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Respiratory electrophysiologic studies in chronic obstructive pulmonary disease

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Abstract

Respiratory failure is common during acute exacerbation of chronic obstructive pulmonary disease (AE-COPD). Phrenic nerve conduction (PNC), transcranial magnetic stimulation (TMS), and cervical magnetic stimulation (CMS) are of great value in identifying the feature and site of AE-COPD.

PNC, TMS, and CMS were performed in 20 AE-COPD patients with respiratory failure, and re-examined after weaning. Latencies and amplitudes of the diaphragmatic compound muscle action potential (dCMAP), motor evoked potential of the diaphragm (dMEP) evoked by TMS and CMS, and central motor conduction time (CMCT) were measured. Blood gas analysis and serum electrolyte levels were also evaluated. The results were compared with those from 20 healthy subjects.

AE-COPD patients showed prolonged CMCT and latencies of dCMAP and dMEP, decreased amplitudes of dCMAP and dMEP evoked by CMS, while CMCT and the latency of dMEP evoked by TMS were shortened after weaning. Significant correlation was identified between arterial blood gas analysis, serum electrolyte levels, disease duration, the duration of mechanical ventilation and the electrophysiological findings in AE-COPD patients prior to weaning.

The central and peripheral respiratory pathway is involved in AE-COPD. Central respiratory pathway function is improved after weaning in AE-COPD patients with respiratory failure.

Abbreviations: AE-COPD = acute exacerbation of chronic obstructive pulmonary disease, CIP = critical illness polyneuropathy, CMCT = central motor conduction time, CMS = cervical magnetic stimulation, COLD = chronic obstructive lung disease, COPD = chronic obstructive pulmonary disease, dCMAP = diaphragmatic compound muscle action potential, dMEP = diaphragmatic motor evoked potential of the diaphragm, GABA = gamma-aminobutyric acid, ICU = intensive care unit, MVD = duration of mechanical ventilation, $PaCO_2$ = partial pressure of arterial carbon dioxide, PaO_2 = partial pressure of arterial oxygen, PNC = phrenic nerve conduction, SD = standard deviation, SIRS = systemic inflammatory response syndrome, TMS = transcranial magnetic stimulation, XP = xiphoid process.

Keywords: chronic obstructive, electrophysiology, magnetic stimulation, phrenic nerve conduction, pulmonary disease, respiratory insufficiency

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a pulmonary disease characterized by chronic airflow limitation that is progressive and usually not easily reversible.[1] Frequent exacerbation of chronic obstructive pulmonary disease are associated with irreversible hypoxemia and hypercapnia with progressive decline in lung function, impaired quality of life, and frequent hospital admissions for exacerbation account for a large proportion of the expenditure of COPD.[2,3] Some patients during acute exacerbation of COPD (AE-COPD) experience acute respiratory failure, which requires mechanical ventilation. Its reasons often involve specific dysfunction of the nervous system, either lack of central respiratory drive or weakness of the respiratory muscles. Lack of central respiratory drive may be due to various types of encephalopathies and high-level cervical spinal cord injury.[4] Electromyographic techniques are of great value in more precisely pinpointing the nervous system cause for respiratory insufficiency.[5]

Phrenic nerve conduction (PNC) is useful for detecting respiratory involvement in the evaluation of patients with respiratory failure and suspected neuromuscular disorders in peripheral respiratory pathway. Transcutaneous unilateral electrical phrenic nerve stimulation in the neck with recording of the diaphragmatic compound muscle action potential (dCMAP) using surface electrodes is a reproducible and

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noninvasive method to study PNC.[6–8] dCMAP is an electrical study of diaphragmatic function. Patients that suffer from critical illness myopathy have prolonged dCMAP. Transcranial magnetic stimulation (TMS) and cervical magnetic stimulation (CMS) are non-invasive procedures that can be used to access the central inspiratory pathway to phrenic motor neurons. They can also be used routinely to diagnose and monitor patients with central respiratory pathway.[9]

The present study is designed to: assess the central and peripheral respiratory pathway using TMS, CMS, and PNC in patients with COPD who were admitted to the hospital for acute exacerbation with respiratory failure; analyze the respiratory electrophysiological changes after weaning from mechanical ventilation. The relationship between the electrophysiological parameters and arterial blood gas analysis, serum electrolyte levels, disease duration, the duration of mechanical ventilation were also determined.

2. Materials and methods

2.1. Subjects

Twenty patients (9 men and 11 women, mean age of 72.9 ± 8.7 years, mean height of 166.9 ± 8.1 cm) with AE-COPD according to the diagnostic criteria of the Global Initiative for Chronic Obstructive Lung Disease (COLD) were included in this study. They experienced acute respiratory failure requiring admission to intensive care unit (ICU). The mean disease duration was 18.1 years (range from 5 to 34 years). The results were compared with 20 age-, sex-, and height-matched healthy control subjects, including 11 men and 9 women, at the mean age of 69.5 ± 5.4 years and the mean height of 166.2 ± 8.5 cm. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000. All subjects received written informed consent, and the study was approved by the local ethics committee. The excluded from this work were patients with neurological or other medical illnesses such as diabetes mellitus, hyperthyreosis, hypothyrosis, cerebral vascular disease, uremia or hepatic failure, chronic medications other than those used for COPD, morbid obesity, neurosurgical operation, neurotoxic medications, and contraindications for TMS such as the presence of history for epilepsy, cranial surgery, or pacemaker use.

2.2. Study design

Here, we designed an observational, prospective case-control respiratory electrophysiological study in 20 AE-COPD patients with respiratory failure, re-examined after weaning and 20 healthy controls. PNC, CMS, TMS, arterial blood gas analysis, and serum electrolyte levels were carried out within 24 hours of mechanical ventilation and re-examined after weaning within 24 hours. All the electrophysiological explorations were made by the same investigator.

2.3. Transcranial and cervical magnetic stimulation

A MagPro Compact magnetic stimulator equipped with a C-100 circular coil (Alpine Biomed ApS, Skovlunde, Denmark) was used for all subjects. The outer diameter of the coil was 110 mm; the inner diameter of the coil was 55 mm; the maximum magnetic flux density at the coil surface was 3.9 Tesla. Clockwise coil current (side B of the coil facing upward) was used to stimulate the right hemisphere. The coil was centered over C4, as determined by the 10 to 20 electroencephalograph system, flat against the skull. TMS was performed at 80% of the maximal magnetic output, CMS was performed with the coil centered over the spinous process of the seventh cervical vertebra.[10] Anticlockwise coil current (side A of the coil facing upward) was used for CMS. CMS at 50% of maximal magnetic output. Higher stimulation at the neck often resulted in large stimulation artifacts. All stimulations were repeated 5 times and the best of 3 recordings was selected for measurement. The values corresponded to the average of 3 stimulations. The time interval between each stimulation was 45 to 60 seconds. TMS and CMS were delivered at the end of expiration by carefully observing chest movement with the patients in the supine position. TMS and CMS were utilized to assess the amplitudes and latencies of motor evoked potential of the diaphragm (dMEP). The central motor conduction time (CMCT) was the conduction time from the cerebral cortex to the spinal cord anterior horn motor neurons, mainly reflect on motor neurons and spinal cord anterior horn cell function, which was calculated by subtracting the cervical onset latency from the cortical onset latency.

2.4. Phrenic nerve stimulation

Phrenic nerve stimulation (PNS) was performed according to the technique established by Markand et al.[11] Phrenic nerve was stimulated at the posterior border of the left sternocleidomastoid muscles, at the level of the upper border of the thyroid cartilage, by a bipolar stimulator with saline-soaked felt tips 8 mm in diameter, with 1.5 cm between electrodes (Alpine Biomed ApS, Skovlunde, Denmark). The cathode was placed at the lower level. Subjects lied supine in a warm room with the head in midline. Current intensity was gradually increased to a supramaximal dCMAP, a current that was 20% higher than the current needed to generate a maximal dCMAP. The stimulator was set to deliver square-wave pulses of 0.2 ms duration, conventionally at 2 Hz. Stimulation was performed at the end of expiration by carefully observing chest movement. Care was taken to avoid co-activating the brachial plexus during stimulation by observing for muscle contractions and arm movement. Recording was rejected if a short latency with an initially positive response was detected, which related to the unnoticed brachial plexus coactivation, and the stimulation was repeated. Phrenic nerve stimulation was repeated 5 times and the best amplitude obtained was used for data analysis.

2.5. Recording

The dCMAPs were recorded with adhesive disposable surface electrodes (7×4 cm; Alpine Biomed ApS, Skovlunde, Denmark). The active recording electrode (G1) was placed 5 cm superior to the tip of the xiphoid process (XP) while the reference electrode (G2) was placed 16 cm inferolaterally from G1 along the ribcage over the chest wall on the left side and connected to a Keypoint 4 electromyogram machine (Alpine Biomed ApS, Skovlunde, Denmark). A ground electrode was placed between the stimulation and recording points. Recordings were rejected if electrocardiogram artifacts were encountered and the stimulation had to be repeated. Filters were set at 2 Hz to 10 kHz. Initial sensitivity was set at 0.2 mV and sweep speed at 5 ms/div. The onset latency was determined from the onset of the negative peak, that as the amplitude from the baseline (or initial positivity if present) to the negative peak.

Table 1

Results of arterial blood gas analysis and serum electrolyte levels in AE-COPD patients, COPD patients after weaning and controls.

	AE-COPD patients ($n=20$)	COPD patients after weaning (n=20)	Controls ($n=20$)	*P* value*		
				P1	P2	P3
pH	7.33±0.05	7.39±0.04	7.41±0.03	<.001	NS	<.001
$PaCO_2$, mmHg	59.4±8.9	44.2±6.3	40.3±2.9	<.001	.019	<.001
PaO_2, mmHg	47.0±10.3	84.8±18.4	96.6±1.9	<.001	.010	<.001
HCO_3^-, mmol/L	35.4±5.9	27.0±2.7	25.1±2.3	<.001	.017	<.001
Na^+, mmol/L	139.6±5.2	138.1±2.8	139.2±2.1	NS	NS	NS
K^+, mmol/L	4.2±0.6	3.7±0.3	3.8±0.2	.036	NS	<.001
Cl^-, mmol/L	92.9±10.4	102.0±3.7	103.3±3.2	<.001	NS	<.001

AE-COPD = acute exacerbation of COPD, Cl^- = chloride, COPD = chronic obstructive pulmonary disease, HCO_3^- = bicarbonate, K^+ = potassium, P1 = AE-COPD patients versus controls, P2 = COPD patients after weaning versus controls, P3 = AE-COPD patients versus COPD patients after weaning, Na^+ = sodium, NS = not significant, $PaCO_2$ = partial pressure of arterial carbon dioxide, PaO_2 = partial pressure of arterial oxygen.

* Significance was considered at $P<.05$.

2.6. Arterial blood gas tests and serum electrolyte levels

Arterial blood gas is a method to detect the saturation level of oxygen in the patient's blood, which was analyzed with a Rapidlab 860 blood gas analyzer (Bayer AG, Leverkusen, Germany), including pH, partial pressure of arterial oxygen (PaO_2), and partial pressure of arterial carbon dioxide ($PaCO_2$). The primary ions of serum electrolytes are sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), chloride (Cl^-), hydrogen phosphate (HPO_4^{2-}), and hydrogen carbonate (HCO_3^-), which are involved in fluid balance and blood pressure control. Serum electrolyte levels were studied using a Modular P800 system (Roche Diagnostics, Basel, Switzerland), including Na^+, K^+, Cl^-, and HCO_3^-.

2.7. Duration of mechanical ventilation

A measurement of the duration of mechanical ventilation (MVD) was defined as the time from intubation to the time of final extubation. Patients requiring reinstitution of mechanical ventilation after weaning were not considered separately but their total MVD was counted.

2.8. Statistical analysis

Statistical analyses were performed using SPSS statistical software version 16.0 (Chicago, IL). Data were expressed as mean ± standard deviation (SD) unless otherwise stated. Patients and controls were compared using the two-tailed Student unpaired *t* test; AE-COPD patients, and COPD patients after weaning were compared using the two-tailed Student paired *t* test. For continuous variables, Pearson correlation coefficient was used to correlate the electrophysiological data with clinical parameters. Variables that had a skewed distribution, such as dCMAP and dMEP amplitudes, MVD were analyzed separately: comparisons between patients and controls were performed using the Mann–Whitney *U* test and Spearman Rho correlation; comparisons between AE-COPD patients and COPD patients after weaning were performed using the Wilcoxon matched-pairs signed-ranks test. Differences were considered statistically significant if $P<.05$.

3. Results

This study included 20 AE-COPD patients with respiratory failure and 20 healthy controls. The median duration of mechanical ventilation was 7 days for the AE-COPD group (first quartile 6 days; third quartile 11 days). Arterial blood gas analysis and serum electrolyte levels of all participants were given in Table 1. Compared with the control group, AE-COPD patients had a significant hypoxia and hypercapnia as recorded in $PaCO_2$ ($P<.001$ for both). The serum HCO_3^- concentration was higher and the pH value was lower in the AE-COPD group than control ($P<.001$ for both). AE-COPD patients demonstrated marked reduced serum Cl^- ($P<.001$), and increased serum K^+ ($P<.05$) compared with control subjects, while Na^+ showed no statistical differences between 2 groups. The PaO_2 value was lower but $PaCO_2$ value and the serum HCO_3^- concentration were higher in COPD patients after weaning compared with the control ($P<.05$ for all). In addition, serum Na^+, K^+, Cl^- concentrations and pH values showed no statistical differences between 2 groups. After weaning from mechanical ventilation in the AE-COPD group, the $PaCO_2$ value and serum K^+ decreased, PaO_2, pH value, and serum Cl^- increased compared with the baseline ($P<.001$ for all). Still, there were no statistical differences in serum Na^+ between the baseline and after weaning in the AE-COPD group.

The electrophysiological findings in COPD patients during acute exacerbation and after weaning were presented in Table 2. The latencies of dCMAP, dMEP, and CMCT were delayed, and the amplitudes of dCMAP and dMEP evoked by CMS were decreased in AE-COPD patients compared with controls ($P<.001$ for all). After weaning from mechanical ventilation in the AE-COPD group, there were no statistical differences in the latency and amplitude of dCMAP, the latency of dMEP evoked by CMS and the amplitude of dMEP evoked by TMS compared with the baseline. Besides, the amplitude of dMEP evoked by CMS was lower ($P<.05$), and CMCT and the latency of dMEP evoked by TMS were shorter compared with the baseline ($P<.001$ and $P<.01$). The latencies of dCMAP and dMEP evoked by CMS and TMS were still prolonged in AE-COPD patients after weaning compared with the control group ($P<.01$ for all), but it showed no statistical difference in CMCT and the amplitude of dMEP evoked by TMS between COPD patients after weaning in the control group. Finally, significant correlation was identified between arterial blood gas analysis, serum electrolyte levels, disease duration, the duration of mechanical ventilation, and the electrophysiological findings in AE-COPD patients prior to weaning (Table 3).

4. Discussion

Chronic hypoxemia and COPD have been reported to cause peripheral neuropathy.[12] However, only a few studies have

Table 2

Electrophysiological findings in COPD patients during acute exacerbation and after weaning.

	AE-COPD patients ($n=20$)	COPD patients after weaning ($n=20$)	Controls ($n=20$)	*P* value†		
				P1	P2	P3
PNC						
Latency, ms	9.0±1.3	8.9±1.4	7.2±0.9	<.001	<.001	NS
Amplitude, μV	423±217	362±169	694±298	.004	<.001	NS
Responses to CMS						
Latency, ms	7.5±1.0	7.4±0.9	6.4±1.0	.001	.003	NS
Amplitude, μV	122±77	83±51	254±164	.001	<.001	.028
Responses to TMS						
Latency, ms	17.6±1.5	15.8±1.8	14.4±1.1	<.001	.004	.001
Amplitude, μV	220±148	206±127	339±256	NS	NS	NS
CMCT, ms	10.1±1.7	8.4±1.9	7.9±1.7	<.001	NS	.009

AE-COPD = acute exacerbation of COPD, CMCT = central motor conduction time, COPD = chronic obstructive pulmonary disease, CMS = cervical magnetic stimulation, NS = not significant, P1 = AE-COPD patients versus controls, P2 = COPD patients after weaning versus controls, P3 = AE-COPD patients versus COPD patients after weaning, PNC = phrenic nerve conduction, TMS = transcranial magnetic stimulation.

† Significance was considered at $P < .05$.

reported the electrophysiological features of the cortico-diaphragmatic pathway involvement in AE-COPD patients.[13–15]

Normal breathing requires the integrity of cerebral cortex, brain stem, descending nerve pathways, motor nerves (especially the phrenic nerve), neuromuscular junction, and respiratory muscles section. Disturbances at any one of these sites can lead to abnormalities in coordination of the system or to muscle weakness.[5] The present study investigated the central and peripheral respiratory pathway by means of TMS, CMS, and PNC.

Phrenic nerve conduction is most helpful in evaluating patients with respiratory difficulties. It can be applied to evaluate the integrity of the neuromuscular respiratory apparatus and enable us to eliminate the effect of the central nervous system.[11] In this study, the mean value of dCMAP latency was longer but the mean value of dCMAP amplitude was lower in AE-COPD patients, the same findings were found in COPD patients after weaning. Our results indicated the involvement of the phrenic nerve in AE-COPD patients with respiratory dysfunction and the electrophysiological changes of PNC cannot return to normal after weaning. The latency of dCMAP is one of the most useful indexes in detecting demyelination of the phrenic nerve.[6,11] The amplitude of dCMAP is a useful parameter for evaluating the function of the diaphragm. It provides a measure of the number of diaphragmatic muscle fibers activated by PNS.[11] In addition to the impairment of the phrenic nerve, diaphragm abnormalities may also lead to a reduction in the amplitude of dCMAP. COPD patients may undergo chronic inflammatory states and irreversible airway obstruction. Additionally, direct inflammatory-mediator effects on malnutrition, blood-gas abnormalities, electrolyte imbalances, drugs, and comorbid conditions can lead to skeletal-muscle (both respiratory and limb) abnormalities.[16,17] They may cause the decrease in the amplitude of dCMAP. Podnar et al[7] reported that patients with COPD often had increased amplitudes of dCMAP, and the possible cause was considered that greater diaphragmatic muscle mass or flattening of the diaphragm associated with lung hyperinflation. However, contrary to findings of them, we found that dCMAP amplitude was comparatively lower in AE-COPD patients prior to weaning. The most possible reason may be that the subjects were COPD patients with different degrees of severity. Our subjects were COPD patients at the acute stage of exacerbation, who

Table 3

Correlation between arterial blood gas analysis, serum electrolyte levels, and the electrophysiological findings in AE-COPD patients prior to weaning‡.

	PNC latency	PNC amplitude	Latency of CMS	Amplitude of CMS	Latency of TMS	Amplitude of TMS	CMCT
PaO_2							
r	−0.331	0.124	0.229	0.383	−0.605	−0.030	−0.667
P	NS	NS	NS	NS	0.005	NS	0.001
Cl^-							
r	0.274	−0.172	0.434	0.438	−0.734	−0.140	−0.898
P	NS	NS	NS	NS	<0.001	NS	<0.001
Duration							
r	0.676	−0.660	0.384	−0.071	−0.112	−0.111	−0.316
P	0.001	0.002	NS	NS	NS	NS	NS
MVD							
r	0.682	−0.493	0.328	0.195	0.169	−0.129	−0.124
P	0.001	0.027	NS	NS	NS	NS	NS

pH, $PaCO_2$, HCO_3^-, Na^+, and K^+ did not show significant correlations with any of the electrophysiological measures.Cl^- = chloride, CMS = cervical magnetic stimulation, CMCT = central motor conduction time, HCO_3^- = bicarbonate, K^+ = potassium, MVD = the duration of mechanical ventilation, Na^+ = sodium, NS = not significant, PNC = phrenic nerve conduction, $PaCO_2$ = partial pressure of arterial carbon dioxide, PaO_2 = partial pressure of arterial oxygen, *r* = correlation coefficient, TMS = transcranial magnetic stimulation.

‡ Significance was considered at $P < .05$.

consistently exhibited severe hypoxemia and/or hypercapnia and needed mechanical ventilation. Under such conditions, the diaphragm and phrenic nerve were prone to get affected.

The motor control of the respiratory muscles is controlled by respiratory centers in the medulla oblongata and pons and efferent pathways. Normal quiet breathing impulses are transmitted from respiratory centers down to the diaphragm, intercostal muscles, and accessory muscles of inspiration in the neck. Behavioral or voluntary control of breathing takes its origins from the motor cortex, with impulses descending via corticospinal tracts.[18] In addition to cortico-diaphragmatic pathway dysfunction, skin thickness, subcutaneous tissue, distortion of the shape of the diaphragm caused by the shape change of chest wall during expansion and flattening of the diaphragm and so on can affect the amplitude of dMEP.[19]

In this study, dysfunction of the corticospinal motor pathway was prominent during AE-COPD. This was evidenced by the prolonged CMCT value and dMEP latency evoked by TMS. In addition, the longer dMEP latency and lower amplitude of dMEP evoked by CMS indicated peripheral phrenic damage, and possible diaphragm abnormalities were also demonstrated by PNC. After weaning, the value of CMCT and the latency of dMEP evoked by TMS were shortened, though not normalized, which indicated that the central control of diaphragm had been improved, but did not return back to normal after rectifying the respiratory failure. Prolonged CMCT usually implies demyelination, 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 AE-COPD patients could be due to corticospinal tract abnormality or I-wave recruitment abnormalities.[20] After weaning, the impairment was partially reversible, and the possible mechanisms could be due to the clinical status of patients, such as hypoxemia, hypercapnia, and electrolytes disturbance. PNC and CMS can both explore the peripheral respiratory pathway; however, we found that the mean amplitude of dMEP evoked by CMS was lower than dCMAP in our study. The most probable cause was that CMS was not supramaximal in our study. We performed CMS at 50% of maximal magnetic output, considering higher intensity stimulation often resulted in large stimulation artifacts. The mean amplitude of dMEP evoked by CMS was decreased and turned lower than dCMAP after weaning, which indicated that the phrenic nerve and/or diaphragm abnormalities were worsen during mechanical ventilation. In addition, large variability of dMEP may also cause the differences between the amplitudes of dCMAP and dMEP evoked by CMS post-weaning (Table 4).[21]

Agrawal et al[22] found subclinical peripheral neuropathy in stable middle-aged patients with COPD, therefore, phrenic nerve or generalized peripheral nerve dysfunction may also be present before including the patients in the study. The cortico-diaphragmatic pathway abnormalities are difficult to interpret in isolation. However, we did not perform peripheral nerve conduction studies and upper limb muscles needle electromyogram, and thus cannot determine whether central and peripheral respiratory pathway dysfunction was specific or it represented a more generalized finding in AE-COPD patients. Our subjects were AE-COPD patients with acute respiratory failure enough to require mechanical ventilation. They were so critically ill that we had to reduce our measurement and focus on the evaluation of the central and peripheral respiratory pathway. The most common causes of an exacerbation of COPD are respiratory infections and air pollution,[23] therefore, sepsis or systemic inflammatory response syndrome (SIRS) may exist in AE-COPD patients. As is well known, sepsis or SIRS is thought to be significant risk factor of critical illness polyneuropathy (CIP).[24] Consequently, CIP may also cause or worsen the central and peripheral respiratory pathway abnormalities in addition to COPD.

We further compared the electrophysiological findings obtained by electrical PNS, TMS, and CMS with arterial blood gas values, serum electrolyte concentrations, disease duration, and the duration of mechanical ventilation. In agreement with previous study, the changes in CMCT and the latency of dMEP evoked by TMS were proportionate to the degree of hypoxemia.[14] The same results were observed in obstructive sleep apnea syndrome.[25] The reduction in Cl^- was associated with prolonged CMCT and the latency of dMEP evoked by TMS. This indicated that the hypoxemia impairs the function of respiratory central motor conduction. As is known to all, cortical excitability in humans is normally modulated by gamma-aminobutyric acid (GABA) ergic inhibitory interneurons.[26] There are 2 main classes of GABA receptors: GABA(A) and GABA(B). GABA(A) receptors are fast, ligand-gated chloride ion channels; while GABA(B) receptors are metabotropic transmembrane receptors,[27,28] and GABAergic activation can modulate neuronal K^+ channels.[29] In our study, the elevation of K^+ level was also observed. The reduction in Cl^- and increase in K^+ levels among our patients with AE-COPD suggested that ion channels and GABAergic transmission were altered; hypoxia was the possible cause.[30] Further studies are needed to evaluate the cortical excitability changes by TMS in AE-COPD patients.

In our research we found a positive correlation between the duration of the disease and the latency of dCMAP, as well as a negative correlation between the duration of the disease and the amplitude of dCMAP. The same associations were found between MVD and the electrophysiological parameters of PNC. This suggested that poor phrenic nerve and diaphragmatic functions led to longer MVD. Respiratory muscle weakness and decreased endurance have been observed following mechanical ventilation. It may be a manifestation of neuromuscular disorders such as CIP, critical illness myopathy, and disuse atrophy.[31] The correlation between MVD and the electrophysiological parameters of PNC may support that the degree of weakness could be related to the MVD.[32]

In conclusion, the present study used central and peripheral electrophysiological approaches and provided an easy and detailed assessment of the nervous system control of respiration in AE-COPD patients. The use of both neurophysiological and respiratory tests would collect useful complementary information on central and peripheral respiratory pathway function. These parameters may be used as potential predictors for weaning from mechanical ventilation in the future.

Our study has several limitations. Firstly, needle electromyography of the diaphragm was not performed. Needle electromyography is helpful to evaluate the presence of motor neuron degeneration and can distinguish myogenic, neurogenic, or mixed lesions of the muscle. However, we could not justify patients to the potential risk of pneumothorax.[5] Secondly, we did not identify the involvement of the incidence of phrenic nerve, the diaphragm, and the corticospinal motor pathway. Thirdly, we did not perform peripheral nerve conduction studies and needle electromyography of the limb muscles, and thus cannot make sure whether the central and peripheral respiratory pathway dysfunction is specific, or accompanied with generalized

Table 4

The introduction of PNC, TMS, and CMS.

Methods	How function	Clinical application	Electrophysiological evaluation
PNC	Phrenic nerve was stimulated at the posterior border of the left sternocleidomastoid muscles, at the level of the upper border of the thyroid cartilage, by a bipolar stimulator with saline-soaked felt tips 8 mm in diameter, with 1.5 cm between electrodes (Alpine Biomed ApS, Skovlunde, Denmark). The cathode was placed at the lower level. Subjects lied supine in a warm room with the head in midline. Current intensity was gradually increased to a supramaximal dCMAP, a current that is >20% than the current needed to generate a maximal dCMAP. The stimulator was set to deliver square-wave pulses of 0.2-ms duration, conventionally at 2 Hz. Stimulation was performed at end expiration by carefully observing chest movement. Care was taken to avoid coactivating the brachial plexus during stimulation by observing for muscle contractions and arm movement. Recording was rejected if a short latency with an initially positive response was detected, which related to the unnoticed brachial plexus coactivation, and the stimulation was repeated. Phrenic nerve stimulation was repeated 5 times and the best amplitude obtained was used for data analysis.	Reveal the causes of respiratory disturbance in peripheral neuropathy, and provide the basis for defining the phrenic nerve injury secondary to some operations and judging whether the phrenic nerve pacemaker can be successfully installed.	Detection of respiratory dysfunction caused by phrenic nerve or diaphragm of a patient with acute exacerbation of COPD.
TMS	A MagPro Compact magnetic stimulator equipped with a C-100 circular coil (Alpine Biomed ApS, Skovlunde, Denmark) was used for all subjects. The outer diameter of the coil was 110 mm; the inner diameter of the coil was 55 mm; the maximum magnetic flux density at the coil surface was 3.9 Tesla. Clockwise coil current (side B of the coil facing upward) was used to stimulate the right hemisphere. The coil was centered over C4, as determined by the 10–20 electroencephalograph system, flat against the skull. TMS was performed at 80% of the maximal magnetic output. All stimulations were repeated 5 times and the best of 3 recordings was selected for measurement. The values corresponded to the average of 3 stimulations. The time interval between each stimulation was 45–60 seconds. TMS was delivered at end expiration by carefully observing chest movement with the patients in the supine position.	Detect the diaphragmatic motor evoked potential of the diaphragm and evaluate the pathway from cortical motor center to diaphragm motor neuron.	Diagnosis and detection of respiratory dysfunction due to insufficient respiratory center movement of a patient with acute exacerbation of COPD.
CMS	CMS was performed with the coil centered over the spinous process of the seventh cervical vertebra. Anticlockwise coil current (side A of the coil facing upward) was used for CMS. CMS was performed at 50% of maximal magnetic output. Higher stimulation at the neck often resulted in large stimulation artifacts. CMS was also delivered at end expiration by carefully observing chest movement with the patients in the supine position.	Detect the diaphragmatic motor evoked potential of the diaphragm and evaluate the pathway from cortical motor center to diaphragm motor neuron.	Diagnosis and detection of respiratory dysfunction due to insufficient respiratory center movement of a patient with acute exacerbation of COPD.

COPD = chronic obstructive pulmonary disease, CMS = cervical magnetic stimulation, dCMAP = diaphragmatic compound muscle action potential, PNC = phrenic nerve conduction, TMS = transcranial magnetic stimulation.

peripheral nerve dysfunction. Lastly, it still requires extension in measurement of maximal inspiratory pressure and TMS parameters related with cortical excitability in AE-COPD patients.

Author contributions

Conceptualization: Yu Wang, Zhecheng Zhang.
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