestation of chronic obstructive pulmonary disease (COPD), it is associated with many extrapulmonary features that contribute to the morbidity, reduced quality of life, and, possibly, mortality of this disease.[1–5] Cognitive impairment have been documented as one of the important extrapulmonary manifestation in patients with COPD.[6–14] Arterial oxygen desaturation may develop in patients with COPD as a result of their disease. This decline in arterial oxygen content could subsequently result in a decrease in oxygen transport to the brain. Global ischemia leads to a variable degree of impairment of cognitive abilities.[15–17] Much research has typically indicated that COPD individuals experience declines in a number of cognitive functions, such as memory reaction time, memory, abstract reasoning skills, and complex visual-motor processes.[18–21] Many studies evaluated the correlation between neuropsychological dysfunction and pulmonary function or arterial blood gases in COPD patients.[10,11,13,22,23] Recently, metabolic brain studies with MR spectroscopy have been reported.[24–26] However, to date and to our knowledge only one study has evaluated

Received March 17, 2004, revision accepted November 2, 2005.

For reprint contact: Hulya Ortapamuk, M.D., Cigdem mah. 357. sok. 4/38 Karakusunlar, Ankara, TURKEY.

E-mail: hortapamuk@yahoo.com

the cerebral perfusion pattern using SPECT in COPD.[27] Therefore, the purpose of the present study is to documented the cerebral perfusion pattern using SPECT and to investigate the relationship between perfusion index and cognitive performance in a sample of COPD patients.

PATIENTS AND METHODS

Patients

Eight patients with stable hypoxemic and hypercapnic COPD (HC) (mean age 52.6 ± 5.4 years, range 47–64 years) and 10 patients with stable nonhypoxemic COPD (NHC) (mean age 54.8 ± 6.9 years, range 45–65 years) were included in the study. The patients' age ranged from 45 to 65 years, with a mean age of 55.1 ± 6.1 years. There were 8 women and 10 men. Ten volunteers (6 males and 4 females) comprised the control group. The control subjects with comparable age, sex and educational status were asymptomatic, nonsmokers, not having any metabolic, psychiatric or neurologic disease and they were taking no medications. All patients gave their informed consent to the study. Ethical approval for the study was obtained from the local ethics committees. The diagnosis of COPD was made according to the criteria defined by the American Thoracic Society.[28] Spirometry and blood gas analysis were done on the day of the scintigraphic study for all patients. After 30 minutes rest, arterial blood gas samples were drawn from radial artery and analyzed immediately. The spirometry data were analyzed using both absolute values and percent of normal predicted values according to the guidelines of the American Thoracic Society.[28] Standardized inhaled therapy to prevent the confounding effect of different dosages was given to all patients: inhaled salbutamol, 200 mg twice a day; ipratropium bromide, 250 mg three times a day and; beclomethasone, 250 mg three times a day. Cognitive test and brain perfusion SPECT were made under the stable conditions. Conditions that can affect the results of cognitive tests and cause cerebral perfusion changes were excluded: 1. a history of head trauma, alcohol or drug abuse, 2. taking medicine which affects the cognitive status and cerebral perfusion and other coexistent pulmonary diseases, congestive heart failure, cirrhosis, dementia, and recent or old stroke, carotid artery stenosis over 50%, renal disorders, thyroid dysfunction, anemia, vitamin B_{12} and folate deficieny, diabetes mellitus or other chronic disease or any visual and hearing impairment, 3. psychiatric disorders. Because depression may influence performance on a cognitive functioning test,[29] depressed subjects according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders III-revised were excluded from the study,[30] 4. patients unable or unwilling to perform the test were also excluded.

All the subjects underwent an extensive physical and laboratory examination, including routine blood and urine analysis, serum assays for vitamin B_{12}, thyroid hormones, NH_4, VDRL, ECG, and chest radiograph. All patients underwent structural imaging by MRI. A 1.5-T unit (Siemens Medical Systems) was used to acquire a standard set of images. Subjects with morphological abnormality or cortical atrophy were not included in the study.

Cognitive Tests

Cognitive functions were assessed by means of mental deterioration battery (MDB) and the battery of neuropsychological tests described below. MDB was proved very effective in discriminating normal from abnormal cognitive performance and characterizing disease-related patterns of mental deterioration. It includes tasks of episodic memory [Rey's Auditory Verbal Learning Test (RAVLT)], language (Word Fluency and Phrase Construction), immediate visual memory, visual-spatial intelligence (Raven's Coloured Matrices) and constructional apraxia (Copying Drawings with and without landmarks).[30] Three additional more comprehensive neuropsy chological tests were used in the present study: Wechsler memory scale-revised (WMS-R), the grooved pegboard test (GPT) and, the color trail test (CTT). The WMS-R is used as a very effective neuropsychological test for memory and learning ability. It yields age-adjusted and education-adjusted standardized scores containing five subcategories: general memory, verbal memory, visual memory, delayed recall, and attention.[31] The GPT test is used for evaluation of visuomotor coordination and motor control of each hand.[32] The CTT is a neuropsychological test for attention and visuospatial scanning ability and it is less affected by cultural or educational levels.[33] All subjects were given psychometric tests by the same medical personnel.

Cerebral Perfusion (SPECT)

Seven hundred and forty MBq of technetium-99m-hexamethylpropylene amine oxime (HMPAO) (Nycomed-Amersham, S.A.) was injected intravenously in a semidark room with reduced visual and auditory stimulus. SPECT imaging was performed using a single head gamma camera (Elscint SPX-6, Haifa, ISRAEL) equipped with a high resolution collimator. Acquisition was started 15 minutes after the injection. The head of the patients was fixed and remained immobile throughout the study. The data were acquired in a 64 × 64 matrix through 360° rotation at 6° intervals for 30 second per projection with a 1.2 zoom and total 60 projections were collected. Total acquisition time was 30 minutes. Approximately 6 million counts were collected for each study. Filtered back projection with a Metz filter was used for reconstruction. Chang's method was applied for attenuation correction with a coefficient factor of 0.075. No scatter correction was performed. The full-width at maximum in the transaxial plane was 8.3 mm. Image slices were arranged parallel to the orbitomeatal line and slices were obtained in the coronal, sagittal and oblique planes. Quantitative analysis was performed by a

ROI-based method according to the report of Tran Dinh et al. 16 transverse slices reoriented parallel to the orbitomeatal plane were obtained using anatomically defined regions of interest.[34] For this study, the following ROIs were drawn semiautomatically over the orbitomeatal plane at vertex cerebral, mid-cerebral and basal cerebral slices: three bilateral ROIs over the superior frontal, central and parietal regions on vertex cerebral slices; six bilateral ROIs over the anterior frontal, middle frontal, temporoparietooccipital, occipital, sylvian, and thalamic regions on mid-cerebral slices; two bilateral ROIs over the anterior temporal, hemicerebellar regions and one middle ROI over the pons on basal cerebral slices. For detailed evaluation of the temporal structures, two transverse slices were reconstructed along the major axis of the temporal lobe and two additional ROIs over the mesial and lateral temporal regions were drawn. The ROI template used was shown in Figure 1. For each cerebral area, mean counts per pixel of the corresponding ROIs in two consecutive slices were averaged. The average number of counts for each region was normalized to the mean cerebellar uptake. ROI semiquantitative analysis was performed by the same investigator, who was blinded to the clinical data. Reference values were obtained from the healthy control group (95% confidence interval of the mean). Regions outside the reference limits were considered abnormal.

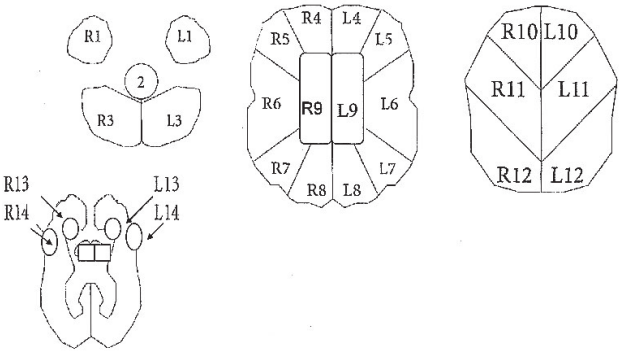


Fig. 1 Representative template of ROIs. R: right, L: left, 1: anterior temporal, 2: pons, 3: cerebellum, 4: anterior frontal, 5: middle frontal, 6: sylvian, 7: temporo-parieto-occipital, 8: occipital, 9: thalamus, 10: superior frontal, 11: central, 12: parietal, 13: mesial temporal, 14: lateral temporal.

Statistical Analysis

Data were analyzed by statistical packages (SPSS for Windows, version 11.5; SPSS, Inc., Chicago; and BMDP, Berkeley, Calif.). Quantitative variables data are expressed as the mean ± SD. The data of the patients and controls in terms of age, duration of education and pulmonary function parameters were statistically analyzed using Mann-Whitney U test. The comparison of cognitive tests between groups was made by Mann-Whitney U test. The significance of the difference in each ROI between

Table 1 Demographic features, blood gas and spirometry results of the groups

	Mean age (years)	Sex M/F	Duration of education (year)	PaO_2 mmHg	$PaCO_2$ mmHg	FEV_1, *l*/min	FEV_1, % predicted
Control subjects n = 10	54.1 ± 8.7	6/4	10.28 ± 3.6	—	—	2.9 ± 0.7	110 ± 10
HC n = 8	52.6 ± 5.4	5/3	9.00 ± 3.8	51.6 ± 4.1*	47.6 ± 7.9[#]	0.77 ± 0.32	34 ± 9.2
NHC n = 10	54.8 ± 6.9	5/5	10.4 ± 2.8	67.5 ± 4.9*	39.9 ± 5.1[#]	1.08 ± 0.55	33.9 ± 13

* $p < 0.05$ for HC versus NHC and [#] $p < 0.01$ HC versus NHC

Table 2 Mean scores (standard deviation) of COPD patients and of control subjects on the tasks of the mental deterioration battery

Tasks	NHC	HC	Control
Visual memory	14.3 (3.1)	14.1 (3.3)	14.6 (2.3)
Immediate recall	33.8 (3.7)	27.1 (5.9)	35.2 (8.3)
Delayed recall	7.8 (2.9)	4.1 (2.7)[#]	8.6 (3.1)[#]
Delayed recognition	77.3 (8.0)	76.9 (7.7)	79.5 (6.8)
Phonological verbal fluency	26.8 (8.8)	25.9 (7.8)	27.8 (9.1)
Word generation	13.7 (4.2)	14.1 (5.5)	15.3 (3.5)
Copying drawings	7.0 (3.6)	6.9 (3.0)	7.2 (2.8)
Copying drawings with landmarks	60.1 (8.9)	59.6 (7.5)	61.6 (5.2)
Digit span forward	6.9 (1.7)	7.0 (0.9)	7.1 (1.2)
Digit span backward	5.1 (1.1)	4.8 (1.3)	5.3 (0.8)
Raven's colored progressive matrices	15.4 (5.4)	14.8 (4.5)	17.2 (3.7)
Temporal rule induction	15.3 (5.4)	17.6 (4.9)	17.7 (5.1)

[#] HC versus control $p < 0.01$

Table 3 Other neuropsychological tests scores obtained by groups

Neuropsychological tests	HC	NHC	Control
WMS-R			
general memory	92 ± 12	95 ± 10	100 ± 15
verbal memory	77 ± 3*	96 ± 4	100 ± 15*
visual memory	93 ± 11	94 ± 13	100 ± 15
attention/concentration	79 ± 2*	91 ± 12	100 ± 15*
delayed recall	66 ± 3*	91 ± 17	100 ± 15*
CTT			
CTT1	37 ± 13*	46 ± 9	50 ± 10*
CTT2	45 ± 16	47 ± 11	50 ± 10
GPT			
dominant hand	47 ± 14	48 ± 9	50 ± 10
nondominant hand	46 ± 10	47 ± 12	50 ± 10

* HC versus control $p < 0.01$

patients groups and controls was evaluated by Student's t test for independent groups. Bonferroni's correction was used to control the probability of type I errors when performing multiple comparisons. We considered the significance for differences between groups in neuropsychological tests and counts on ROIs at $p < 0.01$. The correlation between cognitive test scores and cerebral perfusion index was performed by Pearson correlation test.

RESULTS

The general characteristics of the patients and control subjects were given in Table 1. Educational level, sex disturbance and age were uniform across groups, according to criteria of selection. No significant difference in these parameters was found between the groups ($p > 0.05$). Table 2 shows the mean scores obtained by COPD patients and control subjects on the various tasks forming the MDB. The results of the other neuropsychological function tests in the patients and controls are listed in Table 3. Compared with the results of control subjects, COPD patients scored less on selected tasks exploring verbal memory, delayed recall, and attention. These three domains were below the threshold of significance in HC patients, while NHC patients had significantly lower scores of verbal memory. No significant difference between the COPD groups and controls was found in any other task of neuropsychological tests.

The mean counts in cerebral ROIs of patients and control subjects are listed in Table 4. Comparison of perfusion indexes between NHC patients and controls, and HC patients and controls showed that one ROI had significantly reduced perfusion in NHC patients than in that of the controls: left anterior frontal; and five ROIs in HC patients than that of the controls: left superior frontal, left anterior frontal, left middle frontal, right superior frontal, and left parietal. Comparison of perfusion indexes between NHC and HC patients showed a significant reduction in perfusion in the following ROIs in HC patients: left middle frontal, left superior frontal, right superior frontal, and left parietal. Perfusion index of left anterior frontal in HC and NHC patients did not show any differences. Examples of perfusion patterns in COPD patients are shown in Figure 2.

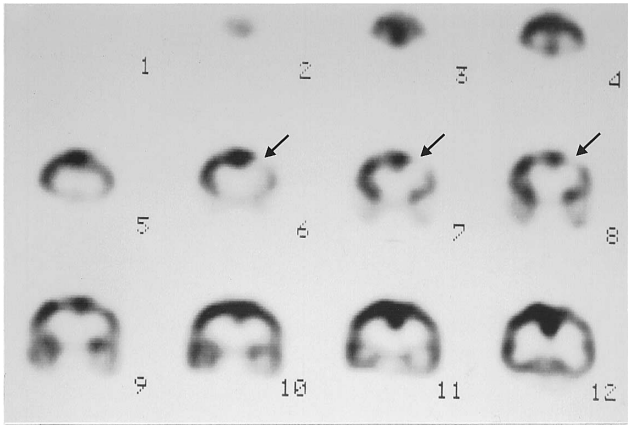
Table 4 Mean counts (SD) in the 27 ROIs of controls, HC patients and NHC patients

ROIs	CS (n = 10)	HC (n = 8)	NHC (n = 10)
R Anterior frontal	0.755 (0.06)	0.715 (0.09)	0.741 (0.06)
L Anterior frontal	0.723 (0.05)*	0.690 (0.06)*,#	0.719 (0.07)*,#
R Middle frontal	0.737 (0.03)	0.729 (0.05)	0.728 (0.08)
L Middle frontal	0.738 (0.08)*	0.694 (0.02)*	0.733 (0.08)
R Sylvian	0.752 (0.05)	0.749 (0.08)	0.750 (0.05)
L Sylvian	0.736 (0.04)	0.732 (0.09)	0.734 (0.09)
R Anterior temporal	0.737 (0.08)	0.747 (0.08)	0.739 (0.10)
L Anterior temporal	0.695 (0.10)	0.682 (0.09)	0.690 (0.10)
Pons	0.793 (0.09)	0.783 (0.09)	0.786 (0.07)
R Hemicerebellar	0.896 (0.07)	0.891 (0.09)	0.887 (0.1)
L Hemicerebellar	0.965 (0.03)	0.953 (0.02)	0.961 (0.03)
R Temporal-parietal	0.752 (0.04)	0.747 (0.08)	0.744 (0.1)
L Temporal-parietal	0.718 (0.05)	0.711 (0.03)	0.716 (0.08)
R Occipital	0.775 (0.05)	0.770 (0.06)	0.769 (0.11)
L Occipital	0.772 (0.05)	0.765 (0.06)	0.769 (0.10)
R Thalamus	0.726 (0.10)	0.715 (0.10)	0.721 (0.09)
L Thalamus	0.689 (0.12)	0.677 (0.08)	0.684 (0.10)
R Superior frontal	0.753 (0.06)	0.750 (0.06)	0.749 (0.11)
L Superior frontal	0.721 (0.04)*	0.650 (0.06)*	0.715 (0.11)
R Central	0.703 (0.05)	0.700 (0.04)	0.695 (0.12)
L Central	0.744 (0.03)	0.748 (0.04)	0.739 (0.12)
R Parietal	0.761 (0.05)	0.763 (0.08)	0.758 (0.13)
L Parietal	0.729 (0.05)*	0.590 (0.03)*	0.724 (0.12)
R Mesial temporal	0.832 (0.32)	0.828 (0.07)	0.830 (0.12)
L Mesial temporal	0.862 (0.39)	0.871 (0.08)	0.871 (0.11)
R Lateral temporal	0.815 (0.04)	0.820 (0.09)	0.824 (0.08)
L Lateral temporal	0.934 (0.05)	0.941 (0.06)	0.939 (0.06)

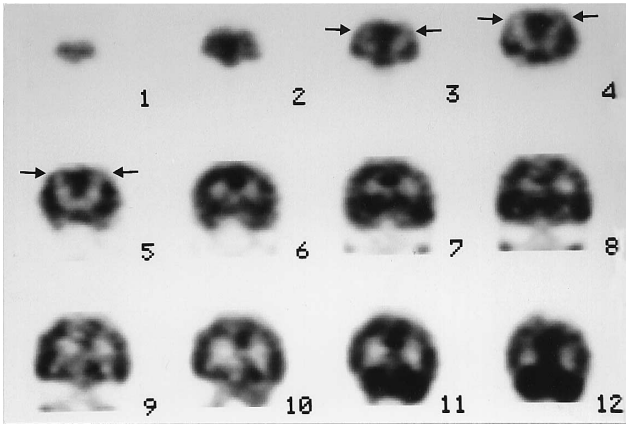
Significant differences: * HC versus CS $p < 0.01$, # NHC versus CS $p < 0.01$

Table 5 Correlation of cognitive functions and cerebral perfusion in HC and NHC patients

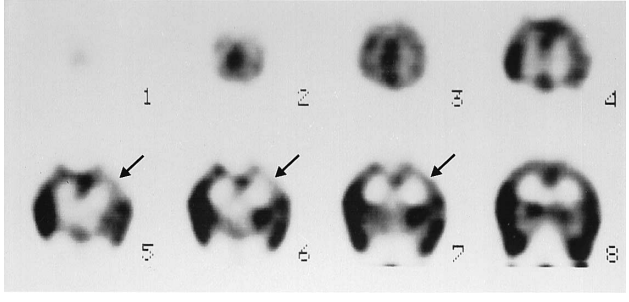
Cognitive function	Perfusion	p	r
HC patients			
Verbal memory	Decreasing in left anterior frontal	0.05	–0.700
Attention	Decreasing in left middle frontal	0.05	–0.86
Delay recall	Decreasing in left middle frontal	0.01	–0.952
NHC patients			
Verbal memory	Decreasing in left anterior frontal	0.05	–0.902



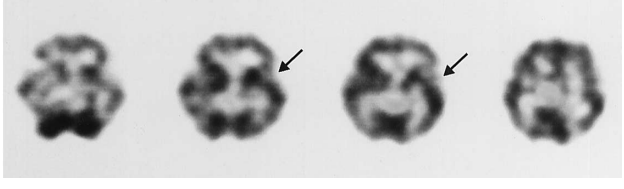
A



B



C



D

Fig. 2 Representative Tc-99m HMPAO SPECT images of brain perfusion abnormalities in COPD patients. (A) SPECT shows reduced cerebral perfusion in left frontal region (*arrow*) in a 55-year-old man with nonhypoxemic COPD. (B) Images of Tc-99m HMPAO shows bilateral hypoperfusion of frontal regions (*arrows*) in a hypoxemic patient. (C) Coronal views of the brain of a 36-year-old woman with hypoxemic COPD shows hypoperfusion of left parietal region (*arrow*). (D) Selected transaxial slices in a hypoxemic patients reveals decreased perfusion in left temporo-parietal region.

Perfusion indexes on frontal ROI in NHC patients and both frontal and parietal ROIs in HC patients were significantly correlated with the results of neuropsychological tests. Remaining ROIs did not show any correlation with the cognitive performance. Verbal memory function was inversely correlated with left anterior frontal perfusion in HC and NHC patients ($r = -0.700$, $p = 0.05$; $r = -0.902$, $p = 0.05$, respectively). Attention function was negatively correlated with left middle frontal lobe perfusion ($r = -0.86$, $p = 0.05$) and a statistically significant correlation was found between the delay recall and left parietal perfusion ($r = -0.952$, $p = 0.01$) in HC patients (Table 5).

DISCUSSION

Individuals with COPD may show both age-related declines in blood flow and disease-related declines in arterial oxygen content. Consequently, the combination of these factors leads to impairment in cognitive function. Although cognitive impairment in COPD patients was reported in many studies,[10,11,13,20,35] this impairment was reported in different subtests. Recall has been frequently reported to be the most affected cognitive function in hypoxemic COPD.[13,20,35,36] Significant impairment has also been found in high cognitive domains, such as abstraction and complex motor integration.[37] Decline of verbal memory has been reported as to parallel the decline of the active recall and passive recognition of learned material.[38] Incalzi et al. showed that 48.5% of patients with COPD had a specific pattern of cognitive deterioration characterized by a dramatic impairment in verbal and verbal memory tasks, well-preserved visual attention, and diffuse worsening of the other functions.[12] Stuss et al. reported that hypoxia in COPD results in a relatively focused pattern of impairment in measures of memory function and tasks requiring attention allocation.[13] Results of the present study showed that verbal memory, delay recall, and attention were impaired in COPD patients. While all these subtest scores were significantly lower in HC patients, NHC patients scored significantly lower than controls only on verbal memory ability. These results are more consistent with the data previously reported, in which, hypoxemic patients showed more deterioration in cognitive functions than nonhypoxemic ones.[11,13,40] The findings of cognitive deterioration in patients having no hypoxemia in this study suggests that the possibility of mental deterioration should be tested in nonhypoxemic COPD patients who are at higher risk than the normal population.

Because of the proposed link between cognitive dysfunction and decreased blood flow, we aimed to clarify cerebral perfusion distribution in COPD and investigate if there is a relationship between cognitive impairment and cerebral perfusion index. Our analysis of cerebral perfusion in NHC patients showed significantly decreased

perfusion in left frontal regions. HC patients showed perfusion decline in both frontal and parietal regions. These results suggested that the hypoxia level of COPD is reflected in different patterns of psychological and CBF changes.

We found that decreasing perfusion indexes correlated with the neuropsychological test results. Deficit in verbal memory, delay recall and, attention may be explained by the decreased perfusion in these task-related cerebral regions. Huang et al. reported that attention was negatively correlated with left prefrontal perfusion index in their study population with mild cognitive impairment.[39] When we considered the role of the frontal region in the regulation of verbal memory and attention, this can emphatically help to explain the relevance between our findings of frontal type cognitive problems and frontal hypoperfusion. Besides frontal hypoperfusion we also detected parietal hypoperfusion which may support the results of Shim et al.[26] They found that the levels of cerebral metabolites of COPD patients were significantly altered, and especially that the choline level in the parietal regions correlated with memory function using ^{1}H MRS. This metobolic changes may be compatible with the perfusion decline in parietal regions as shown in our patients. ^{31}P MR spectra obtained from patients with stable COPD showed that phosphorus-containing metabolites within cerebral cells provide evidence of extensive use of anaerobic metabolism in hypoxemic COPD patients.[24] Blood flow can not be a marker of cerebral metabolism, but reduction in cerebral perfusion in NHC patients can be related to depressed cerebral metabolism.

Only one study has reported the perfusion changes in COPD.[27] The authors noted decreased perfusion in only frontal regions and impairment in only verbal memory. Hypoxemic patients showed perfusion changes in that study, whereas NH patients had normal cerebral perfusion. However, we showed the perfusion changes in both frontal and parietal regions and demonstrated impairment in more cognitive tasks than they did. Moreover, we observed cerebral hypoperfusion in NHC patients besides HC patients. In that study no structural imaging was applied to exclude cerebral pathology which can result in perfusion changes. But in our study all patients and controls underwent MRI to prevent confusion related to other structural changes affecting cerebral perfusion. The discrepancies in the results of these two studies on impaired tasks and perfusion could be the consequence of either patient features or conceptual problems.

Although our study did not establish causality, it is likely that the changes we observed in cerebral blood flow in COPD patients were a consequence of chronic changes in arterial blood gases. After acute CO poisoning, a diffuse, but frontal-dominant hypoperfusion pattern involving both the gray and white matter was reported by Maeda et al.[41] Watanabe et al. reported significantly decreased regional cerebral blood flow extensively in the bilateral frontal lobes as well as the bilateral insula and apart of the right temporal lobe in patients with delayed neuropsychiatric sequelae after carbon monoxide intoxication as compared with normal volunteers.[42] On the bases of these studies we speculated that the frontal-dominant perfusion decrease in our COPD patients may be the result of the greater sensitivity of the frontal regions to hypoxia than the other cerebral regions. But, the observed relationship might be coincidental and has to be proven by more detailed studies focusing on that topic.

CONCLUSION

The present study offers an insight into the relationship between the cerebral perfusion changes and cognitive functions in patients with COPD. Most of the hypoxemic COPD patients and a number of nonhypoxemic patients were found to have cognitive dysfunction and cerebral perfusion abnormalities. More significant results can be obtained if further study is conducted in a larger number of COPD patients. So additional studies will be required to document the clinical significance of cerebral perfusion changes in COPD patients.

REFERENCES

1. Wouters EF, Creutzberg EC, Schols AM. Systemic effects in COPD. *Chest* 2002; 121: 127–130.
2. Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J* 1994; 7: 1793–1797.
3. Engelen MP, Deutz NE, Wouters EF, Schols AM. Enhanced levels of whole-body protein turnover in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 1488–1492.
4. Gross NJ. Extrapulmonary effects of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2001; 7 (2): 84–92.
5. Ambrosino N, Bruletti G, Scala V, Porta R, Vitacca M. Cognitive and perceived health status in patient with chronic obstructive pulmonary disease surviving acute on chronic respiratory failure: a controlled study. *Intensive Care Med* 2002; 28 (2): 170–177.
6. Meek PM, Lareau SC, Anderson D. Memory for symptoms in COPD patients: how accurate are their reports? *Eur Respir J* 2001; 18 (3): 474–481.
7. Kozora E, Filley CM, Julian LJ, Cullum CM. Cognitive functioning in patients with chronic obstructive pulmonary disease and mild hypoxemia compared with patients with mild Alzheimer disease and normal controls. *Neuropsychiatry Neuropsychol Behav Neurol* 1999; 12 (3): 178–183.
8. Etnier J, Johnston R, Dagenbach D, Pollard RJ, Rejeski WJ, Berry M. The relationships among pulmonary function, aerobic fitness, and cognitive functioning in older COPD patients. *Chest* 1999; 116 (4): 953–960.
9. Prigatano GP, Parsons O, Wright E, Levin DC, Hawryluk G. Neuropsychological test performance in mildly hypoxemic patients with chronic obstructive pulmonary disease.

J Consult Clin Psychol 1983; 51 (1): 108–116.
10. Fix AJ, Golden CJ, Daughton D, Kass I, Bell CW. Neuropsychological deficits among patients with chronic obstructive pulmonary disease. *Int J Neurosci* 1982; 16 (2): 99–105.
11. Grant I, Heaton RK, McSweeny AJ, Adams KM, Timms RM. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Arch Intern Med* 1982; 142 (8): 1470–1476.
12. Antonelli Incalzi R, Chiappini F, Fuso L, Torrice MP, Gemma A, Pistelli R. Predicting cognitive decline in patients with hypoxaemic COPD. *Respir Med* 1998; 92 (3): 527–533.
13. Stuss DT, Peterkin I, Guzman DA, Guzman C, Troyer AK. Chronic obstructive pulmonary disease: effects of hypoxia on neurological and neuropsychological measures. *J Clin Exp Neuropsychol* 1997; 19 (4): 515–524.
14. Antanoelli Incalzi R, Gemma A, Marra C, Muzzolon R, Capparella O, Carbonin P. Chronic obstructive pulmonary disease. An original model of cognitive decline. *Am Rev Respir Dis* 1993; 148 (2): 418–424.
15. Dustman RE, Emmerson R, Shearer D. Physical activity, age, and cognitive neuropsychological function. *J Aging Phys Act* 1994; 2: 143–181.
16. Hansen P. Pathophysiology of chronic diseases and exercise training. Durstine JL ed. *Resource manual for guidelines for exercise testing and prescription 2nd ed*., Philadelphia, PA; Lea & Febiger, 1993: 187–197.
17. Marchal G, Rioux P, Petit-Taboue MC. Regional cerebral oxygen consumption, blood flow, and blood volume in healthy human aging. *Arch Neurol* 1992; 49: 1013–1020.
18. Della Sala S, Donner CF, Sacco C, Spinnler H. Does chronic lung failure lead to cognitive failure? *Schweiz Arch Neurol Psychiatr* 1992; 143: 343–354.
19. Crews WD, Jefferson AL, Bolduc T, Elliott JB, Ferro NM, Broshek DK, et al. Neuropsychological dysfunction in patients suffering from end-stage chronic obstructive pulmonary disease. *Arch Clin Neuropsychol* 2001; 16 (7): 643–652.
20. Fioravanti M, Nacca D, Amati S, Buckley AE, Bisetti A. Chronic obstructive pulmonary disease and associated patterns of memory decline. *Dementia* 1995; 6 (1): 39–48.
21. Huppert FA. Memory impairment associated with chronic hypoxia. *Thorax* 1982; 37 (11): 858–860.
22. Mulloy E, McNicholas WT. Ventilation and gas exchange during sleep and exercise in severe COPD. *Chest* 1996; 109: 387–394.
23. Grant I, Prigatano GP, Heaton RK, McSweeny AJ, Wright EC, Adams KM. Progressive neuropsychologic impairment and hypoxemia: relationship in chronic obstructive pulmonary disease. *Arch Gen Psychiatr* 1987; 44 (11): 999–1006.
24. Mathur R, Cox IJ, Oatridge A, Shephard DT, Shaw RJ, Taylor-Robinson SD. Cerebral bioenergetics in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160 (6): 1994–1999.
25. Hamilton G, Mathur R, Allsop JM, Forton DM, Dhanjal NS, Shaw RJ, et al. Changes in brain intracellular pH and membrane phospholipids on oxygen therapy in hypoxic patients with chronic obstructive pulmonary disease. *Metab Brain Dis* 2003; 18 (1): 95–109.
26. Shim TS, Lee JH, Kim SY, Lim TH, Kim SJ, Kim DS, et al. Cerebral metabolic abnormalities in COPD patients detected by localized proton magnetic resonance spectroscopy. *Chest* 2001; 120 (5): 1506–1513.
27. Incalzi RA, Marra C, Giordano A, Calcagni ML, Cappa A, Basso S, et al. Cognitive impairment in chronic obstructive pulmonary disease. A neuropsychological and SPECT study. *J Neurol* 2003; 250: 325–332.
28. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152: 1107–1135.
29. Kennelly KJ, Hayslip B, Richardson SK. Depression and helplessness-induced cognitive deficits in the aged. *Exp Aging Res* 1985; 11 (3–4): 169–173.
30. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, fourth ed.* Washington; American Psychiatric Editors, 1994.
31. Wechsler D. *Wechsler Adult Intelligence Scale—Revised Manual*. San Antonio, TX; Psychological Corp., 1981.
32. Maj M, D'Elia L, Satz P, Janssen R, Zaudig M, Uchiyama C, et al. World Health Organization, Division of Mental Health/Global Programme on AIDS, Evaluation of two new neuropsychological tests designed to minimize cultural bias in the assessment of HIV-1 seropositive persons: a WHO study. *Arch Clin Neuropsychol* 1993; 8 (2): 123–135.
33. Mitrushin MN, Boone KB, D'Elia LF. *Handbook of normative data for neuropsychological assessment*. New York, NY; Oxford University Press, 1999: 428–447.
34. Tran Dinh YR, Mamo H, Cervoni J, Caulin C, Saimot AC. Disturbances in the cerebral perfusion of human immune deficiency virus-1 seropositive asymptomatic subjects: a quantitative tomography study of 18 cases. *J Nucl Med* 1990; 31: 1601–1607.
35. Stulbarg MS, Carrieri-Kohlman V, Gormley JM, Tsang A, Paul S. Accuracy of recall of dyspnea after exercise training sessions. *J Cardiopulm Rehabil* 1999; 19 (4): 242–248.
36. Isoaho R, Puolijoki H, Huhti E, Laippala P, Kivela SL. Chronic obstructive pulmonary disease and cognitive impairment in the elderly. *Int Psychogeriatr* 1996; 8 (1): 113–125.
37. Lisansky DP, Clough DH. A cognitive-behavioral self-help educational program for patients with COPD. A pilot study. *Psychother Psychosom* 1996; 65 (2): 97–101.
38. Incalzi RA, Gemma A, Marra C, Capparella O, Fuso L, Carbonin P. Verbal memory impairment in COPD. Its mechanisms and clinical relevance. *Chest* 1997; 112 (6): 1506–1513.
39. Huang C, Wahlund LO, Almkvist O, Elehu D, Svensson L, Jonsson T, et al. Voxel- and VOI-based analysis of SPECT CBF in relation to clinical and psychological heterogeneity of mild cognitive impairment. *Neuroimage* 2003; 19 (3): 1137–1144.
40. Dulfano MJ, Ishikawa S. Hypercapnia: mental changes and extrapulmonary complication: an expanded concept of the "CO_2 intoxication" syndrome. *Ann Intern Med* 1965; 63 (5): 829–841.
41. Maeda Y, Kawasaki Y, Jibiki I, Yamaguchi N, Matsuda H, Hisada K. Effect of therapy with oxygen under high pressure on regional cerebral blood flow in the interval form of carbon monoxide poisoning: observation from subtraction of technetium-99m HMPAO SPECT brain imaging. *Eur*

Neurol 1991; 31 (6): 380–383.
42. Watanabe N, Nohara S, Matsuda H, Sumiya H, Noguchi K, Shimizu M, et al. Statistical parametric mapping in brain single photon computed emission tomography after carbon monoxide intoxication. *Nucl Med Commun* 2002; 23 (4): 355–366.