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Central Nervous System Involvement in Chronic Obstructive Pulmonary Disease

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Abstract

Background Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous disease. Studies evaluating both peripheral and central nervous system involvement in patients with COPD at the same time are rare. Transcranial magnetic stimulation (TMS) assesses excitability of the motor cortex and corticospinal pathway function. Diaphragmatic contractile function had been assessed by cortical and cervical magnetic stimulation of the phrenic nerve roots in COPD patients.

Objective To investigate electrophysiologically central nervous system involvement in COPD as compared to healthy controls, to study the central neural derive of the diaphragm by assessing TMS-MEP parameters of the phrenic nerve in patients with COPD and compare these with healthy controls.

Methods The present study is a case control study was conducted in Al-Imamein Al-Kadhimein Medical City, from November 2019 to October 2021 included 40 COPD patients and 40 healthy volunteers who were subjected to blood gas and biochemical analysis and pulmonary function test before commencement of neurophysiological analysis.

Results Statistically significant prolongation of the cortical motor latencies as well as peripheral motor conduction times of both phrenic nerves in COPD patients compared to control subjects ($p<0.001$). The means of the central motor conduction times in the both phrenic nerves were higher in COPD patients compared to controls, yet, the difference was only significant in the right phrenic nerve. There was statistically significant increase in the means of the motor threshold of both phrenic nerve in some patients with COPD in comparison with control group. The phrenic nerve cortical latencies showed the most sensitive and specific parameters to study the involvement of nervous system in COPD, while the peripheral motor conduction time was the second most sensitive and specific parameter. No correlations observed between body mass index, SpO_2 with phrenic nerves TMS parameters.

Conclusion The central neuropathy is one of the complications in COPD patients. Motor threshold of phrenic nerves was significantly higher in COPD patients reflecting significant decrease in excitability of motor cortex affecting excitatory contact with subcortical neurons. Results of the cortical and radicular MEP latencies of both phrenic nerves were of high sensitivity and specificity in diagnosing nervous system involvement in COPD.

Keywords Chronic obstructive pulmonary disease, phrenic nerve, TMS

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List of abbreviations: BMI = Body mass index, CMAP = Compound motor action potential, CMCT = Central Motor conduction time, COPD = Chronic obstructive pulmonary disease, CRP = C-reactive protein, EMG = Electromyography, MEP = Motor evoked potential, PMEP = Peripheral motor evoked potential, ROC = Receiver operating characteristic, SCV = Sensory conduction velocity, SPSS = Statistical package for social sciences, TMS = Transcranial magnetic stimulation

Introduction

Chronic obstructive pulmonary disease (COPD) is mainly presented with dyspnea and exercise limitation secondary to irreversible airflow obstruction;

however, nowadays COPD is considered as multi-systemic inflammatory disorder rather than simple respiratory disease. Several studies have reported the presence of peripheral neuropathy (PNP) in COPD. Some patients with COPD show neuropathic changes that are distally predominant, mainly sensory, and characterized pathologically by axonal loss, accompanied in some cases by demyelination [1]. Little is known about the efficacy of the neural drive to the diaphragm and its possible involvement in diaphragmatic decompensation in patients with COPD [2].

The principle of transcranial magnetic stimulation (TMS) is based on induction of an electromagnetic field in the brain of sufficient magnitude and density to depolarize the neurons [3]. TMS pulse applied over the primary motor cortex, induces action potentials in cortical axons that spreads transsynaptically to neurons along the corticospinal tract and peripheral motor nerve. These excitation signals elicit responses in targeted muscles recorded as motor evoked potentials (MEPs). TMS has been used as an investigation tool for assessing the respiratory corticospinal pathways and studying of diaphragmatic MEPs [4].

In the last decade, a study demonstrated changes in the excitability of the motor cortex controlling respiratory muscles in COPD especially diaphragm [5]. Recently, other studies found dysfunction of the corticospinal motor pathway assessed by TMS [6,7]. However, still little research has been conducted in COPD to assess central neural drive to the diaphragm and its possible involvement in physiological derangement in COPD patients.

This study aimed to investigate electrophysiologically central nervous system involvement in COPD as compared to healthy controls. Also, to study the central neural derive of the diaphragm by assessing TMS-MEP parameters of the phrenic nerve in patients with COPD and compare these with healthy controls.

Methods

This is a case control study was conducted in Al-Imamein Al-Kadhimein Medical City, Baghdad, Iraq for the period extended from November 2019 to October 2021.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by the Institute Review Board of the College of Medicine, Al-Nahrain University according to the document number (268) in 15/10/2019.

Forty patients with clinically documented COPD, being diagnosed and referred by a pulmonologist. History and information are taken from the patients, which included the patient's name, age, sex, weight, height, occupation, past medical history, disease duration. Those were compared with 40 age and sex matched healthy controls with no history of any medical disease. All participants would be subjected to O_2 saturation analysis by oxymeter, C-reactive protein (CRP) analysis and perform pulmonary function test (PFT) before commencement of electrophysiological study. TMS-MEP study of bilateral phrenic nerves were made for all studied subjects.

Routine computerized electromyography (EMG) equipment (Micromed, 8-channel elecromyograph, serial no. GH17H9NW315431 B, model 1715, code GH17ESSM/EDC, Italy) was used. The Magstim 200 stimulator (The Magstim Company Ltd., Spring Gardens, Whitland, UK) was employed. For magnetic stimulation of the motor cortex, the coil would be applied to the scalp region for stimulation of the diaphragm. The coil would be held tangentially to the skull at Cz point of the international 10-20 electroencephalography (EEG) system, which is located at the vertex. The stimulus intensity was adjusted to obtain the largest reproducible responses (range: 65-100% stimulator output). The angle of the coil around an optimal site was changed until the highest diaphragmatic compound motor potential was recorded. The average point of

optimal excitability was determined to be 3 cm lateral to mid-line and 2-3 cm anterior to auricular plane [8]. For cervical root magnetic stimulation of the phrenic nerve; subjects were seated comfortably with the neck flexed. Stimuli were delivered at end-expiration with the glottis closed to preclude lung volume influence on diaphragm EMG. The optimal site of stimulation was identified by gradually moving the coil along cervical vertebrae C3-C7 until the largest Compound motor action potential (CMAP) amplitude was observed at submaximal stimulation intensities [9]. For cortical magnetic stimulation of phrenic nerves at both sides the following parameters showed be measured: Motor threshold (MT) of phrenic nerves, cortical motor evoked potential latency (CMEPL), CMEP amplitude (CMEPA). For cervical magnetic stimulation of phrenic nerves at both sides the following parameters showed be measured: Peripheral motor evoked potential (PMEP) amplitude, peripheral motor evoked potential latency (PMEPL), a representation of the phrenic nerve conduction time (PNCT). Central motor conduction time (CMCT) was calculated as follow: (CMCT = CMEPL – PMEPL) [7].

Statistical analysis

Most of data were continuous and expressed as mean ± standard deviation, comparison of these data was done by using unpaired Student t-test. Only sex and CRP were expressed as frequency and percentage, comparison of these data was done using Fisher exact test. P value less than 0.5 was considered as significant. The sensitivity and specificity of all studied diaphragmatic TMS parameters were evaluated by using receiver operating characteristics curve (ROC) test. Pearson correlation was studied between above mentioned parameters and certain pathophysiologic parameters namely (SpO_2, body mass index and CRP). The software used where Microsoft excel 2016 and SPSS (statistical package for social sciences) version 23.

Results

Eighty subjects were enrolled in this study; 40 patients diagnosed with COPD and 40 apparently healthy volunteers. The mean age of patients was (60.83±9.34 years) comprising (30) males and (10) females, as compared to (62.9±5.98 years) of apparently healthy volunteers comprising (30) males and (10) females, too. No significant difference was noticed regarding age, sex, weight, height or body mass index between COPD patients and control group. Seven out of forty patients had CRP positive results, as compared to none in the control group and the difference was significant (p value = 0.012). Finally, results of SpO_2 were significantly lower in COPD patients as compared to control group (p value <0.001) (Table 1).

There was statistically significant prolongation of the cortical motor latencies as well as peripheral motor conduction times of both phrenic nerves in COPD patients compared to control subjects. The means of the Lt. phrenic cortical conduction time compared to control were (20.6±2.98 msec versus 16.29±2.83 msec; p<0.001). On the other hand, the Rt. phrenic mean cortical conduction time compared to control was (20.97±3.0 msec versus 16.34±2.33 msec; p<0.001). In a similar manner, the means of the peripheral motor conduction time in patients with COPD compared to controls were (11.93±3.17 msec versus 8.64±2.25 msec and 12.74±3.04 msec versus 8.99±2.07 msec; p<0.001) for the Lt. and Rt. phrenic nerves; respectively. The means of the CMCT in the both phrenic nerves were higher in COPD patients compared to controls, yet, the differences was only significant in the Rt. phrenic nerve (8.25±1.79 msec and 7.32±1.77 msec; p= 0.022). (Table 2).

Table 1. Comparison of demographic parameters, SpO_2 and C-reactive protein between COPD patients and control group

Parameter		Patients N=40 mean±SD	Control N=40 mean±SD	P value
Age (yr)		60.83±9.34	62.9±5.98	0.241*
Weight (kg)		80.3±17.51	83.58±12.63	0.340*
Height (cm)		165.83±9.22	168.43±10.58	0.245*
BMI (kg/m^2)		29.03±5.17	29.46±3.52	0.669*
SpO_2 (%)		95.0±5.48	98.68±0.53	<0.001*
		N (%)	N (%)	
Sex	Male	30 (75.0)	30 (75.0)	1.000**
	Female	10 (25.0)	10 (25.0)	
CRP	Negative	33 (82.5)	40 (100)	0.012**
	Positive	7 (17.5)	0 (0.0)	

BMI= Body mass index, CRP= C-reactive protein, * p value by unpaired ttest, ** p value by Fisher Exact test

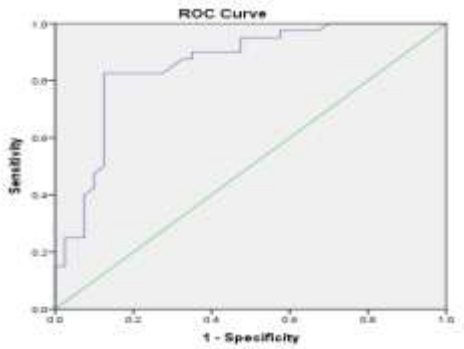
Table 2 also shows statistically significant increase in the means of the motor threshold of the Rt. phrenic nerve in patients with COPD in comparison with control group (64.23%±3.97 versus 54.95% ±3.37; p<0.001). Lastly, the mean of the cortical MEP amplitudes of the Lt. phrenic nerve was significantly higher in COPD patients than controls (p=0.025). Nevertheless, the differences between means of the radicular Lt. phrenic nerve amplitudes and those of the Rt. phrenic nerve counterpart amplitudes were all not significant (p=0.439, p=0.450 and p=0.173; respectively)

Table 2. Comparison of TMS and MEP parameters between COPD patients and control

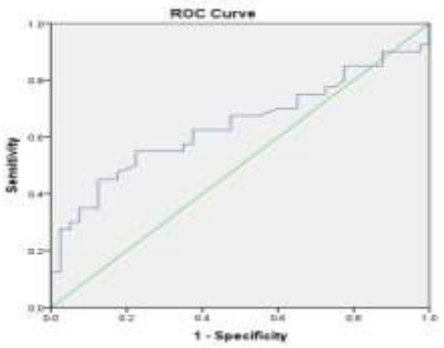
Parameter	Patients N=40 mean±SD	Control N=40 mean±SD	P value
Motor threshold (%)	64.23±3.97	54.95±3.37	<0.001
Lt. phrenic cortical MEP latency (msec)	20.6±2.98	16.29±2.83	<0.001
Lt. phrenic cortical MEP amplitude (mV)	0.65±0.3	0.52±0.2	0.025
Lt. phrenic peripheral motor conduction time (msec)	11.93±3.17	8.64±2.25	<0.001
Lt. phrenic radicular MEP amplitude (mV)	1.16±0.51	1.08±0.42	0.439
Lt. phrenic central motor conduction time (msec)	8.42±2.27	7.72±1.97	0.145
Rt. phrenic cortical MEP latency (msec)	20.97±3	16.34±2.33	<0.001
Rt. phrenic cortical MEP amplitude (mV)	0.66±0.31	0.61±0.29	0.450
Rt. phrenic peripheral motor conduction time (msec)	12.74±3.04	8.99±2.07	<0.001
Rt. phrenic radicular MEP amplitude (mV)	1.31±0.7	1.12±0.45	0.173
Rt. phrenic central motor conduction time (msec)	8.25±1.79	7.32±1.77	0.022

MEP= motor evoked potential, msec= millisecond, mV= millivolt, P value by unpaired t-test

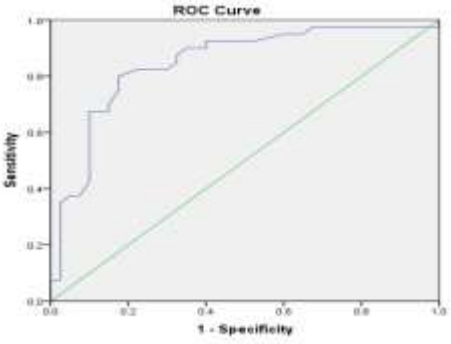
According to ROC test (Figure 1 and 2), phrenic nerve cortical latencies were the most sensitive and specific parameters with both sensitivity and specificity percentages equal (82.5%, 87.5%; respectively at cutoff value 18.35msec for Lt. phrenic nerve and 80.0%, 85% at a cutoff value 10.55 msec for Rt. phrenic nerve). The peripheral motor conduction time was the second most sensitive and specific parameter with both sensitivity and specificity equals (80.0%, 82.5%; respectively at cutoff value 9.7 msec for Lt. phrenic nerve and with sensitivity and specificity equals both (80.0%) at cutoff value 10.55 msec for Rt. phrenic nerve). Other phrenic nerve TMS parameters were of low sensitivity and specificity percentages (Tables 3 and 4).



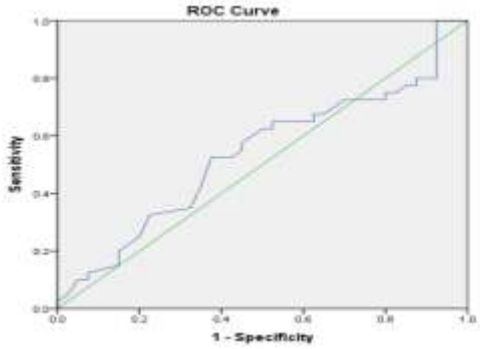
Lt. phrenic cortical MEP latency



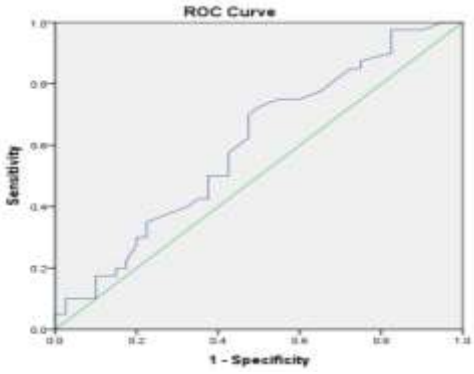
Lt. phrenic cortical MEP amplitude



Lt. phrenic peripheral motor conduction time

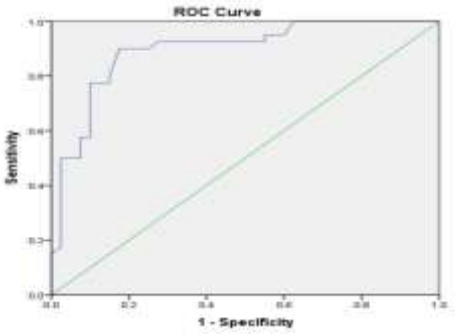


Lt. phrenic radicular MEP amplitude

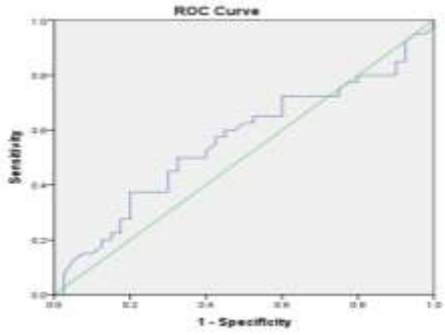


Lt. phrenic central motor conduction time

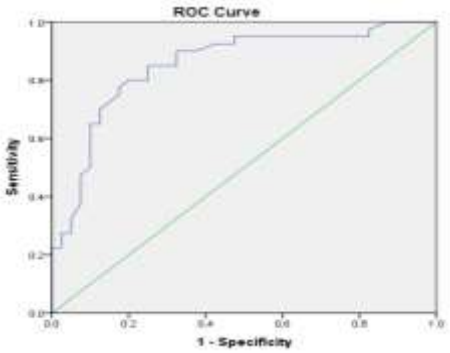
Figure 1. ROC Curve of the Lt. Phrenic Parameters in Patients with COPD



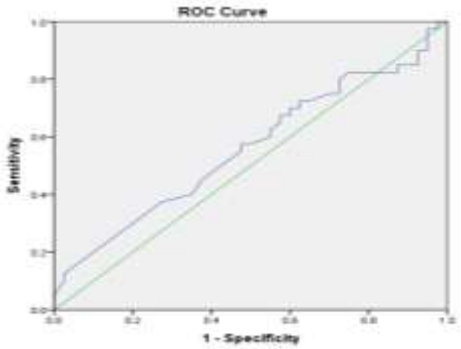
Rt. phrenic cortical MEP latency



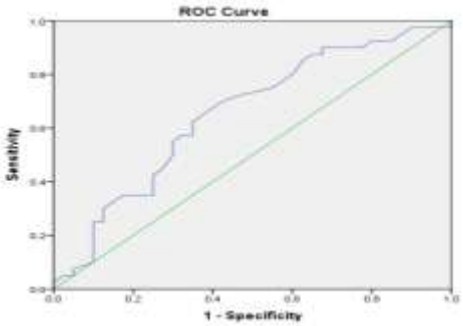
Rt. phrenic cortical MEP amplitude



Rt. phrenic peripheral motor conduction time



Rt. phrenic radicular MEP amplitude



Rt. phrenic central motor conduction time

Figure 2. ROC Curve of the Rt. Phrenic Parameters in Patients with COPD

Table 3. Area under curve, sensitivity, specificity and cutoff value of the Lt. phrenic parameters in COPD Patients

Parameter	Area under curve	Sensitivity	Specificity	Cutoff value
Lt. phrenic cortical MEP latency	0.857	82.5%	87.5%	18.35
Lt. phrenic cortical MEP amplitude	0.641	62.5%	62.5%	0.59
Lt. phrenic peripheral motor conduction time	0.847	80.0%	82.5%	9.7
Lt. phrenic radicular MEP amplitude	0.536	55.0%	55.0%	0.98
Lt. phrenic central motor conduction time	0.601	57.5%	57.5%	7.65

Table 4. Area under curve, sensitivity, specificity and cutoff value of the Rt. phrenic parameters in COPD Patients

Parameter	Area under curve	Sensitivity	Specificity	Cutoff value
Rt. phrenic cortical MEP latency	0.895	80.0%	85.0%	18.25
Rt. phrenic cortical MEP amplitude	0.560	57.5%	57.5%	0.64
Rt. phrenic peripheral motor conduction time	0.853	80.0%	80.0%	10.55
Rt. phrenic radicular MEP amplitude	0.560	55.0%	52.5%	1.15
Rt. phrenic central motor conduction time	0.654	62.5%	65.0%	7.5

No correlations were found between body mass index, SpO_2 with phrenic nerve TMS parameters in COPD patients and control groups. Finally, comparison between phrenic nerve TMS findings in COPD patients with positive CRP level and those with negative level showed no significant difference between the two groups (Tables 5, 6 and 7).

Table 5. Correlation of body mass index with phrenic nerve conduction study parameters in COPD patients and control groups

Parameter		Body mass index	
		Patients	Control
Motor threshold	r	0.158	-0.102
	p	0.330	0.529
Lt. phrenic cortical MEP latency	r	0.123	0.043
	p	0.450	0.791
Lt. phrenic cortical MEP amplitude	r	-0.151	0.151
	p	0.353	0.353
Lt. phrenic peripheral motor conduction time	r	0.261	0.205
	p	0.104	0.204
Lt. phrenic radicular MEP amplitude	r	0.312	-0.115
	p	0.050	0.481
Lt. phrenic central motor conduction time	r	-0.189	-0.130
	p	0.243	0.425
Rt. phrenic cortical MEP latency	r	0.092	-0.055
	p	0.573	0.738
Rt. phrenic cortical MEP amplitude	r	-0.135	-0.149
	p	0.405	0.358
Rt. phrenic cortical MEP amplitude	r	0.222	0.057
	p	0.169	0.726
Rt. phrenic radicular MEP amplitude	r	0.150	0.091
	p	0.355	0.579
Rt. phrenic central motor conduction time	r	-0.198	-0.151
	p	0.221	0.352

Table 6. Correlation of SpO_2 with phrenic nerve conduction study parameters in COPD patients

Parameter		Body mass index	
		Patients	Control
Motor threshold	r	-0.200	-0.009
	p	0.215	0.954
Lt. phrenic cortical MEP latency	r	0.205	0.041
	p	0.204	0.800
Lt. phrenic cortical MEP amplitude	r	0.260	-0.197
	p	0.105	0.222
Lt. phrenic peripheral motor conduction time	r	0.076	0.102
	p	0.642	0.530
Lt. phrenic radicular MEP amplitude	r	0.184	-0.131
	p	0.257	0.422
Lt. phrenic central motor conduction time	r	0.180	-0.084
	p	0.267	0.605
Rt. phrenic cortical MEP latency	r	-0.004	0.099
	p	0.979	0.542
Rt. phrenic cortical MEP amplitude	r	0.166	-0.116
	p	0.307	0.477
Rt. phrenic cortical MEP amplitude	r	0.022	0.185
	p	0.893	0.252
Rt. phrenic radicular MEP amplitude	r	0.130	0.017
	p	0.423	0.915
Rt. phrenic central motor conduction time	r	-0.051	-0.065
	p	0.754	0.688

Table 7. Comparison of phrenic nerve parameters in patients group according to positivity of C-reactive protein

Parameter	Negative N=33 mean±SD	Positive N=7 mean±SD	P value
Motor threshold	64.3±3.8	63.86±5.01	0.791
Lt. phrenic cortical MEP latency	20.67±2.64	20.29±4.53	0.762
Lt. phrenic cortical MEP amplitude	0.69±0.29	0.48±0.32	0.097
Lt. phrenic peripheral motor conduction time	11.93±3.21	11.91±3.21	0.991
Lt. phrenic radicular MEP amplitude	1.21±0.53	0.94±0.3	0.211
Lt. phrenic central motor conduction time	8.42±2.32	8.37±2.2	0.956
Rt. phrenic cortical MEP latency	20.85±3.07	21.51±2.76	0.600
Rt. phrenic cortical MEP amplitude	0.7±0.32	0.47±0.21	0.081
Rt. phrenic cortical MEP amplitude	12.82±3.13	12.36±2.77	0.722
Rt. phrenic radicular MEP amplitude	1.36±0.75	1.07±0.35	0.325
Rt. phrenic central motor conduction time	8.06±1.56	9.16±2.58	0.142

Discussion

No significant differences were noticed regarding sex, height or age between the two studied groups, which would exclude any possible source of error that might be anticipated if any significant differences were present in these parameters, and this is important to exclude their effects as co-factors that would compromise study results. In addition, no significant differences were observed regarding weight and hence, body mass index results between patients and control group. This can be explained that all of the patient included in the study were not in the advanced severe stages of the disease, and most of them were overweight, thus, malnutrition was not found in all of the studied patients and therefore, no statistically significant differences were found regarding weight and body mass index as compared to control subjects.

However, the significant decrease in SpO_2 percentages observed in COPD patients as compared to control subjects, which could be explained by the effects of hypoxemia, which is a major complication of COPD compared to controls. Gas exchange abnormalities in COPD result in hypoxemia and hypercapnia [10]. Finally, CRP was positive in seven patients compared to none in the control group, which is statistically significant and might ring a bell about the possible effect of inflammation in the pathophysiology of the disease. A study by Agarwal and his colleagues revealed the circulating levels of the inflammatory marker highly sensitive-CRP are significantly elevated in patients with COPD, supporting the view that COPD is in part an inflammatory disorder [11].

Statistically significant prolongation of the cortical motor latencies as well as peripheral motor conduction times of both phrenic nerves was witnessed in COPD patients compared to control subjects. On the other hand, the means of the CMCT in the same nerves were higher in COPD patients compared to controls, yet, the difference was only significant in the Rt. Phrenic nerve. These findings prove the possible role of the central nervous system (CNS) in the disease process, with the possibility of chronic axonal degeneration affecting CNS, these finding were in harmony with several studies [6,12,13]. Hopkinson and his co-workers found that diaphragmatic PMEPL was significantly longer in COPD patients than healthy controls. Also, reported bilateral increase in CMEPL and CMCT in their studied COPD patients compared to healthy control group [12].

Further, Wang and his colleagues reported bilateral increase in CMEPL and CMCT in their studied COPD patients compared to healthy control group [6]. Prolonged CMCT usually implies degeneration of fast-conducting corticospinal fibers, with transmission via small myelinated fibers or by some other oligosynaptic pathways, failure of activation of large, fast conducting pyramidal cells by TMS. It was suggested that CMCT prolongation in COPD patients could be due to corticospinal tract abnormality or I-wave recruitment abnormalities [14]. Stimulation of the motor area of cerebral cortex will cause multiple descending volleys; corticospinal neurons will transmit those impulses which are asynchronous. A temporal and spatial summation is required for alpha motor neurons firing [15]. Reduction of total number of intact corticospinal neurons, the temporal summation and hence the time taken by alpha motoneurons firing off will be longer; consequently, the CMCT will be prolonged [13].

CNS involvement in patients with COPD might be further underlined by the finding of statistically significant increment in motor threshold of both phrenic nerves compared to healthy controls, which reflect significant decreased excitability of the motor cortex. The decreased excitability affects excitatory contact with the corticospinal neurons, there initial axon segments as well as excitability of the spinal cord, phrenic nerve and diaphragm [16]. This finding is in disagreement with other authors who found that diaphragmatic motor threshold was significantly lower in stable COPD than healthy controls, reflecting hyperexcitability of the diaphragm motor area in COPD patients [8,12]. However, these studies included either mild –moderate COPD patients [12] or stable COPD patients [12]; while in the present study, all types of COPD were included,

which might bring to light that the involvement of CNS in the pathophysiology of COPD would be in the severe unstable stages of the disease.

The means of amplitudes of MEP of both phrenic nerves, whether cortical or radicular amplitudes, in patients of COPD were paradoxical. Although these means of both phrenic nerves were higher in COPD patients than control group the differences were not significant apart from the left phrenic MEP amplitude. Such controversial results would weaken the validity of TMS-MEP amplitude measurements in studying the involvement of CNS in patients with COPD. MEP amplitude represents the overall excitability of cortical interneurons, provides an estimate of the extent of corticospinal tract and spinal motor neuron activation [17]. The amplitude equivocal results can be explained by the complex relationship between neuronal pathways in CNS, with the influence of multiple interneurons and lots of convergence and divergence which could probably cause minor amplitude changes that were not statistically significant, at least for both phrenic nerves. Literature provides paradoxical findings regarding MEP amplitudes of phrenic nerves in COPD patients. Some studies have found significant decrement in COPD patients compared to controls [6,13], others have found significant increment as compared to controls [18]. Podnar and Harlander reported that the amplitude of dCMAP provides a measure of the number of diaphragmatic muscle fibers activated by peripheral nervous system. They reported that patients with COPD often had increased amplitudes of dCMAP, explaining that the possible cause could be the greater diaphragmatic muscle mass or flattening of the diaphragm associated with lung hyperinflation [18].

ROC analysis of the Rt. and Lt. phrenic nerve TMS and MEP parameters was performed to study the involvement of nervous system in COPD; phrenic nerve cortical latencies were the most sensitive and specific parameters; the peripheral motor conduction time was the second most sensitive and specific parameter in these patients with both sensitivity and specificity. Other phrenic nerve TMS parameters were of low sensitivity and specificity percentages.

These results further strengthen previous findings and point to the importance of the axonal neuropathic changes in both phrenic nerves as well as their CNS influence of the higher cortical centers and subcortical pathways (cortical MEP latencies were even more sensitive and specific than peripheral "radicular" latencies) in the pathophysiology of COPD and their valuable role in diagnosing COPD in affected patients. These findings corroborate the results of Elnemr and his colleagues who proposed that CMEPs (i.e. CMEPL, CMCT, CMEPA, and DRMT) had good diagnostic accuracy and sensitivity for predicting corticospinal pathway affection in case of COPD patients [13]. Findings of the present study showed no relations between body mass index, SpO_2 or CRP with phrenic nerve TMS parameters in COPD patients and control groups. These finding are in agreement with Aras and his co-workers who found no significant correlations with EMG and VEP abnormalities and PFT parameters, biochemical parameters, age, body mass index, or disease duration [1]. The inability to find correlations of the above-mentioned parameters with the disease severity can be explained that COPD patients with different levels of severity were included, not to mention the small number of the studied population of COPD patients, because of COVID-19 pandemic circumstances, which would probably affect the correlation studies and compromise the study results.

Kahnert and his co-worker found no significant associations between CRP concentrations, as a systemic marker of inflammation, and peripheral neuropathy, after adjustments for age, sex, height, ethnicity, body mass index, smoking status and history, suggesting that systemic inflammation plays a secondary role for neuropathy [19]. Oxygen tension is better estimated using arterial blood gas analysis, which is an invasive method and could cause serious complications, and should be performed in the respiratory care unit, and since most patients included in the present study were outpatients, only SpO_2 could be performed with the possible lower diagnostic

relations with the studied parameters. Finally, no relations were found between body mass index in patients with COPD and the studied TMS parameters, which can be explained that most patients included in the current study were not in the advanced severe stages of the disease, and definitely not malnourished, which most likely would affect the possible correlations with the studied parameters. This is in harmony with current previous finding that no statistically significant differences were found regarding weight and body mass index between the studied COPD patients and the control subjects.

In conclusion, the current study found that central neuropathy is one of the complications in COPD patients. Motor threshold of phrenic nerves was significantly higher in COPD patients reflecting significant decrease in excitability of motor cortex affecting excitatory contact with subcortical neurons. Results of the cortical and radicular MEP latencies of both phrenic nerves were of high sensitivity and specificity in diagnosing nervous system involvement in COPD.

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Author contribution

Dr. Kareem: conducting the study, collected the data and performed the statistical analysis and drafting the manuscript. Dr. Al-Hashimi: contributed in the designing, organization and finalization of the manuscript. Dr. Al-Kadhimi: referring the COPD cases.

Conflict of interest

The authors declare there is no conflicts of interest.

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