patients, respectively) and the mean oxygen flow was 1.2 l/min (1.1 l/min and 1.4 l/min for male and female patients, respectively). There were no significant differences between male and female patients among these values. However, male patients had a significantly higher rate of COPD (71% vs 47%, $p = 0.001$) and lower values of forced expiratory volume in one second (FEV_1) (49.7 ± 10.3 [standard deviation, S.D.] vs 66.0 ± 7.5% predicted, $p = 0.002$) compared with female patients (Table 1).

The proportion of patients with cognitive impairment (MMSE, lower than 23 points) was significantly higher in female patients than in male patients with long-term DOT (14[41%] vs 15[15%], respectively; $p = 0.01$, after correction for differences in age, education, and disease duration). In contrast, there were no significant differences between male and female controls in these data (Table 2). The relation between MMSE score and age is illustrated in Fig. 1. There were significant negative correlations between MMSE

TABLE 1. *Clinical characteristics*

Variable	Controls		Patients		p value*
	Male ($n = 301$)	Female ($n = 417$)	Male ($n = 101$)	Female ($n = 34$)	
Age (yr)	77.4 ± 8.2	78.3 ± 9.2	77.4 ± 8.3	79.0 ± 7.3	0.96
Education (yr)	11.4 ± 2.7	10.8 ± 2.1	11.3 ± 1.9	10.9 ± 2.2	0.08
COPD diagnosed - No. (%)	36(12)	25(6)	72(71)	16(47)	0.001
FEV1.0 (% predicted)	82.7 ± 19.6	87.5 ± 24.6	49.7 ± 10.3	66.0 ± 7.5	0.002
Blood gas analysis					
PaO_2 (mmHg)	85.2 ± 3.6	84.4 ± 5.3	71.0 ± 6.8	69.0 ± 7.3	0.23
$PaCO_2$ (mmHg)	42.8 ± 2.7	41.2 ± 3.4	48.9 ± 2.2	47.6 ± 3.1	0.44
PH	7.41 ± 0.2	7.42 ± 0.1	7.37 ± 0.1	7.36 ± 0.1	0.88

Plus-minus values are means ± S.D. *Comparisons were made between male patients and female patients with long-term DOT.

Blood gas data refer to the patient breathing oxygen at the usual therapeutic concentration via nasal prongs. COPD and FEV1.0 denote chronic obstructive pulmonary disease and forced expiratory volume in one second.

TABLE 2. *Clinical outcomes*

Variable	Controls		Patients		p value*
	Male ($n = 301$)	Female ($n = 417$)	Male ($n = 101$)	Female ($n = 34$)	
MMSE score	27.0 ± 3.0	26.4 ± 3.4	26.0 ± 2.4	23.4 ± 2.1	0.02
≦ 23 No. (%)	18(6)	29(7)	15(15)	14(41)	0.01
> 24 No. (%)	283(94)	388(93)	86(85)	20(59)	
GDS score	4.4 ± 2.8	4.2 ± 2.9	6.2 ± 3.4	5.9 ± 2.6	0.16
Functional/performance status (Katz index)	6.2 ± 1.8	6.2 ± 2.1	7.7 ± 3.3	7.0 ± 2.4	0.17
Borg score	1.1 ± 1.0	1.2 ± 1.1	3.2 ± 0.8	1.4 ± 0.6	0.01

Plus-minus values are means ± S.D. *Comparisons were made between male patients and female patients with long-term DOT.

MMSE and GDS denote Mini-Mental State Examination and Geriatric depression scale.

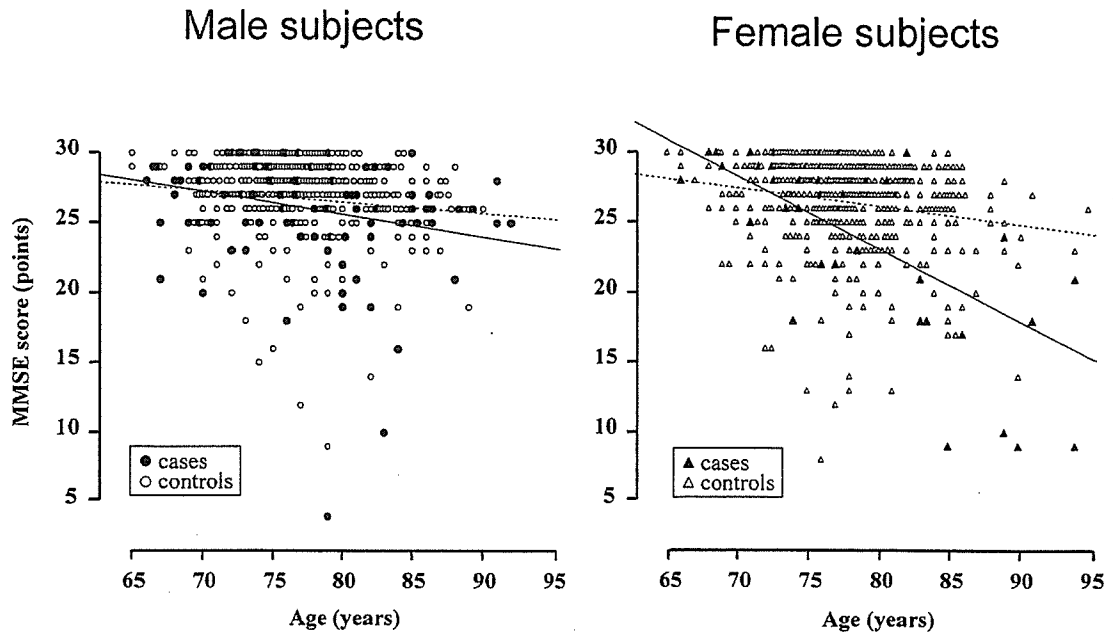

Fig. 1. Correlation between MMSE score and age in male and female subjects.
Open circles indicate male controls and closed circles indicate male patients receiving long-term DOT. Open triangles indicate female controls and closed triangles indicate female patients receiving long-term DOT. The straight lines are fitted to patients with long-term DOT and dashed lines to controls. MMSE denotes Mini-Mental State Examination and DOT denotes domiciliary oxygen therapy.

score and age in both controls and patients receiving long-term DOT. There was no significant difference in declining rate of MMSE score between male controls and patients (–0.077/year, R^2 = 0.016 vs –0.156/year, R^2 = 0.054, respectively, p = 0.231) (Fig. 1). By contrast, a significant difference in declining rate of MMSE score was observed between female controls and patients (–0.120/year, R^2 = 0.027 vs –0.524/year, R^2 = 0.426, respectively, $p < 0.0001$). Furthermore, although there was no significant difference in declining rate of MMSE score between male and female controls, a significant difference was observed between male and female patients (–0.156/year, R^2 = 0.054 vs –0.524/year, R^2 = 0.426, respectively, p = 0.021), which demonstrated age-related cognitive decline was more pronounced in female patients receiving long-term DOT (Fig. 1). Male patients had a significantly higher Borg score during daily exercise compared with female patients (3.2 ± 0.8 [S.D.] vs 1.4 ± 0.6, p = 0.01, respectively) (Table 2). There seemed to be a positive correlation between the MMSE score and the Borg score in both male and female patients, whereas it was not statistically significant (data not shown). There were no correlations between the MMSE score and the FEV_1%, GDS score, Katz index, PaO_2, $PaCO_2$ or the duration of DOT by multi-regression analysis in male and female patients with long-term DOT (Table 2).

Discussion

Oxyhemoglobin desaturation is reported to be an important determination of mental deterioration (Heaton et al. 1983; Incalzi et al. 1993). A previous study has shown that 6 months oxygen treatment is associated with small but definite improvement in brain functioning among patients with hypoxemic COPD (Heaton et al. 1983). However, cognitive function in patients receiving long-term oxygen treatment and its gender differ-

ence has not been studied. The present study demonstrated that age-related cognitive decline was more pronounced in female patients receiving long-term DOT, while cognitive function in male patients was fairly preserved compared with control subjects of the same age. To the best of our knowledge, there are no published data concerning interactions between sex and cognitive outcome after long-term DOT. There were no significant differences among several clinical parameters except the Borg score, probably due to the difference in the lung function, between male and female patients. Despite the lack of clear knowledge of the mechanism for the interaction of sex and cognitive outcome after long-term DOT, a possible explanation for this finding might be a contribution of substance P (SP) in the CNS. Several findings indicate involvement of tachykinins in stress-related anxiety and depressive states (Megens et al. 2002). Especially, SP plays a role in dyspnea perception and in some autonomic reflexes and behaviors (Megens et al. 2002). SP release is suggested in stressful situations in the CNS (Culman and Unger 1995) and the NK_1 receptor antagonist has been shown to improve anxiety and depression rating scales in depressed patients (Rupniak and Kramer 1999). SP might be released significantly in the CNS in male patients with long-term DOT and an increased release of SP might up-regulate neprilysin (Stefano et al. 1992), a major amyloid-β peptide degrading enzyme in the brain, leading to protection against cognitive decline in male patients (Iwata et al. 2000).

That continuous oxygen therapy did not provide a complete protection against the deteriorating cognition in both male and female patients is not surprising, since several factors related chronic respiratory failure other than hypoxemia are known to affect cognition. Among these factors, hypercapnia, acidosis, and hypocapnia resulting from hypoxemia-induced hyperventilation should be taken into consideration (Heaton et al. 1983; Incalzi et al. 1993).

The limitation of the present study should be discussed. First, we did not conduct a longitudinal but a cross-sectional analysis of the cognitive and psychologic functions in patients receiving long-term DOT. A longitudinal study for a long-term period may provide more detail information about the age-related cognitive decline in each subject. Second, the absolute number of the female patients with long-term DOT is limited, which is pointed out in other previous reports (Heaton et al. 1983; Incalzi et al. 1993). This is probably due to a gender difference in the prevalence of pulmonary diseases such as COPD, which require DOT in the case of disease progression. Third, although a significant negative correlation between MMSE scores and age in both controls and patients with long-term DOT was found, the correlation coefficient values were low in individual groups. A further study with a large number of patients is needed to translate the present findings to patients with DOT in general. However, we believe that our data provide sufficient grounds for a reexamination of the effect of long-term DOT on cognitive function in those patients.

In conclusion, the current study demonstrates that the effect of long-term DOT on cognitive outcome differs between men and women. The increased life expectancy of patients with chronic respiratory failure after the introduction of the oxygen therapy implies that a growing fraction of physically disabled and to a various extent mentally impaired patients can be alive until old age especially in female patients (Sasaki et al. 1998; Kubo et al. 2005). Thus, end-stage pulmonary diseases will become a growing geriatric problem, and health care systems should be prepared to deal with it.

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