Altered axonal excitability properties and nerve enlargement in POEMS syndrome

（POEMS症候群における軸索特性の変化と神経浮腫）

千葉大学大学院医学薬学府
先端生命科学専攻
（主任：桑原聡教授）
三津間さつき

Clinical Neurophysiology, Research paper

Altered axonal excitability properties and nerve edema in POEMS syndrome

Satsuki Mitsuma, Sonoko Misawa, Kazumoto Shibuya, Sagiri Isose, Yukari Sekiguchi, Yuta Iwai, Minako Beppu, Keisuke Watanabe, Hiroshi Amino, Satoshi Kuwabara*

Departments of Neurology, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 260-8670, Japan

*Corresponding author:

Satoshi Kuwabara, MD

Department of Neurology, Graduate School of Medicine, Chiba University

1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

Tel. +81-43-222-7171 Ext. 5414 Fax. +81-43-226-2160

E-mail kuwabara-s@faculty.chiba-u.jp

Key words: POEMS syndrome; axonal excitability; nerve ultrasound; ion channel

Potential financial interests: None

Acknowledgement: This study was supported in part by a grant for research on intractable diseases from the Ministry of Health, Labour and Welfare of Japan (S.K.).

Conflict of interest: None

Word count: title, 10 (78 spaces); abstract, 191; text, 1684

Highlights:

- Axonal excitability and its correlation with serum VEGF and nerve edema detected by ultrasound were studied in POEMS syndrome.
- Excitability testing showed altered sodium, potassium, and inward rectifying corrents, some of which were correlated with VEGF levels and nerve edema.
- In addition to structural changes (demyelination), nerve edema induced by upregulated VEGF, and upregulated inflammatory cytokines can modulate profiles of POEMS neuropathy.

Abstract:

Objective: POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating neuropathy with upregulation of vascular endothelial growth factor (VEGF). This study aimed to elucidate axonal excitability properties and their relation to VEGF levels and nerve edema in POEMS neuropathy.

Methods: Axonal excitability measurement and nerve ultrasound were performed in the median nerve of 33 patients with POEMS syndrome. Serum VEGF levels were measured by ELISA.

Results: Compared with normal subjects (n=87), POEMS patients showed longer strength-duration time constant, fanning-out of threshold electrotonus curves, and greater threshold changes in a hyperpolarizing current-threshold relationship. Nerve ultrasound showed significant enlargement in POEMS patients. Serum VEGF levels and the extent of nerve edema partly correlated with nerve conduction slowing, as well as persistent sodium currents and inward rectification.

Conclusions: In POEMS syndrome, patterns of changes in excitability properties could suggest increased persistent sodium currents, and impaired potassium and inward rectifying channels. The findings were not consistent with depolarization due to nerve edema and compression ischaemia.

Significance: In addition to demyelination, nerve edema induced by upregulated VEGF, and upregulated inflammatory cytokines could modulate profiles of POEMS neuropathy.

1. Introduction

POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating polyneuropathy associated with monoclonal plasma cell proliferation and multi-organ involvement (Bardwick et al., 1980; Kuwabara et al., 2008a; Dispenzieri, 2014). Serum levels of vascular endothelial growth factor (VEGF) are markedly increased in POEMS syndrome, and increased vascular permeability and neovasculization mediated by VEGF are likely to cause characteristic symptoms such as edema, pleural effusion/ascites, organomegaly and skin angiomata (Watanabe et al., 1996). However, mechanisms for neuropathy in POEMS syndrome have not yet been elucidated, whereas pathological studies have shown perineurial edema, and segmental demyelination with uncompacted myelin and secondary axonal degeneration (Kanda, 2013).

The proposed mechanisms for POEMS neuropathy include that the combination of blood-nerve barrier breakdown by VEGF and following invasion of other inflammatory cytokines such as interleukin-12, and tumor necrosis-α causes nerve demyelination (Kanai et al., 2012), and that nerve edema mediated by VEGF leads to compression ischaemia and axonal depolarization (Kanda, 2013), but these hypotheses still need confirmation.

Axonal excitability testing using threshold tracking was developed to investigate ion channel function, membrane potential, and passive membrane properties of human axons *in vivo* (Bostock et al., 1998; Burke et al., 2001), and over the past two decades, the technique has been extensively applied to the study of the biophysical properties of human peripheral nerves and have provided important insights into axonal ion channel function in health and disease (Nodera and Kaji, 2006; Sawai et al., 2008).

Separately, nerve ultrasound are also becoming increasingly important in the diagnosis and evaluation of peripheral neuropathies particularly in the 2000's (Padua et al., 2012) providing new insights into macroscopic nerve morphology. In this study, we aimed to elucidate axonal excitability properties and their relation to nerve morphology and serum VEGF levels in patients with POEMS syndrome.

2. Methods

2.1. Subjects

This study prospectively enrolled 33 consecutive patients (25 men; age range 36–75 years, mean 55 years) with newly diagnosed POEMS syndrome, who fulfilled published criteria (Kuwabara et al., 2008a) seen at a single tertiary hospital (Chiba University Hospital) in Japan from January 2012 to September 2014. We excluded patients with renal failure because serum K^+ levels can significantly alter membrane potential and axonal excitability properties (Kiernan et al., 2000).

Normal control data for axonal excitability testing were obtained from 87 age-matched healthy subjects (49 men; age range 38–76 years, mean 56 years). Serum VEGF levels were measured by ELISA commercially (Special Reference Laboratory Co. Ltd., Tokyo, Japan). All the patients and normal control subjects gave informed consent to the study procedures, which was approved by the Ethics Committee of Chiba University Graduate School of Medicine.

2.2. Neurophysiological assessment

Neurophysiological evaluation was performed before thalidomide treatment, and in 9 patients, follow-up studies were done 3 months later. Nerve conduction studies were conducted using conventional procedures and a standard electromyography machine (Viking 4, Nicolet Biomedical Japan, Tokyo, Japan). Nerve excitability testing was performed on the median nerve at the wrist (3 cm proximal to the wrist crease) using a computerized program (QTRAC® with multiple excitability protocol, TRONDNF, Institute of Neurology, London, UK) as described previously (Kiernan et al., 2000; Nasu et al., 2014). Compound muscle action potentials (CMAPs) were recorded from the abductor pollicis brevis. Skin temperature was measured near the stimulating site and maintained above 32.0°C (using extra heating, if necessary). Excitability indices included strength–duration time constant, threshold electrotonus, and refractoriness, supernormality, and late subnormality of the recovery cycle of axonal excitability with a single supramaximal conditioning stimulus, and a current-threshold relationship.

2.3. Nerve ultrasound

Ultrasound examination was performed with Logiq E9 (GE Healthcare Japan, Tokyo, Japan) with a 6-12MHz electronic linear array probe at the wrist, forearm, and elbow portion of the median nerve trunk. Cross-sectional area were measured at the inner

border of the thin hyperechoic epineural rim by the continuous tracing technique and the average values were calculated after serially measuring three times (Kerasnoudis et al., 2014). No additional force was applied other than the weight of the transducer and the extremities were kept in the neutral position to avoid causing any artificial nerve deformity.

2.5. Statistical analysis

All statistical tests were two-sided. The comparison of paired parameters of nerve conduction studies or excitability testing between baseline and the second examination was evaluated via the paired t-test with Bonferroni's correction for multiple testing. Regression analysis was performed by Pearson's correlation coefficient test. All statistical analyses were performed using JMP software, version 5.1.1 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Nerve excitability testing and ultrasound

Table 1 shows results of nerve conduction studies, and excitability testing. Nerve conduction velocities were significantly slowed consistent with primary demyelinating neuropathy. In excitability testing, strength-duration time constant was significantly longer and current required for produce 50% of the maximal CMAP was greater for POEMS patients than for normal controls. In the recovery cycle of axonal excitability, POEMS patients had greater superexcitability and smaller late subexcitability. POEMS patients showed fanning-out in threshold electrotonus particularly in the hyperpolarizing direction, and greater threshold changes to hyperpolarizing currents in current-threshold relationships (**Figure 1**).

Nerve ultrasonography showed significantly greater cross-sectional area at the wrist, forearm, and elbow portion of the median nerve in patients with POEMS syndrome than in normal subjects.

3.2. Correlation with serum VEGF levels and nerve enlargement

Before treatment, serum VEGF levels were greatly increased in all patients with POEMS syndrome; the mean value was 5143 pg/ml (normal<1000 pg/ml), ranging from 1080 to

16400 pg/ml. **Table 2** shows correlation of electrophysiological indices with serum VEGF levels and cross-sectional area at the elbow. Higher serum VEGF levels were associated with longer distal motor latency, and smaller CMAP amplitude in nerve conduction studies, and greater threshold changes to long hyperpolarizing conditioning currents.

Separately larger cross-sectional area on nerve ultrasound was associated with slower nerve conduction velocity, smaller CMAP amplitude, and loner strength-duration time constant. Serum VEGF levels and nerve cross-sectional area at the time of examination did not show significant correlation.

3.3. Serial changes after treatment

Sequential examinations on nerve excitability and ultrasound were performed before and 3 months after thalidomide treatment in 9 patients. **Table 3** shows serial changes. Serum VEGF levels decreased. Nerve cross-sectional area significantly reduced after treatment, suggesting edema was a major cause of nerve enlargement Significant improvement was observed in distal latency in nerve conduction studies. In excitability testing, superexcitability and and threshold change to 100% hyperpolarizing conditioning currents in current-threshold relationship significantly changed towards normal (**Figure 2**).

4. Discussion

Our results show that axonal excitability properties in POEMS neuropathy is characterized by prolonged strength-duration time constant, increased superexcitability, reduced late subexcitability, fanning-out in threshold electrotonus, and greater threshold changes to 100% hyperpolarizing conditioning current in current-threshold relationships. These findings could suggest altered nodal persistent sodium currents, reduced potassium and inward rectifying conductances,respectively (Burke et al., 2001; Nodera and Kaji, 2006; Howells et al., 2012). However, their interpretations are difficult because of multiple factors such as segmental demyelination, nerve edema, and upregulated inflammatory cytokines could contribute to altered channel function. The excitability indices and nerve conduction parameters are partly correlated with serum VEGF levels and the extent of nerve enlargement.

Pathological studies have shown segmental demyelination and remyelination,

uncompacted myelin, and perineirial edema in sural nerve specimen of patients with POEMS syndrome (Koike et al., 2008). The short-internode associated with remyelination, and altered myelin resistance may affect the input resistance and lead to fanning-out in threshold electrotonus, but again other factors could modulate a total findings of excitability testing.

The pattern of excitability changes are different from those in chronic inflammatory demyelinating polyneuropathy (CIDP); previous reports on CIDP have shown that compared with normal subjects, strength-duration time constant was significantly shorter, and in the recovery cycle, CIDP patients had less refractoriness, supernormality and late subnormality than healthy controls (Cappelen-Smith et al., 2000; Sung et al., 2004). Current-threshold relationships did not show significant changes. Particularly, strength-duration time constant and superexcitability change to the opposite direction in POEMS syndrome and CIDP. It is important to differentiate the two conditions because POEMS syndrome is often misdiagnosed as CIDP (Nasu et al., 2012), but treatments are substantially different. In this regard, whether nerve excitability testing is helpful for the differential diagnosis of POEMS syndrome and CIDP, needs to be studied in a prospective fashion.

In the present study, serum VEGF levels were invariably elevated in POEMS patients, consistent with previous reports (Kuwabara et al., 2008a, 2008b), and correlated, although weakly, with distal latency and hyperpolarizing threshold electrotonus and current-threshold relationships (**Table 2**). These findings might not reflect the direct effects of VEGF alone, because multiple inflammatory cytokines such as interleukin-12, and tumor necrosis-α are simultaneously and markedly upregulated in the active phase of POEMS syndrome (Kanai et al., 2012), and it is possible such cytokines other than VEGF affect ion channel function, although this should be investigated in further studies. Nevertheless, increased vascular permeability mediated by VEGF presumably responsible for nerve edema, frequently found on pathological examination (Kanda, 2013). We initially expected membrane depolarization due to edema-induced compression ischaemia in POEMS syndrome, and nerve edema detected by ultrasound partly correlated with axonal excitability. However, a combination of the nerve excitability changes did not support axonal depolarization. Different from an acute compression/ischaemia model, compensatory mechanisms in response to

depolarization might act, leading to resulted in a steady state during chronic exposure of VEGF and nerve edema. Our study did not reach a conclusion on whether membrane potential is altered in POEMS syndrome, because multiple factors in POEMS syndrome such as demyelination, and cytokine activation would also largely affect membrane properties.

There are several limitations in this study. We could examine sequential changes in a small number of patients (n=9) and relatively short period of follow-up (3 months). Secondly, both nerve excitability testing and ultrasound works only in the restricted portion of the nerve (e.g., superficially located portion of the nerve). Finally, among the inflammatory cytokines elevated in POEMS syndrome, only VEGF was measured. The effects of cytokines should be evaluated as a network based on measurements of multiple cytokines.

The pathophysiology of POEMS neuropathy is still unclear, and a complex interaction of multiple factors could contribute to development of neuropathy in POEMS syndrome. Further multidisciplinary approach using electrophysiological, morphological, and biochemical methodology would be required to elucidate the pathogenesis of peripheral neuropathy in POEMS syndrome, and we would like to do so in future studies.

References

Bardwick PA, Zvaifler NJ, Gill GN, Newman D, Greenway GD, Resnick DL. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. Medicine (Baltimore) 1980;59:311-22.

Bostock H, Cikurel K, Burke D. Threshold tracking techniques in the study of human peripheral nerve. Muscle Nerve 1998;21:137-158.

Burke D, Kiernan MC, Bostock H. Excitability of human axons. Clin Neurophysiol 2001;112:1575-85.

Cappelen-Smith C, Kuwabara S, Lin CS, Mogyoros I, Burke D. Activity-dependent hyperpolarization and conduction block in chronic inflammatory demyelinating polyneuropathy. Ann Neurol 2000 Dec;48:826-32.

Dispenzieri A. POEMS syndrome: 2014 update on diagnosis, risk-stratification, and management. Am J Hematol 2014;89:214-23.

Howells J, Trevillion L, Bostock H, Burke D. The voltage dependence of I(h) in human myelinated axons. J Physiol 2012;590:1625-40.

Kanai K, Sawai S, Sogawa K, Mori M, Misawa S, Shibuya K, et al. Markedly upregulated serum interleukin-12 as a novel biomarker in POEMS syndrome. Neurology 2012;79:575-82.

Kanda T. Biology of the blood-nerve barrier and its alteration in immune mediated neuropathies. J Neurol Neurosurg Psychiatry 2013;84:208-12.

Kerasnoudis A, Pitarokoili K, Behrendt V, Gold R, Yoon MS. Nerve ultrasound score in distinguishing chronic from acute inflammatory demyelinating polyneuropathy. Clin Neurophysiol 2014;125:635-41.

Kiernan MC, Burke D, Andersen KV, Bostock H. Multiple measures of axonal excitability: a new approach in clinical testing. Muscle Nerve 2000;23:399-409.

Koike H, Iijima M, Mori K, Yamamoto M, Hattori N, Watanabe H, et al. Neuropathic pain correlates with myelinated fibre loss and cytokine profile in POEMS syndrome. J Neurol Neurosurg Psychiatry 2008;79:1171-9.

Kuwabara S, Dispenzieri A, Arimura K, Misawa S, Nakaseko C. Treatment for POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome. Cochrane Database Syst Rev 2008a Oct 8;(4):CD006828.

Kuwabara S, Misawa S, Kanai K, Suzuki Y, Kikkawa Y, Sawai S, et al. Neurologic improvement after peripheral blood stem cell transplantation in POEMS syndrome. Neurology 2008b;71:1691-5.

Nasu S, Misawa S, Nakaseko C, Shibuya K, Isose S, Sekiguchi Y, et al. Bortezomib-induced neuropathy: axonal membrane depolarization precedes development of neuropathy. Clin Neurophysiol. 2014;125:381-7.

Nasu S, Misawa S, Sekiguchi Y, Shibuya K, Kanai K, Fujimaki Y, et al.. Different neurological and physiological profiles in POEMS syndrome and chronic inflammatory demyelinating polyneuropathy. J Neurol Neurosurg Psychiatry 2012;83:476-9.

Nodera H, Kaji R. Nerve excitability testing and its clinical application to neuromuscular diseases. Clin Neurophysiol 2006;117:1902-16.

Padua L, Liotta G, Di Pasquale A, Granata G, Pazzaglia C, Martinoli C, et al. Contribution of ultrasound in the assessment of nerve diseases. Eur J Neurol 2012;19:47-54.

Sawai S, Kanai K, Nakata M, Hiraga A, Misawa S, Isose S, et al. Changes in excitability properties associated with axonal regeneration in human neuropathy and mouse Wallerian degeneration. Clin Neurophysiol. 2008;119:1097-105.

Sung JY, Kuwabara S, Kaji R, Ogawara K, Mori M, Kanai K, et al. Threshold electrotonus in chronic inflammatory demyelinating polyneuropathy: correlation with clinical profiles. Muscle Nerve 2004;29:28-37.

Watanabe O, Arimura K, Kitajima I, Osame M, Maruyama I. Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. Lancet 1996;347:702.

Table 1. Results of nerve conduction studies, axonal excitability, and ultrasound.

		Normal	POEMS syndrome	P-value
		(n=85)	(n=31)	
Nerve conduction study				
Distal latency	(ms)	3.6 (0.4)	5.3 (1.0)	<0.0001
CMAP amplitude	(mV)	10.8 (1.2)	5.7 (1.0)	<0.0001
Conduction velocity	(m/s)	57.7 (6.3)	34.2 (6.1)	<0.0001
Nerve excitability testing		(n=87)	(n=33)	
Strength-duration property				
Strength-duration time constant	(ms)	0.42 (0.008)	0.50 (0.02)	0.0002
Current for 50% CMAP	(mA)	4.5 (0.2)	9.6 (0.8)	<0.0001
Recovery cycle				
Refractorines (2.0 ms)	(%)	47.9 (4.5)	38.5 (4.5)	0.06
Superexcitability (6.3 ms)	(%)	-20.6 (1.3)	-26.0 (1.3)	0.04
Late subnormality (42 ms)	(%)	18.5 (1.1)	9.2 (0.9)	<0.001
Threshold electrotonus				
TEd 10-20ms	(%)	69.2 (0.6)	70.7 (1.4)	0.3
TEd 90-100ms	(%)	46.1 (0.6)	48.4 (1.1)	0.07
TEh 90-100ms	(%)	-124.4 (2.4)	-136.9 (4.7)	0.02
Current threshold relationship				
50% depolarizing current	(%)	51.9 (0.9)	56.3 (1.6)	0.02
100% hyperpolarizing current	(%)	-309.6 (6.1)	-350.6 (13.9)	0.01
Hyperpolarizing I/V slope		0.42 (0.01)	0.36 (0.02)	0.01
Nerve ultrasound				
Cross sectional area		(n=23)	(n=19)	
Wrist	(cm^2)	0.07 (0.01)	0.10 (0.02)	0.001
Forearm	(cm^2)	0.06 (0.01)	0.08 (0.02)	<0.0001
Elbow	(cm^2)	0.07 (0.01)	0.11 (0.03)	<0.0001

Data are given as mean (SEM).

Table 2. Correlation of electrophysiological index with VEGF and nerve edema

	Serum VEGF level		Area (Ultrasound)	
	R^2	P-value*	R^2	P-value*
Nerve conduction study				
Motor nerve conduction velocity	0.0593	NS	0.389	0.03
Distal latency	0.133	0.04	0.3344	NS
CMAP amplitude	0.2082	0.01	0.2203	0.04
Nerve excitability testing				
Stimulus (mA) for 50% max response	0.05	NS	0.1616	NS
Strength-duration time constant (ms)	0.14	NS	0.3211	0.04
Refractoriness at 2 ms (%)	0.0098	NS	0.0241	NS
Superexcitability (%)	0.015	NS	0.0042	NS
Subexcitability (%)	0.0238	NS	0.0372	NS
TEd(10-20ms)	0.0001	NS	0.005	NS
TEd(90-100ms)	0.0164	NS	0.01	NS
TEh(90-100ms)	0.0185	NS	0.0125	NS
TEh(slope 101-140ms)	0.1941	0.01	0.0241	NS
Hyperpol. I/V slope	0.2007	0.03	0.015	NS
Nerve ultrasound (cross-sectional area)				
wrist	0.0218	NS		
Forearm	0.0987	NS		
Elbow	0.0208	NS		

*P-value < 0.05, considered as statistically significant; NS, not significant.

Table 3. Serum VEGF level, electrophysiology, and nerve ultrasound before and after treatment.

		Before	3 months	P-value
Serum VEGF	(pg/mL)	6061 (1667)	3600 (1406)	0.2
Nerve conduction study (n=9)				
Distal latency	(ms)	5.6 (0.5)	5.2 (0.5)	0.01
CMAP amplitude	(mV)	5.2 (1.2)	5.1 (1.5)	0.9
Conduction velocity	(m/s)	36.2 (3.6)	37.4 (3.4)	0.3
Nerve excitability testing (n=9)				
Strength-duration time constant				
Strength-duration time constant	(ms)	0.49 (0.01)	0.52 (0.04)	0.5
Current for 50% CMAP	(mA)	11.3 (1.9)	8.7 (1.3)	0.2
Recovery cycle				
Refractoriness (2.5 ms)	(%)	16.0 (4.2)	8.4 (6.1)	0.3
Superexcitability (7.9 ms)	(%)	-27.1 (1.4)	-23.5 (1.6)	0.036
Late subnormality (42 ms)	(%)	8.8 (1.2)	11.3 (1.7)	0.2
Threshold electrotonus				
TEd 10-20ms	(%)	74.4 (1.9)	74.8 (2.2)	1.0
TEd 90-100ms	(%)	51.5 (2.2)	51.5 (1.9)	1.0
TEh 90-100ms	(%)	-150.8 (10.4)	-154.0 (11.5)	0.8
Current threshold relationship (I/V)				
50% depolarizing current	(%)	57.1 (2.0)	56.8 (2.0)	0.8
100% hyperpolarizing current	(%)	-395.5 (19.6)	-331.8 (18.0)	0.006
Hyperpolarizing I/V slope		0.32 (0.01)	0.41 (0.04)	0.03
Nerve ultrasound (n=13)				
Cross sectional area				
Wrist	(cm^2)	0.11 (0.03)	0.10 (0.03)	0.02
Forearm	(cm^2)	0.09 (0.02)	0.08 (0.02)	0.18
Elbow	(cm^2)	0.12 (0.03)	0.10 (0.01)	0.01

Data are given as mean (SEM).

Figure legends

Figure 1.

Nerve excitability testing in patients with POEMS syndrome and in age-matched normal subjects. A. Strength-duration time constant. B. Recovery cycle of axonal excitability after supramaximal conditioning stimulus. C. Threshold electrotonus. D. Current-threshold relationship. Open and filled circles indicate normal subjects and POEMS patients respectively. Data are given as mean, and error bars indicate standard error.

Figure 2.

Sequential changes in nerve excitability testing before and 3 months after the start of thalidomide or steroid treatment in patients with POEMS syndrome. A. Recovery cycle of axonal excitability after supramaximal conditioning stimulus. B. Current-threshold relationship. Filled and open circles indicate before and after treatment respectively. Data are given as mean, and error bars indicate standard error.

Figure 1.

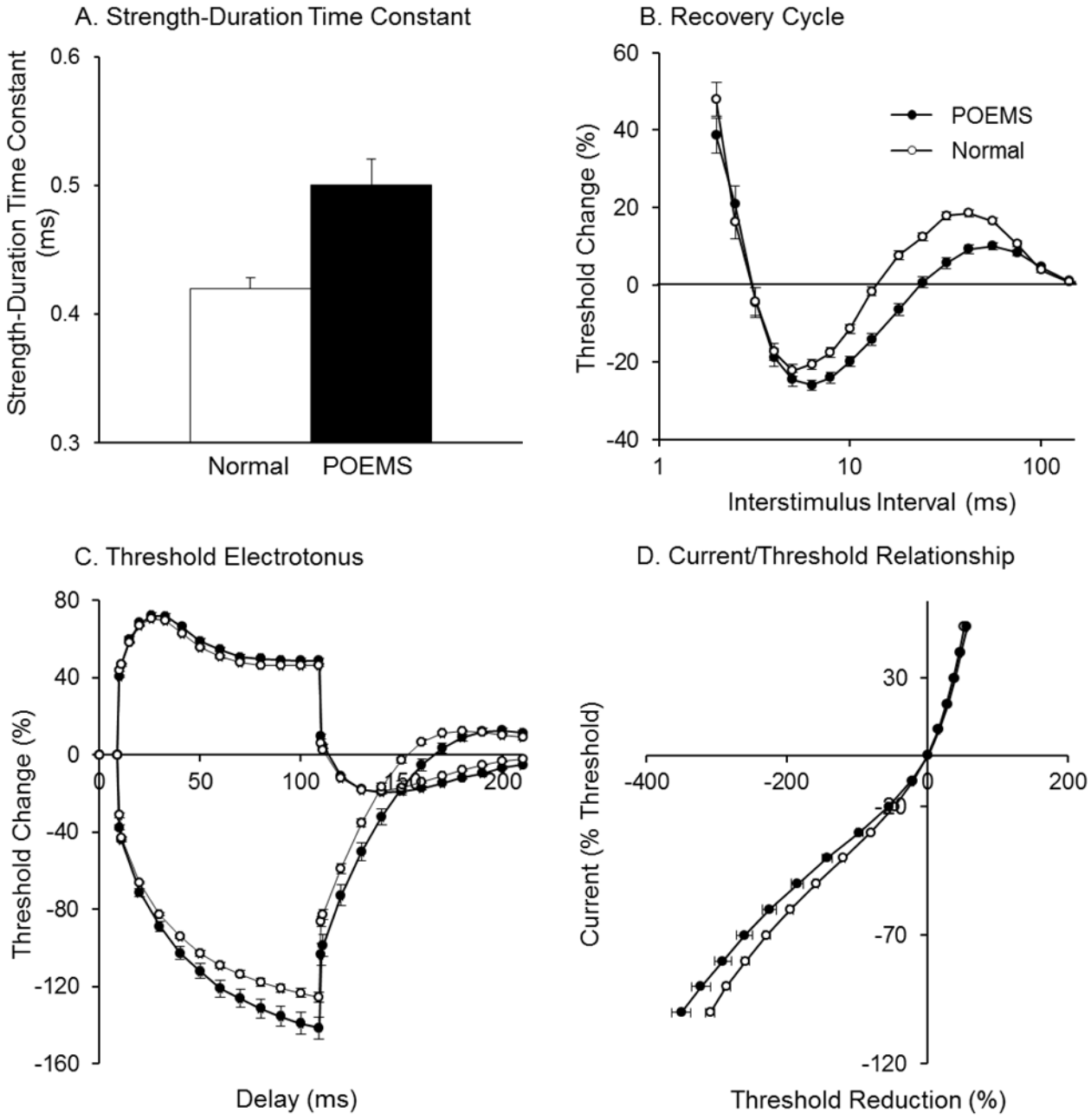
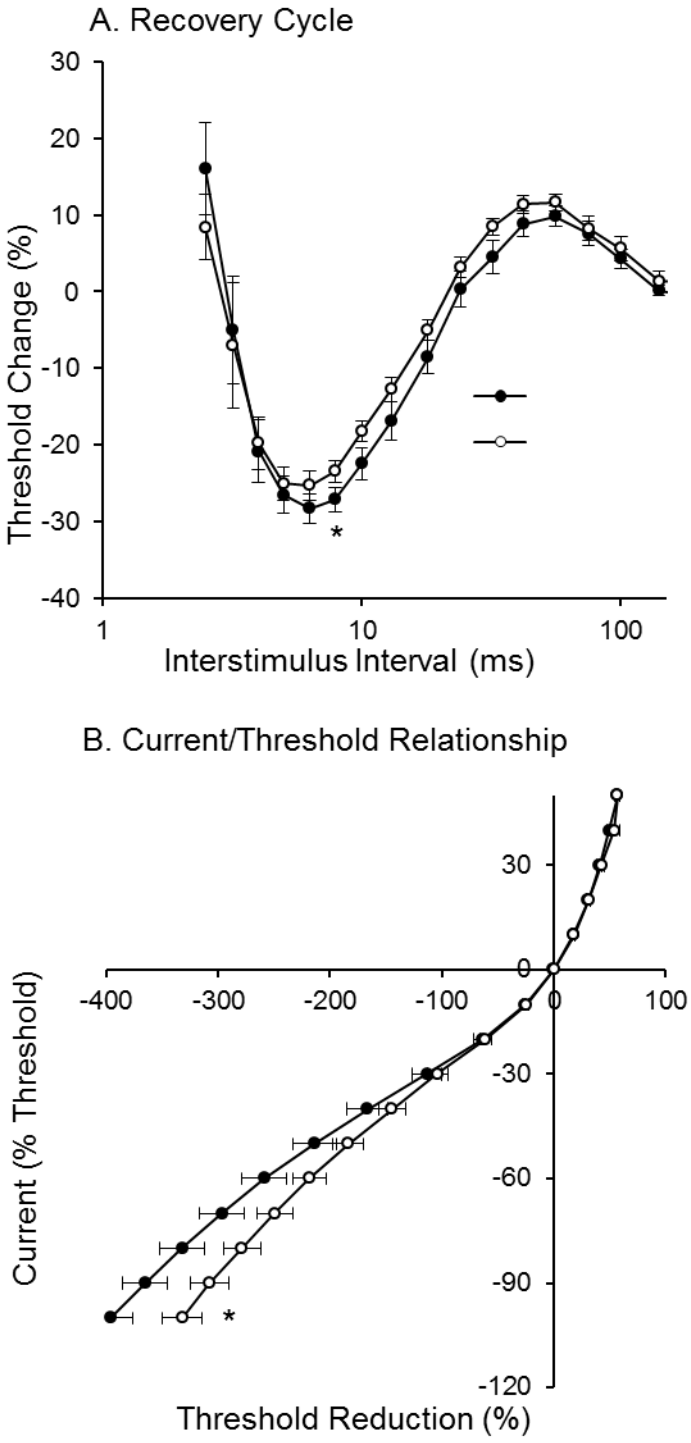

A. Strength-Duration Time Constant
Strength-Duration Time Constant (ms)
0.6
0.5
0.4
0.3
Normal
POEMS
B. Recovery Cycle
Threshold Change (%)
60
40
20
0
-20
-40
1
10
100
Interstimulus Interval (ms)
POEMS
Normal
C. Threshold Electrotonus
Threshold Change (%)
80
40
0
-40
-80
-120
-160
0
50
100
150
200
Delay (ms)
D. Current/Threshold Relationship
Current (% Threshold)
30
-70
-120
-400
-200
0
200
Threshold Reduction (%)

Figure 2.


A. Recovery Cycle
Threshold Change (%)
30
20
10
0
-10
-20
-30
-40
1
10
100
Interstimulus Interval (ms)
*
B. Current/Threshold Relationship
Current (% Threshold)
30
0
-30
-60
-90
-120
-400
-300
-200
-100
0
100
Threshold Reduction (%)
*

Clinical Neurophysiology
平成 27 年 2 月　公表済