Magnetic resonance spectroscopy in evaluating cerebral metabolite imbalance in chronic obstructive pulmonary disease

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Rationale Magnetic resonance spectroscopy (MRS) is a powerful research tool and has been proved to provide additional clinically relevant information for several diseases such as brain tumors, metabolic disorders, and systemic diseases.

Aim The aims of this study were to evaluate cerebral metabolic imbalance in chronic obstructive pulmonary disease (COPD) and to correlate the abnormalities with spirometric and gasometric parameters.

Patients and methods In a case–control study, eight COPD patients and eight age-matched and sex-matched healthy control individuals were compared. ^{1}H-MRS was performed using 1.5-T MRI/MRS scanner. Using ^{1}H-MRS single-voxel technique, *N*-acetyl aspartate/choline (NAA/Cho), choline/creatine (Cho/Cr), and *N*-acetyl aspartate/creatine (NAA/Cr) ratios were estimated and compared in both groups.

Results There were significant differences regarding the distribution of neurotransmitters in the temporal lobe only between COPD and control groups; there were significant positive correlations between the NAA/Cho ratio at the thalamus with both partial pressure of arterial carbon dioxide and base excess or base deficit. However, there was a significant positive correlation between the Cho/Cr ratio at the thalamus and forced vital capacity (l), and a significant positive correlation between the NAA/Cr ratio at the thalamus and BMI, and a negative correlation between the NAA/Cr ratio at the thalamus and partial pressure of arterial oxygen. There was a significant negative correlation between the NAA/Cr ratio at the temporal lobe and partial pressure of arterial carbon dioxide.

Conclusion MRS provided an insight to study the neurochemical changes that occur in COPD patients. Chronic hypoxemia and hypercapnia seem to play a key role in the pathophysiology of neurochemical changes in COPD.

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Introduction

Magnetic resonance spectroscopy (MRS) is a modality that is available on most state-of-the-art clinical magnetic resonance (MR) scanners. For the brain in particular; MRS has been a powerful research tool and has also been proven to provide additional clinically relevant information for several diseases such as brain tumors; metabolic disorders; and systemic diseases. the most widely available MRS method; proton (^{1}H; hydrogen) spectroscopy; is an FDA-approved procedure that can be ordered by clinicians for their patients if indicated. other methods such as phosphorous-31; carbon-13; or fluorine-19 MRS have been successfully applied to humans. however; with the ever-increasing importance of clinical MRI; these exotic and time-consuming applications have been pushed to the side and are only available at a few academic centers. in addition; ^{1}H *MRS* does not require any additional hardware beyond what is already being used for MRI [1].

Single-voxel MRS measures the MR signal of a single selected region of interest, whereas signal outside this area is suppressed. For single-voxel MRS, the magnetic field and other parameters are optimized to get the best possible spectrum from a relatively small region of the brain [2]. Each metabolite appears at a specific frequency (ppm), and each reflects specific cellular and biochemical processes. *N*-acetyl aspartate (NAA) is a neuronal marker and decreases with any disease that adversely affects neuronal integrity. Creatine provides a measure of energy stores. Choline is a measure of increased cellular turnover and is elevated in tumors and inflammatory processes. The observable MR metabolites provide powerful information, but unfortunately many notable metabolites are not represented in brain MR spectra [3].

In the present study, we aimed to demonstrate the difference in the cerebral metabolic profile of chronic obstructive pulmonary disease (COPD) patients in comparison with age-matched and sex-matched healthy controls.

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Patients and methods

Ethical consideration

The present study was approved by the Institutional Ethics Committee of Assiut University. In addition, written informed consent was obtained from all patients.

Patients

This study was conducted in Assiut University Hospital at the Chest Diseases and Tuberculosis Department and the Neurology and Psychiatry Department during the period between May 2013 and October 2015. We enrolled eight stable COPD patients and eight adult age-matched and sex-matched healthy controls.

Inclusion and exclusion criteria

Stable COPD patients aged 45–75 years who were admitted to the Chest Diseases and Tuberculosis Department in Assiut University Hospital and COPD patients who attended outpatient clinics as well as healthy voluntaries of the same age, area of residence, smoking habits, and educational level were eligible to participate in the present study.

Exclusion criteria

COPD patients with any of the following comorbidities:

(1) Left-sided heart failure, renal insufficiency, or liver impairment.
(2) COPD patients with exacerbation.
(3) Electrolyte disturbance or diabetic patients.
(4) Chronic use of systemic steroids or any other drug affecting the results.
(5) Severe decompensated respiratory failure interfering with the study protocol.
(6) Previous cerebral stroke or any neuropsychiatric condition.

All patients were subjected to careful history taking. Height, body weight, and BMI were recorded, and full chest and neurological examinations were performed. All routine investigations related to exclusion criteria were performed.

All patients eligible to participate were subjected to the following:

(1) Spirometric evaluation: conventional spirometry using Zan 300 (Company nSpire Health^{TM}, Sensor Medics MGA USB, Oberthulba, Germany) was performed for COPD and control groups. The reference values used were those of the American Thoracic Society standards. The following parameters were observed and recorded for the study – forced expiratory volume in the first second percentage predicted and volume in liters, forced expiratory volume in the first second/forced vital capacity (FVC) ratio, and FVC percentage predicted and volume in liters.
(2) Gasometric evaluation: arterial blood gases samples were analyzed by Radiometer blood gas analyzer (Radiometer Medical ApS Company, Åkandevej, Demark). Arterial blood acidity (pH), partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide ($PaCO_2$), arterial oxygen saturation (SaO_2), arterial bicarbonate level (HCO_3^-), and base excess or deficit were recorded.
(3) MRS: ^{1}H-MRS was carried out using a 1.5-T MRI/MRS scanner (Siemens, Erlangen, Germany). After scout images in three orthogonal planes, multislice T_2-weighted axial images of the whole brain were acquired. The single-voxel technique was used for two areas – namely, the parietotemporal lobe and the thalamus. The metabolic ratios *N*-acetyl aspartate/creatine (NAA/Cr), *N*-acetyl aspartate/choline (NAA/Cho), and choline/creatine (Cho/Cr) were calculated by integrating area under each peak.

Statistical analysis

Sampling

Sampling was performed using nonprobability convenient sampling technique. Patients were selected from those consecutively attending the Chest Diseases and Tuberculosis Department and those attending the outpatient clinic.

Sample size

The estimated sample size was eight COPD patients and eight controls because of financial issues.

Data were recorded and analyzed using statistical package for social science software computer program version 20 (SPSS; SPSS Inc., Chicago, Illinois, USA), Medcalc v.11.6 (MedCalc Software Company, Ostend, Belgium), and Open Epi V.3.01 (Open Source Programe, Atlanta, USA). Quantitative data are described using mean±SD, and qualitative data are described using frequencies. Nonparametric tests were used in the present study as follows:

(1) The Mann–Whitney *U*-test was used to compare results between the COPD group and the control group.
(2) Spearman's correlation coefficient was used to determine the correlation between cognitive dysfunction and spirometric and gasometric parameters of COPD patients.
(3) *P*-value below 0.05 was accepted as significant.

Results

We enrolled eight stable COPD patients and compared them with eight age-matched and sex-matched healthy controls. Distribution of age and sex in both groups were as follows: 60.62±6.75 years and six males in the COPD group and 56.12±7.35 years and seven males in the control group. Detailed demographic data of both groups are represented in Table 1.

Spirometric and gasometric evaluation showed that there was a significant difference between the COPD group and the control group in all parameters except blood acidity. Detailed spirometric and gasometric evaluation are represented in Table 2.

MRI spectroscopy measurements in the COPD group and the control group showed that there was no significant difference in the distribution of neurotransmitters in the thalamus, but there was a significant difference regarding the distribution of neurotransmitters in the temporal lobe. Table 3 shows the detailed results of the MRS.

There were significant negative correlations between NAA/Cho at the thalamus and both $PaCO_2$ and base excess or base deficit, whereas there was a significant positive correlation between Cho/Cr at the thalamus and FVC (l). Moreover, there was a significant positive correlation between NAA/Cr at the thalamus and BMI, and a negative correlation between NAA/Cr at the thalamus and SaO_2 as shown in Table 4.

The level of neurotransmitters in the temporal lobe and spirometric and gasometric parameters showed that there was a significant negative correlation between NAA/Cr and $PaCO_2$ as shown in Fig. 1.

Discussion

The study of specific patterns of cerebral metabolites in COPD is still novel, and most of the few studies carried out thus far have shown three landmarks of cerebral metabolite imbalance in COPD.

Elevation of choline

The most pronounced neurochemical changes in COPD is the elevation of choline [4,5]. We propose that frequent oxygen desaturation during everyday activity of COPD patients may be a key mechanism underlying the damage of brain tissue reflected in elevated brain choline. Similar choline elevations observed in systemic diseases were associated with brain tissue breakdown and cognitive impairment [6,7] and appeared to reflect damage to myelin and increased turnover of neuronal membrane precursors [8]. These results are consistent with the finding of our results in the pariototemboral lobe.

Decrease in *N*-acetyl aspartate

The second landmark in neurochemical changes in COPD was a decrease in NAA. Neuronal cell death is generally considered an irreversible process accompanying aging, and decreased levels of NAA are reported frequently in healthy aged persons.

Table 1 Demographic data of chronic obstructive pulmonary disease patients and controls undergoing spectroscopy

	COPD group (*N*=8) [*N* (%)]	Control group (*N*=8) [*N* (%)]	*P*-value
Sex			
Male	6 (75.0)	7 (87.5)	0.32
Female	2 (25.0)	1 (12.5)	
Age (years)			
Mean±SD	60.62±6.75	56.12±7.35	0.61
Smoking			
Smoker	2 (25.0)	3 (37.5)	0.51
Ex-smoker	6 (75.0)	5 (62.5)	
Residence			
Urban	2 (25.0)	3 (37.5)	0.93
Rural	6 (75.0)	5 (62.5)	
Dominant hand			
Right handed	7 (88.0)	6 (75.0)	0.87
Left handed	1 (12.0)	2 (25.0)	
Education			
Literate	2 (25.0)	3 (37.5)	0.92
Illiterate	6 (75.0)	5 (62.5)	
Duration of illness (years)			
Mean		16±6.6	
Range		7–26	

COPD, chronic obstructive pulmonary disease.

Table 2 Gasometric and spirometric data of chronic obstructive pulmonary disease and control groups undergoing spectroscopy

	COPD group (*n*=8) (mean±SD)	Control group (*n*=8) (mean±SD)	*P*-value
FEV_1 (l)	1.4±0.84	2.93±0.92	<0.004*
FEV_1%	48±24.1	93±10	<0.0001*
FVC (l)	2.7±1.11	3.4±0.96	0.001*
FVC%	79.5±26.1	96.6±9.3	0.003*
FEV_1/FVC%	52.2±16.5	82.3±2.55	<0.0001*
BMI (kg/m^2)	23.9±8.6	27.96±6.11	0.001*
pH	7.40±0.035	7.42±0.01	0.143
$PaCO_2$ (mmHg)	65±10.71	38.25±3.37	<0.0001*
PaO_2 (mmHg)	62.8±7.47	87.12±5.5	<0.0001*
SaO_2%	91.87±2.53	96.75±1.16	<0.0001*
HCO_3 (mEq/l)	37±6.21	16.87±1.55	<0.0001*
BE/BD (mmol/l)	12.1±6.4	1.163±1.1	<0.0001*

BE/BD, base excess or base deficit; COPD, chronic obstructive pulmonary disease; FEV_1%, forced expiratory volume percentage predicted; FEV_1, forced expiratory volume in the first second; FVC%, forced vital capacity percentage predicted; FVC, forced vital capacity; HCO_3, serum biocarbonate level; $PaCO_2$, partial arterial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; pH, blood arterial acidity; SaO_2, arterial oxygen saturation percent. *Significant difference.

Table 3 Magnetic resonance spectroscopy measurements in chronic obstructive pulmonary disease and control groups at the thalamus and the parietotemporal area

	COPD group (*n*=8) (mean±SD)	Control group (*n*=8) (mean±SD)	*P*-value
NAA/Cho at thalamus	0.41±0.14	0.38±0.11	0.562
Cho/Cr at thalamus	0.75±0.22	0.76±0.19	0.916
NAA/Cr at thalamus	1.57±0.38	2.09±0.66	0.059
NAA/Cho at parietotemporal area	0.64±0.32	1.72±0.41	0.001*
Cho/Cr at parietotemporal area	0.71±0.24	1.22±0.38	0.002*
NAA/Cr at parietotemporal area	2.31±0.45	1.65±0.39	0.009*

Cho/Cr, choline/creatine ratio; COPD, chronic obstructive pulmonary disease; NAA/Cho, *N*-acetyl aspartate/choline ratio; NAA/Cr, *N*-acetyl aspartate/creatine ratio. *Significant difference.

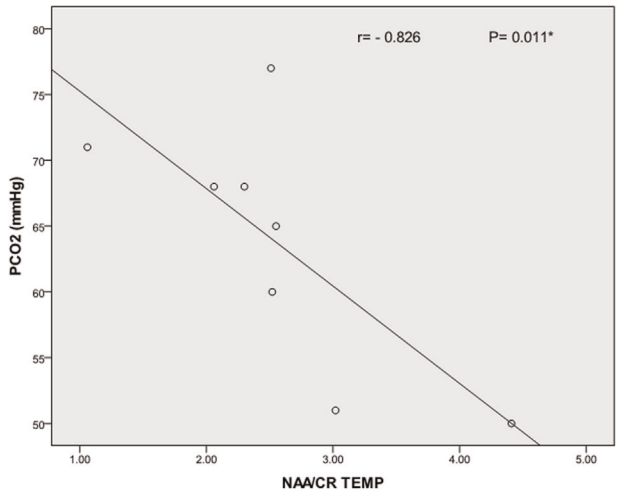
Table 4 Correlation between neurotransmitter levels in the thalamus and spirometric and gasometric parameters using Spearman's correlation

	NAA/Cho THA		Cho/CR THA		NAA/CR THA	
	r	*P*	*r*	*P*	*r*	*P*
FEV_1 (l)	0.295	0.478	0.560	0.149	0.060	0.888
FEV_1%	0.430	0.287	0.661	0.075	0.169	0.690
FVC (l)	0.371	0.365	**0.719**	**0.045***	–0.476	0.233
FVC%	0.398	0.329	0.681	0.063	–0.611	0.108
FEV_1/FVC	0.060	0.888	0.180	0.670	0.595	0.120
BMI (kg/m^2)	0.006	0.989	0.030	0.943	**0.723**	**0.043***
pH	–0.134	0.751	–0.049	0.909	–0.158	0.709
$PaCO_2$ (mmHg)	**–0.765**	**0.027***	–0.578	0.133	0.108	0.799
SaO_2%	0.245	0.558	0.000	1.000	**–0.854**	**0.007***
PaO_2 (mmHg)	0.096	0.820	–0.078	0.854	–0.611	0.108
HCO_3 (mEq/l)	–0.669	0.070	–0.470	0.240	–0.275	0.509
BE/BD (mmol/l)	**–0.778**	**0.023***	–0.515	0.192	–0.262	0.531

BE/BD, base excess or base deficit expressed; Cho/Cr, choline/creatine ratio; FEV_1%, forced expiratory volume percentage predicted; FEV_1, forced expiratory volume in the first second; FVC%, forced vital capacity percentage predicted; FVC, forced vital capacity; HCO_3, serum biocarbonate level; NAA/Cho, *N*-acetyl aspartate/choline ratio; NAA/Cr, *N*-acetyl aspartate/creatine ratio; $PaCO_2$, partial arterial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; SaO_2, arterial oxygen saturation percent; THA, thalamus. *Significant correlation. Bold values stands for significant correlation.

NAA is the acetylated form of the amino acid aspartate, which is found in high concentrations in neurons and is a marker of neuronal viability. It is therefore reduced in any process that destroys neurons, and this is concomitant with our results.

Figure 1



Shows there was a significant negative correlation between *N*-acetyl aspartate/creatine, at parietotemporal lobe, and partial pressure of arterial carbon dioxide

Increase in cerebral neurochemical markers of oxidative stress and anaerobic respiration

The third landmark was the unique study performed by Mathur *et al*. [9], which correlates chronic hypoxemia to the increase in cerebral neurochemical markers of oxidative stress and anerobic respiration – namely, inorganic phosphate and phosphomonoesters – evaluated using the ^{31}P-MRS technique. In our study, we did not use the ^{31}P-MRS technique.

In agreement with our results, a study by Shim *et al*. [10] evaluated the clinical significance of cerebral metabolic abnormalities in COPD patients using MRS, including 17 symptomatic COPD patients and 21 age-matched healthy volunteers. NAA, Cr, and Cho levels in the parietal white matter were all significantly lower in COPD patients than in control subjects ($P<0.0125$).

In agreement with our results, another study by Karakas *et al*. [11] investigated cerebral metabolism with proton MRS using the multivoxel technique, in which 30 male patients aged 45–70 years with moderate-level COPD and an age-matched group of 30 healthy males as controls were included. The results showed 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 compared with the control group. The findings of this study using MRS confirmed that most patients with symptomatic COPD have cerebral metabolic abnormalities.

In concomitance with our results, Sinha *et al*. [12] investigated changes in the cerebral metabolism of nondiabetic and normolipidemic patients with COPD using ^{1}H-MRS (28 symptomatic COPD patients and 19 healthy controls). They also proved that COPD patients have cerebral metabolic abnormalities.

In agreement with our study, El-Helbawy *et al*. [13] enrolled 20 symptomatic COPD patients (16 male and four female) and an age-matched group of 20 healthy controls (11 male and nine female). Pulmonary function, respiratory muscle strength, and resting arterial blood gas tests and ^{1}H-MRS of the brain were carried out on all subjects. The parietotemporal and the occipital regions were localized for ^{1}H-MRS. The metabolic ratios of NAA/Cr and Cho/Cr were calculated by the single-voxel technique. The result of the study proved that in comparison with healthy controls the mean values of Cho/Cr in COPD patients were lower in the parietotemporal and occipital areas, respectively, whereas the mean values of NAA/Cr in COPD patients were higher in both parietotemporal and occipital areas of the brain, respectively.

Two studies were performed to study the effect of smoking on brain [14,15]. They used MRS to compare smokers and nonsmokers matched for age, sex, and educational level. NAA (a neuronal marker that may reflect synaptic density) concentrations in the left hippocampus, but not in the anterior cingulate gyrus, were reduced in tobacco smokers.

Animal experiments that assessed the effect of hypoxia on brain [16] showed that NAA, Cr, and Cho were found to be unchanged during the first few hours of ischemia but altered after 24 h. NAA and Cr levels decreased several hours later.

A study evaluating the effects of induced low pH levels and hypercapnia and hypothermia in experimental animals [17] showed marked decrease in NAA and creatine levels during hypercapnia. This fact also supports the neurochemical changes observed in COPD patients with chronic hypercapnia.

Many studies with similar results have been carried on obstructive sleep apnea syndrome (OSAS) patients, which may resemble COPD in the state of chronic hypoxemia and the results were similar to the results of the present study. Among these studies, the study of Tonon *et al*. [18] enrolled 14 OSAS patients without cardiovascular or cerebrovascular impairment who underwent the same protocol before and after 6 months of continuous positive air way pressure

(CPAP). Before CPAP treatment, cortical NAA in OSAS was significantly lower than in controls and positively correlated with minimum SaO_2 during sleep. Cortical NAA reduction persisted after CPAP therapy.

In conclusion, MRS provides insight into the neurochemical changes that occur in COPD patients. Chronic hypoxemia and hypercapnia seem to play a key role in the pathophysiology of neurochemical changes in COPD. A limitation of the present study was that MRI spectroscopy was only applied to small number of patients and controls because of financial issues. We recommend future studies to combine functional MRI and perfusion MRI together with MRI spectroscopy to obtain a greater understanding of the cerebral metabolic changes in COPD.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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