Value of proton magnetic resonance spectroscopy of brain to study the cerebral metabolic abnormalities in COPD: Initial experience

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Received 2 October 2013; accepted 9 October 2013
Available online 14 November 2013

Abstract Background: Chronic obstructive pulmonary disease (COPD) patients were found to have cerebral metabolic abnormalities. Proton magnetic resonance spectroscopy (1H MRS) is a sensitive technique that detects metabolic changes of the brain.

Objective: To study the cerebral metabolic changes in COPD patients using 1H MRS.

Methods: This study was carried out on twenty symptomatic COPD patients (16 male and 4 female) and age matched group of 20 healthy controls (11 male and 19 female). Pulmonary function tests, respiratory muscle strength, resting arterial blood gases, and 1H MRS of the brain were carried out on all subjects. The parieto-temporal and occipital regions were localized for 1H MRS. The metabolic ratios of N-acetyl aspartate to creatine (NAA/Cr) and choline to creatine (Cho/Cr) were calculated by the single voxel technique.

Results: In comparison with healthy control subjects, the mean values of Cho/Cr in COPD patients were lower in parieto-temporal and occipital areas (0.99 ± 0.21 vs. 1.10 ± 0.31; P = 0.22) (0.81 ± 0.26 vs. 0.88 ± 0.21; P = 0.37), respectively while, the mean values of NAA/Cr in COPD patients were higher in both parieto-temporal and occipital areas of the brain (1.82 ± 0.35 vs. 1.68 ± 0.22; P = 0.14) (1.59 ± 0.31 vs. 1.39 ± 0.39; P = 0.08), respectively. In COPD patients, significant positive correlations were observed between maximal expiratory pressure (MEP) and NAA/Cr in parieto-temporal area of the brain.

Conclusions: The cerebral metabolites, arterial blood gases, respiratory muscle strength, and pulmonary function tests are altered in symptomatic COPD patients. 1H MRS is a non invasive technique that detects cerebral metabolic changes in COPD patients.

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only characterized by progressive and largely irreversible limitation of air flow, shortness of breath, cough and expectoration, but also by adverse effects on brain function [2]. Exacerbations of COPD accounted for over half of all acute medical admissions for respiratory diseases [3]. Although COPD is a slowly progressive disease, acute infective exacerbations are associated with worsening hypoxia, hypercapnia, and respiratory acidosis [4]. Normal cerebral cell function is critically dependent on intracellular energy metabolism via oxidative phosphorylation and the production of adenosine triphosphate (ATP) [5]. (1H MRS) is a sensitive technique that detects metabolic changes of the brain. Using 1H MRS different metabolites present in the brain can be measured. They are, N-acetyl aspartate (NAA), total creatine, choline containing compound (Cho), glutamate, glutamine, aspartate, alanine, myo-inositol, lactate and glucose [6]. NAA is a neuronal marker the concentration of which decreases with neuronal cell death. It is an intraneuronal molecule and it is found only in neurons and axons of the mature brain. It is reduced in many brain disorders, in the presence of neuronal and/or axonal loss or dysfunction, such as infarcts, dementia, brain tumors, hypoxic encephalopathy and multiple sclerosis [7,8]. Cho is associated with myelination, Choline containing compounds are an integral part of the neuronal membranes. Their signal strength participates in energy metabolism. Cr is assumed to be a relatively stable brain metabolite both in normal and pathological conditions; it is often used as an internal standard in the in vivo evaluation of relative concentrations of metabolites [10,11]. Hydrogen 1 (1H) magnetic resonance (MR) spectroscopy enables noninvasive quantification of in vivo metabolite concentrations in the brain. It has proved to be a powerful addition to the clinical assessment tools for numerous pathologic conditions, including epilepsy, multiple sclerosis, stroke, cancer, and metabolic diseases [12]. It has been approved by the U.S. Food and Drug Administration and is widely used for the evaluation of the brain and the prostate gland [13]. In this study, we suggest that cerebral metabolism may be disturbed in COPD patients due to chronic hypoxia/hypercapnia and this may have an influence on the levels of cerebral metabolites. This may have some clinical significance.

Subjects and methods

Twenty symptomatic COPD patients and age matched group of 20 healthy control subjects were recruited from Chest and Radiology Departments Menoufia University Hospital Egypt, from October 2012 to January 2013. COPD was defined as evidence of chronic and generalized air-flow limitation (FEV1 < 80% predicted and FEV1/FVC < 70%) with long-term variability in FEV1 or peak expiratory flow rate of <20% and acute B2-agonist reversibility of <15% [14]. No patient had an acute exacerbation of COPD (defined as hospital admission or prescription of antibiotics/systemic corticosteroids by a general practitioner) over 3 months prior to the study. Patients with other, coexistent pulmonary diseases, congestive heart failure, cirrhosis, dementia, and recent or old stroke, and those with claustrophobia, cardiac pacemakers, and ferromagnetic implants were excluded. The control subjects were asymptomatic, healthy nonsmokers, and were taking no medications. All subjects gave written informed consent, and ethical approval for the study was obtained from the local ethics committees. Measures of pulmonary function included spirometry, pulse oximetry at rest and change during a 6-minute walk, and distance walked [15], arterial blood gas measurements and respiratory muscle strength were done on the day of the study for all patients. The MRS examination requires an obligatory period during which each subject lies flat within the bore of the magnet, which presents technical difficulties for COPD patients. Our study protocol was therefore intended to minimize the time in the magnet; it was not possible to measure absolute concentrations of metabolites in mmol/g wet weight of tissue in the present study because absolute quantitation of metabolites with reference to a known concentration of an external reference standard requires further sequences. This would have unavoidably prolonged the examination time beyond that which was ethically permissible and practically possible for the patient population studied.

Pulmonary function test and respiratory muscle strength

Pulmonary function including forced vital capacity (FVC), Forced expiratory volume in the first second (FEV1), peak expiratory flow rate (PEFR) and FEV1/FVC was measured by spirometer according to ATS criteria. Using severity classification of COPD Global initiative for chronic obstructive lung disease guidelines (GOLD), via measurement of FEV1 as percent predicted. Ia (FEV1 < 50–79% predicted), Ib (FEV1 < 30–49% predicted), and III (FEV1 < 30% predicted) were characterized in moderate and severe COPD patients. Clinical assessment of the global function of respiratory muscle was performed by measuring maximal inspiratory and expiratory mouth pressure. Maximal static inspiratory (MIP) and maximal expiratory pressure (MEP) were measured in sitting position. The MIP was measured near residual volume and MEP was measured near total lung capacity. Best of three satisfactory readings was taken for analysis.

1H magnetic resonance spectroscopy (MRS) of the brain

The 1H MRS was carried out using a 1.5 Tesla MRI scanner (Toshiba Excelart Vantage). Spectroscopy was performed following a routine brain MRI analysis, and the T2-weighted images were used for localization. Using these images well-defined regions of the brain namely, parieto-temporal and occipital regions were localized for 1H MRS (Fig. 1). The single voxel method was employed using sequence PRESS at an echo-time (TE) of 136 ms and with a repetition time (TR) of 2000 ms, field of view 2, matrix: 1x1024 was used for 1H MRS. The metabolic ratios NAA/Cr and Cho/Cr were calculated by integrating area under each peak. One experienced MRS operator undertook the careful placement of the localization-voxel in the same region for all subjects, thereby increasing the consistency of region selection see (Fig. 2).

Results

The base line clinical characteristics are presented in Table 1. The mean age of COPD patients was 59.30 ± 8.12 years. There were 4/20 (20%) female and 16/20 (80%) male. All COPD patients had dyspnea on exertion. 15/20 (75%) were

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current smokers. 8/20 (40%) patients were being treated with theophylline and inhaled corticosteroid (ICS), 3/20 (15%) with diuretics, and 9/20 (45%) patients with ipratropium bromide inhaler. The degree of airway obstruction was moderate IIa in 6/20 (30%) patients, moderate IIb in 7/20 (35%) patients, and severe in another 7/20 (35%) patients. All patients had PaO2 of >60 mm Hg at the resting state. The measured PCO2 for the patients was >45 mm Hg in 10/20 (50%) patients, and <45 mm Hg in another 10/20 (50%) patients. 9/20 (45%) COPD participants were on long-term continuous O2 therapy. The mean values of PCO2 were (49.9 ± 13.2 vs. 37.3 ± 8.1 mm Hg) in COPD patients compared with healthy
control subjects. In COPD participants FEV1/FVC, FEV1, and FVC values were (68.9 ± 7.9), (39.5 ± 12.4), and (42.7 ± 12.9) of predicted, respectively. While in controls were, (83.3 ± 13.6), (83.8 ± 10.7), and (76.9 ± 8.3) of predicted, respectively. While in controls and FVC values were (68.9 ± 7.9), (39.5 ± 12.4), and (1.59 ± 0.31 vs. 1.39 ± 0.39; \( P = 0.08 \)), respectively of controls and occipital areas (1.82 ± 0.35 vs. 1.68 ± 0.22; \( P = 0.057 \)), respectively. The mean values of MIP were (4.2 ± 0.7), (7.5 ± 1.7), and (83.3 ± 13.6), (83.8 ± 10.7), and (76.9 ± 8.3) of predicted, respectively. While in controls and FVC values were (68.9 ± 7.9), (39.5 ± 12.4), and (0.81 ± 0.26 vs. 0.88 ± 0.21; \( P = 0.099 \)), respectively. Significant negative correlation between 6MWD feet and PO2. Significant positive correlation between arterial PH and PO2. Significant positive correlation between arterial PH and PO2.

Peak spectroscopic data were transferred to a computer workstation and were processed by a special software.
Impaired brain function has long been recognized as a complication of COPD [16]. Patients with mild to moderate hypoxia have previously been found to have abnormalities on testing for psychometric functions, activities of daily living, and electroencephalography [17,18]. We therefore postulated abnormalities in brain bioenergetics in patients with chronic stable hypoxia. The aims of the present study were to identify changes in 1H MRS spectra obtained from the brains of patients with stable COPD, and to compare the results with MR spectra from the same areas of the brain in healthy control subjects. This study examined the brain dysfunction in a carefully selected group of COPD patients and matched controls, using disease-specific measures of disease severity, disability, and validated measures of neurochemical of brain integrity. In the present work Cho/Cr cerebral metabolites in COPD patients were lower in both parieto-temporal and occipital areas of the brain (0.99 ± 0.21 vs. 1.10 ± 0.31) and (0.81 ± 0.26 vs. 0.88 ± 0.21 \( P = 0.3 \)), respectively, in comparison to healthy control subjects. However, this difference did not attain statistical significance. While, a general non-significant increase of NAA/Cr cerebral metabolite was observed in similar areas of the brain of COPD patients as compared to healthy control. Cerebral metabolism was investigated with proton magnetic resonance spectroscopy (MRS) using the multivoxel technique in another study [19] which comprised 30 male patients, aged 45–70 years, with moderate level COPD and an aged matched group of 30 healthy males as the control group. Karakas and his colleagues [19] reported that the frontal and parietal white matter in patients with COPD showed an overall reduction in cerebral metabolites. The NAA/Cr, and Cho/Cr ratios of the cerebral frontal and parietal white matter regions in the COPD group were significantly lower than the control group. The findings of this study through the use of MRS confirmed that most patients with symptomatic COPD have cerebral metabolic abnormalities. Sinha et al. [20] had investigated changes in the cerebral metabolism of non diabetic and normo-lipidaemic patients with chronic obstructive pulmonary disease (COPD) using 1H MRS, 28 symptomatic COPD patients and 19 healthy controls. The mean values of NAA/Cr and Cho/Cr in parieto-temporal area in COPD patients were 1.86 ± 0.54 and 0.77 ± 0.23, respectively. The mean values of NAA/Cr and Cho/Cr in occipital area in COPD patients were 1.75 ± 0.44 and 0.61 ± 0.25, respectively. Compared with healthy control subjects, the mean values of Cho/Cr in COPD patients were lower, both in parieto-temporal (0.77 ± 0.23 vs. 0.89 ± 0.35; \( P = 0.17 \)) and occipital (0.61 ± 0.25 vs. 0.67 ± 0.08; \( P = 0.36 \)) areas of the brain. To evaluate the clinical significance of cerebral metabolic abnormalities in COPD patients Shim et al [7] using the MRS, examined seventeen symptomatic COPD patients and 21 age-matched healthy volunteers. The mean FEV1 was 38 ± 10% predicted, the PaCO2 was 39 ± 7 mm Hg, and the PaO2 was 89 ± 18 mm Hg, and these values did not exhibit a statistical correlation with the levels of cerebral metabolites. NAA, Cr, and Cho levels in parietal white matter (PWM) were all significantly lower in COPD patients than in control subjects (\( P < 0.0125 \)). They suggested that decreased in vivo Cho levels indicate loss of myelin lipids or phospholipid metabolism dysfunction. On the other hand, Borson et al. [21] reported that frontal choline was significantly higher in oxygen dependent COPD subjects, consistent with evidence of brain damage in this most impaired group. Neurochemical measures of frontal choline were 3.96 ± 0.38, 3.30 ± 0.46 and 4.50 ± 0.71 in control, COPD and O2 dependent group of COPD, respectively, whereas NAA or creatine revealed no significant statistical difference between different studied groups. Elevation of frontal choline in oxygen-dependent COPD patients is consistent with the work of Incalzi et al. [25] using a different (perfusion) imaging approach. In that comprehensive mapping study, substantial perfusion deficits were identified in frontal lobes and were most marked in oxygen-dependent subjects. We propose that frequent oxygen desaturation during everyday activity of COPD patients may be a key mechanism underlying the damage to brain tissue reflected in elevated brain choline. Similar choline elevations are observed in systemic diseases secondarily associated with brain tissue breakdown and cognitive impairment (Friedman et al. [22], Forton et al. [23]), and appear to reflect damage to myelin and increased turnover of neuronal membrane precursors (Ross and Michaelis [24]). It is likely that increases in choline in advanced hypoxemic COPD reflect such a combination of membrane breakdown and turnover changes in the brain, and that these are eventually manifested as white matter hyperintensities on structural imaging. Other spectroscopy approaches (eg, decoupled 31P MRS) to measure individual constituents of the choline peak could be helpful in refining and further interpreting these results. In diseases in which there is increased cell repair like in COPD, there is an increase in choline resonance. This is because the normal equilibrium that exists between cell membrane synthetic products (like phos-
phocholine) and breakdown products (like glycerolphosphocholine) is altered in favor of cell membrane degradation synthesis. Under these circumstances the cell membrane degradation products would be recirculated into synthetic pathways, this would therefore result in increasing choline resonance [26]. However, Shim et al. [7] and Sinha et al. [20] studies, excluded oxygen dependent subjects, participants were younger, analyses were not adjusted for age and education, and the brain regions sampled were different from those used in the previous study and possibly less likely to be related to changes in mood and cognition. Their results matched with our work as regards reduced Cho/Cr metabolites in COPD patients. Although our study did not establish causality, it is likely that the changes we observed in cerebral bioenergetics in COPD patients were a consequence of chronic changes in arterial blood gases. It is also unclear whether these changes in cerebral bioenergetics are a consequence of chronic hypoxia, hypercapnia, or both [28]. A study by Alchanatis et al., [29] showed that patients with hypoxia in obstructive sleep apnea and without a medical history of cardiac disease or cardiovascular risk factors had significantly depressed NAA/Cr and Cho/Cr ratios, as well as a diminished Cho concentration in brain white matter, when compared to controls. This finding suggests that hypoxia may promote brain metabolic impairment even in the absence of hypercapnia or other co-morbidities. Different pathophysiological abnormalities associated with various diseases may induce their own characteristic changes in the brain. Co-morbid diseases such as congestive heart failure (CHF), diabetes mellitus (DM), Chronic liver diseases (CLD), and other risk factors like smoking associated with COPD patients may have different effects on the cerebral metabolites. In patients with DM, the cholin level increases in both the parietal white matter and the occipital gray matter, whereas a significant reduction of NAA is found in the parietal cortex [28] while chronic hepatic encephalopathy, reduced the Cho levels in the cerebral parietal white matter. Patients with CHF showed a more prominent decrease of brain metabolites [28,29]. MR-based metabolomics had ability in discriminating patients exposed to same risk factors, smoking habit: 50 current smokers without COPD, COPD smokers analyzed by a mean of MR. MR spectra of exhaled breath condensate discriminate COPD patients from healthy subjects in smoking habit related disease. Cerebral metabolites were prominently reduced in COPD smoker than healthy smoker. MR offers a powerful tool for assessing the evolution of airway disease even in the presence of strong common factors [30–32]. Neuronal cell death is generally considered to be an irreversible process accompanying aging, and decreased levels of NAA are reported frequently in healthy aged persons [30]. Mathur et al. [27] reported that there is an accumulation of cerebral lactate and a reduction in N-acetyl aspartate in proton MRS spectra in patients with COPD. Karakas and his colleagues [19], Shim et al. [7] and Sinha et al. [20] results were matched with the previous results. In the present work NAA/Cr ratio increased, however COPD participants were younger, analyses were not adjusted for age. Also 9/20 (45%) were oxygen dependent subjects, it is not known whether the spectroscopic abnormalities observed in hypoxic patients are correctable with supplemental oxygen or, indeed, are inducible in normal human subjects with controlled experimental hypoxia and weather earlier oxygen supplementation, could help to prevent irreversible brain damage in COPD patients. The possibility of cerebral NAA restoration might be expected using long term oxygen therapy for these COPD patients. Further studies are needed to confirm whether these increases represent actual neural regeneration. Also the brain regions sampled in previous studies were different from those used in the present study. This association in COPD patients between blood pH and arterial PO2 suggests that at least as far as these patients are concerned, the metabolites of anaerobic metabolism do have an impact on blood pH. In a hypoxic intracellular environment, the cell relies chiefly on glycolysis for ATP generation as both Kreb’s cycle and oxidative phosphorylation become inefficient. With acceleration of glycolysis, intracellular lactate is expected to accumulate. This is expected to result in a decrease in blood pH as the cell becomes overwhelmed with excess lactate. The linear relationship observed between PaO2 and pH (although still within normal range) in our study seems to support this notion. This finding supports our speculation that the switch to anaerobic metabolism in hypoxic patients tends to result in lactate accumulation, which is in turn buffered by cationic proteins. Patients with chronic stable hypoxia seem to fully compensate for developing intracellular brain acidosis either through active ion transport of protons outside the cell [33,34] or by retention of bicarbonate [35]. It is interesting to speculate that as hypoxia increases, the ability of the neuron to buffer lactate, pump out protons, and retain bicarbonate might fail, resulting in acidosis. This may be the mechanism underlying the decompensation in cerebral function with agitation, confusion, and ultimate unconsciousness that is characteristic of severe respiratory failure. In the present work expected statistically significant differences in the main lung disease related predictor (independent) variables between control and the COPD group were found for several measures (I) pulmonary function test: FEV1, FVC, FEV1/FVC, PEFR, 6MW distance, resting arterial oxygen saturation (Spo2) and minimal arterial oxygen saturation during 6MWT. (II) Arterial blood gases: PH, arterial oxygen tension (PO2) and arterial carbon dioxide tension (PCO2). (III) Respiratory muscle strength: MIP and MEP. Tarrega et al. [13] stated that patients with severe COPD became chronically hypoxicemic and hypercapnic. Delclaux et al. [36] posted that, patients with COPD in chronically stable conditions expected to have an increased oxygen alveolar-arterial gradient, and therefore lowered PaO2 compared with healthy subjects. Moderate COPD patients were hypoxicemic only during modest exercise, and as the disease worsened, they were unable to exercise at all. They also reported a persistent, irreversible low FEV1 which was the most characteristic objective finding in COPD. Clinical assessment of the global function of the respiratory muscle was performed by measuring maximal inspiratory and expiratory mouth pressure, although these measurements were very effort dependent. They stated that patients with COPD had an impaired value of MIP and MEP. Gosselink and his colleagues in a meta-analysis included 32 randomized controlled trials on the effects of inspiratory muscle training in COPD they announced that maximal inspiratory muscle strength was reduced ( + 7 cm H2O) and a significant improvement was found in MIP, endurance time and walking distance after training modality (strength or endurance training, added to general exercise training). Our data revealed that, significant negative correlations were observed between MEP and NAA/Cr in parieto-temporal area of the
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...brain (r = 0.66, P < 0.05) and between 6MW distance and NAA/Cr in occipital area of the brain. These results were in agreement with Shim et al. [7] and Sinha et al. [20] results.

In conclusion, the results of our study demonstrate that the cerebral metabolism, pulmonary functions, arterial blood gases and respiratory muscle strength are altered in symptomatic COPD patients. The present study offers insight into the complex biochemical changes in the brains of patients with moderate and severe COPD. Further work needs to be done (with 31P MRS and 1H MRS) to correlate the cerebral bioenergetic abnormalities in these patients with other evaluations of cerebral function, and to directly measure levels of intracellular brain lactate and PH. It is now possible to combine MRS with near-infrared spectrophotometry in the same examination in order to assess changes in cerebral blood flow. Further studies should combine both modalities, since it is not known whether the spectroscopic abnormalities observed in hypoxic patients are correctable with supplemental oxygen or, indeed, are inducible in normal human subjects with controlled experimental hypoxia and hypercapnia. Correction of such cerebral bioenergetic abnormalities with administered pharmacological agents, independent of any changes in ventilatory status and both in patients with stable COPD and patients with acute exacerbation of this disease may pave the way for novel modalities of therapy to support cerebral compensation in these patients. Routine identification of episodic desaturation with everyday activity, and/or sleep, and earlier oxygen supplementation, could help to prevent irreversible brain damage in COPD patients. Further studies will be required to document the mechanism and clinical significance of cerebral metabolic abnormalities in COPD patients and to confirm the effect of therapeutic interventions on the cerebral metabolism. Limitation of this study: Small sample size technical difficulties for COPD patients and inability to measure absolute concentrations of cerebral metabolites were the main obstacles in the present work.

Conflict of interest

We have no conflict of interest to declare.

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