

Skin sympathetic outflow in Buerger's disease

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Abstract

To clarify if sympathetic outflow is altered in Buerger's disease (thromboangitis obliterans, TAO), we measured skin sympathetic nerve activity (SSNA) in TAO patients, and observed the sweating and vasoconstrictive responses during resting and with activating maneuvers. Multiunit postganglionic sympathetic activity was recorded in a skin fascicle of the tibial nerve innervating the skin of the sole (glabrous skin) and peroneal nerve innervating the skin of the dorsum pedis (hairy skin) from five TAO patients and five healthy subjects simultaneously with skin blood flow and sweat expulsion. TAO patients showed significantly less vasoconstrictor SSNA than healthy subjects (17.0 ± 1.9 vs. 31.5 ± 5.8 bursts/min, $P < 0.001$). Moreover, we found no relationship between vasoconstrictor SSNA and skin blood flow in some patients, while they were well correlated in healthy subjects. There was no evidence for increased sympathetic activity in TAO patients, and no hypersensitive relationship was found between SSNA and skin blood flow. These observations suggested that these TAO patients exhibiting no relationship between skin blood flow reduction and vasoconstrictor activity might not respond to sympathectomy, which is generally expected to result in an increase in skin blood flow. The absence of increased sympathetic nerve activity provides further indirect evidence of a local vascular abnormality in TAO. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

At present, direct arterial surgery is not frequently feasible for patients with Buerger's disease, i.e. thromboangitis obliterans (TAO), because of multiple and diffuse occlusion of the arteries distal to the popliteal artery (Shionoya et al., 1980). As a procedure that produces vasodilatation, sympathectomy has been widely employed for relief of vasospasm in TAO.

The cause of TAO has not been fully elucidated. One of the pathophysiological features of this disease is vasospasm (Shionoya, 1990). Vasospastic phenomena in TAO lead to Raynaud's phenomenon and are believed to result from an increase in vasoconstrictor tone at the more proximal vessels (Shionoya, 1990). This increase in vasoconstrictor tone was observed as marked vasospasm of the arteries and veins during surgical procedures, as delayed visualization of the distal arteries, and as a 'corrugate' or 'accordion-like' appearance of arteries of the lower ex-

trimities arteries by angiography. In these vasospastic phenomena of the vessels of the limbs, high sympathetic activity or responsiveness is assumed to contribute to TAO (Shionoya, 1990), which was supported by some reports of increased urinary excretion of catecholamines in TAO patients (Iwase, 1963; Ono, 1989). This assumption of sympathetic hyperactivity in TAO patients has been strengthened by the relief of skin symptoms, e.g. coldness, rest pain, and ischemic ulcers (Shionoya et al., 1980), by sympathectomy.

Since the introduction of microneurography (Hagbarth and Vallbo, 1968; Vallbo et al., 1979), recording of muscle sympathetic nerve activity (MSNA) has contributed to elucidation of the pathophysiology of the various disease (Wallin and Fagius, 1988). We reported previously that reduced resting MSNA and hyperresponsiveness to the cold pressor test in TAO patients (Yamamoto et al., 1993). Since the major symptoms of TAO are associated with the skin, the evaluation of SSNA in TAO patients is necessary to assess the sympathetic function in this disease.

The purpose of the present study was to determine the skin sympathetic outflow at rest to assess SSNA in TAO patients. The SSNA can be classified into vasoconstrictor

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and sudomotor components by its effector response (Bini et al., 1980a,b; Sugeno et al., 1990; Iwase et al., 1988, 1995). Since the vasoconstrictor response might be more clearly linked with the skin symptoms, these two components were measured both in *SSNA from the tibial nerve innervating the sole (glabrous skin) and SSNA from the peroneal nerve innervating the dorsum pedis (hairy skin)*, using the double recording technique of microneurography (Iwase et al., 1995; Okamoto et al., 1994). Furthermore, regression analysis between SSNA and responses of effector organs (Iwase et al., 2000), i.e. skin blood flow and sweat expulsion, were examined in TAO patients.

2. Subjects and methods

2.1. Subjects

Five patients with Buerger's disease (TAO) who met the following clinical criteria (Shionoya, 1989) for diagnosis of TAO comprised the TAO group. Briefly they are; (1) smoking history, (2) onset before the age of 50 years, (3) infrapopliteal arterial occlusive lesions, (4) either upper limb involvement or phlebitis migrans, (5) absence of atherosclerotic risk factors other than smoking. All patients were male, mean age was 35 years old (range: 27 to 42 years old), and the mean duration of symptoms was 3.65 years (range: 3 to 6 years). No patients underwent lumbar sympathectomy, nor had they taken any medication for at least 1 week at the time of the examination (Table 1). Their symptoms were ischemic ulcer of the toes in three patients and intermittent claudication after 100–200 m walking for two patients who have already been treated due to TAO for several years. The two patients were smokers, onset in young age, and have phlebitis migrant, lower extremity pain. Their arteriographic findings showed typical findings of TAO. All patients were normotensive, and none had any other disease by physical laboratory examination. Phlebitis migrans was observed in two patients. Five normal healthy volunteers who were age-matched males with a mean age of 29 years (27 to 35 years old) comprised the control group (Table 1). All subjects were informed of the aim and the risks involved in the examination and gave written consent. This study was

approved by the Committee on Human Research, Research Institute of Environmental Medicine, Nagoya University.

2.2. Protocol

The subjects were examined in a supine position. They were required to lie down on a bed with a hole at the popliteal fossa to access the tibial and peroneal nerves. Skin blood flow of the sole was measured by laser Doppler flowmeter (Advance ALF 21, Tokyo, Japan), and sweating was monitored by the ventilated capsule method with Perspiro (Kenz-OSS100, Suzuken, Nagoya, Japan).

2.3. Skin sympathetic nerve activity

Skin sympathetic nerve activity was recorded from the tibial and peroneal nerves simultaneously by the double recording technique at the popliteal fossa using tungsten microelectrodes with a tip diameter of 1 μm and an impedance of 3–5 M Ω (26-05-1, Frederic Haer, Bowdoinham, ME) percutaneously without anesthesia. The criteria for identification of the nerve activity were described elsewhere (Mano, 1990, 1998). Briefly, the nerve activity (1) consisted of spontaneous, irregular, pulse asynchronous efferent burst discharges, recorded from the skin nerve fascicles; (2) was followed by peripheral vasoconstriction or perspiration; (3) was elicited following an almost constant latency (0.8–1.1 s) by mental stress and sensory stimuli (sound, pain, electrical stimulation of the peripheral nerve trunk, etc.); and (4) was elicited by deep breathing (Vallbo et al., 1979; Iwase et al., 1995; Mano, 1990, 1998). The sympathetic nerve signals were fed into two high impedance input preamplifiers (Kohno III, Kohno Instruments, Nagoya, Japan), and band-pass filters (500–5000 Hz, NF Circuit Design, Yokohama, Japan). Neurograms were monitored on a cathode ray oscilloscope (Hitachi VC6023) and a sound amplifier with a loud speaker, and were stored in a DAT tape recorder (Sony Precision Technology Inc., PC-216Ax) for later analysis. Nerve signals were also full rectified, integrated with a time constant of 0.1 s, and displayed by a thermal pen recorder (NEC-San-ei, Recti-Horiz, Tokyo, Japan) as a mean-voltage neurogram. The SSNA was quantified as the

Table 1
Characteristics of TAO patients, TAO Group

Case	Age	Smoking	Phlebitis migrans	Site of occlusion	Ulcer
1	45	+	–	rt. A. anterior tibiariis & poplita lt.A. anterior & posterior tibialis	+
2	42	+	+	rt. F-P graft	–
3	37	+	+	rt. A. femoralis	–
4	32	+	–	rt. Crural arteries lt. Crural arteries	+
5	27	+	–	rt. A. anterior tibiariis & poplita lt. Crural arteries	+

integrated value of the mean voltage neurogram and was expressed as SSNA bursts/min (burst rate).

2.4. Quantification of sweating

The ventilated capsule method was employed for determination of sweat expulsion (Iwase et al., 1995; Sugeno et al., 1990; Okamoto et al., 1994), and for the effector response, the maximal rate of rise of the sweat expulsion (sweat acceleration) was taken as described by Sugeno et al. (1990). Two plastic capsules each with an open surface area of 1 cm² were fixed to the sole and dorsum pedis ipsilateral to the recording side. Dry air was introduced into the capsules at a rate of 0.2 l/min, and drained to highly sensitive capacitance hygrometers to determine humidity. Sweating was quantified by injecting 1 µl of distilled water into the capsule for calibration.

2.5. Measurement of skin blood flow

Laser Doppler flowmetry was employed to measure skin blood flow as an indicator of vasoconstriction (Iwase et al., 1995; Sugeno et al., 1990; Okamoto et al., 1994), and for the effector response, reduction in skin blood flow was taken as described by Iwase et al. (1995). Two probes were attached to the sole and the dorsum pedis ipsilateral to the microneurography.

2.6. Identification of sudomotor and vasoconstrictor nerve activity

SSNA burst followed by a sweat expulsion with latencies of 2.4–3.0 s was classified as a sudomotor (SM) burst (Iwase et al., 1995; Sugeno et al., 1990; Okamoto et al., 1994). SSNA burst followed by a reduction in skin blood flow with latencies of 5–6 s was classified as a vasoconstrictor (VC) burst (Iwase et al., 1995; Okamoto et al., 1994), and SSNA that we were unable to identify as neither sweat expulsion nor reduction in skin blood flow was classified as unidentified activity.

2.7. Experimental protocol

The subjects reclined on a bed in a sound- and light-proof room. Ambient temperature was initially maintained at 25°C for 30 min, during which spontaneous SSNAs from the two nerves were recorded for 20 min. To activate the SSNA, mental arithmetic, supramaximal electric stimulation at the wrist, acoustic stimulation by starting pistol sound, and cold pressor test were loaded to the subjects.

2.8. Statistical analysis

Statistical analysis was assessed by using simple regression, unpaired Student's *t*-tests, and the Chi-square test. *P*

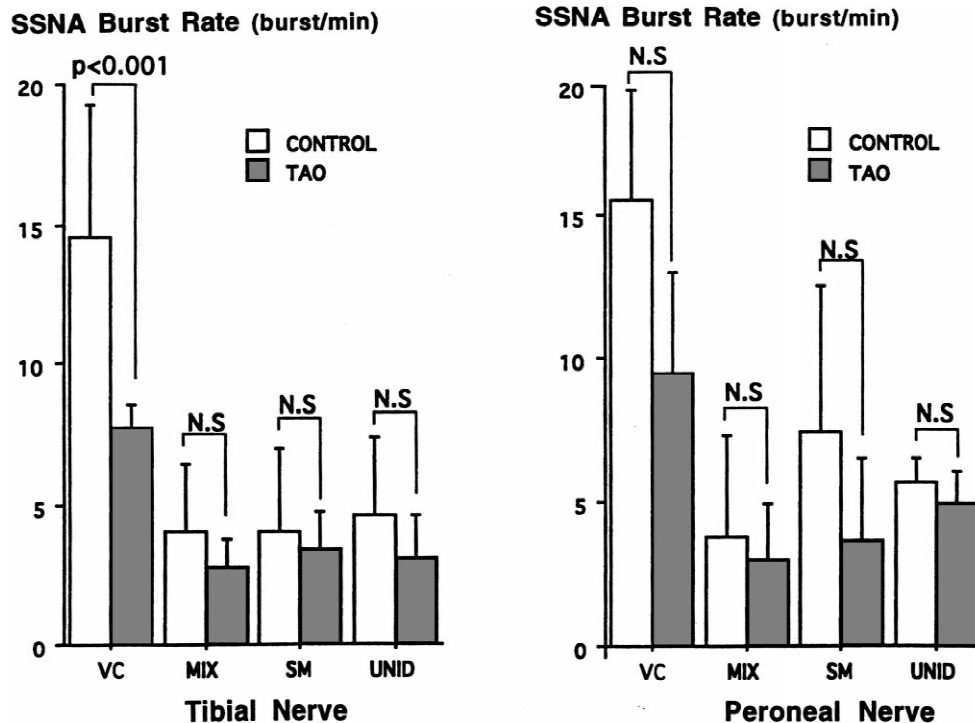


Fig. 1. Burst rate of skin sympathetic nerve activity (SSNA) from the tibial and peroneal nerves. There were significant differences in total and VC of the tibial nerve analysis ($P < 0.001$). The other components of SSNA exhibited no significant differences. Abbreviations: VC – vasoconstrictor burst of SSNA, Mix – mixed burst of VC and SM, SM – sudomotor burst of SSNA, UNID – unidentified burst of SSNA.

values <0.05 are considered significant. Data were shown as mean \pm S.D.

3. Results

3.1. Skin sympathetic nerve activity at rest

Resting SSNA from the tibial nerve for 10 min was significantly lower in the patients with TAO (17.0 ± 1.9 bursts/min) than in control subjects (31.5 ± 5.8 bursts/min, $P < 0.001$). The mean tibial VC burst rate was 7.7 ± 0.8 for TAO, which was significantly lower than that for control (16.7 ± 3.6 bursts/min). The other components of SSNA from the tibial nerve and peroneal nerves did not differ significantly between groups (Fig. 1). The typical traces of SSNA and skin blood flow and sweat expulsion between TAO and control group are shown in Fig. 2. The record-

ings from the control subjects and from the peroneal nerve of the TAO patients have good correspondence to the sweat expulsions or the reduction in skin blood flow following the SSNA bursts, however, the recordings from the tibial nerve of TAO exhibited no correspondence to the responses in the effector organs.

3.2. Vasoconstrictor nerve activity and vasoconstriction

When burst amplitude of vasoconstrictor nerve activity was plotted against the change in skin blood flow during rest, a significant correlation was observed in the control subjects, while no relationship was found in three out of five TAO patients between burst amplitude of SSNA and resulting vasoconstriction in the tibial nerve (Fig. 3). Moreover, there was a significant difference of correlation coefficient for skin blood flow reduction between TAO patients and the control subjects for tibial nerve recording ($P < 0.01$). However, there was no significant difference in correlation coefficient for skin blood flow reduction between TAO patients and the control in the peroneal nerve (Fig. 4).

3.3. Sudomotor nerve activity and sweat expulsion

When the amplitude of tibial SM was plotted against the sweat expulsion of plantar during rest, a significant correlation was observed for all healthy subjects, while not for three out of five TAO patients. There was a significant difference for correlation coefficients of the tibial SSNA and the plantar sweat expulsion between TAO and control subjects during rest ($P < 0.05$, Fig. 4). There was no significant difference for the peroneal SSNA and the dorsal sweat expulsion.

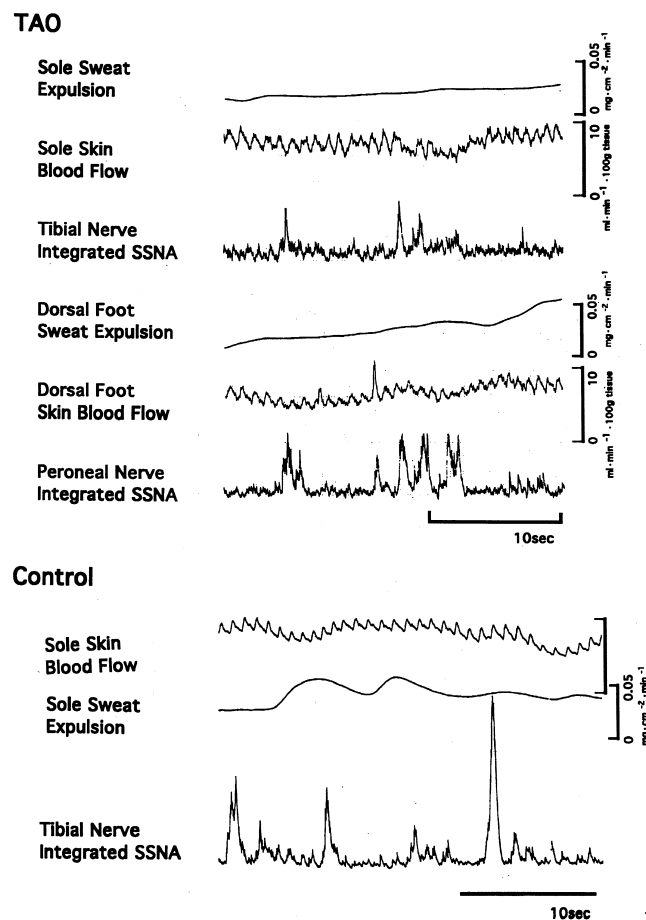


Fig. 2. Comparison of a typical case of skin sympathetic nerve activity (SSNA) and skin blood flow (SBF) and sweat expulsion between TAO group and control group. The upper trace is a recording from the peroneal nerve and dorsal side of the foot of a patient with TAO. Bottom trace is a recording from the tibial nerve and plantar of a healthy subject. Upper trace indicates no correspondence between SSNA and SBF; however, in the other traces, SSNA corresponds to reduction of SBF and sweat expulsion.

4. Discussion

The present study demonstrated that resting vasoconstrictor SSNA discharge from the tibial nerve *innervating to the sole (glabrous skin)* was lowered in the patients with Buerger's disease (thromboangitis obliterans, TAO) while SSNA from the peroneal SSNA *innervating to the dorsum pedis (hairy skin)* exhibited no significant difference between TAO and the control subjects. We also observed that neuroeffector response (Iwase et al., 2000) of vasoconstrictor SSNA to reduction in skin blood flow and of sudomotor SSNA to sweat expulsion was diminished in TAO patients.

Skin sympathetic nerves consist mainly of vasomotor (vasoconstrictor) fibers which innervate vascular smooth muscle to control blood flow, and sudomotor fibers which innervate sweat glands in the skin (Bini et al., 1980a,b; Iwase et al., 1988, 1995; Sugeno et al., 1990). A recent report documented vasodilator fibers in the sudomotor nerve activities to the hairy skin (Sugeno et al., 1998).

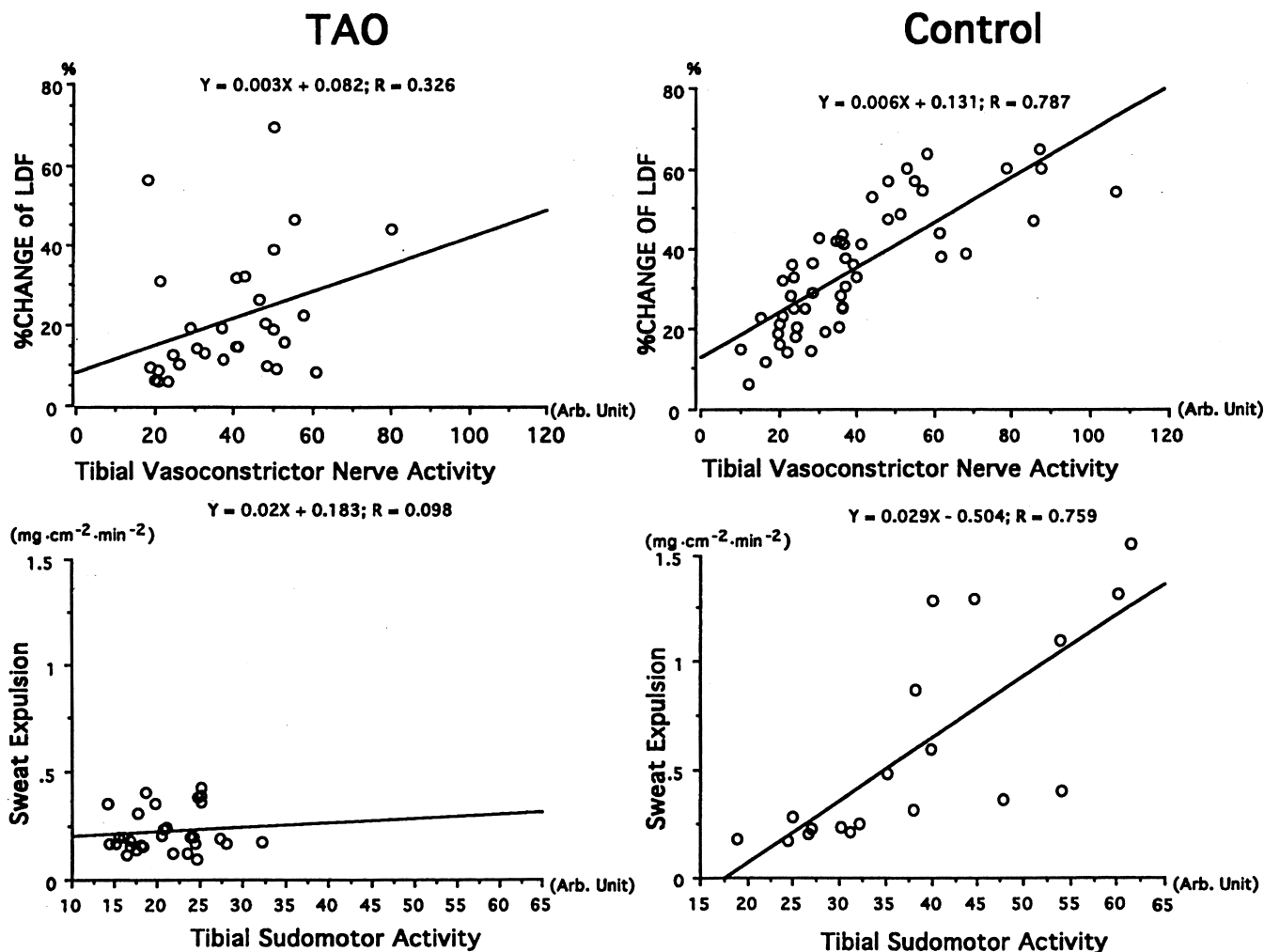


Fig. 3. Relationship between tibial SSNA and effector responses. Upper panels show relationships between SSNA and reduction of skin blood flow, and lower panels are the relationships between SSNA and sweat expulsion. The slopes of the regression lines were significantly greater for control subject than TAO patient.

We observed a linear relationship in healthy subjects between the strength of sympathetic activity (measured as burst amplitude in the mean voltage neurogram) and sweat expulsion, and skin blood flow reduction with much interindividual variability. This linear relationship was also observed in peroneal SSNA in TAO patients, however, not in the tibial. In TAO patients with long history, there was no abnormal sympathetic enhancement, but rather a decrease in SSNA to the lower extremities at rest, especially in vasoconstrictor activity from the tibial. Furthermore, neither a more profound nor a prolonged vasoconstriction was elicited by a single, strong sympathetic burst. Yamamoto et al. (1993) found that the resting muscle sympathetic nerve activity (MSNA) decreased in the tibial nerve of TAO patients. These findings support that the primary sympathetic hyperactivity as a cause of vasospasm is unlikely. It was supposed that the findings showed the tendency to dilate vessels by sympathetic vasomotor regulation under the ischemic condition of skin.

The regional differentiation of human SSNA to the glabrous and hairy skin was firstly demonstrated by Bini et al. (1980b). Since SSNA innervating to the glabrous skin (e.g. tibial SSNA) is easily influenced by mental or emotional activation, it might be natural that the tibial SSNA differs from the peroneal SSNA *innervating to the hairy skin* as observed in the palmoplantar hyperhidrosis (Iwase et al., 1997).

The lack of vasomotion in the microcirculation is characteristic for TAO patients (Shionoya, 1990). The absence of vasomotion would be expected under ischemic conditions requiring maximal vasodilatation while it is controversial whether all arterioles in the critically ischemic area are already maximally dilated. The dependent rubor, a peculiar bluish of the toe and forepart of the foot in TAO indicates vasodilatation and repletion in the subpapillary plexus of the skin, namely stagnation of arterial circulation in the microcirculatory system. As such a stagnant and atonic status in the microvascular system is

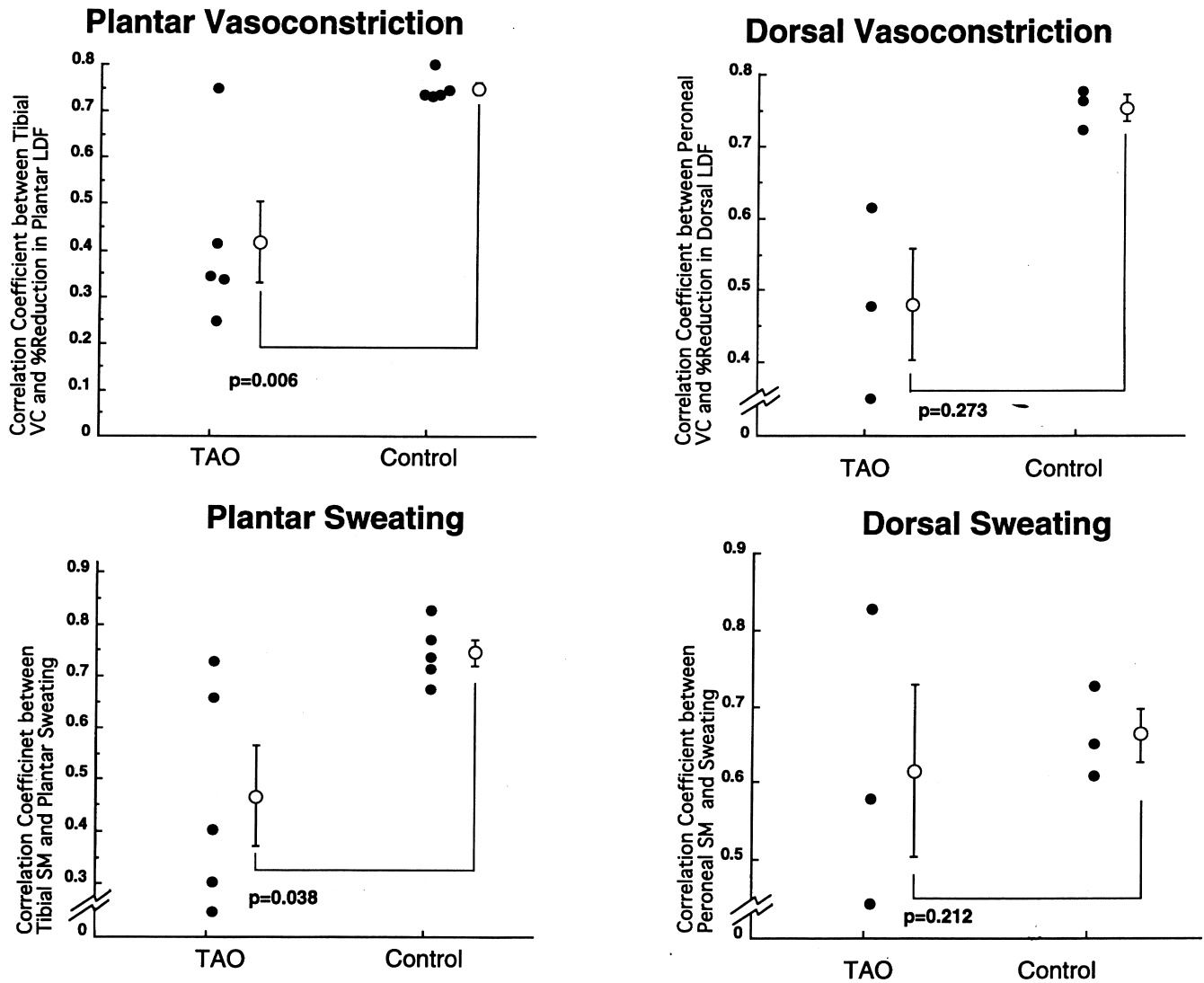


Fig. 4. Logistic regression analysis of correlation coefficient between TAO and control groups. Upper plots were analyzed concerning with plantar vasoconstriction and sweating, lower plots were concerning dorsal vasoconstriction and sweating.

beyond sympathetic vasomotor regulation, the rubor often persists after arterial reconstruction and sympathetic denervation (Shionoya, 1990).

An examination of the relationship between amplitude of SSNA and skin blood flow reduction, and sweat expulsion revealed that the significant difference found between TAO patients and healthy subjects at planter area. Although it could indicate an increased response of vessels to sustained sympathetic activity, we found a lack of correlation in the TAO patient group. In this study, there was a lack of normal neuroeffector response at the tibial innervation area of the sole (glabrous skin), where is a highly developed area of arteriovenous anastomosis in the skin. It is suggested that there is mainly influenced lesion at the microcirculation in the plantar skin.

We have confirmed the vascular response of TAO patients on the level of sympathetic nerve activity; however, it might be an ordinary sympathetic vasomotor

regulative response for the ischemic limbs. We suggest that sympathectomy might induce neither a decrease in the resistance nor vasodilatation of the peripheral vessel, if the sympathetic vasoconstriction rising peripheral vascular resistance is reduced by a certain level. This lack of correlation may indicate a disturbance of the ordinary relationship between sympathetic nerve activity and target vessels in patients with TAO. In this type of TAO patients, the blood flow in the skin of the affected limbs might not increase after sympathectomy because of the vessels of digits have already dilated by reduction in vasoconstrictor activity. However, TAO patients who exhibit a good correlation between sympathetic activity and blood flow in the skin of the affected limbs, may expect clinical improvement of vasospastic symptoms after sympathectomy.

In conclusion, the evidence of decreased vasoconstrictor activity in SSNA of the TAO patients was found using microneurography, and a primary hypersensitivity of the

vessels to strong sympathetic outflow could not be observed, although there might be some kind of changes in the functional relationship between nerves and vessels. In this type of patient, blood flow in the skin of the affected limbs might not increase after sympathectomy while all vessels in the clinical ischemic area are already maximally dilated.

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