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ORIGINAL RESEARCH

Evaluation of Peripheral Neuropathy in Patient with Stable Chronic Obstructive Pulmonary Disease: A Hospital-Based Study from North India

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ABSTRACT

Background:Chronic obstructive pulmonary disease (COPD) is characterized by obstruction in airflow; however, COPD is a systemic illness. Neurophysiological alterations, such as nerve conduction (monosynaptic reflex test) and strength, have been correlated with smoking, the severity of the disease, hypoxemia, age, hypercapnia and peak expiratory flow. In this study, we aimed to evaluate the peripheral nervous system (PNS) with electromyography (EMG) method in patients with COPD and to examine their relationship with each other.

Materials and Methods: The study was conducted in the Department of Physiology in collaboration with the Department of Pulmonary Medicine in New Delhi Medical College and Hospital in Delhi. Our study was conducted among two groups: patient group (included COPD cases) and control group (included healthy volunteers). Spirometry was done using MEDGRAPHICS body plethysmograph. Nerve conduction studies were performed on median, ulnar, peroneal, tibial and sural nerves using NEURO– MEP–NET EMG/NCV/EP (NEUROSOFT TM) Equipment. The data for each nerve parameter in the two groups were analyzed Students' T test.

Results: 39 patients with stable COPD in addition to 39 healthy volunteers as a control were included in this study. The mean age for patient group was 62.78±7.11 years and for control group it was 60.13±9.83 years. Males in the patient group were 89.7% and in control group they were 87.2%. The pulmonary function tests revealed a significant decrease of FEV1, and FEV1/FVC in the COPD group when compared to the control group. The patient of COPD was grouped in accordance with these GOLD criteria and 28.2% of patients were having Mild COPD, while 35.9% of patients each were having moderate and severe COPD. Results of the nerve conduction study showed that there was a statistically significant decrease in amplitude (mv) and velocity (m/s) and increase in latency (ms) of peripheral nerve motor and sensory in the COPD group when compared to the control group.

Conclusion: This study shows that advancement in severity of disease predisposes to neuropathy. Hence, sensory nerve conduction study can be advised routinely and at regular intervals to the patients suffering from increasing severity of COPD for early detection of neuropathy.

Keywords: Nerve conduction velocity, peripheral neuropathy, Chronic obstructive pulmonary disease, Spirometry, Electromyography.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by obstruction in airflow; however, COPD is a systemic illness.[1] Lung impairment is only one of the symptoms, and mechanisms such as oxidative stress and inflammation may be involved in the development of the systemic effects. The skeletal musculature is affected, and there are alterations regarding the type of fiber and muscle mass, enzymatic metabolism and capillarization of blood vessels.[2,3,4] Other abnormalities are seen in these patients and are related to neurophysiological aspects. Electromyography (EMG) is useful in the detection of abnormal electrical activity in muscles, in which a substantial reduction in the speed of the reflex response may correspond to a nerve conduction pathology, such as a peripheral neuropathy.[5,6,7]

Neurophysiological alterations, such as nerve conduction (monosynaptic reflex test) and strength, have been correlated with smoking, the severity of the disease, hypoxemia, age, hypercapnia and peak expiratory flow.[8] However, these aspects have not been compared with functional capacity and other predictors, such as the BODE Index, described as a survival prognosis score for patients with COPD.[9]

The presence of neurophysiological alterations was first described by Appenzeller et al. in 1968.[10]Kayacan et al. found neurophysiological alterations in 93.8% of patients with COPD [11]. Jann et al. found a slight reduction in both nerve conduction speed and the range of action potential of the motor unit in chronic respiratory failure, thereby suggesting the occurrence of peripheral neuropathy.[12] Another study found a reduction in muscle strength, mobility and coordination in hypoxemic patients at rest.[13]

Peripheral muscle strength has been studied in the realm of pulmonary rehabilitation. However, O'Shea et al. suggest that further investigations should be carried out on the impact of strength on functional performance in individuals with COPD as well as the results of an increase in strength regarding an improvement in functional activity, including the measurement of balance.[14] Other examinations have sought the same efficacy as the walk test, but in a smaller space, thereby facilitating their execution. One such examination is the SST. Ozalevli et al. compared both tests and concluded that the SST determines the functional condition of patients with moderate to severe COPD as well as the 6MWT, while offering lesser hemodynamic stress.[15]

We hypothesized that patients with COPD show a slowing of the monosynaptic reflexes and functional alterations compared with healthy individuals of similar age. In this study, we aimed to evaluate the peripheral nervous system (PNS) with electromyography (EMG) method in patients with COPD and to examine their relationship with each other.

MATERIALS & METHODS

The study was conducted in the Department of Physiology in collaboration with the Department of Pulmonary Medicine in New Delhi Medical College and Hospital in Delhi with prior permission of ethical committee. Our study was conducted among two groups: patient group (included COPD cases) and control group (included healthy volunteers). Diagnosis of COPD was done on the basis of history of cough, sputum production, and exertional dyspnea. General physical examination followed by respiratory system examination was done to detect for cyanosis, signs of hyperinflation including barrel chest, enlarged lung volume, and poor diaphragmatic excursion prolonged expiratory phase, use of accessory muscles of respiration, sitting in characteristic "tripod" position to facilitate sternocleidomastoid, scalene and intercostal muscles, expiratory wheezing, and odor of smoke or nicotine staining of fingernails. COPD was confirmed by performing spirometry and bronchodilator reversibility testing on patients suspected clinically to be suffering from disease.[16]

Through relevant history and neurological examination – patients with conditions adversely affecting nerve conduction (severe anemia, chronic renal failure, liver failure, chronic alcoholism, congestive cardiac failure, diabetes mellitus, thyroid disorders, neuromuscular disorders, rheumatoid arthritis, and drug abuse) or patients on antiretroviral/ antitubercular drugs which may lead to PNP were excluded.[17] After applying these inclusion and exclusion criteria, 39 cases of COPD (patient group) and 39 healthy volunteers (control group) in the age group of 25–65 years were selected. Subjects were briefly explained about the procedure and voluntary informed consent was taken.

Spirometry was done using MEDGRAPHICS body plethysmograph. COPD patients classically show a decrease in both FEV and forced vital capacity (FVC). With worsening of the disease severity, there were an increase in lung volumes, total lung capacity, functional residual capacity, and residual volume. Airflow limitation seen in COPD patients is defined as a post- bronchodilator FEV in 1 s (FEV1) to FVC (forced vital capacity) ratio <0.70, without reversibility to bronchodilators. The severity of airflow limitation in COPD is classified based on Global Initiative for Obstructive Lung Disease (GOLD) criteria.[18]

Nerve conduction studies were performed on median, ulnar, peroneal, tibial and sural nerves using standard protocol and settings as described by Misra et al. using NEURO– MEP–NET EMG/NCV/EP (NEUROSOFT TM) Equipment.[19] The apparatus works on a computer with Windows 98 operating system having MS Office 97 package. The recording electrode, ground electrode, and stimulating electrode are applied to the skin after application of electrode paste. For motor nerve conduction study, the low-frequency filter was set at 2 Hz and high-frequency filter at 10 kHz. For sensory nerve conduction study, the low-frequency filter was set at 5 Hz and high-frequency filter at 3 kHz. The sweep speed was set at 2 ms/division.

The active and reference electrodes, placed 3 cm apart, make up the recording electrode. The active electrode was placed over motor point of the muscle (midpoint between the origin and insertion of the muscle) or nerve segment to be studied. The reference electrode for motor response was positioned on the muscle tendon and for sensory response was placed on the nerve segment to be studied. A skin surface ground electrode was placed between the recording electrode and stimulating electrode. The stimulating electrode, placed on the skin at appropriate sites, was used for stimulation of the nerve with supramaximal stimulus (20–40 mA) at constant current pulses.[19]

Motor nerve conduction velocity, latency, and amplitude of median, ulnar, tibial and peroneal nerves were recorded for patient and control groups. Similarly, sensory conduction velocity, latency, and amplitude in median, ulnar, and sural nerves were recorded. Normality test of the sample was conducted using Kolmogorov–Smirnov test in SPSS following which the data for each nerve parameter in the two groups were analyzed Students' T test in SPSS Version 14 and Microsoft Excel database. P value < 0.05 was considered as significant.

RESULTS

Table 1. Shows that in our study the demographic characteristics of the patient group and control group were comparable (p>0.05). The mean age for patient group was 62.78±7.11 years and for control group it was 60.13±9.83 years. The mean BMI for patient and control groups were 23.5±4.3 kg/m2 and 23.8±4.5 kg/m2 respectively. The mean haemoglobin for patient and control groups were 13.76±1.66 g/dl and 13.90±1.34 g/dl respectively. The patient of COPD was grouped in accordance with these GOLD criteria and 28.2% of patients were having Mild COPD, while 35.9% of patients each were having moderate and severe COPD.

Table 1: Demographic characteristics of the patient and control groups (N=78)

Variables	Number (%)/Mean±SD		P-value
	Patients (n=39)	Controls (n=39)	
Age (years)	62.78±7.11	60.13±9.83	0.177
Gender			
Male	35 (89.7)	34 (87.2)	0.723
Female	4 (10.3)	5 (12.8)	
Weight (kg)	67.15±11.6	66.57±10.45	0.817
BMI (kg/m^2)	23.5±4.3	23.8±4.5	0.764
Hemoglobin (g/dl)	13.76±1.66	13.90±1.34	0.683
Iron (mg/dl)	69.64±13.94	72.53±12.83	0.344
Urea (mg/dl)	28.7±6.8	27.3±6.6	0.359
Creatine (mg/dl)	0.68±0.23	0.69±0.21	0.842
COPD class			
Mild	11 (28.2)	–	–
Moderate	14 (35.9)	–	–
Severe	14 (35.9)	–	–
FeV_1/FVC	58.97±8.32	88.21±2.43	<0.0001
FeV_1	45.50±18.44	80.66±2.72	<0.0001
Disease duration (years)	11.43±9.23	–	

Table 2. shows the electromyography results of motor nerve among patient group and control group and the right median motor amplitude among patient group and control group were 10.98±3.89 mv and 13.24±4.28 mv respectively; latency among patient group and control group were 3.96±0.51 ms and 2.87±0.65 ms respectively; and conduction velocity among patient group and control group were 57.62±7.17 m/s and 60.43±8.11 m/s respectively. Right ulnar motor amplitude among patient group and control group were 10.21±2.51 mv and 13.04±3.50 mv respectively; latency among patient group and control group were 3.32±0.56 ms and 2.57±0.42 ms respectively; and conduction velocity among patient group and control group were 58.38±9.01 m/s and 66.46±8.49 m/s respectively. The differences for Amplitude (mv), Latency (ms), and Conduction velocity (m/s) for Right median, right ulnar, right peroneal, right tibial, left median and left ulnar motor nerves among patient group and control group were statistically significant ($p<0.05$), except for the right median motor nerve conduction velocity ($p>0.05$).

Table 2: Electromyography results of Motor nerve among patient group and control group (N=78).

Motor nerve electromyography	Mean±SD		P-value
	Patients (n=39)	Controls (n=39)	
Right median motor			
Amplitude (mv)	10.98±3.89	13.24±4.28	0.017
Latency (ms)	3.96±0.51	2.87±0.65	<0.0001
Conduction velocity (m/s)	57.62±7.17	60.43±8.11	0.109
Right ulnar motor			
Amplitude (mv)	10.21±2.51	13.04±3.50	<0.0001
Latency (ms)	3.32±0.56	2.57±0.42	<0.0001
Conduction velocity (m/s)	58.38±9.01	66.46±8.49	0.0001

Right peroneal motor			
Amplitude (mv)	3.29±2.51	4.87±3.68	0.030
Latency (ms)	4.67±0.48	4.10±0.39	<0.0001
Conduction velocity (m/s)	44.68±6.04	51.79±6.16	<0.0001
Right tibial motor			
Amplitude (mv)	7.87±4.81	12.28±5.54	0.0003
Latency (ms)	4.58±0.96	3.50±0.48	<0.0001
Conduction velocity (m/s)	44.67±7.04	50.75±5.71	0.0001
Left median motor			
Amplitude (mv)	10.46±3.19	15.78±6.51	<0.0001
Latency (ms)	4.40±0.64	3.53±0.65	<0.0001
Conduction velocity (m/s)	56.86±7.72	60.96±7.41	0.019
Left ulnar motor			
Amplitude (mv)	11.09±4.70	15.50±5.34	0.0002
Latency (ms)	3.45±0.47	2.67±0.42	<0.0001
Conduction velocity (m/s)	60.14±7.07	70.31±10.53	<0.0001

Table 3. shows the electromyography results of sensory nerve among patient group and control group and the right median sensory amplitude among patient group and control group were 11.87±6.42 mv and 21.26±8.16 mv respectively; latency among patient group and control group were 3.40±0.54 ms and 2.55±0.63 ms respectively; and conduction velocity among patient group and control group were 52.45±7.04 m/s and 56.09±6.97 m/s respectively. Right ulnar sensory amplitude among patient group and control group were 11.81±7.75 mv and 22.10±8.75 mv respectively; latency among patient group and control group were 2.87±0.54 ms and 2.43±0.21 ms respectively; and conduction velocity among patient group and control group were 50.18±6.01 m/s and 54.37±5.60 m/s respectively. The differences for Amplitude (mv), Latency (ms), and Conduction velocity (m/s) for Right median, right ulnar, right sural, left median and left ulnar sensory nerves among patient group and control group were statistically significant ($p<0.05$), except for the right median motor nerve conduction velocity ($p>0.05$).

Table 3: Electromyography results of Sensory nerve among patient group and control group (N=78).

Motor nerve electromyography	**Mean±SD**		**P-Value**
	Patients (n=39)	**Controls (n=39)**	
Right median sensory			
Amplitude (mv)	11.87±6.42	21.26±8.16	<0.0001
Latency (ms)	3.40±0.54	2.55±0.63	<0.001
Conduction velocity (m/s)	52.45±7.04	56.09±6.97	0.025
Right ulnar sensory			
Amplitude (mv)	11.81±7.75	22.10±8.75	<0.0001
Latency (ms)	2.87±0.54	2.43±0.21	<0.0001
Conduction velocity (m/s)	50.18±6.01	54.37±5.60	0.002
Right sural sensory			
Amplitude (mv)	11.25±3.29	16.85±4.68	<0.0001
Latency (ms)	3.31±0.25	3.09±0.18	<0.0001
Conduction velocity (m/s)	45.04±7.75	52.70±8.23	0.0001
Left median sensory			
Amplitude (mv)	14.48±7.20	23.04±9.52	<0.0001

Latency (ms)	3.34±0.34	2.57±0.25	<0.0001
Conduction velocity (m/s)	53.84±7.21	57.29±7.89	0.047
Left ulnar sensory			
Amplitude (mv)	11.65±6.86	23.93±8.83	<0.0001
Latency (ms)	2.78±0.56	2.43±0.29	0.001
Conduction velocity (m/s)	52.56±6.46	57.16±6.42	0.002

DISCUSSION

39 patients with stable COPD in addition to 39 healthy volunteers as a control were included in this study. The mean age for patient group was 62.78±7.11 years and for control group it was 60.13±9.83 years. Males in the patient group were 89.7% and in control group they were 87.2%.

The pulmonary function tests revealed a significant decrease of FEV1, and FEV1/FVC in the COPD group when compared to the control group. These results are similar to those stated by Calik-Kutukcu et al. who described that FVC, FEV1, FEV1/FVC, FEF25-75% and PEF values of patients with COPD were statistically significantly lower than those of healthy people (P = 0.001).[20]

The patient of COPD was grouped in accordance with these GOLD criteria and 28.2% of patients were having Mild COPD, while 35.9% of patients each were having moderate and severe COPD. Similarly, a study by Calik-Kutukcu et al. described that 5% of COPD patients had mild, 45% moderate, 30% severe, and 20% very severe concerning to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[18,20] In addition, Karthikkeyan et al. described that the severity of mild, moderate type-IIA and moderate type-IIB forms of the disease were established to happen in 17, 63, and 20 percent, respectively, in the sample population.[21]

The most important cause of peripheral nervous system involvement is hypoxemia,[11] as it causes peripheral-nerve damage, harming the Vasonervorum.[22] In addition, Karthikkeyan et al. has described that the reason for peripheral neuropathy in patients with COPD is reduced spirometric measurements besides chronic severe hypoxemia.[21]

Furthermore, Agrawal et al. suggested that malnutrition, tobacco smoking, besides drugs used in COPD management, may be probably linked with neuropathy seen in patients with COPD.[8] Jindal et al. and Poza et. detected a greater prevalence of peripheral neuropathy in patients with severe hypoxemia and/ or hypercapnia discovered by neurophysiological analysis.[23,24]Stoebner et al. reported that hypoxia is linked to nerve capillary endothelial cell hyperplasia and hypertrophy, prompting luminal occlusion that causes microangiopathy in peripheral nerves in COPD patients.[25]

In different studies conducted by Agrawal et al. and Kayacan et al. have suggested the prevalence of peripheral neuropathy varied markedly from one study to another which can be explained by non-uniformity between study subjects from different studies.[7,11]

Gupta et al. stated that about one-third of patients with COPD have clinical confirmation of polyneuropathy, also two-thirds have abnormalities on electrophysiological studies, in addition, some patients with no clinical evidence of polyneuropathy still have electrophysiological deficit suggestive of polyneuropathy.[26] In addition, concluded that polyneuropathy is not an uncommon systemic manifestation of COPD. Knowledge of its coexistence may be valuable in early diagnosis of poly- neuropathy, thereby framing the preventive strategies and well-controlled chronic airway obstruction, keeping the PaO2 levels above the definition of hypoxemia (i.e., PaO2 > 60 mmHg) may probably help prevent or

slow down the manifestations of polyneuropathy in COPD patients, and avoid another disability.

Results of the nerve conduction study showed that there was a statistically significant decrease in amplitude (mv) and velocity (m/s) and increase in latency (ms) of peripheral nerve motor and sensory in the COPD group when compared to the control group. In addition, COPD affecting sensory fibers more than motor fibers and causing axonal sensory neuropathy. These results are equivalent to those described by Kayacan et al. and Ozge et al. who reported that the incidence of sub-clinical or clinical peripheral neuropathy in COPD was 28–95%.[11,22] In addition, Kazi et al. stated that, 96% of the patients with COPD were having neuropathy mainly subclinical detected by nerve conduction study, as most of the patients did not have any signs and symptoms of neuropathy.[27] In addition, the neuropathy involved was sensory nerves; mainly the sural nerve and the most common changes of neuropathy were of axonal type. They added, there was a significant association and correlation between stages of COPD (according to FEV1%) with sural NCV and amplitude.

In addition, our results co agree with those described by El-Shinnawya et al. who stated that the incidence of neuropathy is high, and a statistically significant positive correlation between the severity of neuropathy and the degree of hypoxemia, while it showed a negative correlation between spirometry values (FEV1 and FEV1 / FVC ratio) and median nerve distal latency.[28]

Demir et al. noticed peripheral neuropathy in (93.5%) of the studied patients (31 subjects) on EMG the sensory nerve conduction abnormalities were the most common, the sural nerve affected in (29 subjects), the ulnar nerve (26), median nerve (28), and motor nerve conduction abnormalities; peroneal (7), median nerve (2), tibial and ulnar nerve (1) and they concluded that the frequency of neuropathy, particularly sensorial, was more than expected, with a significant positive correlation between the degree of hypoxemia and the severity of neuropathy. In addition, they advise the use of electro- physiological studies for the detection of peripheral neuropathy in patients with COPD.[29]

CONCLUSION

This study shows that advancement in severity of disease predisposes to neuropathy. Hence, sensory nerve conduction study can be advised routinely and at regular intervals to the patients suffering from increasing severity of COPD for early detection of neuropathy. With this, neuropathic drug can be avoided and supportive therapy added in treatment protocol of these patients. Second, further studies can be undertaken to delineate causative role of inflammatory cytokines in PNP in larger sample size of these patients.

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