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Research Article

Acute and Chronic Effects of Smoking on the Peripheral Nervous System

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Abstract

Objectives: The symptoms of the predominantly sensory neuropathy related to smoking are similar to those observed in toxic states. The acute and chronic effects of cigarette smoking on the peripheral nervous system are different. We aimed to evaluate the axonal exitability properties of the two different states.

Methods: We investigated the axonal excitability of 16 cases with chronic obstructive pulmonary disease and a history of smoking cigarettes. These cases were divided into two groups according to polyneuropathy presence. Six of them had sensory polyneuropathy. Seventeen healthy cases who were smokers were examined by threshold tracking before and after smoking.

Results: The relative refractory period and superexcitability parameters had statistically significant differences in chronic obstructive pulmonary disease cases. Hyperpolarization related threshold electrotonus and superexcitability values were significantly different after smoking in the acute stage.

Discussion: Sensory polyneuropathy and axonal depolarization are the prominent findings in the chronic stages. However, the acute effects of smoking on axonal excitability might be related to the blocking of inward rectifying channels by the metal Caesium.

Keywords: Cigarette smoking; Chronic obstructive pulmonary disease; Axonal excitability; Polyneuropathy; Caesium-like toxic effect

Introduction

Smoking related diseases are major public health issues [1]. Smoking is the most important and prominent risk factor for Chronic Obstructive Pulmonary Disease (COPD). Few studies mention the comorbidity of polyneuropathy in COPD [2]. The findings of these studies mainly point to axonal polyneuropathy with sensory fibre involvement and an incidence of 16-20% [3]. In COPD patients, primarily sensory neuropathy was detected and a link was shown between the consumption of cigarettes and the findings of polyneuropathy [4-7]. There are also studies that mention the correlation between hypercapnia and hypoxemia and the severity of COPD [4]. However, in the literature, there are no studies showing either the direct or the acute effects on the peripheral nervous system, even though cigarette smoke can be expected to have a direct toxic effect with chronic polyneuropathic consequences. The well-known effects of smoking are hypoxia and hypercapnia [2]. Hypercapnia is one of the major factors that change the blood pH. A shift in blood pH to acidosis modifies the excitability properties of the peripheral nerve, as with ischemia, and has the potential to disturb the functions of the nerve [8]. In addition, some alterations in the axon and myelin structures of the peripheral nerve can be expected due to the consequences of smoking on the vasa nervorum and vasa vasorum in the vascular bed [9]. However, smoking related predominantly sensory neuropathy mostly resembles a toxic situation. In this situation it can be considered that some of the substances in smoke have a directly axonotoxic effect on nerve tissue. Axonal excitability studies have been used effectively in recent years to evaluate alterations in peripheral nerves and the mechanisms of action of these processes [10-12]. Detailed information about the involvement of peripheral nerves in diabetic polyneuropathy, in demyelinating diseases and in chronic renal failure has been obtained [13,14]. It is expected that the chemical substances in smoke have an effect on peripheral nerve excitability. We predict that in addition to the toxic substance effects of smoking, the alterations in blood pH could lead to peripheral nerve damage and variances in axonal excitability similar to an ischeamic situation. For this purpose, we investigated the variances of axonal excitability parameters in COPD patients and alterations in COPD polyneuropathy.

Methods

Study

This study was designed as a prospective cohort study and approved by the local Ethics Committee.

Patients

For investigating the chronic effects of smoking, COPD patients from the Pulmonary Diseases Unit who were smokers were included in the study. The patients were evaluated in two groups. One of the groups consisted of the patients with polyneuropathy according to electrophysiological findings. The other group of patients did not

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have polyneuropathy. The pulmonary function test (PFT) value of FEV_1 was <50% in all of the COPD patients with polyneuropathy and all the patients were over 40 years of age. COPD patients without polyneuropathy had the same PFT values and age distribution. None of the patients in the former group had any comorbidity to cause polyneuropathy, the conditon was diagnosed electrophysiologically in every case. Sixteen (3 female, 13 male) COPD patients of the Pulmonary Diseases Unit in 2015 were included in the study. The mean duration of the disease was 59 ± 47 months. The patients had a history of 38 ± 16 pack/year smoking. In our cases, five were smokers whilst the others had quit smoking 4.5 ± 4 years previously. The 17 healthy smokers included in the study investigating the acute effects of smoking had a mean age of 42 ± 3 years. Axonal excitability studies were performed on this group after a 12 hour cigarette free period. The control cases were 10 healthy non-smokers who were over 40 years of age and had never smoked.

Assessment of respiratory functions and COPD diagnosis

In newly diagnosed patients; COPD diagnosis is based on the presence of risk factors, chronic coughing, progressive shortness of breath and productive sputum. In PFT, the value of $FEV_1/FVC<70\%$ after bronchodilator therapy significantly confirmed the diagnosis. Pulmonary function tests were measured with a spirometer. The spirometer was manually calibrated once a day. The respiratory function test was performed with the spirometer 3 times and the best value was recorded. The disease severity was evaluated according to the FEV value during PFT after bronchodilator therapy. In the patients already diagnosed with COPD, previous records were evaluated and the same values were checked. All of the patients were diagnosed as COPD according to GOLD 2014 diagnosis criteria (The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (https://goldcopd.org.) [15]. The evaluation of symptoms (according to the modified Medical Research Council (mMRC) scale) and combined assessment of attacks in the last year, the ABCD staging, were carried out according to the GOLD Guidelines for COPD Staging. Patients with few symptoms (mMRC score of 0-1) and a low number of attacks (0 in the last year or 1 attack requiring no hospitalization) were considered as A stage, patients with a higher rate of symptoms (mMRC ≥2) and lower number of attacks (0 or 0 in the last year) were considered as B stage, patients with a history of low-grade symptoms (mMRC score 0-1) with a high number of episodes (at least 1 hospital admission in the last year or at least 2 episodes) were considered as C stage, patients with high symptoms (mMRC ≥2) and those with a high number of episodes (at least 1 hospital admission in the last year or at least 2 episodes) were considered as D stage.

Evaluation of smoking status

Never a smoker: A participant who had never smoked with no history of passive exposure. Smoker: A participant who smoked prior to the diagnosis. Ex-smoker: A participant who had smoked previously but had not smoked or had a history of passive exposure in the 3 month period before the diagnosis.

Evaluation of neurological findings and polyneuropathy

The sensory and motor complaints of the patients medical history were defined. Sensory negative and positive symptoms like pain, paraesthesia, tingling and motor symptoms like muscle weakness and fasciculation were investigated. Nerve conduction studies to investigate polyneuropathy were performed on all patients. Median, peroneal and tibial motor conduction velocities and median and sural sensory conduction velocities were evaluated in the upper and lower extremities. The findings were considered to be compatible with polyneuropathy if areflexia and sensory findings were observed in neurological examination and the involvement of more than two nerves were detected in upper and lower extremities during electrophysiological studies. We evaluated the acute consequences of cigarettes on axonal excitability. The cases were all healthy smokers; they had no complaints and their neurological examinations were normal. In these cases, axonal excitability was evaluated before and after cigarette smoking. We evaluated the cases after a minimum 12-hour cigarette free period (at night) and again immediately after they had smoked a cigarette.

Evaluation of axonal excitability

Our EMG and Axonal excitability laboratory was on the first floor of the hospital. All of the cases being evaluated for the effects on axonal excitability properties after smoking went downstairs and smoked in the garden. They each smoked one cigarette, which they had brought with them. The duration between leaving the laboratory and starting to record was approximately 20 minutes. The electrodes were secured tightly and their position was never altered between recordings. The temperature of the upper limb was measured from the inner surface of the wrist by an electronic probe during the axonal excitability study as a threshold tracking technique. The motor nerve axonal excitability study was performed on the left upper limb. The cathode electrode was placed on the Abductor Pollicis Brevis (APB) muscle and the reference electrode placed 3 cm. Distal to the cathode electrode on the metacarpophalangeal joint. The left median nerve was stimulated at the wrist. The surface disc electrode was placed on the wrist approximately 3 cm. Above and proximal to the wrist line and the anode electrode placed 10 cm. Proximal and lateral out of the nerve trace. Compound Muscle Action Potentials (CMAP) were recorded from the APB muscle with surface electrodes. The QTRAC-S system was used for stimulation and the TROND protocol performed in all cases [16]. In this protocol, a stimulus-response recording is attained first and 40% of the supramaximal response in this curve is used as the target amplitude in threshold monitoring. After attaining the stimulus-response recording, the Strength Duration Time Constant (SDTC) is measured. Then the threshold electrotonus, voltage-current relationship and recovery cycle were recorded respectively. While recording we did not change the places of the electrodes. The temperature of the limb was kept at approximately 32°C during the study. Statistical difference analysis was performed between groups using a packet computer program in the TROND protocol and the values below 0.05 accepted as significant in parametric weighted tests. The Nonparametric Kruskal-Wallis test and Wilcoxon signed test were used in group comparisons and t-tests performed while comparing the blood gases and electrophysiological parameters for unequal variance. The values of pH, pCO_2 and K+ in blood venous gas analysis were analyzed just before axonal excitability studies in the COPD patients and in the smoker control group cases before and after smoking a cigarette.

Results

The COPD diagnosis criteria are covered in detail in the method section. Other systemic diseases such as Diabetes Mellitus (DM) and Chronic Renal Failure (CRF) were excluded. The patients had a history of 38 ± 16 packets of cigarettes per year. In our cases, 5 of them were still smoking and the others had stopped smoking 4.5 ± 4 years previously. In 6 (1 female, 5 male) of the patients with COPD, we

diagnosed Polyneuropathy (PNP) in an EMNG (Table 1). The mean duration of the COPD was 89 ± 32 months in this group. In the group without PNP, 5 of the patients were still smoking. The mean duration of the COPD was 42 ± 47 months in the group without PNP. The mean age for the group with polyneuropathy was 64 ± 3 years, the mean age for the group without PNP was 61 ± 3 years. There was no significant difference in gender distribution between the two groups. In the polyneuropathy group there were no stage A patients. Stage B, C and D patients were equally distributed in both groups. The mean FEV was 37 ± 16.9, the mean FEV_1/FVC was 53.4 ± 8.5 (Table 1). When we evaluated the electrophysiological findings, we could not obtain sural action potentials in 4 of the patients in the PNP group. In all of the patients, disturbances of low amplitude and extended duration were observed in median sensory action potentials. The median motor nerve distal latency was extended in duration in one of the patients and the tibialis CMAP was lower in amplitude in another patient. In one case, a prolongation of tibialis F-wave latency was observed. These findings supported predominantly sensory polyneuropathy. There was a statistically significant difference in the average amplitudes of median nerve sensory action potentials when compared with the group without PNP. Only in tibialis nerve CMAPs, were the motor conduction velocities significantly different, when compared with the group without PNP (p = 0.01; tibialis CMAP was 5.6 mV ± 3.6 mV in the group with PNP and 11.4 mV ± 3.5 mV in the group without PNP). When we considered the median nerve, there were no significant differences in CMAP amplitudes and conduction velocities. The mean values of pH = 7.39 ± 0.04, pCO_2 = 50.74 mmHg ±11.31 mmHg and K = 3.97 mmol/L ± 0.69 mmol/L in blood venous gas analysis just before axonal excitability studies in the COPD patients. There were no statistically significant differences in terms of pH, PCO_2 and K values between the groups with and without PNP (p values were respectively 0.23, 0.53 and 0.43). In the smoker control group cases without COPD the values before cigarette smoking were pH = 7.39 ± 0.03, pCO_2 = 44.89 mmHg ± 7.02 mmHg, K = 4.11 mmol/L ± 0.39 mmol/L. The values after smoking were pH = 7.37 ± 0.03, pCO_2 = 47.76 mmHg ± 5.59 mmHg, K = 4.16 mmol/L ± 0.36 mmol/L. The differences in alterations in pH were statistically significant (p = 0.032), meanwhile for the other blood gas analysis alterations the differences were found to be statistically insignificant. Axonal excitability studies were performed by the threshold tracking technique in 5 cases with PNP and in 9 cases without PNP amongst COPD patients. We excluded one patient in each group due to technical issues. In COPD patients we observed an alteration in supernormality, when compared to the groups with PNP and without PNP. However, this alteration was not statistically significant. When the findings of 10 cases who were never smokers and older than 40 years of age (median age = 58.6 ± 3.6) were compared with the patient group, a decrease in the superexcitability (%) was observed in the patient group (p = 0.003) and also a significant decrease in superexcitability of 5 and 7 miliseconds was observed in the same group (respectively p = 0.004 and p = 0.003) (Table 2) (Figure 1). These differences were evaluated as statistically significant with the Kruskal-Wallis test (non-parametric Anova test). These findings showed that the median nerve displayed a more depolarized state in COPD patients compared with the healthy subjects. At the same time, a more depolarized axonal excitability pattern existed in the patients with PNP in COPD. The history of cigarette smoking was present in all of the COPD patients and it seemed to be a risk factor. It is not ethical to design pre- and post-cigarette smoking studies in COPD patients to evaluate the effects of cigarettes on axonal excitability. For that reason, we designed a pre- and post-smoking recordings study with the cases who applied to the hospital because of their smoking addiction seeking support to stop smoking. 17 cases included in the study had a mean age of 42 ± 3 years with no other complaints. After a period of 12 hours cigarette free, the axonal excitability studies were performed. The electrode places were stationary. Axonal excitability studies were performed just after smoking with each patient smoking the same brand of cigarette that she/he usually smoked. When we compared the recordings before and after smoking, we observed a hyperpolarized fanning-out pattern in threshold electrotonus and an increase in supernormality (Figure 2). The values were supernormality (%) (p = 0.03), Teh (10 ms - 20 ms) (p = 0.005), Teh (20 ms - 40 ms) (p = 0.04), Teh (90 ms - 100 ms) (p = 0.018) and Teh slope (101-140) (p = 0.02). The differences of superexcitability values in 5 miliseconds were found to be statistically significant in the paired t-test (Table 2).

Table 1: General features of patients with COPD.

		PNP (-)	PNP (+)	Total
Smoking (pack/year) (mean±sd)		41±18	34±11	38±16
Duration of COPD (month) (mean±sd)		42±47	89±31	59±47
RFT (mean±sd)	FEV_1	36.6±15.2	38.0±23	37.0±16.9
	FVC	43.4±18.1	55.0±27.5	46.7±20.2
	FEV_1/FVC	53.3±9.3	53.5±7.0	53.4±8.5
Stage (n, %)	A	2 (100%)	-	2 (12.5%)
	B	3 (60%)	2 (40%)	5 (31.1%)
	C	3 (40%)	2 (60%)	5 (31.1%)
	D	2 (50%)	2 (50%)	4 (25.3%)
Gender (n, %)	Woman	2 (66.7%)	1 (33.3%)	3 (17.4%)
	Man	8 (61%)	5 (39%)	13 (82.6%)
Total		10 (62.5%)	6 (37.5%)	16 (100%)

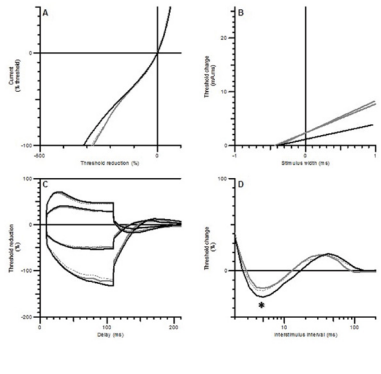

Figure 1: Kruskal-Wallis test.

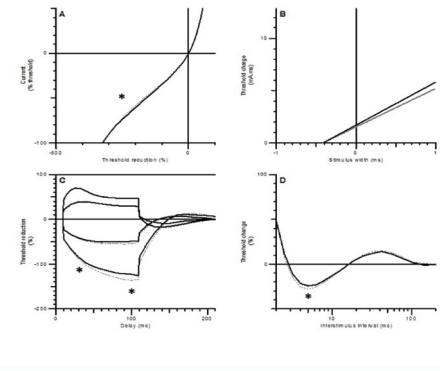

Figure 2: Hyperpolarized fanning-out pattern in threshold electrotonus and an increase in supernormality.

Table 2: Median nerve axonal excitability findings in groups (mean ± sd).

	Normal subjects A	COPD without PNP B	COPD with PNP C	p	Before smoking	After smoking	p
Variable	*Mean ± SE (n=10)*	*Mean ± SE (n=9)*	*Mean ± SE (n=5)*	*Groups (A,B,C)*	*Mean ± SE (n=17)*		*Paired*
Stimulus (mA) for 50% m	4.097 ± 1.14	6.654 ± 1.32	7.065 ± 1.34	0.18	5.598 ± 1.1	5.241 ± 1.08	0.45
Strength-duration\time	0.431 ± 0.019	0.446 ± 0.030	0.486 ± 0.050	0.79	0.420 ± 0.015	0.414 ± 0.012	0.64
Rheobase (mA)	2.603 ± 1.15	4.205 ± 1.34	4.447 ± 1.36	0.18	3.77 ± 1.11	3.49 ± 1.09	0.42
Stimulus-response\slope	3.831 ± 1.15	3.958 ± 1.13	4.352 ± 1.18	0.82	4.555 ± 1.07	4.145 ± 1.08	0.13
Peak response\(mv)	3.046 ± 1.81	2.212 ± 1.39	2.049 ± 1.61	0.23	2.673 ± 1.23	2.612 ± 1.2	0.49
Resting I/V slope	0.525 ± 0.020	0.623 ± 0.062	0.614 ± 0.054	0.22	0.568 ± 0.030	0.562 ± 0.021	0.82
Minimum I/V slope	0.280 ± 0.024	0.270 ± 0.026	0.277 ± 0.029	0.96	0.231 ± 0.005	0.228 ± 0.010	0.70
Temperature (C)	33.17 ± 0.3	32.72 ± 0.302	32.98 ± 0.648	0.57	32.32 ± 0.259	32.44 ± 0.211	0.63
RRP (ms)	2.551 ± 1.03	2.676 ± 1.04	2.777 ± 1.08	0.38	2.838 ± 1.04	2.706 ± 1.02	0.21
TEh (90-100 ms)	-131.8 ± 5.07	-117.8 ± 7.91	-122 ± 11.3	0.43	-124.4 ± 6.08	-135.5 ± 5.62	0.018*
TEd (10-20ms)	69.78 ± 1.26	66.9 ± 2.43	68.33 ± 1.51	0.18	68.65 ± 1.04	69.41 ± 1.09	0.48
Superexcitability (%)	-27.49 ± 1.13	-20.2 ± 2.27	-17.89 ± 1.6	0.003*	-23.68 ± 1.71	-26.47 ± 1.56	0.06
Subexcitability (%)	17.02 ± 1.24	16.16 ± 2.72	17.36 ± 5.49	0.78	13.17 ± 1.77	14.64 ± 2.33	0.35
Age (years)	58.6 ± 3.66	60.67 ± 2.82	63.8 ± 2.69	0.55	42.12 ± 3.4		-
TEd (40-60 ms)	51.92 ± 1.15	47.97 ± 2.42	51.32 ± 1.43	0.07	51.33 ± 1.38	50.39 ± 1.2	0.24
TEd (90-100 ms)	47.34 ± 1.1	45.23 ± 2.46	46.89 ± 1.29	0.48	47.01 ± 1.27	46.07 ± 1.18	0.36
TEh (10-20 ms)	-77.51 ± 1.62	-69.89 ± 4.65	-75.73 ± 3.07	0.16	-75.92 ± 1.56	-79.31 ± 1.63	0.005*
TEd (undershoot)	-16.98 ± 1.84	-18.09 ± 1.7	-14.86 ± 0.902	0.50	-18.12 ± 1.51	-18.87 ± 1.58	0.59
TEh (overshoot)	12.91 ± 1.4	13.93 ± 1.45	12.84 ± 1.33	0.93	14.41 ± 1.68	14.62 ± 1.51	0.83
TEd (peak)	69.12 ± 1.14	65.62 ± 2.41	67.32 ± 1.35	0.14	67.86 ± 1.05	68.53 ± 1.07	0.52
S2 accommodation	21.78 ± 1.47	20.39 ± 1.25	20.43 ± 0.844	0.65	20.85 ± 1.2	22.46 ± 1.29	0.23
Accommodation half-time	38.26 ± 1.18	35.36 ± 1.22	36.96 ± 1.91	0.57	36.93 ± 1.29	37.46 ± 0.857	0.60
Hyperpol. I/V slope	0.391 ± 0.027	0.399 ± 0.025	0.455 ± 0.047	0.52	0.547 ± 0.157	0.391 ± 0.022	0.33
Refractoriness at 2.5 m	2.178 ± 3.35	6.581 ± 4.81	11.71 ± 7.2	0.42	11.82 ± 3.66	7.952 ± 2.65	0.35
TEh (20-40 ms)	-98.07 ± 2.86	-90.15 ± 4.96	-96.62 ± 3.89	0.41	-96.43 ± 2.93	-101.8 ± 2.87	0.016*
TEh (slope 101-140 ms)	2.24 ± 0.087	2.009 ± 0.127	2.183 ± 0.141	0.40	2.131 ± 0.138	2.408 ± 0.101	0.02*
Refractoriness at 2 ms	36.17 ± 5.91	41.21 ± 9.3	36.13 ± 10.2	0.97	47.23 ± 4.6	47.72 ± 5.08	0.90
Superexcitability at 7	-23.28 ± 1.66	-16.08 ± 2.27	-15.16 ± 1.61	0.004*	-20.87 ± 1.43	-22.99 ± 1.67	0.10
Superexcitability at 5	-28.56 ± 1.17	-21.6 ± 2.48	-18.79 ± 1.41	0.003*	-24.38 ± 1.87	-27.94 ± 1.5	0.04*
TEd20 (peak)	40.16 ± 0.93	38.59 ± 1.75	38.11 ± 0.854	0.25	38.8 ± 1.13	40.31 ± 0.941	0.12
TEd40 (Accom)	22.26 ± 1.3	21.39 ± 1	20.84 ± 0.865	0.64	21.44 ± 1.13	22.77 ± 1.28	0.25
TEd20 (10-20 ms)	37.69 ± 0.787	36.06 ± 1.23	35.82 ± 0.983	0.24	36.18 ± 0.94	37.41 ± 1.02	0.20
TEh20 (10-20 ms)	-38.26 ± 0.982	-36.9 ± 1.75	-37.7 ± 2.07	0.92	-37.89 ± 0.861	-39.21 ± 1.06	0.10

Discussion

Axonal polyneuropathy with sensory nerve involvement in COPD is reported as 16-20% in the literature[3-7,17]. In our study, in a one-year period we determined distal and predominantly sensory, sensorimotor polyneuropathy in COPD patients as 37%. The polyneuropathy was prominent in the lower extremities. When we compared the COPD patients with the polyneuropathy group to the controls and the COPD patients without the polyneuropathy group, we found that the axonal excitability parameters in the peripheral nerves have a depolarizing pattern in the polyneuropathy group (Figure 1). Kiernan M showed a depolarizing pattern in uremic, mitochondrial and diabetic neuropathies [16,18-20]. We thought that chronic PNP might occur later in the advancing period of COPD. There was no significant difference between the groups with and without PNP in terms of the average age of the patients. This led us to think that personal predispositions and toxic effects might play a role in these findings. The effects of smoking on the peripheral nervous system are unknown and have hardly ever been evaluated in the literature. It is also unclear whether or not the acute effects are equivalent to the chronic effects. Pre-smoking and post-smoking pH alterations indicate the presence of an acidosis tendency after smoking. pH alterations have the potential to cause kinetic changes on axonal channels. It is well known that persistent sodium (Na) channels are particularly sensitive to pH alterations [21,22]. Contrary to the effect observed in hyperventilation, the tendency to acidosis in pH could affect nodal Na channels. We would expect significant Strength Duration Time Constant (SDTC) changes in this situation. However, SDTC change differences before and after cigarette smoking were not statistically significant. The most important differences observed in the axonal excitability parameters were during hyperpolarizing current activation (Figure 2). Influence in this area can only be explained by the modulation of IR channels. Quin Y and colleagues have shown that in the axonal excitability studies regarding diabetic polyneuropathy, the threshold electrotonus might be due to the modulation of Caesium-blocked IR channels by outward opening in hyperpolarization [23]. In our study, similar outward opening after cigarette smoking was observed. We consider the Caesium-like effect might explain the increase in superexcitability that we observed in our study. Superexcitability demonstrated an increase due to Caesium-induced hyperpolarization in axonal excitability studies [24]. There are approximately 4000 substances in cigarette smoke and some of them are non-metallic elements. Caesium is one of them and is known to be 1.27% in cigarette smoke [25,26]. We did not study the

sensorial axonal excitability properties of patients and this is one of the limitations of our study. Obvious sensorial neuropathy in COPD patients has been described in the literature. To understand the electrophysiological characteristics of such sensorial neuropathy, it would need to be measured in further studies. However, the results in our study show a depolarizing pattern in the motor fibers of the median nerve. Additionally, it is important to evaluate the lower extremity motor nerves such as the tibial nerve with which it is possible to study axonal excitability. Another limitation of our study is that we did not measure the Cs+ levels or their bioavailability. We did not anticipate this result and this is why it was not a part of our study. We need further studies to evaluate the relationship between the Cs+ effect and axonal excitability properties. The number of our cases was the most important limitation of our study. As a result, it can be postulated that in smoking related polyneuropathy in COPD patients, a depolarizing pattern was observed in the peripheral nerves. This effect may be due to the toxic effects of non-metallic elements or other substances like Caesium in cigarette smoke. Further studies are needed to investigate the effects of Caesium and non-metallic substances on COPD with PNP.

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