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Chronic Hypoxemia Triggers a Neuropathic Process in Chronic Obstructive Pulmonary Disease: Insight From In Vivo Neurophysiological Assessments

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Background and Purpose Peripheral neuropathies (PNs) are a common but poorly understood complication of chronic obstructive pulmonary disease (COPD). To clarify the initial trigger of a PN in COPD, we investigated the excitability of peripheral nerves in patients with COPD.

Methods The automated nerve excitability test (NET) using the threshold-tracking paradigm was applied to 20 COPD patients. The recording protocol calculated the strength–duration time constant, threshold electrotonus (TE), current–threshold relationship, and recovery cycle (RC). Each NET parameter was compared with two control groups: normal controls group (NC group) and smokers without COPD group (smoker group).

Results In the motor NETs, the change in the threshold in the mid-depolarizing phase of TE (40–60 ms) was smaller in the COPD group (50.7%±1.2%, mean±SEM; n=20) than in the NC group (54.5%±0.7%, n=25; p<0.01), as was the prominence of superexcitability in the RC (-22.6%±1.5% and -26.4%±1.1%, respectively; p=0.04). There were no significant differences in the sensory NETs. Comparisons between the COPD and smoker groups (n=25) also showed no differences in either the motor or sensory NETs.

Conclusions The pattern of excitability in COPD revealed a membrane depolarization attributable to Na^+–K^+–ATPase failure in the axolemma of distal motor nerves. This finding suggests that chronic hypoxemia and adaptative process can alter axonal excitability and trigger a resultant neuropathic process that is antecedent to PN in COPD.

Keywords peripheral nervous system diseases; pulmonary disease, chronic obstructive; hypoxemia; nerve excitability; threshold tracking.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and the lung to noxious particles or gases.[1] Since the first report on the relationship between COPD and peripheral neuropathy (PN),[2] a wide incidence range and various types of PNs have been reported by numerous researchers.[3-11]

Hypoxemia in COPD patients has been considered as the main effect on the peripheral nervous system, while it also affects many other organs. Hypoxemia probably affects the peripheral nerve either by directly acting on nerve fibers or by enhancing the effects of neurotoxic factors.[4] However, the detailed mechanisms acting either systemically (i.e., chronic hypoxemia) or neurophysiologically (i.e., neurotoxically) remain largely unknown.

The recently developed nerve excitability test (NET) using the threshold-tracking technique

can provide insight into the ionic mechanisms underlying the pathophysiology of axonal dysfunction in PN and motor neuron disease.[12-14] Analyses of various parameters and patterns obtained in the NET can reveal the biophysics of ionic conductance in the tested nerves.[15,16] Most of all, this technique has contributed to improving the understanding of the neuropathic process in the early stage of PNs.[17-19]

This study aimed to identify alterations in the excitability of both sensory and motor peripheral nerves in patients with stable COPD utilizing automated NETs, with the intention of clarifying the initial triggering mechanism of PN in COPD.

METHODS

Subjects

We consecutively collected both clinical information and electrophysiological data of COPD patients from September 2020 to February 2022 at Kangdong Sacred Heart Hospital. During this period, two pulmonologists diagnosed COPD by applying the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline:[20] age ≥40 years, presence of airflow limitation that was not fully reversible (quantified as post-bronchodilator forced expiratory volume in 1 second [FEV1]/forced vital capacity [FVC] <70%], smoking history >10 pack-years, and presence of a respiratory symptom such as cough, sputum production, or dyspnea. We excluded any type of PN or other systemic diseases that can affect the peripheral nervous system by performing a detailed review of the results of relevant imaging studies and laboratory testing.

We initially enrolled 25 patients with COPD, 25 normal controls with no history of smoking (NCs), and 25 healthy individuals with a smoking history of more than 20 pack-years (smoker group). We included only patients with GOLD grade 1 or 2 and for whom complete information was available on age, sex, BMI, and smoking status (including pack-years), and recently obtained (within 3 months before NETs) complete information was available on FEV1, FVC, modified Medical Research Council (mMRC) dyspnea score, and COPD assessment test (CAT) score.

We focused on the pure effect of COPD on the peripheral nervous system by completely excluding pre-existing PN. The neurological symptom score (NSS) and neurological disability score (NDS)[21] were used for clinical screening, and cases with either of these scores higher than 2 points were excluded from the final enrollment. Any abnormal findings in a conventional nerve conduction study (NCS) were considered as PN or objective neuropathic changes regardless of the presence of symptoms.

Conventional electrodiagnosis

A conventional NCS was performed in a quiet room by an experienced technician applying standard methods with supramaximal stimulation and surface recording, with the patient in a supine position. The details of the technique and tested nerves are available elsewhere.[22]

Measurement of axonal excitability using the automated NET

The automated NET was implemented using the QTRACW threshold-tracking software (Institute of Neurology, University College London, London, UK) with the TRONDF multiple-excitability recording protocol.[12,14] Motor axons were evaluated by recording compound muscle action potentials (CMAPs) from each muscle after stimulating the median nerve at the wrist (3 cm proximal to the wrist crease).[13] Sensory nerve action potentials (SNAPs) in sensory axons were recorded in an antidromic manner from the index finger after stimulation at the same site as for the motor stimulation.[23] Full details of the technique are available elsewhere.[13,23,24]

The protocol was used to produce stimulus–response curves for stimulus durations of 0.2 ms and 1.0 ms. The strength–duration time constant (SDTC) was determined by applying Weiss' formula to the plots of threshold charge against the stimulation duration, with the SDTC given by the negative intercept on the duration axis.[25,26]

The current required to produce a CMAP whose amplitude was 40% of the maximum was tracked. In the threshold electrotonus (TE) studies, the membrane potential was altered using subthreshold polarizing direct currents that were 40% of the unconditioned threshold. Depolarizing and hyperpolarizing currents lasting 100 ms were applied, and their effects on the threshold current for the test CMAP were examined. In a further test involving subthreshold conditioning currents, the test stimulus was delivered at the end of a polarizing current pulse lasting 200 ms. The intensity of the current pulse was changed systematically from 50% depolarizing to 100% hyperpolarizing in steps of 10% so as to yield a current–threshold relationship, which is analogous to a conventional current–voltage relationship. The recovery cycle (RC) of axonal excitability after a single supramaximal stimulus was measured by delivering the test stimulus at different intervals (from 2 ms to 200 ms) after the conditioning stimulus. Each parameter from the NET was assessed using graphs and raw data.

Standard protocol approvals, registrations, and patient consents

This study was approved by the ethics committees of Kangdong Sacred Heart Hospital (IRB file no. 2019-09-003). All enrolled patients gave written informed consent before being

included in the study.

Statistical analysis

Statistical analysis was performed between groups using a packet computer program in the TRONDF protocol and SPSS program (version 25.0 for Windows, IBM Corp., Armonk, NY, USA). The data are presented as mean±SD or mean±SEM values. *t*-test or Mann-Whitney U test, depending on normality (assessed using the Lilliefors test or Shapiro-Wilk test), were used to compare demographic and clinical information or NET parameters for each group. Spearman's correlation coefficients were used to examine the relationship between parameters. The criterion for statistical significance was set at $p<0.05$.

RESULTS

Demographic and clinical information of the study groups

The 20 COPD patients included in the final analysis had a mean age of 73 years (range: 59–84 years) and were all male. Five of the 25 initially enrolled patients were excluded because of newly diagnosed diabetes mellitus ($n=2$), subclinical carpal tunnel syndrome ($n=2$), and technical factors ($n=1$). Demographic features, pulmonary functions obtained within 3 months from the time of the NET, NSS, and NDS are summarized in Table 1. Four of the 20 patients with COPD complained only of mild distal paresthesia in their feet, and none of the enrolled COPD patients were compatible with PN based on the NSS or NDS.

As the control, we extracted two sets of healthy controls from previous NET data sets of the neurophysiology laboratory at Kangdong Sacred Heart Hospital.[24] Those in the NC group, 71.2±4.3 years of age, were all males with neither a previous history of smoking nor systemic diseases complicating PNs. None of those in the other control group (the smoker group), 67.9±5.1 years of age, who were also all males, had a previous history of COPD or other possible etiologies of PNs. Mean amount of smoking in the smoker group was 29.9±12.5 pack-years. There were no statistically significant differences of age among NC, smoker, and COPD groups ($p>0.05$). There was also no statistically significant differences of the amount of smoking between the smoker and COPD groups ($p>0.05$).

Findings of conventional electrodiagnosis

The CMAP amplitudes in the NCS of the distal median nerve were 7.9±2.0, 8.1±2.2, and 8.4±2.0 mV in the COPD, smoker, and NC groups, respectively; the corresponding distal SNAP amplitudes recorded orthodromically at the wrist were 16.4±4.6, 18.5±4.8, and 17.9±5.1 μV. Neither the CMAP nor the SNAP differed significantly among the three groups ($p>0.05$).

Table 1. Demographic and clinical information of the patients with COPD

Parameter	Value
Number of cases	20
Age (yr)	73.3±3.7
Sex, male	20
BMI (kg/m^2)	23.7±2.6
NSS	1.0±1.3
NDS	1.2±1.0
mMRC dyspnea score	1.3±0.5
CAT score	13.2±6.4
Percentage of predicted FVC	78.3±20.7
Percentage of predicted FEV1	71.3±11.8
FEV1/FVC ratio	56.5±9.3
Smoking amount, pack-years	34.2±11.1

Data are *n* or mean±SD values.
CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council; NDS, neurological disability score; NSS, neurological symptom score.

Multiple excitability measurements and comparisons among groups

The values of the motor NET parameters in the NC, COPD, and smoker groups are listed in Table 2. In the motor NETs, the change in the threshold in the mid-depolarizing phase of TE (TEd) (40–60 ms) was smaller in the COPD group (50.7%±1.2%) than in the NC group (54.5%±0.7%, $p<0.01$) (Figs. 1A and 2A), as was the prominence of superexcitability in the RC (-22.6%±1.5% and -26.4%±1.1%, $p<0.05$) (Figs. 1C and 2B). Other specific parameters of the motor NET showed no significant differences between groups (Fig. 3A and B).

In the sensory NETs, none of the parameters differed significantly between the COPD and NC groups (Table 3). Comparisons between the smoker and NC groups and between the smoker and COPD groups revealed no significant differences in all parameters in both motor and sensory NETs (Tables 2 and 3; Fig. 1B, D, Fig. 2C, D, and Fig. 3).

Correlations between measured multiple excitability parameters and pulmonary function

No significant correlations were found between the parameters of multiple excitability measurements and those of pulmonary function, such as the modified mMRC dyspnea score, CAT score, FEV1/FVC ratio, percentage of predicted FVC, percentage of predicted FEV1, and amount of smoking. For example, no significant correlations were found between TEd 40–60 ms and amount of smoking ($r=0.04$, $p=0.45$) nor between superexcitability and amount of smoking in COPD group ($r=0.07$, $p=0.61$).

Table 2. Comparison of axonal excitability parameters of the median motor nerve among the COPD, smoker, and NC groups

Parameter	NC (*n*=25)	COPD (*n*=20)	Smoker (*n*=25)	p^1	p^2
Stimulus–response and strength–duration relationships					
Stimulus for 50% CMAP (mA)	2.30±1.04	2.79±1.09	2.52±1.07	0.09	0.36
SDTC (ms)	0.49±0.01	0.49±0.03	0.50±0.02	0.73	0.64
Rheobase current (mA)	1.45±1.04	1.82±1.09	1.62±1.07	0.04*	0.30
Stimulus–response slope	4.21±1.06	4.55±1.08	4.49±1.07	0.49	0.32
TE					
$TEd_{(10-20)}$ (%)	71.9±0.7	70.4±0.8	72.6±0.8	0.24	0.58
$TEd_{(40-60)}$ (%)	54.5±0.7	50.7±1.2	54.9±1.0	0.008**	0.67
$TEd_{(90-100)}$ (%)	50.7±0.8	48.1±1.1	52.4±1.1	0.10	0.24
TEd peak (%)	71.6±0.7	69.4±1.0	72.2±0.8	0.08	0.59
S2 accommodation (%)	20.9±0.7	21.3±0.8	19.9±0.6	0.75	0.11
$TEh_{(10-20)}$ (%)	-77.5±1.0	-76.3±1.6	-77.6±1.1	0.91	0.76
$TEh_{(20-40)}$ (%)	-96.3±1.6	-95.5±2.3	-96.7±1.7	0.96	0.65
$TEh_{(90-100)}$ (%)	-127.6±3.2	-126.3±3.7	-127.4±3.3	0.93	0.82
$TEh\ slope_{(101-140)}$	2.08±0.06	2.20±0.10	2.04±0.06	0.30	0.82
CTR					
Resting I/V slope	0.52±0.01	0.56±0.02	0.50±0.02	0.03*	0.46
Minimum I/V slope	0.28±0.01	0.25±0.01	0.25±0.01	0.60	0.72
Hyperpolarizing I/V slope	0.41±0.01	0.42±0.02	0.48±0.04	0.93	0.09
RC					
Superexcitability (%)	-26.4±1.1	-22.6±1.5	-27.4±1.7	0.04*	0.64
Subexcitability (%)	12.7±0.7	13.2±1.0	11.7±0.8	0.73	0.99
Relative refractory period (ms)	3.00±1.02	2.87±1.02	2.87±1.02	0.18	0.17

Data are mean±SEM values. Group comparisons using the Mann-Whitney U test: [1]NC versus COPD, [2]NC versus smoker. Asterisks indicate statistically significant differences: *$p \leq 0.05$; **$p \leq 0.01$.
CMAP, compound muscle action potential; COPD, chronic obstructive pulmonary disease; CTR, current–threshold relationship; I/V, current–voltage relationship; NC, normal control; RC, recovery cycle; SDTC, strength–duration time constant; TE, threshold electrotonus; $TEd_{(10-20)}$, $TEd_{(40-60)}$, and $TEd_{(90-100)}$, depolarizing phases of threshold electrotonus (TEd) after 10–20, 40–60, and 90–100 ms of depolarizing current, respectively; $TEh_{(10-20)}$, $TEh_{(20-40)}$, and $TEh_{(90-100)}$, hyperpolarizing phases of TE (TEh) after 10–20, 20–40, and 90–100 ms of hyperpolarizing current, respectively.

DISCUSSION

This study used the novel technique of automated NETs to investigate the effects of COPD on the peripheral nervous system. Alterations in the excitability of distal motor axons were identified in patients with mild COPD but not PN. Specifically, NETs revealed smaller changes in the threshold during the mid-depolarizing phase of TE (TEd 40–60 ms) and less-prominent superexcitability in the RC. These features were not found in smokers without COPD. Our findings partially reaffirmed those from a previous NET study of COPD, which showed identical changes in the RC in motor NETs.[27] However, that study only applied NETs to motor nerves. Most PNs start with sensory symptoms,[28] and there are previous reports of sensory-dominant PN in COPD.[1,4,8,11] We therefore expected that alterations of excitability would be more prominent in sensory than motor axons. However, we found no significant alteration of sensory axons in COPD. One of the strengths of our study is the identification of the selective involvement of motor nerves in COPD.

In TE, the background membrane depolarization decreases the resistance of the internode by activating paranodal and internodal K^+ channels, thereby decreasing the threshold for changes in both depolarizing and hyperpolarizing directions and producing an appearance of 'fanning in' of TE. In the RC, depolarization of the internodal membrane opens paranodal K^+ channels, which reduces the resistance of the internodal membrane and hence also the size of the depolarizing afterpotential and the extent of supernormality.[14]

Both the present study and that of Uysal et al.[27] identified that superexcitability was significantly less prominent in motor axons in COPD. Uysal et al.[27] hypothesized that this finding reflected the depolarized state of the axolemma of distal motor nerves. In addition to this finding, we found a smaller change in the mid-depolarizing phase of TE (TEd 40–60 ms). Although both studies failed to show a typical 'fanning in' pattern in TE, we considered that the TEd pattern in our study reflected a subtle tendency toward to this pattern. Therefore,

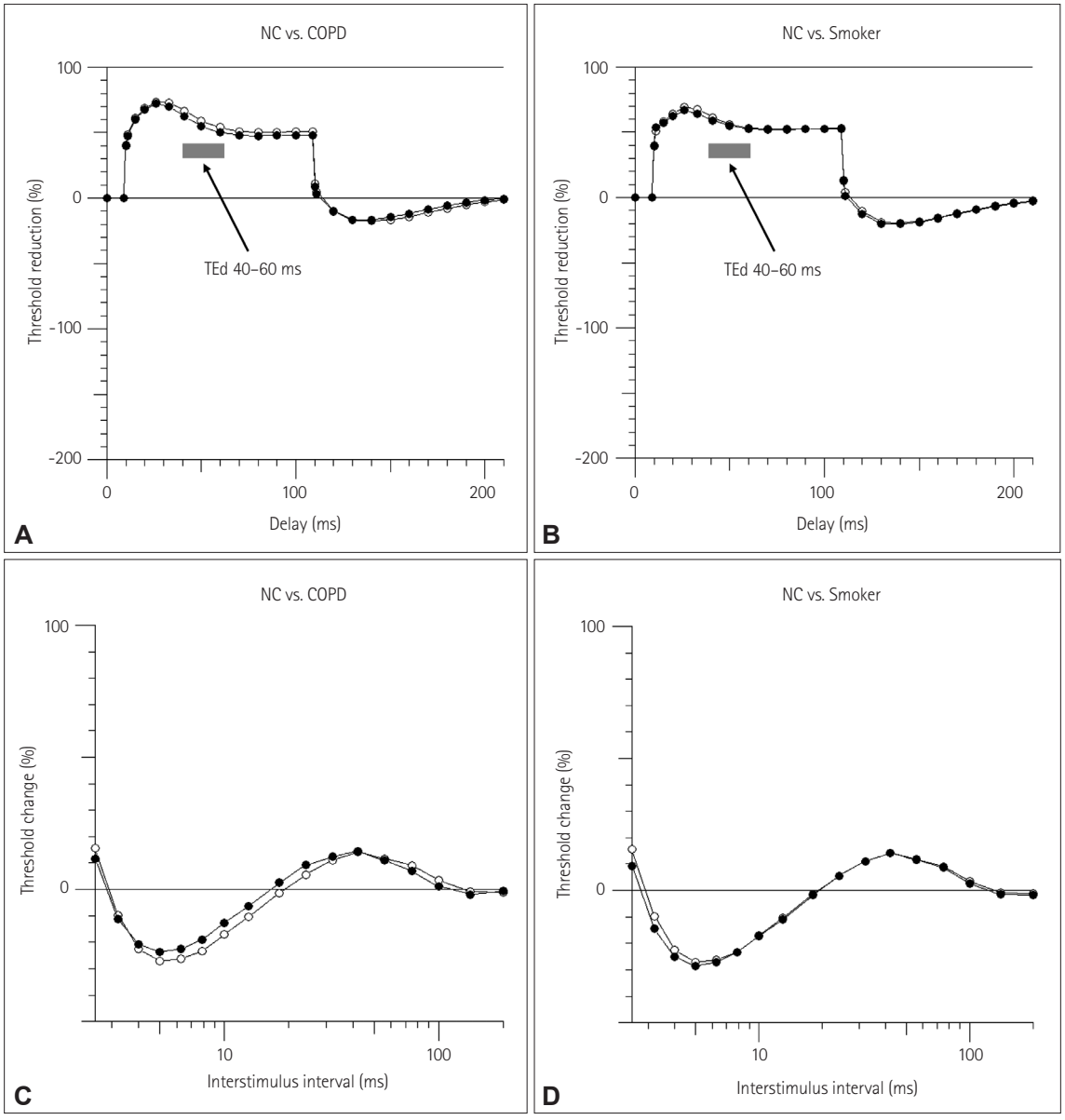

Fig. 1. Waveforms for chronic obstructive pulmonary disease (COPD) and smokers versus normal controls (NCs). The graphs show a depolarizing phase of threshold electrotonus (TEd) (A, B) and a recovery cycle (RC) (C, D). There were significant differences in the mid-depolarizing phase of threshold electrotonus (TEd 40–60 ms) and RC (superexcitability) in the comparison between the COPD and NC groups (A, C) but not between the smoker and NC groups (B, D). The statistical findings pertaining to these data are presented in Table 2. Data are mean values (NC: open circles; COPD: filled circles).

we hypothesize that our findings reflect the membrane depolarization of motor nerves by COPD.

Uysal et al.[27] also investigated an acute effect of smoking on NETs by performing paired testing before and after smoking. It was particularly interesting that they found alteration in hyperpolarizing TE (tendency toward 'fanning out') and increased superexcitability in the RC. They attributed this finding to modulation of the inward rectifier channels and considered the blocking effect of cesium, which is one of the numerous components of smoke. Overall, these findings contrast with the NET findings for COPD suggesting a depolarizing condition.

A depolarized membrane exhibits a decreased resistance and a smaller change in the elicited response, resulting in a 'fanning in' pattern in TE. Therefore, transient ischemia of the axon paralyzes the oxygen-dependent Na^+–K^+–ATPase, resulting in membrane depolarization and a 'fanning in' of the TE response waveform. Meanwhile, postischemia results in compensatory hyperactivity of the pumps leading to membrane hyperpolarization and a 'fanning out' pattern.[14,16]

Based on the above-described observations, we suggest that the NET findings for COPD reflect a chronically adaptive

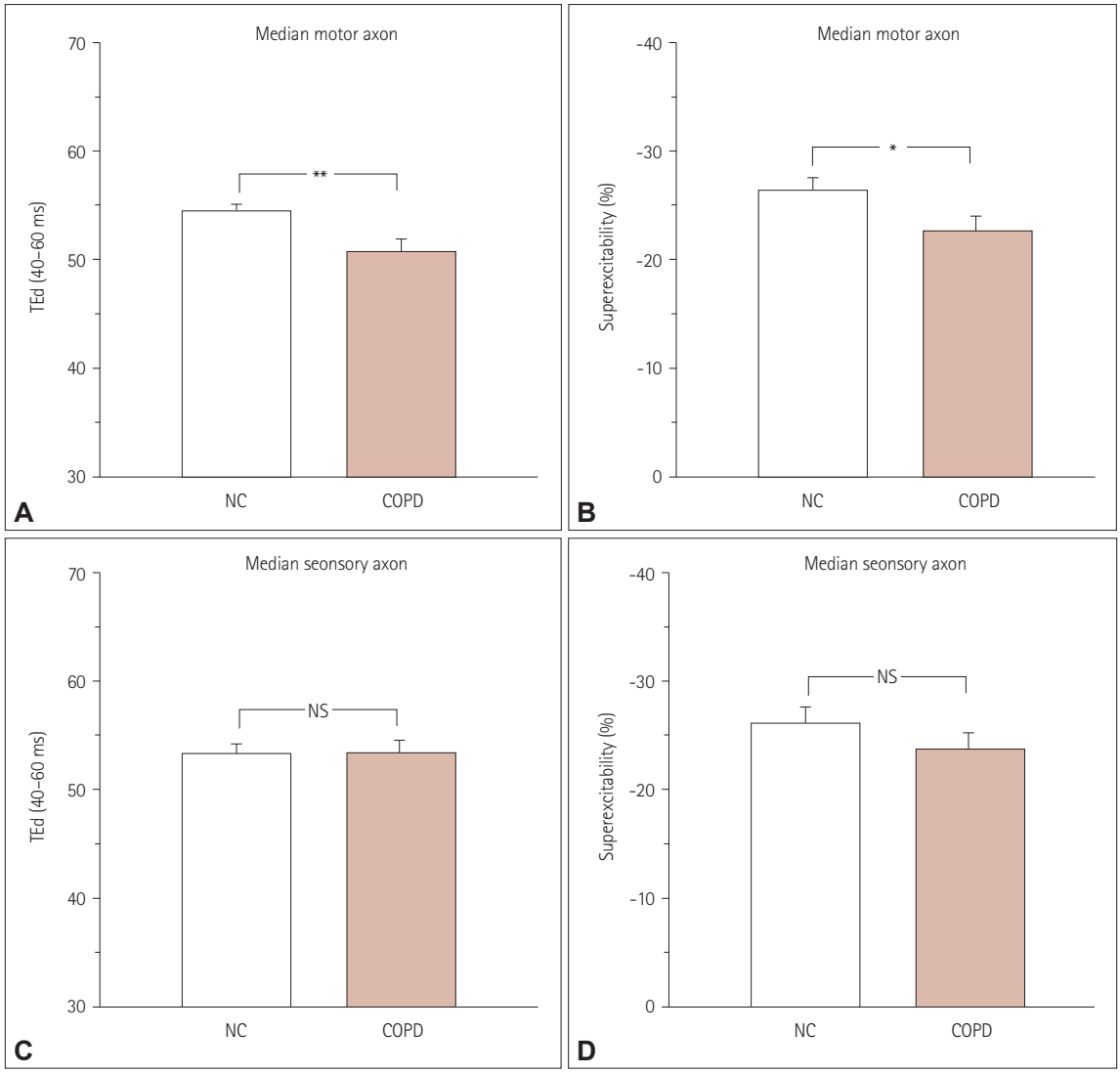

Fig. 2. Mean values of the depolarizing phase of TE (TEd 40–60 ms) and superexcitability between the NC and COPD groups. Comparisons of the TEd 40–60 ms values between the NC and COPD groups using the Mann-Whitney U test revealed a significant difference between the NC and COPD groups (**p<0.01) in axons of the median motor nerve (A) but not in axons of the median sensory nerve (C). Comparisons of the superexcitability values between the NC and COPD groups using the Mann-Whitney U test revealed a significant difference between the NC and COPD groups (*p<0.05) in axons of the median motor nerve (B) but not in axons of the median sensory nerve (D). The statistical findings pertaining to these data are presented in Tables 2 and 3. Data are mean and SEM values. COPD, chronic obstructive pulmonary disease; NC, normal control; NS, nonsignificant; TE, threshold electrotonous.

state of systemic ischemia influencing the vasa nervorum of the peripheral nerve and the resultant pattern of depolarization (i.e., 'fanning in' of TE and decreased superexcitability in the RC). Meanwhile, alteration of the NET parameters between pre- and postsmoking may reflect the effect of postischemia resulting in compensatory hyperactivity of the Na^+–K^+ pump leading to a pattern of membrane hyperpolarization (i.e., 'fanning out' of TE and increased superexcitability in the RC). If this hypothesis is correct, those parameters can be used as neurophysiological biomarkers of the effects of acute and chronic ischemia on the peripheral nervous system.

Because COPD is a chronically devastating disease that affects overall metabolic and systemic pathways of the human body, it can complicate the causative conditions of PNs or neuropathic processes. Nevertheless, we were able to analyze the pure effect by COPD in our study cohort because we exclusively enrolled COPD patients with no apparent clinical or electrophysiological evidence of PN. Therefore, this is the first demonstration of the early neuropathic effect of COPD.

Combined with the previous results of Uysal et al.,[27] it appears that the neuropathic process precedes the overt presentation of PN and might be triggered by membrane depo-

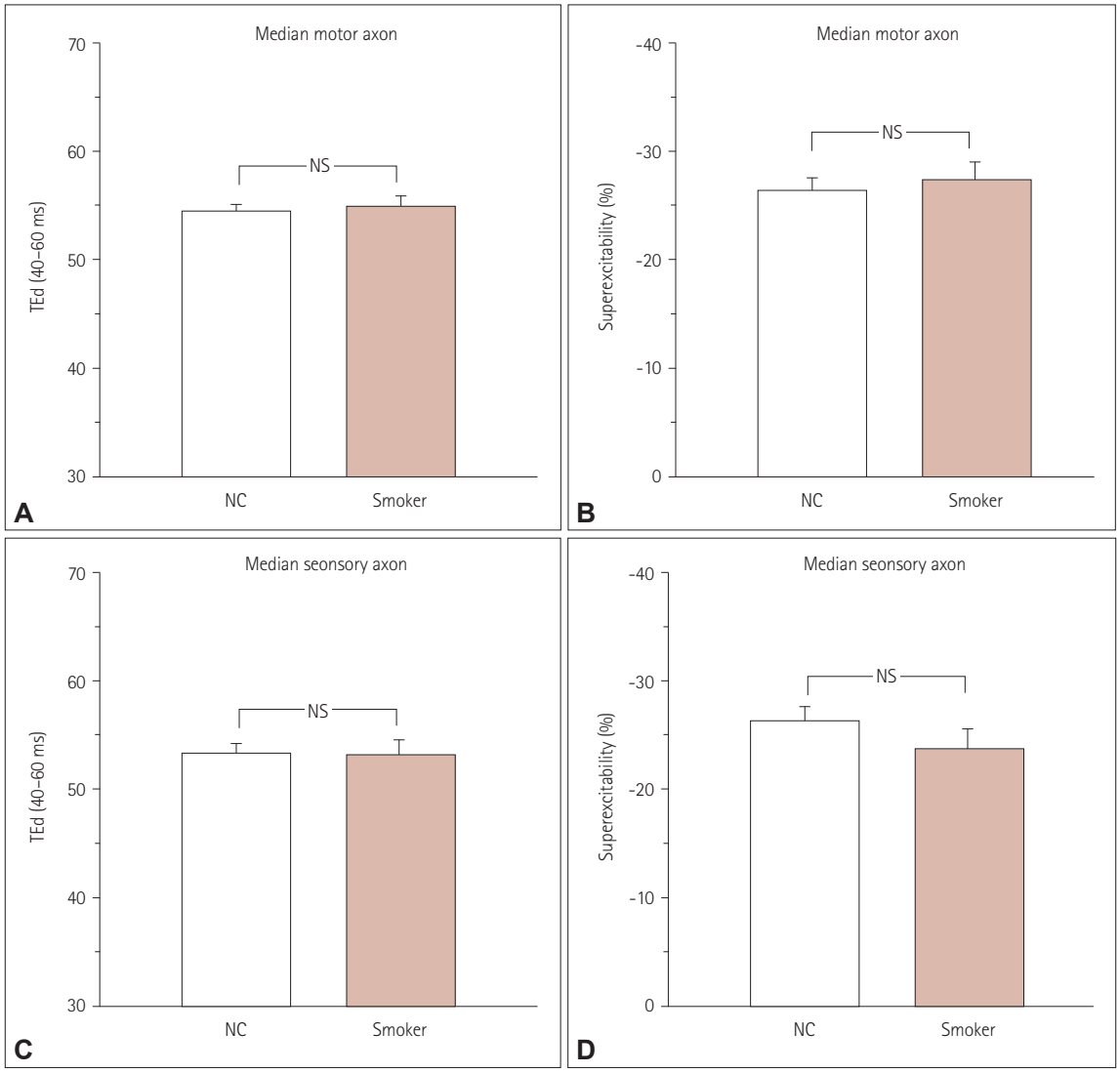

Fig. 3. Mean values of the depolarizing phase of TE (TEd 40–60 ms) and superexcitability between the NC and smoker groups. Comparisons of both the TEd 40–60 ms values and superexcitability between the NC and smoker groups using the Mann-Whitney U test revealed no significant difference between the NC and smoker groups ($p>0.05$) in both axons of the median motor nerve (A, B) and axons of the median sensory nerve (C, D). The statistical findings pertaining to these data are presented in Tables 2 and 3. Data are mean and SEM values. COPD, chronic obstructive pulmonary disease; NC, normal control; NS, nonsignificant; TE, threshold electrotonous.

larization due to chronic hypoxemia in COPD. The absence of this change in smokers without COPD might indicate that the early neuropathic process develops via the effects of COPD per se (i.e., chronic hypoxemia) rather than the effect of smoking (i.e., a neurotoxic effect).

COPD is accompanied by substantial dysregulation of diverse systems involving systemic inflammation and neurohormonal activation, among which hypoxemia and hypercapnia may be the chief mechanisms underlying the systemic pathophysiological effects.[10] This is supported by many adverse neurological affects such as motor neuron diseases, cerebrovascular diseases, and cognitive impairment having been described in patients with COPD.[3,29]

Regarding the effects of COPD on the peripheral nervous system, hypoxemia causes peripheral nerve damage, harming the vasa nervorum.[9] It has been demonstrated pathologically that hypoxemia is linked to nerve capillary endothelial cell hyperplasia and hypertrophy, prompting luminal occlusion that causes microangiopathy in peripheral nerves in COPD patients.[30]

It is also relevant that several animal studies have found that acute and chronic ischemia can lead to peripheral nerve lesions,[31-34] in accordance with clinical observations indicating a higher risk of PN in COPD patients with hypoxemia.[7] These findings are also consistent with the occurrence of even subclinical PN in relation to hypoxemia in COPD.[9]

Table 3. Comparison of axonal excitability parameters of the median sensory nerve among the COPD, smoker, and NC groups

Parameter	NC (*n*=25)	COPD (*n*=20)	Smoker (*n*=25)	p^1	p^2
Stimulus–response and strength–duration relationships					
Stimulus for 50% CMAP (mA)	2.49±1.08	1.98±1.0	2.03±1.08	0.06	0.13
SDTC (ms)	0.50±0.01	0.52±0.02	0.53±0.02	0.64	0.33
Rheobase current (mA)	1.40±1.11	1.02±1.09	1.00±1.10	0.06	0.06
Stimulus–response slope	3.71±1.07	3.31±1.10	3.15±1.10	0.40	0.22
TE					
$TEd_{(10–20)}$ (%)	67.3±1.2	65.0±1.6	64.4±1.7	0.27	0.18
$TEd_{(40–60)}$ (%)	53.4±0.9	53.4±1.3	53.1±1.4	0.95	0.81
$TEd_{(90–100)}$ (%)	53.0±1.0	53.0±1.7	51.5±4.22	0.77	0.84
TEd peak (%)	67.3±1.1	64.4±1.4	69.87±2.74	0.20	0.14
S2 accommodation (%)	14.3±1.3	12.2±1.9	11.4±2.0	0.33	0.20
$TEh_{(10–20)}$ (%)	-83.6±2.0	-86.8±3.1	-89.0±3.1	0.43	0.11
$TEh_{(20–40)}$ (%)	-106.0±2.8	-109.8±4.6	-113.2±4.5	0.57	0.18
$TEh_{(90–100)}$ (%)	-143.4±5.7	-145.6±9.5	-150.9±10.0	0.87	0.70
TEh $slope_{(101–140)}$	2.38±0.12	2.57±0.18	2.68±0.19	0.46	0.15
CTR					
Resting I/V slope	0.47±0.02	0.47±0.02	0.46±0.02	0.95	0.57
Minimum I/V slope	0.23±0.01	0.23±0.01	0.23±0.01	0.84	0.96
Hyperpolarizing I/V slope	0.43±0.03	0.40±0.03	0.40±0.03	0.88	0.95
RC					
Superexcitability (%)	-26.2±1.4	-28.3±1.9	-23.8±1.7	0.25	0.28
Subexcitability (%)	12.5±0.6	11.7±0.8	12.2±0.8	0.38	0.70
Relative refractory period (ms)	3.15±1.03	3.37±1.04	3.42±1.04	0.16	0.09

Data are mean±SEM values. Group comparisons using the Mann-Whitney U test: [1]NC versus COPD, [2]NC versus smoker. There ere no statistically significant intergroup differences.
CMAP, compound muscle action potential; COPD, chronic obstructive pulmonary disease; CTR, current–threshold relationship; I/V, current–voltage relationship; NC, normal control; RC, recovery cycle; SDTC, strength–duration time constant; TE, threshold electrotonus; $TEd_{(10–20)}$, $TEd_{(40–60)}$, and $TEd_{(90–100)}$, depolarizing phases of threshold electrotonus (TEd) after 10–20, 40–60, and 90–100 ms of depolarizing current, respectively; $TEh_{(10–20)}$, $TEh_{(20–40)}$, and $TEh_{(90–100)}$, hyperpolarizing phases of TE (TEh) after 10–20, 20–40, and 90–100 ms of hyperpolarizing current, respectively.

Some limitations of our study need to be considered. The most important limitations are the smallness of the sample and the restricted evaluations of other components of peripheral nerves. Both conventional NCSs and NETs reflect only the large fastest-conducting myelinated axons, and until recently there has been no technique for sensitive and quantitative measurements of lesions of small nerve fibers. Future studies should involve combined evaluations of both large and small nerve fibers in COPD, using emerging specific tools. In addition, advanced study designs with longitudinal follow-ups of neuropathic processes to overt PN are required to reveal the detailed and specific pathogenesis of PN in COPD.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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