Electromyographic Evaluation of Peripheral Nerves in Chronic Obstructive Pulmonary Disease

Gökhan Asal, MD[1]; Aydan Çakan, MD[1]; Ahmet Emin Erbaycu, MD[1]; Şevket Dereli, MD[1]; Ayşe Özsöz, MD[1]; Hakan Edipoğlu, MD[2]; Behiye Özer, MD[3]

[1] *Chest Diseases and Thoracic Surgery Centre, Department of Chest Diseases, İzmir, Turkey*
[2] *Chest Diseases and Thoracic Surgery Centre, Department of Neurology, İzmir, Turkey*
[3] *Department of Neurology, Atatürk Training Hospital, İzmir, Turkey*

Abstract

Background: Hypoxemia is thought to have negative effects on the peripheral nerve system in cases with COPD. This study was designed to investigate the relationship between PN and COPD stage, smoking, severity of chronic hypoxemia by evaluating the velocity and amplitude of conduction in the peripheral sensorial and motor nerves.

Methods: 30 cases with COPD having no other apparent pathology that might cause PN, were included in the study. After a clinical neurological assessment, the velocity and amplitude of conduction in the median sensorial and motor, ulnar sensorial and motor, sural sensorial and fibular motor nerves were measured by electromyography. The patients were divided into subgroups according to their forced expiratory volume, partial arterial oxygen pressure (PaO_2) and smoking history characteristics.

Results: Significant differences were found among the CV of the fibular nerve when the patients were subdivided by their FEV_1 values. Negative correlations were established between sural sensorial nerve CV and duration of smoking, and also between median motor nerve and ulnar motor nerve CV and age. Fibular motor nerve CV and FEV_1 were positively correlated. Clinically, PN was encountered in 40% of the COPD patients. The most frequent electromyography findings were demyelination, and dysfunction of axonal and mixed types.

Conclusion: PN is a frequent problem in patients with COPD, mostly affecting the sural sensorial, ulnar sensorial and fibular motor nerves. Sensorial nerves (40%) are more frequently involved than the motor nerves (6.6%). The electrophysiological findings in COPD appear to be related to age, smoking history, respiratory functions and hypoxemia level.

Turkish Respiratory Journal, 2003;4:(2):51-56

Key words: *chronic obstructive pulmonary disease, electromyography, peripheral neuropathy*

Introduction

Smoking is the most important risk factor in the development of chronic obstructive pulmonary disease (COPD). Cigarette smoking may also have some neurotoxic effects. Hypoxemia in COPD patients is thought to have negative effects on the peripheral nervous system as well as on many other organs. Peripheral neuropathy (PN) has also been reported in patients taking almitrine for COPD, indicating the possible role of drugs in the etiology of PN. It is speculated that almitrine leads to PN by changing a latent neuropathy into an overt condition. While electrophysiological studies in COPD usually reveal a sensorial type neuropathy mostly in the distal parts of the extremities, in severe cases the neuropathy may be characterized by loss of axons which may sometimes be also accompanied by demyelination (1,2).

Correspondence: *Dr. Ahmet Emin Erbaycu*
İzmir Göğüs Hastalıkları Hastanesi,
35110 Yenişehir, İzmir, Türkiye
Tel: +90 (0) 232 433 33 33 / 375
Fax: +90 (0) 232 458 72 62
e-mail: drerbaycu@yahoo.com

The aim of this study was to evaluate the conduction velocity (CV) and amplitude (A) of peripheral motor and sensorial nerves in patients with COPD, as well as to establish the relationships between COPD stage, duration of smoking, and severity of chronic hypoxemia, and the frequency of PN in this group of patients.

Materials and Methods

Thirty patients (M:20, F:10) with COPD who were followed or hospitalized in two centres were included in the study. Patients with conditions such as diabetes mellitus, anemia, chronic renal failure, peripheral circulation disorder, neoplasm, neurotic drug abuse, alcoholism, severe malnutrition and liver problems, which may all lead to PN were excluded. All cases were evaluated in terms of symptoms, physical examination, radiological findings, hemograms, biochemical tests, arterial blood gas levels and respiratory function tests (RFT). RFT could not be performed in one case due to the patient's dysoriented state.

The patients were classified according to their percentage of forced exriratory volume in one secondFEV_1% values (Group 1: mild - $FEV_1 \geq 50\%$, Group 2: moderate - $FEV_1 = 35\text{-}49\%$, and Group 3: severe - $FEV_1 < 35\%$) (3) ; according to their arterial blood gas values (Group 1: those without respiratory insufficiency - $PaO_2 \geq 60$mmHg, and Group 2: those having respiratory insufficiency- $PaO_2 < 60$mmHg); and according to their smoking habits (Group 1: nonsmokers, Group 2: those with a smoking history of 15-59 package year (py), and Group 3: those with a smoking history over 60 py).

All patients examined by a neurologist were asked if they experienced any PN symptoms such as parasthesia or loss of power. Conduction velocity (CV) and amplitude (A) of the median sensorial (MS) and median motor (MM), ulnar sensorial (US) and ulnar motor (UM), sural sensorial (SS) and fibular motor (FM) nerves were unilaterally measured by using a Medelec Saphhine 4 ME electromyography device at a room temperature of 22-24oC. A superficial jet electrode was used for stimulation and recordings. The wrist stimulation antidromic method, applied by placing the superficial electrode on the inner part of the first finger, was used for the assesment of the sensorial fibers of the median nerve. The sensorial fibers of the ulnar nerve were evaluated with "wrist stimulation-five finger" recordings. MM and UM fibers were evaluated by placing superficial electrodes to the distal muscles and wrist stimulation, and also by calculating the percentage difference of latency periods between proximal and distal stimulation in supra maximal stimulation. The CV of the fibular nerves were established by calculating the ratio of the differences between the stimulation level of the nerves at capitulum fibula proximally and at wrist level distally, to the distance. For evaluation of the sural fibers in the lower extremities, the recording electrode was placed on the anterior malleola and the assessment was done antidromically by exercising stimulation of 20MA 10-14cm above malleola. Sensorial conduction value was established by calculating the ratio of the distance of stimulation recording points to obtained latent value. Axion potentials were further measured (μ-mv values). To diagnose neuropathy and the concomitant involvement of more than one nerve, the deviation degrees

Table 1. Conduction velocities and amplitudes of the sensorial nerves (mean and SD)

	MS-CV m/sn	MS-A μv	US-CV m/sn	US-A μv	SS-CV m/sn	SS-A μv
Male (n:20)	46.2±7.3	23.5±10.5	47.4±5.9	19.8±11	43.5±6.3	8.2±4.1
Female (n:10)	42.7±6.8	22±8.9	49.2±6.1	18.5±7.1	43.6±5.4	6.1±3.1
P	0.21	0.7	0.45	0.73	0.98	0.21
Mean values	45.07±7.2	23±9.88	48.03±5.93	19.37±9.81	43.59±5.98	7.59±3.92
Normal values (4)	41-53	10-90	40-61	15-50	40-48	5-30

MS: median sensorial, **US:** ulnar sensorial, **SS:** sural sensorial, **m/sn:** meter/second, **μv:** microvolt

Table 2. Conduction velocities and amplitudes of the motor nerves (mean and SD)

	MS-CV m/sn	MS-A μv	US-CV m/sn	US-A μv	SS-CV m/sn	SS-A μv
Male (n:20)	55.4±4.7	7.2±1.9	58.2±8	7.5±2	48.3±6.7	4.2±1
Female (n:10)	56.2±2.9	7.8±1.9	59.8±7.7	7.7±2.6	45.4±2.8	3.5±1.9
P	0.63	0.47	0.61	0.86	0.11	0.28
Mean values	55.67±4.24	7.43±1.94	58.77±7.85	7.6±2.25	47.31±5.84	3.98±1.43
Normal values (4)	48-58	5-25	49-59	2.3-9.9	40-50	2-15

MM: median motor, **UM:** ulnar motor, **FM:** fibular motor, **m/sn:** meter/second, **μv:** microvolt, **mv:** millivolt

Table 3. Correlations and p values for conduction velocities (CV) and amplitudes (A) of the nerves in groups formed by age, smoking history, $Pa0_2$ and FEV_1%

		MS-CV	MS-A	US-CV	US-A	SS-CV	SS-A	MM-CV	MM-A	UM-CV	UM-A	FM-CV	FM-A
Age	(p)	0.53	0.82	0.46	0.84	0.47	0.22	**0.025**	0.55	**0.019**	0.27	0.31	0.09
	(r)	-0.118	-0.82	-0.138	0.037	0.144	-0.242	**-0.409**	0.113	**-0.426**	-0.205	-0.194	-0.313
Smoking	(p)	0.58	0.85	0.56	0.91	**0.047**	0.69	0.5	0.36	0.37	0.93	0.21	0.31
	(r)	0.126	-0.042	0.133	-0.024	**-0.462**	-0.097	-0.155	-0.209	-0.206	0.019	0.293	-0.238
Pa02	(p)	0.12	0.46	0.89	0.72	0.19	0.82	0.08	0.34	0.1	0.82	0.15	0.3
	(r)	0.288	0.138	0.025	0.333	0.260	-0.044	0.324	0.179	0.306	0.041	0.272	-0.198
FEV1%	(p)	0.96	0.4	0.63	0.98	0.87	0.99	0.51	0.94	0.11	0.61	**0.045**	0.44
	(r)	-0.010	-0.160	-0.092	0.003	-0.034	-0.002	0.126	0.015	0.299	0.098	**0.382**	-0.150

(-) negative correlation, bold figures represent significant correlations

Table 4. Mean values for FEV_1%, PaO_2, smoking history and age in groups formed according to FEV_1%, PaO_2 and smoking history

Groups formed according to FEV_1%	FEV_1%	PaO_2 (mmHg)	Smoking history (py)	Age
1	21.5±8	58.5±13.1	43.7±14.3	58.6±7.7
2	41.2±5.7	69.1±15.2	48±13.5	55.2±13.4
3	55.2±5	65.9±20	62.5±38.8	57.7±8.2
P		0.24	0.34	0.73
Groups formed according to PaO_2				
1	29.4±14.5	51.6±8.2	46±19.8	56.4±9.2
2	33±15.4	77.3±6.6	47.2±12.2	59.6±8.9
P	0.53		0.88	0.34
Groups formed according to smoking history				
1	38.1±17.2	63.1±14	0	55.7±11.1
2	27.3±13.6	63.4±16.6	39.2±9.5	58.8±8.5
3	30.8±12.5	59.9±13.2	70±12.2	58.6±7.8
P	0.25	0.9		0.72

of the lower CV and A values of the nerves, the decrease in both amplitude A and velocity, and some other neurological parameters were assessed in all patients (4).

Th ages, FEV_1% values, PaO_2 values, smoking history and CV and A of the nerves were tested by using Pearson's Movent Product Correlation analysis (direct correlation test). T test was used for the comparison of the male and female patients. A one sided variation analysis (ANOVA) was used in order to establish the presence of any statistically significant difference regarding nerve CV and A, between the patient groups formed according to FEV_1%, PaO_2 and period of smoking. Groups having more than two subgroups were evaluated with the Post Hoc Test (Tukey HSD).

Results

The mean age of the patients was 58.07±9.18 years (range 30-70 years). While 9 patients had never smoked, 16 reported a smoking rate of 15-59 py and 5 a rate of ≥60 py. The mean duration among the smokers was 46.57±16.67 py (range 15-90 py). Mean PaO_2 value was 62.76±14.95 mmHg. and mean FEV_1% value for the 29 patients who underwent RFT was 31.62±16.57. Only two patients questioned for PN complained of paresthesia. These two patients reported a diminution in their deep tendon reflexes. Conduction velocities and amplitudes of the sensorial and motor nerves are shown in Tables 1 and 2.

With the SPSS (10.0 for windows) package program; significantly negative correlations were found between SS-CV and smoking, between MM-CV and age and between UM-CV and age. FM-CV showed a significantly positive correlation with FEV_1%. (Table-3).

A one-way analysis of variance (ANOVA) in patients classified according to FEV_1%, showed no statistically significant differences in age variation (p=0.73), mean py of smoking (p=0.34) and PaO_2 values (p=0.24) among the three groups (Table-4). Also, there was no difference (p>0.05) for PaO_2, age and py between FEV_1% subgroups (1,2,3) and py subgroups (1,2,3) in Post Hoc Test (Tukey HSD).

ANOVA of groups formed according to their smoking period showed no statistically significant difference among age, FEV_1% and PaO_2 values for three groups (p=0.72,

Table 5. Mean conduction velocity and amplitude values of motor and sensorial nerves in groups formed according to FEV_1%, PaO_2 and smoking history

Groups formed according to FEV_1%	MM-CV	MM-A	UM-CV	UM-A	FM-CV	FM-A	MS-CV	MS-A	US-CV	US-A	SS-CV	SS-A
1	54.9±2.9	7.3±2.1	57.3±6	7.6±2.3	45.4 ±3.5	4±1.3	44.2±8	23.2±10.9	48±6.5	18±9	44.3±5	7.5±4.1
2	56.8±5.5	7.2±1.7	59.2±7.3	7.8±2.4	50.5 ±7.6	4±1.7	45.5±4.6	22.4±7	49.4±5.2	21.5±12.7	41.8±6.8	7.8±4.8
3	57.2±7.3	8±2.3	63.7±15.2	7.5±1.9	51.6 ±9.2	3.6±1.5	47.2±9	23.2±12.8	45.2±5.1	18.7±8.5	43±9.8	8±2.4
P	0.47	0.82	0.35	0.96	**0.04**	0.9	0.74	0.98	0.55	0.72	0.7	0.97
Groups formed according to PaO_2												
1	56.5±5	7.5±1.9	59.7±8.7	7.6±1.9	48.5±7.1	3.5±1.5	46.7±7.4	24.4±8.7	47.8±5.7	21.4±9.4	44.3±5.6	7.9±4.1
2	54.5±2.5	7±2.2	57.5±6.6	7.5±2.6	45.5±2.6	4.3±1.6	42.9±6.6	21±11.2	48.3±6.3	16.6±9.9	42.4±6.4	7.6±3.5
P	0.17	0.5	0.46	0.9	0.13	0.15	0.16	0.36	0.15	0.18	0.42	0.84
Groups formed according to smoking History												
1	56.4±3.1	7.7±2.1	60.5±5.6	7.5±2.1	46.8±5	2.9±1.9	43.5±5.7	23.3±8.6	49.5±5.2	20.3±6.5	44.7±5.2	6.5±2.9
2	55.5±5	7.1±2.1	58.6±9.1	7.4±2.5	46.8±6.5	4.3±1.4	44.5±8.4	22.7±10.9	46.8±6.6	18.6±11.9	44.2±6.2	8.3±3.9
3	54.8±3.4	7.4±1.6	55.8±7.1	8.2±1.4	50.2±4.7	4± 0	49.4±3.9	23.2±10.3	49.2±4.2	20±8.6	39.8±5.9	8.4±4.8
P	0.77	0.7	0.57	0.81	0.57	0.24	0.33	0.99	0.49	0.91	0.29	0.64

p=0.25, p=0.9). No statistically significant difference was shown for age, smoking period, and FEV_1% values between groups formed according to PaO_2 values in Student's *t* test. (p=0.34, p=0.88, p=0.53). In groups formed according to FEV_1%; FM-CV was found to be lower in group-1 than group-2 and group-3 (p:0.04) (Table-5).

Neurological assessments revealed that 4 patients had lower and upper sensorial and motor neuropathy, 5 patients had both upper and lower sensorial neuropathy, 1 patient had only upper sensorial neuropathy, 1 patient had only upper sensorial and motor neuropathy and 1 patient had only lower sensorial neuropathy. Out of 30 patients, 9 (30%) had upper and lower, 2 (6.66 %) had only upper, 1 (3.33%) had only neuropathy in the lower extremities. Thus, a total of 12 out of 30 patients had neuropathy (40%) and 10 of these 12 patients had polyneuropathy. Six patients had MS (20%), 2 had MM (6.66%), 8 had US (26.6%), 1 had UM (3.33%), 10 had SS (33.3%) and 3 had FM nerve (10%) involvement.

PN typing was done only electrophysiologically. Of the 30 patients there were 4 with demyelinising MS (13.3%), 1 with MS axional (3.33%), 1 with MS mixed (3.33%), 6 with US axional (20%), 2 with US mixed (6.66%), 4 with SS demyelising (13.3%), 1 with SS axional (3.33%), 5 with SS mixed (16.6%), 2 with MM axional (6.66%), 1 with UM demyelinising (3.33%), 1 with FM demyelising (3.33%), 1 with FM axional (3.33%), and 1 with FM mixed type neuropathy. While 12 patients with neuropathy had sensorial nerve involvement, 5 cases experienced motor nerve involvement. In summary; 12 out of the 30 patients with COPD had pathological values pertaining to their sensorial (40%) and 5 (16.6 %) to their motor nerve CV and/or A. While 2 of these patients had a history and clinical findings of PN, EMG findings were positive for PN in 10 of 28 patients with no clinical signs of neuropathy.

Discussion

COPD patients for PN, may have additional risk factors such as state of an accompanying disease, history of multiple drug use, very old age,and smoking. Smoking and malnutrition have been listed as factors leading to neuropathy in patients with COPD, but hypoxemia ranks first (2). The incidence of neuropathy in cases with COPD varies between 7-88% by clinical assessment, but 58-95% when based on electrophysiological abnormalities (5-10). PN encountered in respiratory insufficiency related to COPD is basically characterised with axonal degeneration, secondary demyelination and abnormal endoneural vessels. PN is reported to occur mostly in the lower extremities (5-7,11,12).

Appenzeller, et al. (13) reported loss of myelin and wallarian degeneration in some fibers in the muscle and sural nerve biopsies of patients having electromyographic and clinical evidence of PN. Since improvement in

peripheral nerve function has been noted in some patients following treatment of the pulmonary disease or malnutrition, neuropathy in COPD could be due to metabolic abnormalities in Schwann cells or to malnutrition. We identified clinical or subclinical neuropathy in 12 of our 30 patients (40%) although none of the patients had cachexia and malnutrition. This ratio is much lower than that reported by Appenzeller, et al. and we believe that the absence of any drug effects or concomitant pathology in our COPD patients with PN may account for this difference.

Smoking is also a risk factor for peripheral nerve pathology. A higher frequency of neuropathy has been reported in ≥60 py smokers. A high carboxyhemoglobin level is a frequent finding in smokers and this has been shown to cause slowing in nerve conduction (2,5,6,11). PN is also reported to have a relation with age in patients with COPD. PN incidence correlates with age while PN severity correlates with hypoxemia. Almitrine bimesilate, a drug used in the treatment of respiratory insufficiency and chronic cerebrovascular insufficiency has an effect as a peripheral chemoreceptor agonist and increases minute ventilation rate by. stimulating afferent carotid body nerves. The most important side effect of this drug is the development of a reversible PN (8,12,14-16).

In our study, PN was shown to involve 6 peripheral nerves in COPD patients.The SS and US nerves were found to be the most commonly involved. While the SS nerve CV was significantly correlated with smoking duration, its amplitude showed no correlation with age, smoking duration, and respiratory functions. No significant correlations were found between the US nerve CV or its A and age, duration of smoking or PaO_2. While the US nerve was the second mostly affected nerve after SS in our study, this finding is not in line with the findings of another study (5).

Faden, et al. (11) assessed the motor functions of median, ulnar and peroneal nerves as well as the sensorial functions of median, radial and sural nerves in 23 patients with COPD. In this study the peroneal nerve was found as the most affected motor nerve, but at the same time, a slowing down in both motor and sensorial conduction was reported in 87% of the cases. Smoking was found to be clearly correlated with electrophysiological abnormalities and this correlation was most significant in those who had smoked over 60 py and sural nerve dysfunction showed the highest correlation. While no correlation was found between nerve conduction and respiratory function, the authors concluded that subclinical neuropathy in these patients was closely correlated with smoking. In our study, we found 80% sensorial nerve involvement and obtained results similar to those reported by Faden, et al. The SS and US nerve involvement observed in our patients was an additional finding which was in terms with the above study. But we could not identify neuropathic differences between upper and lower extremities as reported by Faden, et al. While the FM nerve was the most frequently affected motor nerve, the slowing down CV of this nerve was not correlated with smoking habits. Correlations between MM-CV and MM-A and UM nerve conduction were also not statistically significant among the groups classified by their smoking habits. On the other hand, we found a significant relation between SS-CV and smoking period ($p=0.047$). In groups classified according to their respiratory functions and hypoxemia levels, a statistically significant correlation was found only between FM-CV and respiratory functions ($p=0.04$).

EMG studies have revealed a high ratio of abnormalities in COPD patients (17). Moore, et al. (18) studied MS-CV, axional potential A and peroneal motor CV in 43 patients with COPD and reported at least one abnormal electrophysiological finding in 58% of the patients. Only one abnormality was present in 34.8% of the patients. Of the patients 20.9% had two and 2.32% had three nerve abnormalities. These same authors have identified 7% clinical and 58% subclinical neuropathy cases in their study. Our results show some differences from those of Moore, et al. We identified 6.6% clinic, 33% subclinic neuropathy in our COPD patients. Of these patients, 83.3% had polyneuropathy and 16.6% mononeuropathy.

Paramelle, et al. (8) reported abnormalities in at least two nerves in 74% of their 43 patients with COPD and severe respiratory insufficiency. No risk factors were identified in these patients. In this study, an association between long term hypoxemia and nerve involvement was found. On the other hand, no correlation existed between age, alcoholism, RFT values and peripheric nerve system lesions. In our study, EMG findings in 10 nerves were consistent with demyelination, while findings in 11 nerves showed axonal dysfunction and mixed type electrophysiological findings were present in 9. No differences existed between frequencies of upper and lower extremity involvement (present in 11 and 10 patients respectively). In accordance with Paramelle's study, sensorial nerve involvement was 40%, while the frequency of motor nerve involvement was 16.6%. We did not observe any decrease in nerve CV and/or A which could indicate any significant correlation with hypoxemia.

Brambilla, et al. (9) reported electrophysiological findings of PN in 50 (60%) of 83 patients with COPD. Neuromuscular biopsy findings showed a correlation of PN incidence with age. However, there was no correlation between age and severity of PN. In our study, we established a correlation between severity of PN and hypoxemia and also with smoking habits. On the other hand, no correlations were found between PN incidence and RFT, alcohol intake, weight/height ratio and drug usage. EMG findings consistent

with demyelination and axonal nerve lesions were found in all cases. Brambilla, et al. conclude that PN is frequent in COPD, that the majority of PN cases are subclinical and cite hypoxemia as the pathogenic factor. Our findings also indicate that PN in COPD is not rare. The differences in frequency reported in different studies indicate the need for further studies and the need for exclusion of patients with secondary neuropathy in these studies in order to obtain more accurate data.

In another study (6), frequency of motor deficit was reported in only 12 of the 151 COPD patients having neuropathy. In this multicenter study, PN prevalence was also found to be low as compared to previous reports. It was suggested that the differences among the results of studies could be due to differences in the diagnostic criteria for PN as well as differences pertaining to selection of patients into the study, such as inclusion/exclusion of patients with risk factors for PN other than COPD. In this present study, PN prevalence showed a clear correlation with age and hypoxemia level. Increase in both parameters led to an increase in the frequency of PN. Our study also showed that the frequency of subclinical neuropathy was fivefold as compared to symptomatic PN.

In a research carried out by Demir, et al. (19) on 126 COPD cases, a significant slowing down in CV was noted in the MS, US and SS nerves compared to the controls while the mean CV values for the peroneal and MM nerves were comparable to those of the control group. The results obtained in our study agree with those reported by Demir in that the SS and MS nerves were the most frequently affected nerves in both studies.

While reversible PN due to administration of almitrine has been reported by several researchers (14,16, 20-23), this is not a universal finding, as indicated by Allen, et al (15). There were also no patients using almitrine in our study group.

In conclusion, our study has shown that demyelinisation, axonal or mixed type PN can be encountered in patients with COPD and that subclinical neuropathy occurs at a higher frequency than symptomatic neuropathy in these cases. The study also showed that the involvement of the upper and lower extremities occurs at about the same rate in these patients, that sensorial nerves are affected more frequently and that the FM nerve was the mostly affected motor nerve. We think that age, smoking, respiratory functions and hypoxemia together or alone are effective factors in the development of PN and almitrine may have an additional role as a risk factor.

References

1. Rennard SI, Daughton DM. Cigarette smoking and disease. In: Fishman AP, ed. Fishman's Pulmonary Diseases and Disorders. 3rd ed. New York. Mc Graw Hill; 1998, 8 (45), p. 697-708.
2. Sipahioğlu B, Kızıltan M, Hacıhekimoğlu A, et al. COPD and neuropathy. Solunum 1995; 19: 960-6.
3. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995; 152: 77-83.
4. De Lisa JA, Mackenzie K, Baran EM. Manual of nerve conduction velocity and somatosensory evoked potentials. 2nd ed. New York: Raven Press; 1982, pp 47-51, 54-7, 71-5, 83-6, 137-40.
5. Narayan M, Ferranti R. Nerve conduction impairment in patients with respiratory insufficiency and severe chronic hypoxemia. Arch Phys Med Rehabil 1978; 59: 188-92.
6. Nowak D, Brüch M, Arnaud F, et al. Peripheral neuropathies in patients with chronic obstructive pulmonary disease: a multicenter prevalence study. Lung 1990; 168: 43-51.
7. Jarrat JA, Morgan CN, Twomey JA, et al. Neuropathy in chronic obstructive pulmonary disease: a multicenter electrophysiological and clinical study. Eur Respir J 1992; 5: 517-24.
8. Paramelle B, Vila A, Pollak P, et al. Frequence des polyneuropathies dans les bronchopneumopathies chroniques obsturictives. Presse Med 1986; 15:563-67.
9. Brambilla C, Paramelle B, Vila A, et al. Peripheral neuropathies and chronic obstructive pulmonary disease. Electrophysiological and histopathological study. Am Rev Respir Dis 1986; 133: A-62.
10. Kayabıyıkoğlu G. The changes of pulmonary functions because of smoking in healthy and COPD patients. Solunum Hastalıkları 1994; 5(3): 439-51.
11. Faden A, Mendeza E, Flynn F. Subclinical neuropathy associated with chronic obstructive pulmonary disease, possible pathophysiologic role of smoking. Arch Neurol 1981; 38: 639-42.
12. Stoebner P, Mezin P, Vila A, et al. Microangiopahy of endoneurial vessels in hypoxemic chronic obstructive pulmonary disease. Acta Neuropathologica 1989; 78: 388-95.
13. Appenzeller O, Parks RD, McGee J. Peripheral neuropathy in chronic disease of the respiratory tract. Am J Med 1968; 11: 873-80.
14. Howard P. Hypoxia, almitrine and peripheral neuropathy. Thorax 1989; 44: 247-50.
15. Allen M, Prowse K. Peripheral neuropathy during treatment with almitrine. Br Med J 1985; 290: 1288.
16. Stoebner P, Grosse R, Mezin P, et al. Abnormalities of endoneurial vessels in chronic obstructive lung disease. Pathol Res Pract 1987; 182: 561-2.
17. Valli G, Barbıeri S, Sergi P, et al. Evidence of motor neuron involvement in chronic respiratory insufficiency. J Neurol, Neurosurg and Psych 1984; 47: 1117-21.
18. Moore M, Lerebours G, Senant J, et al. Peripheral neuropathy in chronic obstructive lung disease. Lancet 1985; 2: 1311.
19. Demir O, Zamani A, Gödenelli B: Peripheral neuropathy in chronic obstructive pulmonary disease. J Ankara Med Sch 1996;18(2):79-81.
20. Gherardi R, Lovarn F, Benvenuti C, et al. Peripheral neuropathy in patients treated with almitrine dimesilate. Lancet 1985; I: 1247-50.
21. Suggett AJ, Jarrat JA, Proctor A, et al. Almitrine and peripheral neuropathy. Lancet 1985; ii: 830-1.
22. Alani SM,Twomey JA, Peake MD: Almitrine and peripheral neuropathy. Lancet 1985; ii: 1251
23. Allen MB, Prowse K: Peripheral nerve function in patients with chronic bronchitis receving almitrine or placebo. Thorax 1989;44: 292-7.