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Predicting cognitive decline in patients with hypoxaemic COPD

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The objective was to identify predictors of cognitive decline in patients with hypoxaemic COPD on continuous oxygen therapy.

Eighty-four consecutive ambulatory hypoxaemic COPD patients in stable clinical conditions were prospectively studied over the course of 2 yr. Baseline multidimensional assessment included respiratory function tests, blood gas analysis, Mini Mental Status (MMS) test, Geriatric Depression Scale (GDS), Activities of Daily Living (ADLs) and Charlson's index of comorbidity. Reassessments were made 1 yr and 2 yr thereafter. Sequential changes in MMS, GDS and ADLs were assessed by Friedman's ANOVA by rank test.

Forty patients completed the study (group A), while 44 died or were lost to follow-up (group B). Group B was characterized by more severe respiratory function impairment and worse performances on ADLs and GDS. In group A, MMS deteriorated from baseline to the 1 yr and 2 yr reassessments ($27 \pm 2{\cdot}9$ *vs.* $25{\cdot}8 \pm 4{\cdot}1$ and $25{\cdot}4 \pm 4$, $P<0{\cdot}005$), whereas GDS and ADLs did not change significantly; the 23 patients experiencing a decline of MMS had baseline lower percentage predicted FVC ($52{\cdot}3 \pm 17{\cdot}1$ *vs.* $66{\cdot}9 \pm 13{\cdot}4$, $P<0{\cdot}03$) and FEV_1 ($27{\cdot}2 \pm 8{\cdot}6$ *vs.* $44 \pm 26{\cdot}8$, $P<0{\cdot}02$) values and better affective status (GDS score: $11{\cdot}9 \pm 7{\cdot}7$ *vs.* $16{\cdot}5 \pm 5{\cdot}6$, $P<0{\cdot}04$). Two-year changes in MMS and in GDS scores were inversely correlated (Spearman's $\rho = -0{\cdot}32$, $P=0{\cdot}04$).

Cognitive decline is faster in the presence of severe bronchial obstruction and parallels the worsening of the affective status in COPD patients on oxygen therapy. The onset of depression rather than baseline depressive symptoms seems to be a risk factor for cognitive decline.

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Introduction

A strong relationship is known to link COPD and cognitive dysfunction. Impairment of several neuropsychological functions characterizes hypoxaemic COPD and is partially reversible with the oxygen therapy (1–3). Both defective retrieval and inaccurate recognition affect verbal memory of COPD patients (4). Furthermore, a cross-sectional study showed that peak expiratory flow rate was positively associated with performance on three screening cognitive tests in 3812 old men residing in East Boston (5). A recent longitudinal study correlating midlife pulmonary function with late-life cognitive function demonstrated that depressed FEV_1 was an independent predictor of cognitive dysfunction diagnosed by a screening instrument 23 yr after respiratory function tests had been performed (6).

No information is available regarding the rate of decline of cognitive function in COPD. The indirect evidence from case series studies is consistent with a strong relationship existing between length of history of COPD and neuropsychological impairment (3). Arterial hypercapnia characterizes patients with severe cognitive dysfunction (7). However, comorbid diseases, limitations in social activities and depression, which are very common in COPD patients, can *per se* affect cognition (2). Attempts should be made to disentangle the effects of these conditions on mental status and to identify predictors, if any, of cognitive decline.

The present study aims (1) to assess comparatively over the course of 2 yr changes in cognitive, affective and functional status of hypoxaemic COPD patients without clinically significant cognitive impairment at baseline and (2) to characterize subjects at risk of cognitive decline.

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Subjects and Method

PATIENTS

All the COPD patients listed in the oxygen therapy register of the Pneumology outpatient department of a university hospital in October 1993 were requested to participate in the study. The study protocol was in accord with guidelines provided by the ethics committee of the university.

The diagnosis of COPD conformed with criteria of the American Thoracic Society (8). Sixty-eight patients were on continuous oxygen therapy because they had PaO_2 inferior to 7·3 kPa. Ischaemic heart disease coexisting with COPD was the rationale for prescribing continuous oxygen therapy to the remaining 16 patients, although their PaO_2 ranged from 7·3 to 8·7 kPa. Patients inspired an oxygen-enriched mixture through a Ventimask; the inspired concentration of oxygen ranged from 24% to 31% as required to obtain $SaO_2 \geq 90\%$. During ambulation, most of the patients inhaled oxygen through nasal prongs at a flow ranging between 1 and 4 l min^{-1} as required to achieve $SaO_2 \geq 90\%$; the optimal oxygen flow had been previously defined by performing a 12 min walking test. Liquid oxygen was used; a stroller containing 1000 l was available during ambulation. Compliance with oxygen therapy was checked by analysing records of oxygen use written by the patient and his or her caregivers. Patients using oxygen for less than 19 h were considered to be uncompliant with oxygen therapy. This threshold was chosen because using oxygen for at least 19 h is known to halve mortality when compared with nocturnal oxygen therapy (9).

All the patients lived at home and were ambulant at the time of recruitment and in stable conditions. They regularly attended the Pneumology ambulatory every 4 months.

Criteria for exclusion from the study were as follows: dementia, major depressive syndrome or psychiatric disorders according to DSMIII-r criteria (10); sensory impairment or illiteracy preventing neuropsychological assessment; comorbid diseases, e.g. cerebrovascular disease or hypothyroidism, apt to affect cognitive function (11); bereavement or change in living location in the year before recruitment. Patients recognized to be uncompliant with oxygen therapy were excluded from the follow-up and were considered to be drop-outs. Indeed, regular continuous oxygen therapy is known to slow cognitive, affective and functional decline, so that lack of compliance with oxygen therapy would be a confounding factor (9).

Patients were provided with a standardized therapy including inhaled salbutamol 200 μg t.i.d. and ipratropium bromide 250 μg t.i.d. with beclometasone dipropionate 250 μg t.i.d. added every other month. Nine patients were on continuous low-dose steroid therapy *per os* (prednisone, 5 mg daily). Exacerbations of COPD severe enough to require hospitalization were treated by parenteral antibiotics and steroids. Theophylline was not prescribed.

PROCEDURE

Patients underwent a baseline multidimensional assessment exploring the following areas.

- *Sociodemographic area.* Age, sex, years of formal education, smoking history (previous smoker, actual smoker), occupational role before retirement codified according to Featherman and Hauser (12) and marital status were recorded.
- *Functional capabilities.* The performance in the Activities of Daily Living (ADLs) was directly observed by the examiner and not reported by the patient. ADLs are dressing, bathing, transferring, toileting, walking, eating (13). Each ADL performance was scored in a simplified form: 1, completely independent (performs by himself or herself); 0, performs with some help or is completely dependent on external help. Thus, the whole ADL score can range between 0 and 6. This simplified ADL score was adopted because it is expected to reduce the confounding effect of short-term changes in individual ability due to fluctuations in COPD severity.
- *Affective status.* This was explored by the Geriatric Depression Scale (GDS). This self-administered questionnaire includes 30 questions. Depressed subjects usually score 14 or more (14).
- *Cognitive function.* This was assessed by the Mini Mental Status (MMS) test. This screening instrument, which is used worldwide, explores spatial and temporal orientation, short-term and long-term verbal memory, attention, verbal attainment and praxic abilities. Normal subjects usually score 24 or more (15).
- *Medical area.* Diseases were codified according to the International Classification of Health Problems in Primary Care (16). Charlson's index of comorbidity was computed (17). This index provides a cumulative estimate of the burden of comorbidity which is known to affect the prognosis of homeliving patients with chronic diseases (18).
- *Respiratory function area.* The forced vital capacity manoeuvre was performed by a Baires computerized system (Biomedin, Padova, Italy) according to guidelines provided by ATS in 1987 (19). Reference standards provided by Knudson *et al.* were used (20). Arterial blood gases were measured by a Radiometer ABL 330 (Radiometer, Copenhagen, Denmark) with the patient at rest breathing room air from 1 h.
- *Nutritional area.* Body mass index (weight in kg divided by the square of the of the height in m) was computed. Body weight was measured while the patient was fasting and without shoes and wearing light clothing.

The assessment of cognitive and affective status and of functional capabilities and the measurement of arterial blood gas tensions were repeated yearly for two consecutive years. Alternative forms of questions of GDS and MMS were used, when available, to reduce the effect of practice on the performance. The assessor was unaware of the patient's clinical conditions and respiratory function data as well as of results of previous assessments. The three assessments (baseline, 1 yr and 2 yr) of an individual patient were performed by different assessors (R.A.I., F.C., F.L.) in random order.

STATISTICAL ANALYSIS

The BMDP statistical package was used.

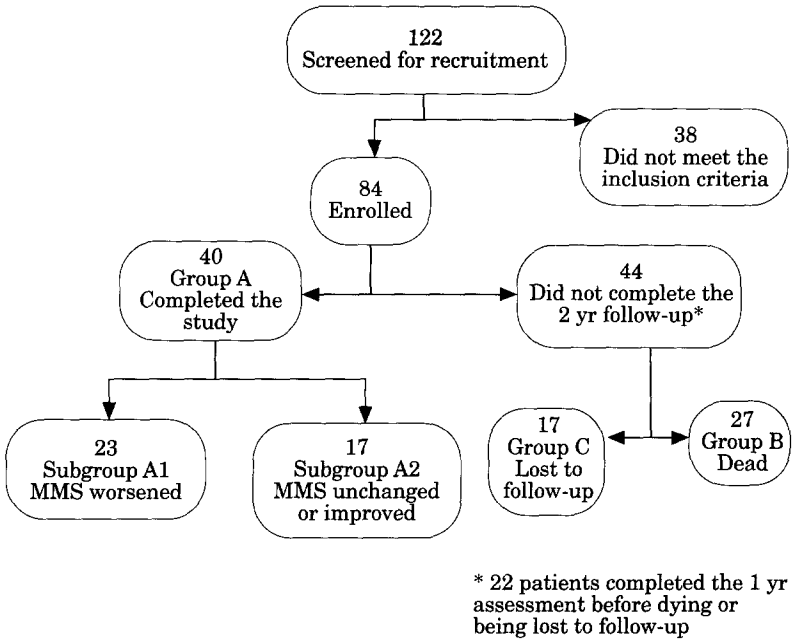

FIG. 1. Partitioning of patients in groups and subgroups.

Baseline characteristics of the 40 patients completing the 2 yr follow-up (group A) were compared with those of the 17 patients lost to follow-up (group B) and of the 27 patients dead (group C). Differences between groups were assessed by the Yates-corrected χ^2 test for dichotomous data and by unpaired t test or Mann–Whitney test for continuous data with or without normal distribution and homogeneous variance, respectively (21).

Changes in MMS, GDS and ADLs were assessed as follows: (1) by the Friedman's ANOVA by rank test (baseline, 1 yr control, 2 yr control) in group A patients (22); (2) by the paired t test or Wilcoxon test, as appropriate, for group B and C patients performing the 1 yr assessment. The correlations between 2 yr changes in MMS (difference between 2 yr and baseline MMS scores) and the corresponding change of ADLs and GDS were assessed by Spearman's ρ test (23). Patients completing the 2 yr follow-up were further divided into two subgroups depending on whether their MMS score worsened (subgroup A1) or was unchanged or improved (subgroup A2). Differences in baseline characteristics between subgroups were assessed by parametric or non-parametric statistics, as appropriate.

Results

Figure 1 shows the partitioning of patients in groups and subgroups. Reasons for drop-outs were as follows: severe functional impairment preventing the patient from attending the Pneumology outpatient department (seven cases); change of address and loss of any contact (four cases); moving to another country (three cases); lack of compliance with oxygen therapy (two cases); refusal of further care (one case).

Table 1 compares the baseline characteristics of the groups with group A, i.e. the patients who completed the 2 yr follow-up, as the reference group. Group B, which included patients who died before completing the follow-up, was characterized by better affective status and higher index of comorbidity than group A. Group C, i.e. patients lost to follow-up, had higher mean age and formal education than group A and more severe functional impairment, as reflected by the ADL score; a higher prevalence of comorbid diseases further characterized group C. Groups had comparable respiratory function data. The last finding shows that group A was representative of the whole COPD population selected for the study, at least with regard to the severity of respiratory function impairment.

Table 2, upper part, summarizes results from Friedman's ANOVA by rank test in group A. The MMS score decreased significantly from the first to the last assessment, while an incremental trend was evident for the GDS score. Given that the GDS score is directly proportional to the severity of depressive symptoms, these findings are consistent with a progressive deterioration of both cognitive and affective status. The worsening of MMS and GDS performances was probably underestimated because the use of alternative forms for several questions cannot completely prevent the improvement in performance due to practice. ADLs declined non-significantly during the 2 yr study period.

Table 2, lower part, compares baseline and 1 yr performances on MMS, GDS and MMS of the 22 patients who underwent the 1 yr reassessment before dying or being lost to follow-up. A slight decline of cognitive and functional capabilities and a dramatic derangement of the affective status characterized these patients.

A significant inverse correlation was found between 2 yr changes in MMS and in GDS scores ($\rho = -0{\cdot}32$, $P = 0{\cdot}04$). Thus, cognitive deterioration paralleled the worsening of the affective status. The correlation between 2 yr changes in MMS and ADLs scores was non-significant ($\rho = -0{\cdot}24$,

TABLE 1. Baseline characteristics of the patients completing the 2 yr follow-up (group A), of the patients dead (group B) and of patients lost to follow-up (group C)

	Group A	Group B	Group C
Number (males)	40 (33)	27 (22)	17 (9)
Age (years) (mean ± SD)	68 ± 9	68 ± 11	73 ± 9*
Years of formal education (mean ± SD)	6 ± 3	7 ± 4	9 ± 3**
Low occupational role before retirement† (%)	57·5	51·8	29·4
Actual smokers (%)	5	11·1	5·9
MMS (mean ± SD)	27 ± 2·9	26·7 ± 3·9	26·3 ± 3·4
ADLs (mean ± SD)	5·7 ± 0·7	5·3 ± 1·4	5·1 ± 1·4*
GDS (mean ± SD)	13·9 ± 7·2	9·9 ± 7·5*	10·3 ± 9
Body mass index (kg m^{-2}) (mean ± SD)	26·6 ± 4·2	25·4 ± 5·9	27·2 ± 5·5
FVC (% predicted) (mean ± SD)	57·5 ± 17·2	58·5 ± 19·8	56·5 ± 25·4
FEV_1 (% predicted) (mean ± SD)	33·2 ± 18·8	34·6 ± 20·1	36·1 ± 19
PaO_2 (kPa) (mean ± SD)	7·06 ± 1	7·19 ± 1·6	7·24 ± 1
$PaCO_2$ (kPa) (mean ± SD)	6·8 ± 1·2	7·01 ± 1·4	6·68 ± 1·2
pH (mean ± SD)	7·38 ± 0·03	7·38 ± 0·03	7·38 ± 0·04
P_A–aO_2 (kPa) (mean ± SD)	4·85 ± 1·1	5·97 ± 3	5·30 ± 2
Charlson's index of comorbidity (mean ± SD)	1·1 ± 0·3	1·4 ± 0·6*	1·5 ± 0·6***
Prevalence of diabetes (%)	5	18·5	29·4**
Prevalence of hypertension (%)	40	37	35·3
Prevalence of CAD–MI (%)	10	22·2	11·8
Prevalence of renal failure (%)	5	3·7	5·9

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; P_A–aO_2, alveolar–arterial oxygen difference; CAD–MI, coronary artery disease–myocardial infarction.
The *t* test or Mann–Whitney test were used for comparing continuous data having or not having normal distribution and homogeneous variance, respectively; the χ^2 test was used for comparing dichotomous data.
*$P<0·05$ *vs.* group A; **$P<0·02$ *vs.* group A; ***$P<0·01$ *vs.* group A.
†Defined according to Featherman and Hauser (11).

$P=-0·13$); on the average, functional capabilities decreased less than cognitive function.

Table 3 compares baseline characteristics of subgroups A1 and A2, i.e. of group A subjects whose MMS worsened (subgroup A1, $n=23$) or was unchanged or improved (subgroup A2, $n=17$) after 2 yr. Patients at risk of cognitive decline were characterized by more severely depressed FEV_1 and FVC values, a tendentially lower occupational role before retirement and a significantly lower GDS score.

Discussion

This study provides the first demonstration that a close parallelism exists between cognitive decline and development of depressive symptoms in COPD patients. The combination of cognitive and affective symptoms is quite common in geriatric populations because patients with organic dementia frequently also become depressed, whereas primarily depressed subjects show cognitive changes severe enough to be referred to as dementia syndrome of depression or pseudodementia (24,25). Pseudodementia is characterized by variable performance across similar tasks, impairment of both recent and remote memory and frequently well-preserved attention and concentration (25). The diagnostic protocol used by us lacks the potential for differentiating true dementia from depressive pseudodementia, which was out of the scope of the present study. However, the cognitive impairment previously observed in COPD patients exempt from clinically relevant depression suggests that neuropsychological function actually deteriorates in these patients (3). Given that depressive symptoms have recently been shown to herald dementia in the elderly, results from the present study might have different explanations (26). The only certain conclusion is that cognitive decline is more evident in patients whose affective status will shift from normality to depression. Thus, the onset of depression rather than its progression seems to be associated with faster cognitive decline.

Loss of functional capabilities did not parallel the decline of neuropsychological functions. The observation by Similowski *et al.* that respiratory muscle strength at FRC level does not suffer from lung hyperinflation in patients with stable COPD provides a likely explanation for this finding: respiratory function at lung volumes needed for performing ADLs is relatively well preserved even in hypoxaemic COPD (27). Thus, functional impairment severe enough to affect performance on ADLs seems to be a very late event in the natural history of COPD. This might

TABLE 2. Changes of cognitive, functional and affective status in the 40 patients completing the 2 yr follow-up and in the 22 patients dead or lost to follow-up after completing the 1 yr assessment*

	Baseline	1 yr	2 yr	*P* value
Completed 2 yr follow-up				
MMS	27 ± 2·9	25·8 ± 4·1	25·4 ± 4	0·003†
ADLs	5·75 ± 0·74	5·65 ± 0·95	5·6 ± 1	0·31†
GDS	13·3 ± 7·2	13·5 ± 6·8	13·8 ± 7·3	0·64†
Dead or lost to follow-up after 1 yr				
MMS	27·6 ± 3	26·2 ± 3·6		0·05‡
ADLs	5·5 ± 1·3	4·9 ± 1·6		0·04‡
GDS	11·9 ± 8·8	14·5 ± 7·6		0·002‡

*Values expressed as mean ± SD.
†Friedman ANOVA by ranks test; ‡Wilcoxon test.

TABLE 3. Baseline characteristics of the 40 patients completing the 2 yr follow-up, subgrouped according to whether their MMS worsened (subgroup A1) or remained unchanged or improved (subgroup A2)

	Subgroup A1	Subgroup A2	*P* value
Number (males)	23 (21)	17 (12)	
Age (years) (mean ± SD)	66 ± 8	70 ± 10	0·17†
Years of formal education (mean ± SD)	6 ± 2	7 ± 3	0·72†
Low occupational role before retirement* (%)	69·6	41·2	0·14‡
Actual smokers (%)	4·3	5·9	0·60‡
MMS (mean ± SD)	27·3 ± 3	26·6 ± 2·9	0·54†
ADLs (mean ± SD)	5·6 ± 0·9	5·9 ± 0·2	0·25§
GDS (mean ± SD)	11·9 ± 7·7	16·5 ± 5·6	0·04†
Body mass index (kg m^{-2}) (mean ± SD)	27·2 ± 3·9	25·7 ± 4·5	0·28†
FVC (% predicted) (mean ± SD)	52·3 ± 17·1	66·9 ± 13·4	0·03†
FEV_1 (% predicted) (mean ± SD)	27·2 ± 8·6	44 ± 26·8	0·09§
PaO_2 (kPa) (mean ± SD)	6·94 ± 1·2	7·22 ± 0·9	0·57†
$PaCO_2$ (kPa) (mean ± SD)	7·10 ± 1·1	6·57 ± 1·3	0·17†
pH (mean ± SD)	7·37 ± 0·03	7·39 ± 0·03	0·07†
P_A–aO_2 (kPa) (mean ± SD)	4·65 ± 1·0	5·12 ± 1·2	0·18†
Charlson's index of comorbidity (mean ± SD)	1·13 ± 0·3	1·06 ± 0·2	0·52†
Prevalence of diabetes (%)	8·7	0	0·61‡
Prevalence of hypertension (%)	34·8	47·1	0·65‡
Prevalence of CAD–MI (%)	13	17·6	0·52‡
Prevalence of renal failure (%)	4·3	5·9	0·61‡

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; P_A–O_2, alveolar–arterial oxygen difference; CAD–MI, coronary artery disease–myocardial infarction.
*Defined according to Featherman and Hauser (11).
†*t* test; ‡χ^2 test; §Mann–Whitney test.

reflect different sensitivities of muscles and brain to hypoxaemia and/or of ADL and MMS to mild variations in performance. The fact that patients had their hypoxaemia corrected and $SaO_2 \geq 90\%$ does not exclude the former hypothesis because a wide range of actual PaO_2 and $PaCO_2$ values characterized the patient population. It remains to be defined whether functional impairment simply reflects the progressive deterioration of respiratory function or is partially attributable to cognitive and affective changes or to non-respiratory muscle wasting. This issue could not be clarified because functional decline prevented some of the patients from attending further the Pneumology outpatient department.

Limitations of the present study are as follows. (1) Aging *per se* might partially account for the observed changes in cognitive and affective status. The lack of a control group of normal elderly prevents us from testing this possibility. However, age-related changes in select cognitive functions

become manifest over a very long time interval (28,29); accordingly, aging is unlikely to be the main determinant of changes recorded in a 2 yr period. Furthermore, the negative trend of cognitive functions was probably smoothed by the practice effect. (2) Results from the present study apply to a COPD population with minimal or no signs of cognitive deterioration at baseline. Indeed, only seven patients had an MMS score inferior to 24. COPD patients with baseline cognitive impairment might experience a more severe neuropsychological involution. (3) We dealt with a selected COPD population regularly attending an outpatient Pneumology department and characterized by a high degree of compliance with oxygen therapy. A more negative trend of both affective and cognitive status is likely to occur in the overall COPD population having comparable baseline characteristics.

These limitations do not weaken the main message from the present study: cognitive decline occurs even in COPD patients regularly performing oxygen therapy and is faster in subjects who belong to lower social class, have more severe bronchial obstruction and experience the onset of depressive symptoms. The possibility should be tested that the regular use of techniques of cognitive activation and occupational therapy, previously proven to slow cognitive decline in select geriatric populations (30), could benefit COPD patients at higher risk of mental deterioration. Future studies should also clarify how individual cognitive functions decline and contribute to the involution of overall cognitive performance. Finally, the possibility that depression simulates cognitive decline in some patients deserves to be explored. Clarifying these issues would allow improvement of the management of COPD patients. Traditional management based on medical therapy and, at most, respiratory physiotherapy is unlikely to meet the needs of care of patients with such a broad and variegated burden of problems affecting quality of life.

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