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Autonomic and cerebrovascular abnormalities in mild COPD are worsened by chronic smoking

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ABSTRACT: Patients with chronic obstructive pulmonary disease (COPD) may develop hypercapnia and hypoxia, two main determinants of cerebral blood flow. The current authors tested whether cerebrovascular regulation was altered in mild COPD, modified by manoeuvres acutely improving autonomic cardiovascular modulation or influenced by smoking habit.

In 15 eucapnic normoxic mild COPD patients (eight smokers) and 28 age-matched controls (14 smokers), midcerebral artery blood flow velocity (MCFV), end-tidal carbon dioxide tension (P_{ET,CO_2}), arterial oxygen saturation (S_{a,O_2}), ECG and blood pressure at rest were monitored during progressive hypercapnic hyperoxia, isocapnic hypoxia, slow breathing and oxygen administration. MCFV, arterial baroreflex and dynamic MCFV–blood pressure relationships were compared by phase analysis.

COPD and control smokers showed higher MCFV (when corrected for P_{ET,CO_2}), lower cerebrovascular resistance index and lower sensitivity to hypercapnia than nonsmokers, with equal sensitivity to S_{a,O_2} and similar phase analysis. Arterial baroreflex was depressed in all COPD patients. Slow breathing and oxygen administration improved baroreflex sensitivity and reduced MCFV in all COPD patients.

Patients with mild chronic obstructive pulmonary disease show autonomic dysfunction. Chronic smoking induces cerebral vasodilation and impairs cerebrovascular control. All abnormalities can be partly corrected by improving the cardio- and cerebrovascular autonomic modulation, suggesting that functional autonomic abnormalities are already present at an early stage of disease.

KEYWORDS: Baroreflex sensitivity, cerebral circulation, chronic obstructive pulmonary disease, cigarette smoking, hypercapnia, hypoxia

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In normal humans and animals, cerebral blood flow is proportional to arterial carbon dioxide tension (P_{a,CO_2}), whereas it is inversely correlated with arterial oxygen tension and oxygen saturation (S_{a,O_2}) [1–3]. Within limitations, cerebral blood flow is linearly correlated with blood flow velocity, as measured by transcranial Doppler ultrasound [1].

Since patients with chronic obstructive pulmonary disease (COPD) have a natural tendency to develop hypercapnia and also show cardiovascular and respiratory control abnormalities [4], it is likely that these combined factors affect cerebral haemodynamics. In turn, alteration in cerebral blood flow may be an important determinant of the cognitive impairment reported in these patients [5, 6], and may also contribute to the worsening of the autonomic and respiratory abnormalities by impairing the perfusion of brainstem regulatory centres. However, smoking is a common habit of COPD patients and, although only few studies (and none in COPD patients) have reported on the chronic effect of smoking on the cerebrovascular dynamics [7–9], smoking seems capable of inducing long-term cerebrovascular changes [9]. Thus, it is possible that chronic smoking may be responsible for or at least contribute to impairment of cerebrovascular regulation.

Despite this potential relevance, very few studies so far have examined the cerebrovascular control in COPD patients [10, 11] and, in particular, comparisons with similar data in healthy control subjects are lacking.

The aims of the present study were to: 1) compare the cerebrovascular haemodynamics in mild

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COPD patients and in healthy controls to assess the presence and the origin (organic *versus* functional) of possible early cardio- and cerebrovascular control abnormalities; 2) test the effect on the cerebrovascular regulation of simple respiratory manoeuvres able to improve the autonomic control of the cardiovascular system; and 3) test the possible interaction with smoking habit.

METHODS

Subjects

The present study was carried out in 15 subjects with mild COPD and 28 age-matched controls. The diagnosis and classification of COPD was made according to the Global Initiative for Chronic Obstructive Lung Disease criteria [12]. The main anthropometric data and post-bronchodilator spirometric data of the patients and controls are presented in table 1. Eight of the COPD and 14 of the controls were active smokers (>10 cigarettes·day^{-1} for ⩾1 yr); none of the remaining COPD patients was an active or previous smoker. The patients were characterised by mild levels of COPD without hypercapnia or hypoxia at rest. For ethical reasons, medications were not discontinued on the day of the tests. These medications included β_2 agonists (10 subjects), anticholinergic agents (11 subjects), theophylline (one subject) and cortisone (seven subjects). Smoking was discontinued during the day of the study. The protocol was approved by the local Ethics Committee (University of Innsbruck, Innsbruck, Austria) and all subjects gave informed written consent to participate in the study.

Protocol

All subjects were examined in a sitting position at a comfortable room temperature and humidity. Midcerebral artery blood flow velocity (MCFV) was monitored by a 2-MHz transcranial Doppler probe at a depth of 35–55 mm through the temporal window (Atys Medical, Soucieu en Jarrest, France) of the nondominant side. The following were also recorded: ECG (by chest leads); continuous noninvasive blood pressure (by the cuff method; Portapres®; Finapres Medical Systems, Amsterdam, the Netherlands); and respiratory movements (by inductive plethysmography). End-tidal carbon dioxide tension (P_{ET,CO_2}) was continuously measured (by COSMOplus; Novametrix, Wallingford, CT, USA), as was S_{a,O_2} (by a pulse oximeter, Ohmeda 3740; Ohmeda, Englewood, CO, USA). Throughout the tests, the subjects were connected to a rebreathing circuit through a mouthpiece, as previously described [13, 14]. In a preliminary study in four COPD patients, the P_{a,CO_2} was compared with the noninvasive end-tidal estimate (mean±SEM 5.05±0.15 kPa (38.0±1.1 mmHg) *versus* 4.69±0.05 kPa (35.3±0.4mmHg), respectively). The absence of hypercapnia in the present study patients was confirmed, and only minimal and expected differences between invasive and noninvasive data were found, all in the range expected for healthy subjects.

In each subject, values were recorded during 4 min of spontaneous breathing (baseline), 2 min of controlled breathing at 15 breaths·min^{-1} and 2 min of controlled breathing at 6 breaths·min^{-1}. The rebreathing tests were performed in random order, in order to evaluate the cerebrovascular sensitivity to hypercapnia and hypoxia, respectively, under the following conditions: 1) progressive hyperoxic hypercapnia (P_{ET,CO_2} raised from baseline by 2.00 kPa (15 mmHg); S_{a,O_2} >98%); and 2) progressive normocapnic hypoxia (S_{a,O_2} from baseline to 80%; P_{ET,CO_2} maintained at a standard level of 5.05 kPa (38 mmHg)).

When the sensitivity to hypercapnia was tested, oxygen was supplied to the rebreathing bag at a very low flow, in order to maintain S_{a,O_2} >98%. During the first 2 min of the procedure, the carbon dioxide was kept constant and the data obtained were compared with baseline data (while breathing room air), in order to test the effect of steady-state oxygen administration. During progressive hypoxia, the carbon dioxide levels were clamped by passing a variable part of the expired air into a reservoir filled with soda lime, under continuous visual control of P_{ET,CO_2}. During all these recordings, all cardiovascular and cerebrovascular signals were continuously recorded.

TABLE 1 Chronic obstructive pulmonary disease (COPD) patients and controls at baseline

	COPD			Healthy controls		
	Smokers	Nonsmokers	All	Smokers	Nonsmokers	All
Subjects n	8	7	15	14	14	28
Sex M/F n	5/3	5/2	10/5	8/6	5/9	13/15
Age yrs	50.6±2.3	54.0±5.1	52.2±2.6	47.6±1.8	46.7±2.9	47.2±1.7
Height cm	177.2±1.7	172.8±3.5	175.2±1.9	170.6±2.1	174.7±1.7	172.6±1.4
Weight kg	79.2±3.3	72.0±3.4	75.8±2.5	72.2±4.8	70.4±2.8	71.3±2.8
BMI kg·m^{-2}	25.3±1.3	24.0±0.5	24.7±2.77	24.7±1.5	22.9±0.7	23.9±0.8
FEV_1 % pred	75.6±3.9	75.5±3.0	75.6±2.1**	82.5±2.6	83.1±2.2	82.8±1.7
FEV_1/FVC	67.7±0.8*	66.1±1.8	67.0±0.9***	89.4±2.1	85.8±2.7	87.6±1.7
Smoking history pack-yrs	20.1±2.7			16.0±2.1		

Data are presented as mean±SEM, unless otherwise stated. M: male; F: female; BMI: body mass index; FEV_1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity. *: p<0.05 *versus* healthy controls; **: p<0.01 *versus* healthy controls; ***: p<0.001 *versus* healthy controls.

Data acquisition and analysis

All signals were continuously acquired on a personal computer at a frequency of 600 samples·channel^{-1}. The cerebrovascular sensitivity to hypoxia or hypercapnia was obtained from the slopes of the linear regression of mean MCFV *versus* S_{a,O_2} or P_{ET,CO_2}, respectively, for each breath. The arterial baroreflex sensitivity was calculated from the time series of RR interval and systolic blood pressure obtained at baseline and during controlled breathing at 15 and 6 breaths·min^{-1}, by the so-called ''alpha index'' (by autoregressive spectral analysis of RR interval and systolic blood pressure) [13, 15]. The MCFV was evaluated during each sequence and the values were corrected for the corresponding P_{ET,CO_2} (MCFV/P_{ET,CO_2}) [15, 16]. The MCFV was also corrected for the contribution of mean blood pressure (MBP/MCFV), thus obtaining an index of cerebrovascular resistance [17], and finally the combined effects of MBP and P_{ET,CO_2} on MCFV (MBP/MCFV/P_{ET,CO_2}) were considered [17].

To test the dynamic relationships between blood pressure and MCFV, transfer function phase analysis was applied. The measurement of the phase delay between MCFV and MBP has been proposed as a method to test dynamic cerebrovascular regulation under undisturbed conditions [18]. According to the high-pass filter model of cerebral regulation, variations in MBP should be transmitted to MCFV [19, 20]. Thus, it was expected that MCFV would lead MBP under normal conditions. In the case of disturbed regulation, the phase shift between both parameters would approach zero, *i.e.* MCFV would follow MBP changes passively [19, 20]. An autoregressive spectral algorithm [19] was used to calculate the amplitudes and phases (expressed in degrees) of the recorded parameters.

Statistical analysis

Data are presented as mean±SEM. Differences between the COPD patients and control subjects and between smokers and nonsmokers were assessed using ANOVA (factorial design on two factors, to test for the effects of COPD and smoking) [21]. Differences between breathing rates in the different groups were assessed using a two-way mixed-design ANOVA (repeated measures for tests within groups and factorial between groups) [21]. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline data

At baseline, significant overall differences were found *via* ANOVA between the four different groups of subjects ($p<0.025$). The differences were essentially due to smoking, which induced a marked resting cerebral vasodilation, evidenced by a significant increase in resting MCFV ($p<0.005$), which remained significant even after correction

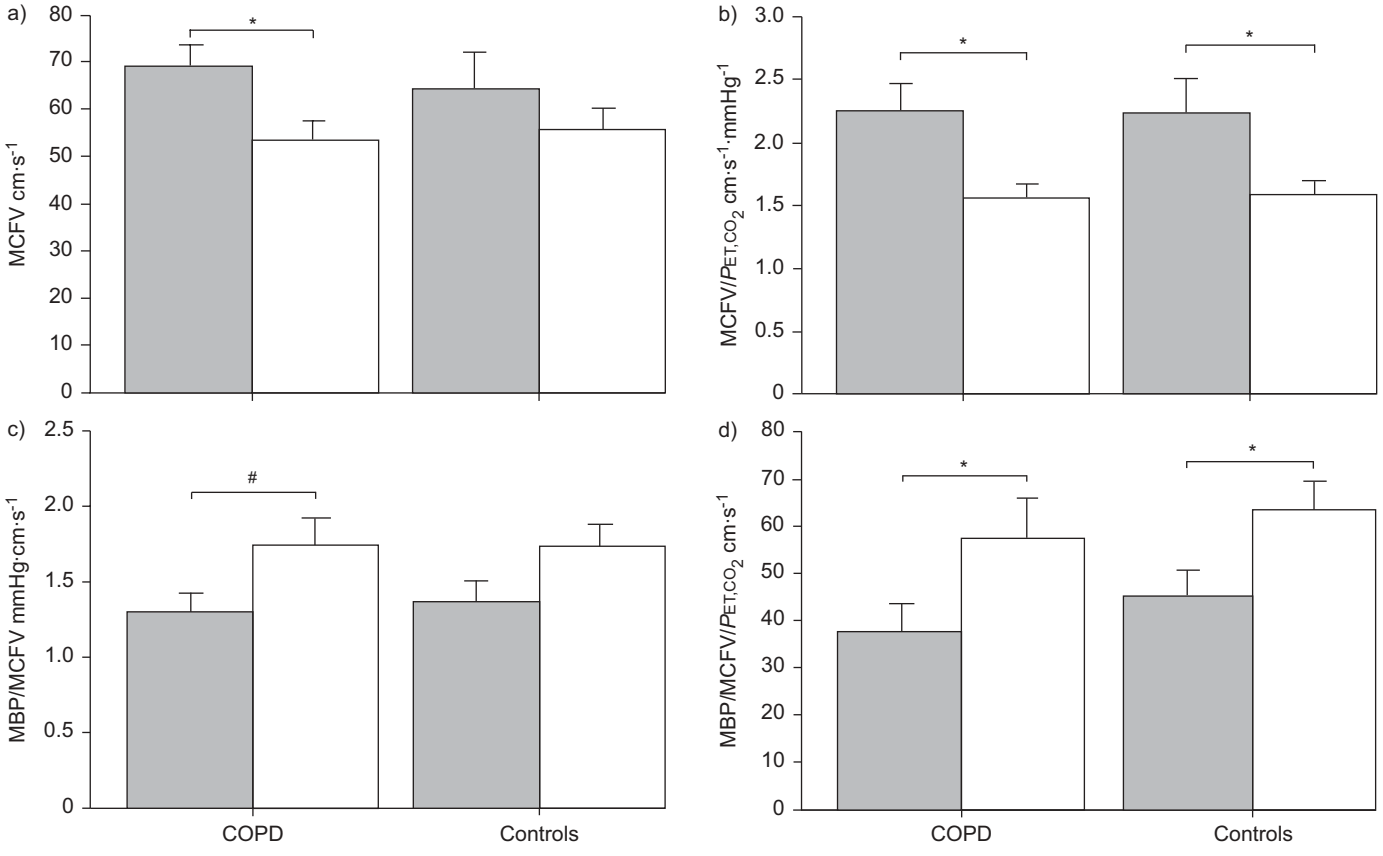

FIGURE 1. Resting levels of a) midcerebral artery blood flow velocity (MCFV), b) MCFV corrected for end-tidal carbon dioxide tension (P_{ET,CO_2}), c) MCFV corrected for mean blood pressure (MBP) and d) MCFV corrected for both P_{ET,CO_2} and MBP, in chronic obstructive pulmonary disease (COPD) patients and healthy controls. No significant differences were observed between COPD patients and controls. Overall comparisons between smokers (■) and nonsmokers (□) gave the following: a and b) $p<0.005$, c) $p<0.05$, d) $p<0.025$. #: $p<0.025$; *: $p<0.05$. 1 mmHg=0.133 kPa.

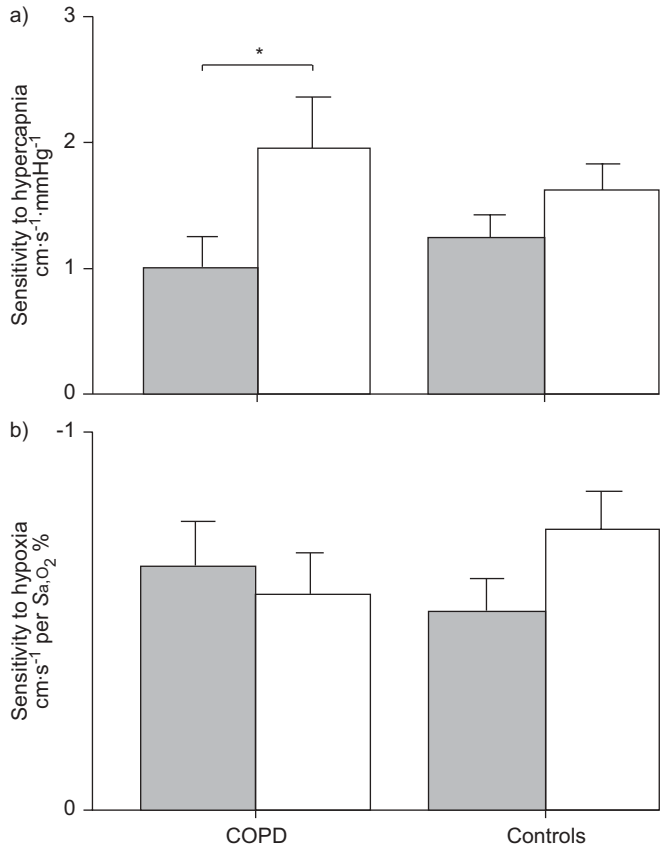

FIGURE 2. Sensitivity to a) hypercapnia and b) hypoxia in chronic obstructive pulmonary disease (COPD) patients and healthy controls. No significant differences were observed between COPD patients and controls. Overall comparisons between smokers (■) and nonsmokers (□) showed a significant difference in sensitivity to hypercapnia ($p<0.025$) but not to hypoxia. *: $p<0.05$. 1 mmHg=0.133 kPa.

for P_{ET,CO_2} levels ($p<0.005$) or MBP (thus expressed in terms of index of cerebrovascular resistance; $p<0.05$), and also when this index was corrected for the effect of P_{ET,CO_2} levels ($p<0.025$; fig. 1). Conversely, no significant differences were seen when considering the presence of COPD.

Sensitivity of MCFV to hypoxia and hypercapnia

Progressive isocapnic hypoxia and progressive hyperoxic hypercapnia increased MCFV in both COPD patients and controls. The average slope of the curves showed no significant differences between the two groups. Conversely, significant differences were observed as an effect of smoking: overall, the smokers showed a significant reduction in hypercapnia sensitivity ($p<0.025$; fig. 2a). Furthermore, during progressive hypercapnia, in five out of eight COPD smokers and in five out of 14 control smokers, a plateau was found at higher levels of P_{ET,CO_2}, indicating a progressively lower sensitivity for higher levels of P_{ET,CO_2}. An example is shown in figure 3. The occurrence of this plateau was also associated with higher resting values of MCFV.

Effect of respiratory manoeuvres

Compared with spontaneous breathing, controlling the breathing rate at 15 breaths·min^{-1} induced a parallel reduction in both the MCFV and P_{ET,CO_2} in both COPD patients and control subjects, thus leaving the MCFV unchanged when corrected for P_{ET,CO_2} (fig. 4). However, when the subjects breathed at 6 breaths·min^{-1}, the drop in MCFV in the COPD group (and to a lower extent in control subjects), remained significant even after correction for P_{ET,CO_2}. At baseline, baroreflex sensitivity was reduced in all COPD patients compared with controls (5.7 ± 0.8 *versus* 10.1 ± 1.0 ms·mmHg^{-1}, respectively; $p<0.01$), but no significant differences were observed between smokers and nonsmokers (6.4 ± 1.1 *versus* 5.2 ± 1.1 ms·mmHg^{-1}, respectively). Controlled breathing at 6 breaths·min^{-1} significantly increased baroreflex

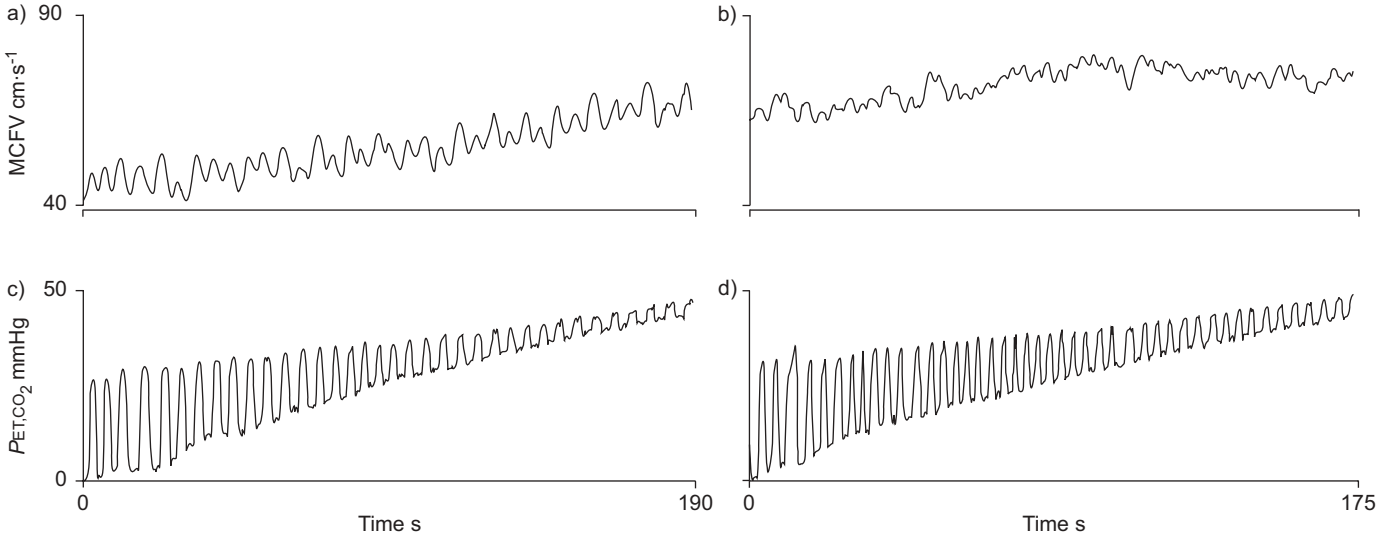

FIGURE 3. Examples of the raw data obtained in one nonsmoker control subject (a and c) and one smoker chronic obstructive pulmonary disease (COPD) patient (b and d) during progressive hypercapnia. Notice the higher starting level of midcerebral artery blood flow velocity (MCFV) in the COPD patient, despite similar starting levels of end-tidal carbon dioxide tension (P_{ET,CO_2}), and the plateau for increasing levels of P_{ET,CO_2} in the COPD patient. 1 mmHg=0.133 kPa.

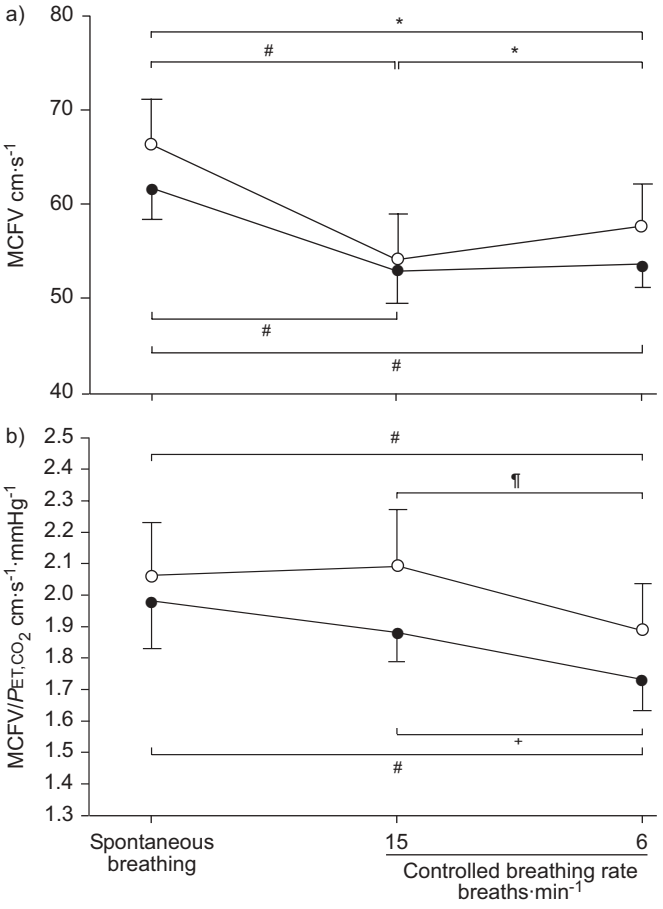

FIGURE 4. Effect of different breathing rates a) on raw midcerebral artery blood flow velocity (MCFV) and b) after correction for end-tidal carbon dioxide tension (P_{ET,CO_2}). Notice that, after correction for the levels of P_{ET,CO_2}, MCFV was decreased only during slow breathing, thus indicating that a modification in the cerebrovascular regulation occurred at this rate independently from P_{ET,CO_2}. ○: chronic obstructive pulmonary disease patients; ●: control subjects. *: $p<0.05$; #: $p<0.005$; ¶: $p<0.0001$; +: $p<0.0025$. 1 mmHg=0.133 kPa.

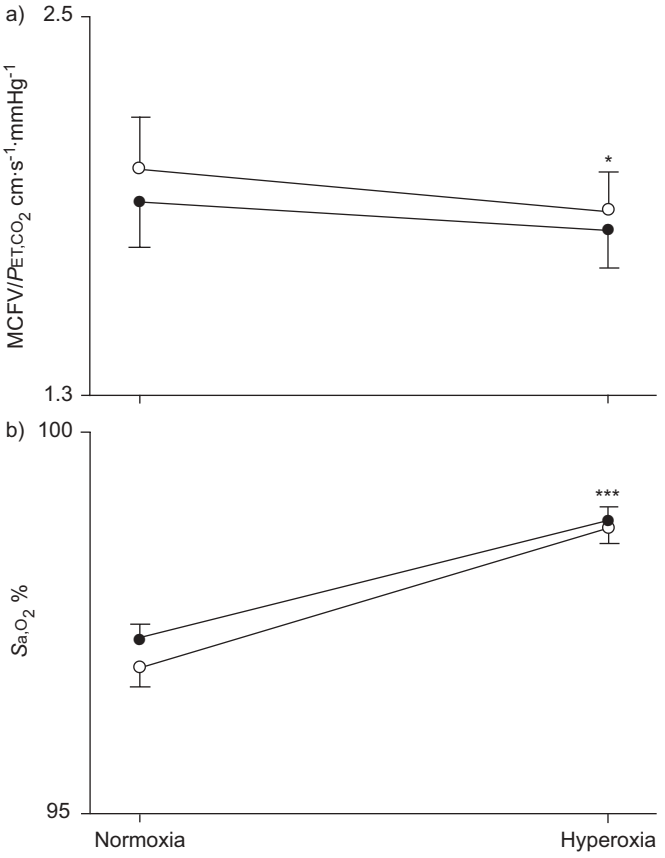

FIGURE 5. Effect of oxygen administration on a) midcerebral artery blood flow velocity (MCFV) corrected for end-tidal carbon dioxide tension (P_{ET,CO_2}) and b) arterial oxygen saturation (S_{a,O_2}). Although all subjects were normoxic, and thus hyperoxia induced only a minor increase in S_{a,O_2}, this intervention reduced MCFV in the chronic obstructive pulmonary disease (○) and control (●) groups. *: $p<0.05$ for both groups compared with normoxia; ***: $p<0.001$ for both groups compared with normoxia. 1 mmHg=0.133 kPa.

sensitivity in all subjects (8.9 ± 1.7 ms·mmHg^{-1} in COPD patients; $p<0.05$ *versus* spontaneous breathing at baseline, not significant *versus* control subjects; and 14.3 ± 2.0 ms·mmHg^{-1} in control subjects, $p<0.01$ *versus* baseline), whereas controlled breathing at 15 breaths·min^{-1} did not induce significant changes compared with spontaneous breathing. Smokers and nonsmokers showed identical trends with respiratory manoeuvres.

Effect of oxygen administration

Although resting S_{a,O_2} levels were normal in both groups, oxygen administration increased S_{a,O_2} in both groups and significantly reduced MCFV/P_{ET,CO_2} (fig. 5). Smokers and nonsmokers showed identical trends.

Phase analysis between MBP and MCFV

In the low-frequency range, MCFV was leading MBP in both groups, with similar phase delays ($65.3\pm8.6^\circ$ *versus* $53.4\pm6.6^\circ$ for COPD and control groups, respectively; nonsignificant; fig. 6). Controlled breathing at 15 and 6 breaths·min^{-1} did not induce significant changes or differences between the two groups. Smokers and nonsmokers showed identical values.

DISCUSSION

Main findings

The present study shows, for the first time, that even patients with mild levels of COPD already have evident alterations in cerebrovascular control, characterised by a higher resting MCFV level and a lower index of cerebrovascular resistance, even after correction for P_{ET,CO_2}. These abnormalities were limited to the subgroup of COPD patients with a smoking history, suggesting that the smoking habit could have been responsible for most of the changes observed in the cerebrovascular modulation. However, baseline baroreflex sensitivity was equally reduced in smokers and nonsmokers, suggesting that autonomic dysfunction was to some extent independent of smoking habit. The sensitivity to hypercapnia was also reduced in the smoking subgroup of COPD patients at higher P_{ET,CO_2} levels. The current authors speculate that these abnormalities might have a potential compensatory role, preventing excessive vasodilation in the presence of hypercapnia. The improvement of these abnormalities by simple respiratory manoeuvres and by oxygen administration indicates that these abnormalities are functional and could be reversed by appropriate therapy.

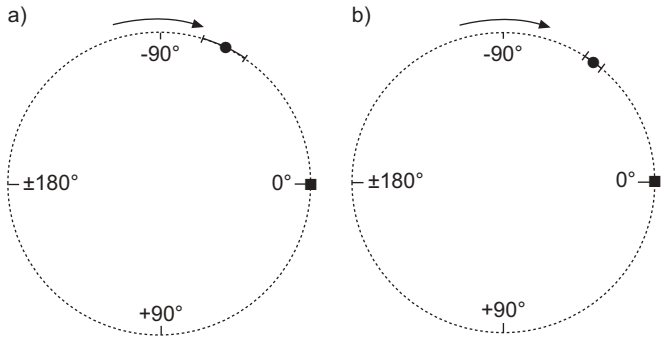

FIGURE 6. Results of phase analysis. The circle (····) indicates the period of the oscillation (0.1 Hz, equivalent to 10 s). Arrows indicate the order of precedence of oscillations. The relative phase delay of the oscillations in midcerebral artery blood flow velocity (MCFV; ●) in relation to those in mean blood pressure (MBP; ■) is shown. Error bars (——) indicate the SEM. The 0.1-Hz oscillations in MCFV always preceded those in MBP, by a similar extent in a) chronic obstructive pulmonary disease patients and b) control subjects.

Increased resting MCFV in mild COPD patients

Even subjects with only mild signs of COPD seem to have a substantial increase in MCFV, suggesting, within the limitations intrinsic in the trans-cranial Doppler measurements [3], an increased cerebral blood flow. This increase is clearly due to the smoking habit, common in COPD patients, as it was also present in smokers with normal spirometry. The increase was more evident when MCFV data were corrected for the value of P_{ET,CO_2}. This is an essential correction, as it is well known that P_{a,CO_2} is the major determinant of MCFV [2, 3, 15, 16], and even a mild hyperventilation may actually induce an artefactual reduction in MCFV. For practical reasons, P_{a,CO_2} had to be estimated from end-tidal values. In theory, due to ventilation/perfusion abnormalities typical of advanced COPD, P_{ET,CO_2} levels could have been underestimated, leading to artefactual increases in MCFV/P_{ET,CO_2} ratio. While this possibility should be taken into account (particularly in more compromised patients), the subjects of the present study were all normocapnic (or even hypocapnic), and only minor and expected differences between intra-arterial and end-tidal values were found in the preliminary testing. Furthermore, all the present study subjects had only minor pulmonary dysfunction, indicating that the estimation of P_{a,CO_2} by end-tidal values was not substantially biased. Additionally, a reduced MBP/MCFV ratio (an index of cerebrovascular resistance) was found in COPD smokers even without correction for P_{ET,CO_2}.

An increase in MCFV may result from an altered sensitivity to hypoxia or hypercapnia. The present results confirm that the subjects showing an increase in resting MCFV (essentially the smoker groups) also had a reduced sensitivity to hypercapnia. In five out of eight of the COPD patients and five out of 14 control smokers, higher resting values were associated with a plateau in the relationship between MCFV and P_{ET,CO_2} (fig. 3). This suggests a lower ability to vasodilate the brain vessels for higher levels of P_{ET,CO_2}. A recent study also showed that a logistic function would better fit the MCFV–P_{ET,CO_2} relationship, indicating a general tendency, even in healthy subjects, towards reduction of the sensitivity for higher levels of P_{ET,CO_2} upon increased MCFV [22]. Therefore, the current finding is probably an amplification of a normal phenomenon, whose finalism could be the prevention of extreme vasodilation at higher levels of CO_2 and/or MCFV. It is well known that extreme cerebral vasodilation, due to hypercapnia or hypoxia (typically occurring at high altitude) can lead to severe headache and even predispose to cerebral oedema [23, 24]. This may be relevant in COPD, as hypercapnia (and often hypoxia) is a common complication in this disease. Conversely, these findings indicate that estimates of sensitivity to CO_2 may vary depending on the range of data used for the calculation. In the present study, since none of the COPD patients were hypercapnic, it was possible to examine the cerebrovascular pattern of response to varying CO_2, from low levels to hypercapnia, thus avoiding all possible bias.

The cerebrovascular changes seen in the present study were essentially confined to the smoker subgroups, with or without COPD. While several studies have evaluated the acute effect of smoking on cerebrovascular dynamics [7–9], only very few have reported baseline comparisons between smoker and nonsmoker subjects. No previous studies of this type in COPD patients exist, to the current authors' knowledge, and in none of the studies were MCFV values corrected for CO_2, ventilation or blood pressure. To the limited extent that data could be compared, the present results are in agreement with previous data reporting an increase in resting MCFV values in smokers at baseline [9].

Autonomic disturbances in COPD patients

Autonomic abnormalities have been consistently found in COPD. These range from a reduction in heart rate variability [25–27], a reduction in respiratory sinus arrhythmia [27] and a reduction in baroreflex sensitivity [28, 29], together with a direct increase in muscle sympathetic nerve activity [30, 31]. In the present study, the COPD patients had depressed baroreflex sensitivity, regardless of their history of smoking and of the current therapy. While the acute effect of smoking is a clear reduction in baroreflex sensitivity [32], the chronic effect is much less evident [33]. Similarly, from the present data, smoking did not emerge as a significant determinant of the observed reduction in baroreflex sensitivity in the COPD patients. In healthy subjects and patients with autonomic dysfunction, reducing the breathing rate was previously found to acutely improve baroreflex sensitivity and improve autonomic function [13, 34, 35]. In the present study, controlled breathing at a slower rate (6 breaths·min^{-1}) induced an evident and significant reduction in MCFV in COPD patients, so that the MCFV became similar to that of controls. This was associated with an increase in baroreflex sensitivity approaching normal levels, suggesting that the changes observed occurred together with an improvement in the autonomic cardiovascular modulation. These findings were not due to a change in P_{ET,CO_2} induced by the change in minute ventilation, as the MCFV changes remained evident after correcting MCFV for P_{ET,CO_2} levels. The reduction in MCFV induced by slower breathing indicates that the autonomic abnormalities were probably functional and not the consequence of an established neuropathy.

During spontaneous breathing, the phase angle between the oscillations in MCFV and MBP, in the 0.1-Hz range, was similar in COPD patients and control subjects, and no changes were seen with controlled breathing at different rates. The interpretation of

this phase angle is controversial: while some investigators consider it a marker of dynamic autoregulation [18], others have previously suggested that it may instead depend upon the autonomic control of the cerebral vessels [19, 36]. A larger phase angle implicates the intervention of some modulating factor (either intrinsic to the vessels or with the implication of the autonomic nervous system), whereas a smaller angle indicates a more passive transmission between main arteries and blood vessels. In fact, a smaller angle is typically seen in severe autonomic neuropathy [19]. In the present study, no reduction in phase angle was found in subjects with COPD, despite depressed baroreflex sensitivity, confirming the finding that the control of cerebrovascular circulation was not markedly affected in the COPD patients. Similarly, COPD subjects had a reduced resting MCFV while breathing oxygen (fig. 5), indicating that, even in the normoxic range, there was an effect of oxygen at the cerebrovascular level.

In conclusion, even patients with mild COPD have autonomic dysfunction that could predispose them to abnormalities in cerebrovascular regulation. In turn, this could potentially amplify the smoke-dependent abnormalities in cerebrovascular dynamics. While a definite neuropathy has been described in severe COPD [37], the present findings of an immediate modification with breathing manoeuvres suggest that these abnormalities resulted from a still functional (and reversible) disturbance in patients with limited clinical involvement. The clinical implications of an alteration in the autonomic nervous system and cerebrovascular dynamics are clear when considering the recently reported high sensitivity of the solitary tract nucleus to changes in blood flow [38]. Additionally, the alteration in cerebrovascular dynamics may affect cognitive performance [5, 6, 39]. This, together with blood gas abnormalities occurring in the natural history of COPD, may be an important factor conditioning cognitive impairment seen in these patients [39].

Limitations of the present study

In the present study, cerebrovascular and autonomic abnormalities in mild COPD are reported. Whether this is the beginning of a progression cannot be established by the current data and further studies are needed in a more compromised population in order to assess whether and to what extent these abnormalities progress, although clinical and technical difficulties involved in correct P_{a,CO_2} assessment make this more difficult in more compromised patients. While an invasive estimation of P_{a,CO_2} could have provided a more reliable measurement, this was performed only in a small subgroup of patients at baseline, and it was impossible to follow the data over time (*e.g.* during rebreathing). Although in theory the current findings could have been influenced by a ventilation/perfusion mismatch typical of advanced COPD, the comparison with invasive data showed normal CO_2 values, ruling out this possibility at least for the group of patients examined. This methodological problem should be taken in due account in more compromised patients. The present results also suggest a possible role of carbon monoxide in the modifications observed, which deserves further clarification. Although the changes observed in cerebrovascular dynamics appear to be a specific effect of smoking, their relationship with the further development of autonomic abnormalities in COPD needs to be studied further. However, due to the importance of smoking in the aetiology and progression of COPD, it appears that the current findings underline the importance of smoke abolition in these patients.

Conclusions

The present study provides evidence that even patients with mild levels of COPD present an initial degree of autonomic dysfunction, which in COPD smokers is associated with impaired cerebrovascular regulation. Functional cerebrovascular abnormalities appear to be typical of smokers, regardless of COPD status. The immediate improvement of the indices of cerebrovascular abnormality after simple manoeuvres that produce a transient improvement in the autonomic modulation of the cardiovascular system suggests that the abnormalities are to a great extent functional and could probably be reversed with appropriate therapy. It is likely that the current data have clinical relevance, as an increase in resting MCFV together with a reduced autonomic control may be one of the factors predisposing these patients to a higher cerebrovascular risk [4, 39]. The other novel finding, the presence of cerebrovascular abnormalities in the COPD smokers, should provide an additional argument in favour of smoking abolition. Further studies are needed to establish the time course of these abnormalities in more severely affected patients.

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