Respiratory Medicine (2006) **100**, 1826–1833

respiratoryMEDICINE

Extracranial carotid Doppler ultrasound evaluation of cerebral blood flow volume in COPD patients

Ramazan Albayrak*, Fatma Fidan, Mehmet Unlu, Murat Sezer, Bumin Degirmenci, Murat Acar, Alpay Haktanir, Mehmet Yaman

Department of Radiology, Faculty of Medicine, Afyon Kocatepe University, 03100, Afyon, Turkey

Received 26 October 2005; accepted 22 January 2006

KEYWORDS
COPD;
Cerebral blood volume;
Doppler ultrasound;
Carotid artery;
Vertebral artery

Summary
Objective: Doppler ultrasound of extracranial internal carotid artery (ICA) and vertebral artery (VA) were performed and total cerebral blood flow volume (tCBFV) was evaluated in chronic obstructive pulmonary disease (COPD) patients. CBFV changes due to blood gas changes were also evaluated.
Methods: Bilateral ICA and VA have been examined with 7.5 MHz linear array transducer in COPD patients. Angle-corrected time averaged flow velocity and cross-sectional areas of vessels have been measured. Flow volumes and tCBFV have been calculated. Flow velocities and waveform parameters have been measured.
Results: tCBFV, anterior–posterior CBFVs, left–right ICA flow volumes, bilateral ICA and VA cross-sectional areas and left ICA peak-systolic velocity were significantly higher in COPD patients than control group. Among COPD patients tCBFVs were highest in hypoxemic–hypercapnic ones, and lowest in normocapnic ones. Bilateral VA flow volumes, bilateral ICA (except left ICA V_{ps}) and VA flow velocities and waveform parameters were not different in COPD patients compared with control group. When compared among the subgroups of COPD patients, there were no significant differences for all parameters.
Conclusion: tCBFVs were found to be significantly higher in COPD patients. This increment which is probably due to balancing the oxygen deficit is low with hypoxemia and high with hypercapnia and hypoxemia. Particularly, bilateral ICA and VA cross-sectional area changes and increased left ICA V_{ps} were considered as the main reason for increased tCBFV in COPD patients.

*Corresponding author. Tel.: +90 272 2136707; fax: +90 272 2144996.
E-mail address: rtalbayrak@yahoo.com (R. Albayrak).

0954-6111/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2006.01.015

Introduction

Studies with healthy humans and animals reported that cerebral blood flow (CBF) increases due to cerebral vasodilatation during hypercapnia and decreases due to cerebral vasoconstriction during hypocapnia.[1,2] In case of hypoxemia, CBF either minimally or markedly increases due to cerebral arteriolar dilatation.[3,4] Changes in CBF during hypercapnia, hypocapnia and hypoxemia in chronic obstructive pulmonary disease (COPD) patients are not clear. Some studies reported elevated levels of CBF,[5,6] whereas other studies reported decreased levels.[7] In other words, some studies showed decreased ventilation although it was expected to increase due to chronic hypercapnia,[8,9] whereas other studies showed decreased arterial carbon dioxide tension (PCO_2) and CBF levels with mechanical ventilation with oxygen (O_2) enrichment.[5,6]

One of the primary aims of cerebrovascular Doppler ultrasound is the analysis and characterization of cerebral hemodynamics under physiologic and pathologic circumstances. Although invasive single positron emission computed tomography (SPECT) and positron emission tomography (PET) studies are the gold standards for the evaluation of CBF, Doppler ultrasound enables simple, easy, prevalent and noninvasive estimation of CBF.[10,11]

CBF and cerebral blood volume (CBV) measurements using PET in normal subjects during hypercapnia and hypocapnia have been reported previously in the literature.[12] Besides, CBV measurement with near-infrared spectroscopy (NIRS) method,[7,13] CBF velocity measurement with transcranial Doppler ultrasound,[5] and CBF measurement with Kety–Schmidt technique[6] were already defined in COPD patients. However, to the best of our knowledge, extracranial carotid Doppler estimation of cerebral blood flow volume (CBFV) in COPD patients has not been reported before.

We aimed to evaluate CBFV and hemodynamic changes that occur in extracranial carotid and vertebral arterial systems with Doppler ultrasound in COPD patients. We also aimed to evaluate the changes in cerebral circulation during normocapnia, chronic hypoxia and chronic hypercapnia–hypoxia in these patients.

Materials and methods

This study is performed in an university hospital setting. From the 29 patients in the study group, two patients with cardiac deficiency, one patients with untreated arterial hypertension, two patients with severe dolicoectasic changes in bilateral internal carotid artery (ICA) and vertebral artery (VA) and four patients with atherosclerotic plaques and stenosis were excluded from the study. Twenty COPD patients (mean age, 66.8 ± 9.6 years) and 22 healthy subjects (mean age, 66.1 ± 9.9 years) were accepted to the study. All the patients and the control subjects were living in the same region. All the patients were selected from outpatient clinic. Hypertensive patients were under treatment with antihypertensive drugs. Arterial blood pressures were within normal limits in all patients and control subjects before the measurements were performed. Eleven patients with COPD were current smokers. The patients with COPD were divided into three groups; four patients with normocapnic COPD ($PaCO_2 > 6.0$ kPa), 10 patients with hypoxemic COPD ($PaO_2 < 8$ kPa) and six patients with hypoxemic–hypercapnic COPD ($PaO_2 < 8$ kPa, $PaCO_2 > 6.0$ kPa).[8]

Control subjects were selected randomly from the volunteers who admitted to the hospital for check-up. Those experiencing significant hemodynamic disturbances and had a history or signs of pulmonary and cerebrovascular disease, or cardiac insufficiency were excluded. All of the subjects were evaluated by the same pulmonologist and their physical examinations were in normal limits. Smoking, alcoholism and alcohol or caffeine use in the last 2 days were other exclusion criteria in the study group. Informed written consent was obtained before the examination.

Doppler ultrasounds were performed in a room with a comfortable temperature after an accommodation period for at least 15 min rest in supine position. It was performed with a 7.5-MHz linear array transducer of a color-coded ultrasound system (Nemio 20; Toshiba, Japan). The volunteers' head slightly elevated and turned to the opposite side by 25–40° for ICA measurements and by 10° for VA measurements. Site of measurement of the ICA was 1.5 cm distal to the carotid bifurcation and the VA was examined between the transverse processes of the vertebrae C4 and C5. All the ultrasound examinations have been performed by the same radiologist. The exam was blinded to whether the subject was a COPD patient or a volunteer.

Measurement of angle-corrected flow velocities was done with the sample volume expanded over the entire vessel diameter. Visual control of the maximal luminal width and acoustic control of an optimum time frequency Doppler signal made certain that the sample volume passed through the center of the vessel. We aimed to keep the angle of insonation as low as possible, in most cases

it was about 60°. Angle-corrected time averaged flow velocity (TAV) was determined as the integral of the mean flow velocities of all moving particles passing the sample volume over three–five complete cardiac cycles. In this way, pulsatile parabolic flow is mathematically transformed into a continuous plug flow. The measurements of TAV, peak-systolic velocity (V_{ps}) and end-diastolic velocity (V_{ed}) were taken in bilateral ICA and VA. In addition, resistance index (RI) was calculated according to $RI = (V_{ps}—V_{ed})/V_{ps}$ and pulsatility index (PI) was calculated as: $PI = (V_{ps}—V_{ed})/\text{time averaged maximum velocity}$. The intravascular flow volume (FV) of each artery was calculated by the formula: FV = TAV × cross-sectional area (A). The cross-sectional area of the circular vessel was calculated from the inner vessel diameter (d) using the formula: $A = (d/2)^2 \times [\pi]$.

We detected ICA and VA intravascular flow volumes. The CBF was calculated as the sum of flow volumes in the ICA and VA of both sides. All measurements were documented by video printer.

Statistical analysis was performed using the SPSS software for Windows (SPSS 10, Chicago, IL, USA). The power of our study was found >95% when the COPD group and its subgroups separately compared with the control group with regard to total cerebral blood flow volume (tCBFV). Mann–Whitney U and Kruskal–Wallis tests were used. All parametric results were expressed as mean ± SD for each group. Local statistical significance was assumed as $P<0.05$ for all parameters.

Results

There was no significant difference between age ($P = 0.950$) and genders ($P = 0.921$) of COPD and control groups. Demographic features, pulmonary function test results and arterial blood gases were shown in Table 1. Pulmonary function tests revealed that absolute and percentage predicted values of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), forced expiratory flow 25–75 ($FEF_{25–75}$) and the value of FEV_1/FVC were significantly higher in control group than COPD patients. tCBFV were significantly higher in COPD patients than control group ($P<0.0001$). In COPD patients, anterior CBFV (aCBFV) which is the sum of bilateral ICA flow volumes ($P<0.0001$), posterior CBFV (pCBFV) which is the sum of bilateral VA flow volumes ($P = 0.005$), left ICA flow volume ($P<0.0001$) and right ICA flow volume ($P = 0.001$) values were significantly higher compared to control group (Table 2). Although left and right VA flow volumes were higher in COPD patients than control group, there were no statistically significant differences between them ($P = 0.052$, 0.059, respectively). However, net VA flow volume [(left VA flow volume+right VA flow volume)/2] was significantly higher in COPD patients than control group ($P = 0.005$). Cross-sectional areas of bilateral ICA and VA were significantly higher in COPD patients than in control group ($P<0.05$) (Table 3). Left ICA V_{ps} was significantly higher in COPD patients than in control group ($P = 0.028$)

Table 1 Demographic features, pulmonary function test results and arterial blood gases of COPD patients.

	Normocapnic COPD ($n = 4$) Mean ± SD	Hipoxic COPD ($n = 10$) Mean ± SD	Hipoxic–hypercapnic COPD ($n = 6$) Mean ± SD	Control ($n = 22$) Mean ± SD	P values
Age	70.7 ± 9.6	63.0 ± 10.4	64.2 ± 8.1	66.1 ± 9.9	0.517
BMI	24.6 ± 3.6	29.2 ± 5.9	24.7 ± 2.5	25.2 ± 2.8	0.556
FVC	2.1 ± 1.1	1.8 ± 0.4	1.8 ± 0.6	4.0 ± 0.5	**0.000**
FEV_1	1.4 ± 1.0	0.9 ± 0.3	1.0 ± 0.5	3.8 ± 0.4	**0.000**
$FEF_{25–75}$	1.2 ± 1.1	0.9 ± 1.1	0.6 ± 0.4	5.1 ± 1.0	**0.000**
FVC%	56.4 ± 20.5	47.5 ± 6.0	52.0 ± 16.1	89.5 ± 9.8	**0.000**
FEV_1%	48.4 ± 24.4	31.8 ± 15.6	37.3 ± 20.3	101.1 ± 10.6	**0.000**
FEV_1/FVC	66.4 ± 15.8	42.0 ± 4.3	53.7 ± 14.9	94.7 ± 4.9	**0.000**
$FEF_{25–75}$%	36.0 ± 29.7	28.5 ± 33.7	20.5 ± 15.9	118.1 ± 22.6	**0.000**
pH	7.44 ± 3.50	7.45 ± 5.30	7.40 ± 5.30	—	0.213
PCO_2 (kPa)	5.2 ± 0.6	5.3 ± 0.6	7.7 ± 1.3	—	**0.005**
PO_2 (kPa)	9.7 ± 0.9	6.5 ± 0.9	6.0 ± 1.5	—	**0.007**
HCO_3 (mmol/L)	25.6 ± 2.0	27.7 ± 2.1	33.2 ± 6.9	—	0.117
$SatO_2$	94.7 ± 1.6	83.9 ± 7.3	73.2 ± 12.7	—	**0.004**

BMI, body-mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; $FEF_{25–75}$, second forced expiratory flow; PCO_2, arterial carbon dioxide tension; PO_2, arterial oxygene tension.

Table 2 tCBFV, anterior–posterior CBFV and flow volumes in internal carotid and vertebral arteries of COPD patients and controls.

	Volume (mL/min)						
	COPD			Controls			*P* values
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
tCBFV	832 ± 169	808.0	632.0	598 ± 56	586.0	181.0	**<0.0001**
aCBFV	628 ± 150	614.0	626.0	441 ± 87	438.5	436.0	**<0.0001**
pCBFV	204 ± 49	192.5	183	157 ± 75	156.5	342.0	**0.005**
LICA	320 ± 101	310.0	385.0	217 ± 60	227.5	256	**<0.0001**
RICA	308 ± 85	307.0	368.0	224 ± 49	218.5	251.0	**0.001**
LVA	108 ± 32	111.5	135	88 ± 61	68.0	228.0	0.052
RVA	96 ± 56	84.0	242.0	68 ± 47	54.0	169.0	0.059

tCBFV, total cerebral blood flow volume; aCBFV, anterior cerebral blood flow volume; pCBFV, posterior cerebral blood flow volume; LICA, left internal carotid artery; RICA, right internal carotid artery; LVA; left vertebral artery; RVA, right vertebral artery. All parameters were expressed as mean ± SD.

Table 3 Cross-sectional area in internal carotid and vertebral arteries of COPD patients and controls and *P* values.

	Cross-sectional area (mm^2)						
	COPD			Controls			*P* values
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
LICA	16.3 ± 4.1	15.0	13.0	13.5 ± 5.1	12.5	22.0	**0.023**
RICA	17.4 ± 3.7	17.5	13.0	13.3 ± 3.9	14.0	16.0	**0.002**
LVA	7.8 ± 2.5	8.0	11.0	5.8 ± 2.2	6.0	8.0	**0.015**
RVA	8.1 ± 2.7	8.0	10.0	5.7 ± 1.8	5.5	8.0	**0.001**

LICA, left internal carotid artery; RICA, right internal carotid artery; LVA, left vertebral artery; RVA, right vertebral artery. All parameters were expressed as mean ± SD.

Table 4 Flow velocities in internal carotid and vertebral arteries of COPD patients and controls.

	Flow velocity (cm/s)						
	COPD			Controls			*P* values
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
LICA V_{ps}	62.1 ± 18.9	65.4	69.2	51.8 ± 14.9	53.9	65.5	**0.028**
LICA V_{ed}	18.9 ± 6.7	20.8	18.6	18.1 ± 6.6	19.9	27.1	0.623
RICA V_{ps}	54.5 ± 18.3	51.3	75.8	54.4 ± 14.4	51.5	51.6	0.880
RICA V_{ed}	16.9 ± 5.4	16.1	23.6	18.1 ± 5.2	17.8	20.2	0.345
LVA V_{ps}	40.9 ± 12.5	39.5	49.8	37.7 ± 12.1	39.4	40.2	0.457
LVA V_{ed}	11.7 ± 4.8	11.3	21.4	11.3 ± 5.6	9.3	21.3	0.435
RVA V_{ps}	38.4 ± 13.9	38.6	53.8	36.6 ± 11.3	33.9	49.2	0.496
RVA V_{ed}	9.9 ± 4.3	11.6	15.3	10.3 ± 4.5	9.5	18.1	0.910

LICA V_{ps}, left internal carotid artery peak-systolic velocity; LICA V_{ed}, left internal carotid artery end-diastolic velocity; RICA V_{ps}, right internal carotid artery peak-systolic velocity; RICA V_{ed}, right internal carotid artery end-diastolic velocity; LVA V_{ps}, left vertebral artery peak-systolic velocity; LVA V_{ed}, left vertebral artery end-diastolic velocity; RVA V_{ps}, right vertebral artery peak-systolic velocity; RVA V_{ed}, right vertebral artery end-diastolic velocity. All parameters were expressed as mean ± SD.

(Table 4). No statistically significant differences were found in (except left ICA V_{ps}) both ICA and VA V_{ps}, V_{ed}, RI and PI values ($P > 0.05$).

The patients with COPD were divided into three groups according to blood gases; normocapnic, hypoxemic and hypoxemic–hypercapnic groups.

Table 5 tCBFV, anterior–posterior CBFV and flow volumes in internal carotid and vertebral arteries of subgroup COPD patients and controls.

	Volume (mL/min)				
	Normocapnic COPD	Hipoxic COPD	Hipoxic–hypercapnic COPD	Controls	*P* values
tCBFV	774±22	814±184	901±195	598±56	**<0.0001**
aCBFV	570±50	613±157	691±179	441±87	**<0.0001**
pCBFV	203±34	200±50	210±61	157±75	**0.048**
LICA	284±23	322±125	340±96	217±60	**0.003**
RICA	286±45	291±81	350±108	224±49	**0.005**
LVA	113±43	110±36	100±18	88±61	0.232
RVA	89±66	90±40	109±78	68±47	0.274

tCBFV, total cerebral blood flow volume; aCBFV, anterior cerebral blood flow volume; pCBFV, posterior cerebral blood flow volume; LICA, left internal carotid artery; RICA, right internal carotid artery; LVA, left vertebral artery; RVA, right vertebral artery. All parameters were expressed as mean±SD.

Table 6 Cross-sectional area in internal carotid and vertebral arteries of subgroup COPD patients and controls.

	Cross-sectional area (mm^2)				
	Normocapnic COPD	Hipoxic COPD	Hipoxic–hypercapnic COPD	Controls	*P* values
LICA	15.0±4.7	17.1±3.6	15.6±4.8	13.5±5.1	0.089
RICA	16.7±4.8	17.6±3.9	17.5±2.9	13.3±3.9	**0.002**
LVA	8.0±2.1	8.5±3.0	6.6±1.5	5.8±2.2	0.059
RVA	8.5±0.5	8.5±2.4	7.3±3.8	5.7±1.8	**0.005**

LICA, left internal carotid artery; RICA, right internal carotid artery; LVA, left vertebral artery; RVA, right vertebral artery. All parameters were expressed as mean±SD.

Among COPD patients tCBFV, aCBFV, pCBFV, left and right ICA flow volumes were highest in hypoxemic–hypercapnic ones and lowest in normocapnic ones (Table 5). Right ICA ($P = 0.02$) and VA ($P = 0.005$) cross-sectional areas were significantly higher in normocapnic, hypoxemic and hypoxemic–hypercapnic COPD patients than in control group (Table 6). Left and right VA flow volumes, left ICA and VA cross-sectional areas, bilateral ICA and VA flow velocities and waveform parameters were statistically insignificant among these three groups ($P > 0.05$).

There were no significant correlations between CBFV and values of PaO_2 and $PaCO_2$. We also did not find significant correlation between CBFV and age, blood pressure, medication.

Discussion

CBF increases due to cerebral arteriolar vasodilatation in hypoxemia, a relation defined in many human and animal studies.[14,15] Levasseur et al.[16] observed vasodilatation in pial arteries in rabbits exposed to long-term hypoxemia. There is a general consideration about a linear relationship between decrease in oxygen and increase in CBF.[17] However, in some studies, a gradual increase whereas in other studies a progressive increase in CBF due to hypoxemia was reported.[18–20] Hasegawa et al.[15] performed continuous CBF measurements with transcranial Doppler ultrasound during hypoxemia and found no differences with mild hypoxemia (18% O_2), whereas an increase in CBF with severe hypoxemia (10% O_2). The increment in CBF due to hypoxemia is minimal in some studies and marked in other studies.[21,22] Dolbec et al.[23] found no regional differences in increased CBF values in response to hypoxemia.

CBF increases in hypercapnia due to vasodilatation in cerebral arterioles, capillaries and venous, resulting in faster removal of CO_2 from the tissue.[24,25] These changes in CBF happen through central chemoreceptors. Some studies suggested that central chemoreceptors play a major role[26] whereas other studies suggested that these receptors are less effective[14] in the regulation.

Hypoxemia together with hypercapnia is a frequent clinical entity. But the effect of this on

CBF and cerebral metabolism is yet controversial. A variety of studies reported increase in CBF during hypoxemia and hypercapnia and decrease during hypocapnia.[27–29] In case of hyperoxia CBF was either decreased or not changed.[30,31]

The effects of acute and chronic changes in blood gases on CBF varies. A decrease in cerebrovascular response to $PaCO_2$ changes in chronic hypercapnia was reported.[32] Levasseur et al.[16] reported a decrease in vasodilatation response of pial arteries after prolonged hypercapnia. Scano et al.[8] reported that CO_2 determines the decreased ventilatory response in COPD patients. Both respiratory muscle impairment and insufficient chemoreceptor response are responsible for this situation in chronic hypercapnic COPD patients. Oca et al. reported that effective ventilation was insufficient in very severe COPD patients.[9] Van de Ven et al.[7] found that CBF during normocapnia and hypercapnia in COPD patients was lower than those in healthy subjects. Either mechanical reasons or a decrease in the effect of CO_2 stimulation on respiratory center in COPD were considered to be the reason. As a result, ventilation was found to be decreased in hypercapnia although it was expected to increase.

Alterations in CBF due to $PaCO_2$ changes were investigated regionally; in hypercapnia marked hyperperfusion was detected in pons, cerebellum, thalamus and putamen and a gradual hypoperfusion was detected in temporal, temporooccipital and occipital cortices.[12] Helou et al.[33] studied sheep fetus and Pelligrino et al.[34] studied rats and they found that vascular response was markedly increased in pons, cerebellum, thalamus and putamen. In some studies, no differences were observed between cerebral cortex and deep white substance during hypercapnia, whereas in other studies cerebrovascular response was found to be more evident in cerebral cortex.[12,35,36]

Hypoxia is a significant cause of cell injury. It can be due to decrease in vascular supply in arterial or venous systems, insufficient oxygenization of blood because of cardiac or pulmonary deficiency, or decrease in oxygen transport capacity of blood because of anemia. In the disturbances where the oxygen demand of the brain is increased, such as COPD and chronic anemia, some modifications in the vasculature are made to supply this demand. These modifications in the vascular system are directed to increase the blood flow to the brain and this increase is achieved by increasing blood flow velocity and vascular lumen diameter, either alone or together. In a study with anemic patients, the increase in CBF was reported to be negatively correlated with hemoglobin. In that study, particularly, VA lumen was increased in anemic patients.[37] In a study with chronic hypercapnic COPD patients, oxygen replacement treatment was shown to decrease CBF velocity, detected with transcranial Doppler ultrasound.[5]

Doppler ultrasound of extracranial carotid and VA is a well-established method to assess cerebrovascular circulation. It has been used for the evaluation of effects of various diseases or conditions. This technique measures tCBFV by applying it to bilateral internal carotid and vertebral arteries, which has been shown to be a precise and reliable approach.[10,11]

To the best of our knowledge, this is the first study that evaluates ICA and VA blood flow volumes separately in patients with COPD by using Doppler ultrasound. In the present study tCBFV, aCBFV, pCBFV, left and right ICA flow volumes, bilateral ICA and VA cross-sectional areas and left ICA V_{ps} were markedly increased in COPD patients. Ellingsen et al.[18] reported that ICA flow rates were directly proportional with blood CO_2 levels. Ito et al.[12] reported that the increase in CBF due to hypercapnia in healthy subjects was related with vascular blood flow velocity. In our study, the flow velocity values were higher in COPD patients, particularly those with hypoxemia and hypercapnia, compared with control group. But only left ICA V_{ps} was statistically significant. Bilateral ICA and VA cross-sectional areas were markedly increased, and in our study, this was the main reason of increased tCBFV in COPD patients.

Increased tCBFV due to blood gas alterations in COPD patients in our study are in agreement with the results of similar studies in healthy human subjects or animals using PET,[12] carotid artery Doppler ultrasound,[18] magnetic resonance imaging,[23] and transcranial Doppler ultrasound methods.[38] Our results are in contrast with the results of the study of Van de Ven et al.[7] in COPD patients with NIRS method.

There are other reasons than blood gas changes, increasing and decreasing CBF in COPD patients. Aging, arterial hypertension, polycythemia, aminophylline and systemic corticosteroids use decreased CBF in COPD patients.[7,10,39–41] But there was no significant correlation between CBFV and age, blood pressure, medication in our study.

Chronic hypercapnia, a reversible syndrome of headache, papilledema and impaired consciousness with tremor of the extremities has been described in patients with chronic pulmonary insufficiency.[42] The headaches are attributed to the increased intracranial pressure. Increased CBF is elevated intracranial pressure in normal population.[43] Blood gases changed in COPD patients can raise

intracranial pressure. The increased intracranial pressure may produce papilledema that can progress to blindness. Ventilatory support and discontinuation of sedative drugs constitute effective treatment. Vigorous hyperventilation must be avoided as renewed obtunation, seizures and even death may result, presumably from hyperventilation-induced cerebral vasoconstriction.[42]

RI is thought to be correlated to vascular resistance, and reported to be a good marker for predicting the prognosis of perinatal asphyxia.[44] Archer et al.[45] found 100% sensitivity of a low RI with increased diastolic flow in the anterior cerebral artery and middle cerebral artery. In our study there were no significant differences in RI and PI values of ICA and VA between COPD patients and control group.

As a conclusion, bilateral ICA and VA cross-sectional areas and left ICA V_{ps} are the basic parameters causing high tCBFV, aCBFV and pCBFV in COPD patients. Increased tCBFV in normocapnic COPD patients, those similar to control group with regard to blood gas values, suggests a possible compensatory mechanism developed for covering the increased oxygen demand. Hypoxia alone and hypoxia with hypercapnia emphasizes the increase in tCBFV. In our study, low number of cases was the major limitation. Further studies of tCBFV measurements using Doppler ultrasound comparing enough COPD patients and control subjects with adjusted blood gases need to be performed.

References

1. Ito H, Kanno I, Ibaraki M, Hatazawa J. Effect of aging on cerebral vascular response to $PaCO_2$ changes in humans as measured by positron emission tomography. *J Cereb Blood Flow Metab* 2002;**22**:997–1003.
2. Massik J, Jones MD, Miyabe M, Tang YL, et al. Hypercapnia and response of cerebral blood flow to hypoxia in newborn lambs. *Am Physiol Soc* 1989:1065–70.
3. Bereczki D, Wei L, Otsuka T, et al. Hypoxia increases velocity of blood flow through parenchymal microvascular systems in rat brain. *J Cereb Blood Flow Metab* 1993;**13**:475–86.
4. Shockley RP, LaManna JC. Determination of rat cerebral cortical blood volume changes by capillary mean transit time analysis during hypoxia, hypercapnia and hyperventilation. *Brain Res* 1988;**454**:170–8.
5. Cannizzaro G, Garbin L, Clivati A, Pesce LI. Correction of hypoxia and hypercapnia in COPD patients: effects on cerebrovascular flow. *Monaldi Arch Chest Dis* 1997;**52**(1): 9–12.
6. Sari A, Oshiata S, Toriumi T, et al. Cerebral blood flow and cerebral oxygen consumption in patients with COPD on mechanical ventilation. *Intens Care Med* 1992;**18**(8):455–8.
7. Van VMJ, Colier WN, Van SMC, et al. Ventilatory and cerebrovascular responses in normocapnic and hypercapnic COPD patients. *Eur Respir J* 2001;**18**:61–8.
8. Scano G, Spinelli A, Duranti R, et al. Carbon dioxide responsiveness in COPD patients with and without chronic hypercapnia. *Eur Respir J* 1995;**8**:78–85.
9. Oca MM, Celli BR. Mouth occlusion pressure, CO_2 response and hypercapnia in severe chronic obstructive pulmonary disease. *Eur Respir J* 1998;**12**:666–71.
10. Dorfler P, Puls I, Schliesser M, et al. Measurement of cerebral blood flow volume by extracranial sonography. *J Cereb Blood Flow Metab* 2000;**20**:269–71.
11. Scheel P, Ruge C, Schoning M. Flow velocity and flow volume measurements in the extracranial carotid and vertebral arteries in healthy adults: reference data and the effects of age. *Ultrasound Med Biol* 2000;**26**:1261–6.
12. Ito H, Kanno I, Ibaraki M, Hatazawa J, Miura S. Changes in human cerebral blood flow and cerebral blood volume during hypercapnia and hypocapnia measured by positron emission tomography. *J Cereb Blood Flow Metab* 2003;**23**:665–70.
13. Van VMJ, Colier WN, Van SMC, et al. Effects of acetazolamide and furosemide on ventilation and cerebral blood volume in normocapnic and hypercapnic patients with COPD. *Chest* 2002;**121**(2):383–92.
14. Poulin MJ, Robbins PA. Influence of cerebral blood flow on the ventilatory response to hypoxia in humans. *Exp Physiol* 1998;**83**:95–106.
15. Hasegawa M, Tatsuno M, Houdou S, et al. Continuous comparison of cerebral blood flow velocity and volume on hypoxia. *Brain Dev* 1991;**13**:433–7.
16. Levasseur JE, Wei EP, Kontos HA, Patterson JL. Responses of pial arterioles after prolonged hypercapnia and hypoxia in the awake rabbit. *J Appl Physiol* 1979;**46**:89–95.
17. Jones MD, Traystman RJ, Simmons MA, Molteni RA. Effects of changes in arterial O_2 content on cerebral blood flow in the lamb. *Am J Physiol* 1981;**240**:209–15.
18. Ellingsen I, Hauge A, Nicolaysen G, Thoresen M, Walloe L. Changes in human cerebral blood flow due to step changes in PaO_2 and $PaCO_2$. *Acta Physiol Scand* 1987;**129**:157–63.
19. Borgstrom L, Johannsson H, Siesjo BK. The influence of acute normovolemic anemia on cerebral blood flow and oxygen consumption of anesthetized rats. *Acta Physiol Scand* 1975;**93**:505–14.
20. Van Beek JH, Berkenbosch A, De Goede J, Olievier CN. Response of vertebral and carotid blood flow to isocapnic changes in end-tidal oxygen tension. *Respir Physiol* 1986;**63**: 65–77.
21. Fortune JB, Feustel PJ, Graca L, Hasselbarth J, Kuehler DH. Effect of hyperventilation, mannitol, and ventriculostomy drainage on cerebral blood flow after head injury. *J Trauma* 1995;**39**:1091–7 (Discussion 1097–1099).
22. D'Arceuil HE, Crespigny AJ, Rother J, Moseley M, Rhine W. Serial magnetic resonance diffusion and hemodynamic imaging in a neonatal rabbit model of hypoxic-ischemic encephalopathy. *NMR Biomed* 1999;**12**:505–14.
23. Dolbec CJ, Tropres I, Montigon O, et al. Regional response of cerebral blood volume to graded hypoxic hypoxia in rat brain. *Br J Anaesth* 2002;**89**:287–93.
24. Feihl F, Perret C. Permissive hypercapnia. How permissive should we be? *Am J Respir Crit Care Med* 1994;**150**:1722–37.
25. Neubauer JA, Melton JE, Edelman NH. Modulation of respiration during brain hypoxia. *J Appl Physiol* 1990;**68**:441–51.
26. Berkenbosch A, Olievier CN, DeGoede J. Respiratory responses to hypoxia peripheral and central effects. Chairman's introductory communication. *Adv Exp Med Biol* 1995; **393**:251–6.
27. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg* 1982;**57**:769–74.

28. Heistad DD, Abboud FM, Dickinson W. Richards Lecture: circulatory adjustments to hypoxia. *Circulation* 1980;**61**: 463–70.
29. Bicher HI. Brain oxygen autoregulation: a protective reflex to hypoxia? *Microvasc Res* 1974;**8**:291–313.
30. Bergo GW, Tyssebotn I. Cerebral blood flow and systemic hemodynamics during exposure to 2 kPa CO_2-300 kPa O_2 in rats. *J Appl Physiol* 1995;**78**:2100–8.
31. Bew SA, Field LM, Droste DW, Razis P. The effect of high concentrations of inspired oxygen on middle cerebral artery blood velocity measured by transcranial Doppler. *Exp Physiol* 1994;**79**:593–6.
32. Clivati A, Ciofetti M, Cavestri R, Longhini E. Cerebral vascular responsiveness in chronic hypercapnia. *Chest* 1992;**102**:135–8.
33. Helou SM, Hudak ML, Jones Jr MD. Cerebral blood flow response to hypercapnia in immature fetal sheep. *Am J Physiol* 1991;**261**:1366–70.
34. Pelligrino DA, Koenig HM, Albrecht RF. Nitric oxide synthesis and regional cerebral blood flow responses to hypercapnia and hypoxia in the rat. *J Cereb Blood Flow Metab* 1993; **13**:80–7.
35. Ramsay SC, Murphy K, Shea SA, et al. Changes in global cerebral blood flow in humans: effect on regional cerebral blood flow during a neural activation task. *J Physiol* 1993; **471**:521–34.
36. McPherson RW, Kirsch JR, Ghaly RF, Traystman RJ. Effect of nitric oxide synthase inhibition on the cerebral vascular response to hypercapnia in primates. *Stroke* 1995;**26**:682–7.
37. Haktanır A, Demir S, Acar M, et al. Doppler ultrasound evaluation of cerebral blood flow in anemia resulting from chronic renal failure. *J Ultrasound Med* 2005;**24**(7):947–52.
38. Vovk A, Cunningham DA, Kowalchuk JM, Paterson DH, Duffin J. Cerebral blood flow responses to changes in oxygen and carbon dioxide in humans. *Can J Physiol Pharmacol* 2002;**80**: 819–27.
39. York EL, Jones RL, Menon D, Sproule BJ. Effects of secondary polycythemia on cerebral blood flow in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1980;**121**(5):813–8.
40. Bowton DL, Alford PT, McLees BD, Prough DS, Stump DA. The effect of aminophylline on cerebral blood flow in patients with chronic obstructive pulmonary disease. *Chest* 1987; **91**(6):874–7.
41. Schraa JC, Dirks JF. The influence of corticosteroids and theophylline on cerebral function. A review. *Chest* 1982; **82**(2):181–5 (Review).
42. Simon RP. Breathing and the nervous system. In: Aminoff MJ, editor. *Neurology and general medicine*. 3rd ed. New York: Churchill Livingstone; 2001. p. 1–17.
43. Muizelaar JP, Fatouros PP, Schroder ML. A new method for quantitative regional cerebral blood volume measurements using computed tomography. *Stroke* 1997;**28**:1998–2005.
44. Stark JE, Seibert JJ. Cerebral artery Doppler ultrasonography for prediction of outcome after perinatal asphyxia. *J Ultrasuond Med* 1994;**35**:595–600.
45. Archer LNJ, Levene ME, Evans DH. Cerebral artery Doppler ultrasonography for prediction of outcome after perinatal asphyxia. *Lancet* 1986;**2**:1116.