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AUTONOMIC RESPONSES TO ENVIRONMENTAL STIMULI IN HUMAN BODY

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ABSTRACT

The author reviewed in this paper current microneurographic findings on the responses of muscle sympathetic nerve activity (MSNA) and skin sympathetic nerve activity (SSNA) to the environment in humans with special reference to vibration-induced white finger (VWF). 1) MSNA was enhanced by +Gz gravitational input, while being suppressed by simulated weightlessness through the baroreflex mechanism to maintain hemodynamic homeostasis. 2) MSNA was enhanced by hypobaric hypoxia through the chemoreflex mechanism. 3) SSNA was lowest under thermoneutral ambient temperature condition. Sudomotor component of SSNA increased under hot ambient temperature, while vasomotor component of SSNA increased under cold ambient temperature. 4) MSNA and vasomotor component of SSNA increased by local cold stimuli such as when a hand was immersed into cold water. 5) SSNA was enhanced by local vibration of the human body. The vibratory frequency of 60 Hz was the most effective for vibration-induced SSNA response. With a constant vibratory frequency of 60 Hz, SSNA increased depending on the vibratory acceleration. MSNA was not enhanced by local vibration of the body. 6) SSNA was markedly enhanced by combined stimuli of local vibration and noise. 7) MSNA increased during handgrip exercise, presumably depending on afferent inputs from muscle metaboreceptors. 8) The sympathetic response to environmental stress was markedly influenced by aging. The basal level of MSNA increased with aging, while the MSNA responsiveness to gravitational stress became reduced by aging. MSNA responsiveness to simulated weightlessness was also reduced by aging. 9) Vibration-induced white finger may be related to complex autonomic dysfunctions including excessive somato-sympathetic reflex induced by local vibration, cold stimuli and handgrip exercise. Gravity-dependent sympathetic nerve responses and the influence of aging may also contribute to the underlying mechanisms of VWF.

Key Words: Autonomic response, Microneurography, Sympathetic nerve activity, Environment, Aging, Vibration-induced white finger, Human.

INTRODUCTION

Autonomic responses to environmental stimuli in human body have been so far studied indirectly by observing the responses of autonomic effector organs (heart rate, blood pressure, skin blood flow, sweating, pupillary responses etc.) or by measuring the plasma level of noradrenalin. Meanwhile, recent advance in microneurographic technique has enabled us to approach more directly the autonomic nervous responses to environmental stimuli in human subjects.

Using microneurography, we can record sympathetic nerve activities leading to muscle (muscle sympathetic nerve activity; MSNA) and skin (skin sympathetic nerve activity; SSNA). MSNA is mainly composed of vasoconstrictor activity leading to blood vessels in skeletal muscle, playing an essential role to maintain homeostasis of the systemic blood pressure. MSNA may also contribute to the control of muscle tone and muscle metabolism. SSNA is composed of sudomotor and vasoconstrictor activities leading to sweat glands and skin blood vessels, con-

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trolling sweating and skin blood flow. SSNA may also modulate the sensitivity of skin sensory receptors.

Vibration-induced white finger (VWF) may be related to complex multifactorial autonomic responses to various kinds of environmental stimuli, including not only vibratory or thermal stimuli, but also gravitational, altitude and exercise (hand gripping) stimuli. Aging may be also an important factor to influence autonomic responses to environment related to VWF. By applying the microneurographic technique, we have so far analyzed how the sympathetic nervous system in humans responds to various kinds of environmental stimuli under normal and abnormal conditions.[1] We have also analyzed how aging influences the sympathetic nerve responses to environmental stimuli.[2–6] In this paper, I would like to review current microneurographic findings on autonomic responses, particularly sympathetic nerve responses to environmental stimuli in human body.

MICRONEUROGRAPHY AS A TOOL TO INVESTIGATE SYMPATHETIC NERVE ACTIVITY IN HUMANS

Microneurography is a method for recording somatosensory afferent discharges and sympathetic efferent activities from human peripheral nerves in situ.[7] The first report concerning the recording of sympathetic nerve impulses was made in Sweden by Hagbarth and Vallbo[8] in 1968. This technique has become used so far as a direct tool to investigate sympathetic nerve activity in human subjects in clinical and research fields. Using this technique, we can record postganglionic sympathetic nerve outflows leading to muscle (muscle sympathetic nerve activity; MSNA) and skin (skin sympathetic nerve activity; SSNA). It has been made clear that these two sympathetic nerves activities discharge independently according to the regional differentiation.

Microneurographic technique to record and identify the sympathetic nerve activity from human peripheral nerve

A tungsten microelectrode with a shaft diameter of about 100 to 200 μm and a tip diameter of about 1 μm, which is insulated by epoxy resin except for the tip, and has an impedance around 1 − 5 MΩ at 1 kHz, is used to record microneurographically the sympathetic nerve activity. Neural traffic is recorded as voltage difference between an intra-neurally inserted recording electrode and a reference electrode placed in the vicinity of the recording electrode. The nerve discharges are fed into a preamplifier with a high impedance input and band-pass filtering between 500 and 5000 Hz. The output of the preamplifier should be amplified and then monitored on a cathode ray oscilloscope. Sound monitoring of the sympathetic nerve activity is also extremely important, because of the characteristic sounds of MSNA and SSNA. The recorded sympathetic nerve activity can be stored in a data recorder using magnetic tapes or discs with other parameters for later analysis.

All peripheral nerves approachable from the skin can be used for microneurographic recording. In general, median or radial nerves in the upper extremities, and tibial or peroneal nerves in the lower extremities are used for microneurographic recording. In rare cases, facial or trigeminal nerves in the face and intercostal nerves can be also used for microneurographic recording.

If the electrode tip is inserted into the muscle nerve fascicle of a nerve, MSNA can be recorded. In this case, sensory afferent discharges from peripheral muscle receptors innervated by the impaled nerve can be also elicited by mechanical stimulations such as tapping, squeezing, or stretching the muscle, but not by gently touching the skin. When the electrode tip is placed in

the skin nerve fascicle, SSNA can be recorded. In this case, afferent discharges from peripheral skin receptors can also be elicited by gently touching or tapping the skin area innervated by the impaled nerve. Muscle and skin sympathetic nerve activities can be recorded by a minute displacement of the electrode tip in the muscle or skin nerve fascicle, respectively.

The identification of muscle and skin sympathetic nerve activities is based on the following discharge characteristics. MSNA: 1) pulse-synchronous spontaneous and rhythmic efferent burst discharges recorded from muscle nerve fascicle; 2) modulation by respiration; 3) increase by a fall and decrease by a rise in systemic blood pressure; and 4) enhancement by maneuvers increasing intra-thoracic pressure such as Valsalva's maneuver. SSNA: 1) spontaneous arrhythmic efferent burst discharges recorded from skin nerve fascicle; 2) being followed by peripheral vasoconstriction or perspiration; and 3) elicitation with almost constant latency by mental stress and sensory stimuli (sound, pain, electrical stimulation of the peripheral nerve trunk etc.).

The identification of the nerve fibers discharging with the above-mentioned characteristics as belonging to the efferent C-fiber group is based on the following findings. 1) The discharges are not modified by local anesthetic infiltration distal to the recording site, blocking simultaneously recorded afferent somatosensory impulses, while they are abolished rapidly by local anesthetic infiltration proximal to the recording site, with an increase in peripheral skin blood flow in the case of vasoconstrictor activity without changing somatosensory afferent activities. 2) The double recording technique using two different sites in the same nerve clearly shows that the discharge recorded in the proximal site always precedes the discharge recorded in the distal site. The conduction velocity measured as inter-electrode distance divided by the interval of two discharges shows the value of the C-fiber range to be around $1 - 2$ m/sec.[1)]

Quantitative evaluation of MSNA and SSNA

MSNA can be evaluated quantitatively as a burst rate, which refers to the number of sympathetic bursts per minute. The burst rate is expressed as the absolute value and is suitable for evaluating inter-individual variations of MSNA, because it has been proved to be reproducible in individual subjects. To evaluate MSNA independently of the heart rate, the number of sympathetic bursts per 100 heart beats has been also used as the term of burst incidence. Burst incidence is also suitable for evaluating inter-individual variations of MSNA. Not only the burst number of MSNA but also the discharge frequency of each sympathetic nerve fiber and recruited number of discharging fibers in the burst are modulated under different conditions. These are expressed as the amplitude of the full-wave rectified and integrated traces of the sympathetic burst discharge. Thus, total MSNA is expressed as burst amplitude multiplied by burst rate. This value, which is expressed as an arbitary unit, is only reliable when the electrode tip is not moved for the duration of the experiment. Under these conditions the total MSNA is the most suitable parameter for evaluation of intra-individual variations of MSNA. SSNA may be expressed as a burst rate as for MSNA, but it seems to be better analyzed as total SSNA, which expresses the total area of the full-wave integrated SSNA bursts, because of the irregularity in frequency, amplitude, and duration of these SSNA bursts.

SYMPATHETIC NERVE RESPONSES TO ENVIRONMENT

The microneurographic technique has been used to analyze directly the responses of MSNA and SSNA to various environmental conditions.[1)] I would like to review here current microneurographic findings on sympathetic nerve responses to different kinds of environmental stimuli in human subject with special reference to the vibration-induced white finger.

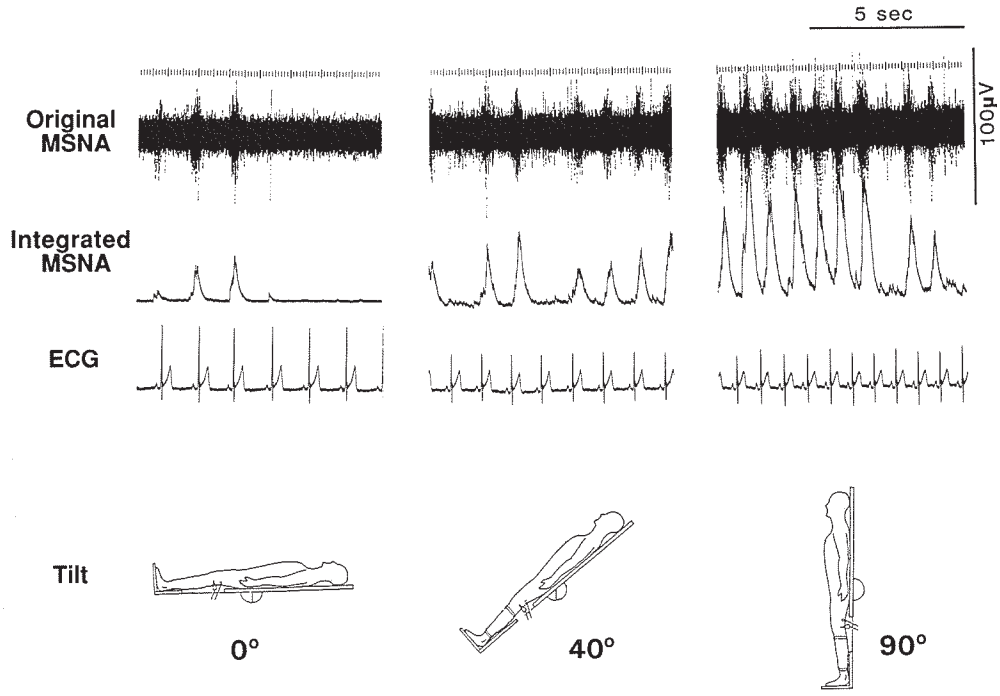

Fig. 1. Response of MSNA to head-up tilting
MSNA is enhanced by head-up tilting depending on the tilt angle, maximally discharging when the subject is kept in upright position. (Modified from Iwase et al. 1987[10])

Sympathetic nerve responses to gravity

One of the most important stimuli to the human body on the earth is terrestrial gravity. When the human being changes his or her posture, gravitational input to the human body becomes altered. The gravitational input from the head to the leg (+Gz) is zero during supine posture, while increasing when changing the posture to the upright position. Burke et al.[9] reported that MSNA recorded from the peroneal nerve was increased by changing the posture from a horizontal supine position to sitting, and from sitting to standing. Iwase et al.[10,11] reported that MSNA recorded from the tibial nerve was increased by head-up tilting from a horizontal supine to an upright posture (Fig. 1). There was a significant positive correlation between the sine function of the tilt angle (+Gz) and the burst rate (burst number/min) of MSNA, but a significant negative correlation between stroke volume and MSNA burst rate. This finding may indicate that MSNA responds to +Gz stimulus in the upright standing posture of the human body, which induces venous pooling in the legs and a decrease in venous return to the heart, thereby reducing the stroke volume. One sympathetic response to this gravitational stimulus is an acceleration of heart rate, which serves to increase the cardiac output. The MSNA response to gravitational stimulus is important in maintaining hemodynamic homeostasis by increasing peripheral vascular resistance. MSNA was also increased by lower body negative pressure[12–14] which had been used to simulate +Gz gravitational stimulus in the human body. In this case, the venous blood is shifted from the upper part of the body to the lower part. This may stimulate not only high pressure (arterial) baroreceptors but also intrathoracic low pressure volume receptors. The unloading of these receptors may be responsible for the activation of MSNA associated with the fluid shift due to gravitational stress.

Sympathetic nerve responses to weightlessness simulated by head-out water immersion

To understand the sympathetic nerve responses to gravity, it may be also interesting to analyze the sympathetic nerve responses to the gravity-free condition. This analysis may be effected under the microgravity condition in space in the near future. However, at the present stage, microneurographic technique remains difficult to apply during space flight. The analysis can be made under a simulated condition of weightlessness. Thermoneutral head-out water immersion has been often used to simulate weightlessness on the earth. In this condition, buoyancy reduces body weight, and hydrostatic pressure to the lower part of the human body induces a cephalad fluid shift, similar to that supposed in space, increasing venous return to the heart and stroke volume. We have reported that MSNA recorded from the tibial nerve in standing human subjects is markedly suppressed by head-out water immersion.[11,15–18] The suppression of MSNA was proportional to the level of immersion up to the neck, being maximally reduced with immersion to the neck. When the MSNA was measured in the course of water immersion simultaneously with leg volume by means of mercury-in-silastic rubber strain gauge plethysmography, stroke volume, cardiac output, systemic blood pressure and total peripheral vascular resistance (mean blood pressure divided by cardiac output), there were significant positive correlations between leg volume or total peripheral vascular resistance and the MSNA, while there were significant negative correlations between stroke volume or cardiac output and the MSNA. There was no significant correlation between systolic, mean, or diastolic blood pressure and MSNA.[18] These findings may suggest that the suppression of MSNA during head-out immersion is related to a reduction in leg volume, which indicates cephalad fluid shift. The suppressive response of MSNA during water immersion may reduce peripheral vascular resistance to compensate for the increase in the stroke volume and cardiac output due to cephalad fluid shift, thus maintaining hemodynamic homeostasis, cooperating with humoral mechanisms such as Gauer-Henry reflex[19] which reduces the secretion of antidiuretic hormone. SSNA, recorded from the tibial nerve which innervates the plantar skin, was also suppressed by head-out thermoneutral water immersion, but much less than MSNA.[16] This may signify that the role of SSNA in controlling hemodynamic homeostasis against fluid shifts is less important than the role of MSNA.

Sympathetic nerve responses to hypobaric hypoxia (simulated high altitude)

Atomospheric pressure and related oxygen supply are also important to modify autonomic responses in the human body. Blumberg and Oberle[20] suggested for the first time that MSNA in humans was increased by hypoxia induced through inhalation of low-oxygen gas. Saito et al.[21] reported that MSNA in humans recorded microneurographically from the tibial nerve while sitting was increased when the subject was exposed to a hypoxic-hypobaric environment in a low pressure chamber. When the simulated altitude was elevated stepwise from 0 m (sea level) to 7,000 m, the MSNA burst rate increased with the altitude. However, there were large variations among individuals in this response of MSNA to hypobaric hypoxia, which increased beyond the altitude of 5,000 m. MSNA was transiently reduced beyond the altitude of 6,000 m concomitantly with the appearance of symptoms of mountain sickness, including bradycardia, arterial hypotension, nausea, facial pallor or faintness. With oxygen inhalation, MSNA increased quickly with the recovery from these clinical symptoms. Rowell and Blackmon[22] measured simultaneous changes in MSNA and plasma norepinephrine levels when the subject inhaled low-oxygen gas. They reported that MSNA was increased by inhalation of gas with oxygen concentrations of 12, 10 and 8%, but there was a discrepancy between MSNA and plasma norepinephrine responses. Under normal atmospheric pressure, MSNA has been reported to correlate with the plasma norepinephrine level.[23,24] Plasma norepinephrine was much less influenced than MSNA by hypoxia. This influence may depend on the inhibition of norepinephrine release at the nerve

terminal due to hypoxemia, or modification of the balance between the release and the metabolism of this substance while under hypoxia. The increase in MSNA under hypoxia may indicate that this activity is regulated not only by baroreceptors but also by chemoreceptors.

With regard to the effects of hypobaric conditions on MSNA, the influence of hypocapnia should be also considered, since the sensitivity of chemoreceptors is modified by arterial hydrogen ion levels (pH) even under the same arterial oxygen saturation. Somer et al.[25] reported that the MSNA recorded from the peroneal nerve increased more during hypocapnic hypoxia than during isocapnic hypoxia, in which condition minute ventilation and blood pressure increased significantly more than during hypocapnic hypoxia. They concluded that sympathetic response to hypoxia depends on the interactions between chemoreceptor stimulation and the associated hyperventilation. The sympathetic nerve response to chemoreceptor stimulation may represent the net effects of the excitatory influence of the chemoreflex and the inhibitory influence of the pulmonary afferents and baroreceptor afferents. The same authors[26] compared the effects of isocapnic hypoxia and hyperoxic hypercapnia on MSNA recorded from the peroneal nerve, and concluded as follows. 1) Hyperoxic hypercapnia caused a greater increase of MSNA than isocapnic hypoxia. 2) Hypercapnia caused a greater increase of MSNA than hypoxia. However, during apnea, hypoxia caused a much greater increase in MSNA than hypercapnia. 3) The inhibitory influence of ventilation on MSNA was greater during hypoxia than hypercapnia. 4) Combined hypoxia with hypercapnia have synergic effects on MSNA.

Sympathetic nerve responses to ambient temperature

The sympathetic nervous system plays an essential role for thermoregulation in the human body. SSNA, which is composed of sudomotor and vasoconstrictor activities, is particularly important for thermoregulation controlling sweating and skin blood flow under various ambient temperature conditions. Bini et al.[27] differentiated vasomotor and sudomotor components of SSNA recorded from the median nerve based on simultaneous recordings of finger plethysmogram and galvanic skin response in the palm. They reported that the vasomotor component of SSNA increased under the ambient temperature of 15°C and was suppressed under the ambient temperature of 43°C. In contrast to this, the sudomotor component of SSNA was reduced under the cold environment of 15°C and was increased under the hot environment of 43°C. Iwase et al.[28] reported that SSNA was lowest at the thermoneutral ambient temperature around 22° to 26°C. At higher than this temperature the sudomotor component was increased, while at lower than this temperature the vasomotor component was increased. Sugenoya et al.[29,30] identified the sudomotor component of SSNA using simultaneous recording of sweat expulsion by means of the ventilated capsule method and reported that the sudomotor activity rose at high ambient temperatures with a close relationship to tympanic temperature, while the vasomotor components, which were followed by reductions of blood flow measured by laser-Doppler flowmetry at the level of the dorsum pedis, were not modified by body temperature.

One of the questions concerning SSNA is whether differences exist between SSNAs leading to glabrous skin, which is dominated by mental sweating, and those leading to hairy skin, which is dominated by thermal sweating. Using double nerve recordings, Bini et al.[31] reported that vasoconstrictor burst activities recorded simultaneously from the median and peroneal nerves during exposure to the cold environment showed a striking similarity with respect to the timing and strength of individual bursts. A similarly strong correlation was observed also among sudomotor bursts recorded simultaneously from the posterior cutaneous antebrachial and superficial radial nerve during exposure to the warm environment. Based on these findings, they concluded that in the distal glabrous skin areas thermoregulatory functions were mainly executed via

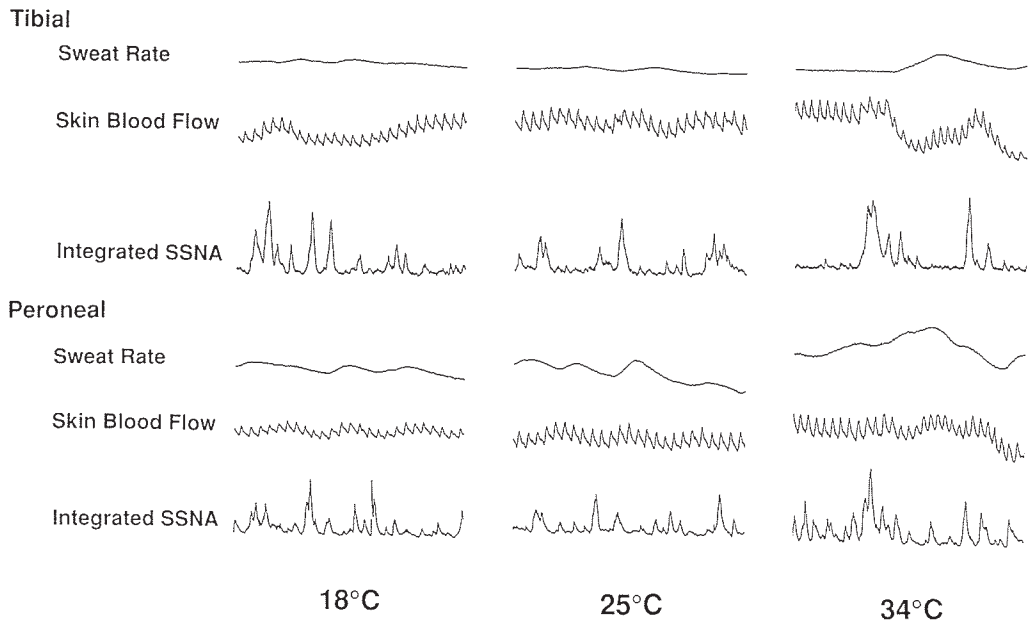

Fig. 2. SSNA under different ambient temperature
SSNAs recorded simultaneously from the tibial and the peroneal nerves were lowest at the ambient temperature of 25°C, while increasing at 18°C and 34°C. (Okamoto et al.[32])

vasoconstrictor fibers whereas sudomotor fibers were activated only at relatively high temperatures. Contrary to this, in hairy skin on the dorsal side of the forearm and hand, reflex thermoregulation was to a large extent executed via sudomotor fibers. Recently, Okamoto et al.[32] compared the SSNA in the peroneal nerve innervating hairy skin with that in the tibial nerve innervating plantar glabrous skin using a technique of simultaneous recording under different ambient temperature conditions. SSNAs in both nerves were lowest under the ambient temperature of 25°C, while increasing under the temperatures of 18°C and 34°C (Fig. 2). However, there were differences in discharges between the sudomotor and vasomotor components of SSNA in both nerves. At the ambient temperature of 30°C, the sudomotor component in the peroneal nerve and the vasomotor component in the tibial nerve were high, while at the ambient temperature of 18°C, the sudomotor components in both the peroneal and tibial nerves were reduced and the vasoconstrictor component in the tibial nerve was increased. These findings may indicate that sudomotor and vasomotor sympathetic activities in the peroneal and tibial nerve are controlled differently under different ambient temperature conditions.

It has been speculated that the skin sympathetic nerve innervates not only the sweat glands and skin blood vessels, but also skin sensory receptors including nociceptors and mechanoreceptors, controlling the receptor sensitivity. Hakusui et al.[33] reported the changes in SSNA recorded in one subject who suffered from Raynaud's phenomenon under the low ambient temperature of 5°C, when sweating and skin blood flow in the finger became almost abolished. In this situation, SSNA was markedly enhanced with the appearance of finger pain, without changing sweating and skin blood flow (Fig. 3). This finding may indicate that enhanced SSNA may be responsible for the painful symptom in Raynaud's phenomenon under the cold environment sensitizing the cutaneous nociceptors.

Regarding MSNA changes in humans related to the ambient temperature, Sugiyama et al.[34]

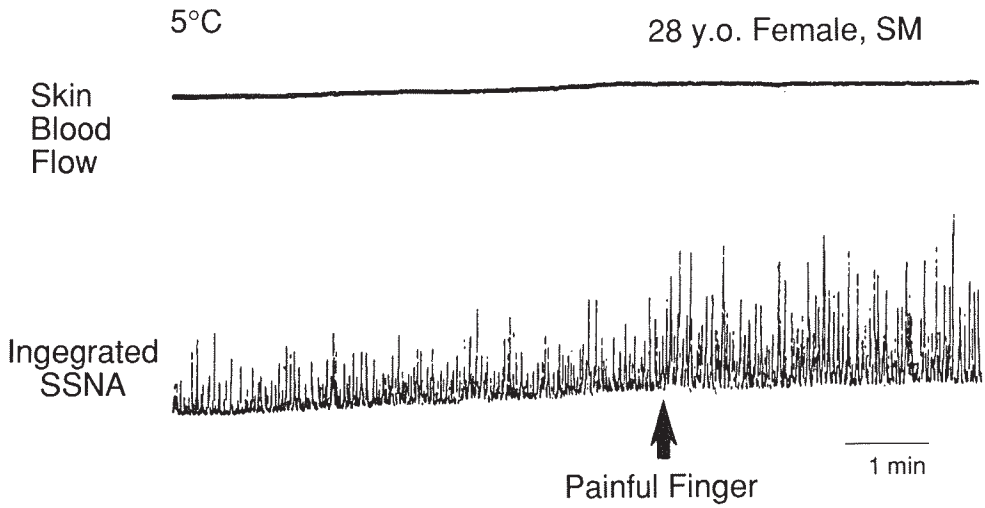

Fig. 3. SSNA recorded from the median nerve at the ambient temperature of 5°C SSNA increased concomitantly with the appearance of Raynaud's phenomenon with finger pain. (Modified from Hakusui et al. 1989[33])

observed the effects of low ambient temperature on MSNA and shivering. MSNA increased at low ambient temperature conditions in all subjects. However, there were large variations among individuals in the MSNA during the shivering. When shivering became manifest, there was a transient suppression of MSNA in some subjects, while an increase of MSNA occurred in other subjects. The MSNA response associated with shivering was related to changes in respiration and blood pressure, which varied with the subject.

Sympathetic nerve responses to local thermal stimuli

The sympathetic nervous system responds not only to the ambient temperature, but also to local thermal stimuli of the human body. There have been studies on sympathetic nerve activities in which the effects of immersion into cold or hot water of a part of the human body are reported. Victor et al.[35] indicated that the cold pressor test maneuver, in which one hand was immersed into ice water for 2 minutes, enhanced MSNA in the peroneal nerve from 30 seconds after the onset of immersion. Fagius et al.[36] also reported an increase of MSNA recorded from the peroneal nerve during the ice water immersion of one hand. This increase was associated with blood pressure elevation, and they concluded that the cold pressor test is a powerful activator of MSNA, i.e., baroreceptor-governed vasoconstrictor outflow. Yamamoto et al.[37] reported that the initial effect of the cold pressor test was due to an increase of cardiac output, while the late effect was attributed to the increase of MSNA. Fagius and Sundlöf[38] reported that MSNA in the peroneal nerve was enhanced by immersing the face into water of 20°C for 12 seconds. This maneuver elicits the so-called diving reflex with a marked response in bradycardia. The enhancement of MSNA occurred before the appearance of bradycardia. These MSNA responses to partial immersion of the human body in cold water seem to be induced by a reflex depending on somatosensory afferent inputs, especially from the skin of the immersed body part.

With regard to SSNA response to partial body immersion, the effects of immersion of a hand into cold and hot water have been studied. Fagius et al.[36] reported that immersion of one hand into cold water did not induce consistent changes in SSNA recorded from the peroneal nerve in

the lower extremities, although the same maneuver did elicit the increase of MSNA in the peroneal nerve. Fagius and Blumberg[39] reported that SSNA recorded from the median nerve was increased when the contralateral hand was immersed into ice water in healthy subjects and in patients with Raynaud's phenomenon. They found no evidence for increased sympathetic activity underlying Raynaud's phenomenon, nor for a primary hypersensitivity of the vessels to sympathetic outflow, although there may have been some changes in the functional relationship between nerve and vessel. They suggested that Raynaud's phenomenon was concerned with some kind of local fault mechanism. This conclusion seems to be contradictory to the above-mentioned finding by Hakusui et al.[33] that in one case who presented Raynaud's phenomenon, SSNA was increased concomitantly with the appearance of finger pain.One of the reasons for this contradiction may be due to the difference in cold stimulus. Hakusui's case was exposed to cold ambient temperature, while Fagius and Blumberg immersed the hand into cold water. Kunimoto and Mannen[40] reported that immersion of a hand into cold water elicited an increase in SSNA recorded from the median nerve with lowering the skin temperature, followed by a decrease in SSNA with a transient elevation of skin temperature. This may suggest that a sympathetic suppressive response is responsible for the mechanism of cold-induced vasodilation (hunting reaction). Nagasaka et al.[41] demonstrated an increase in SSNA recorded from the median nerve during transient vasoconstriction induced by immersion of the hand into a water bath in which the temperature was raised every 10 min by steps of 2°C from 35°C or 37°C to 41°C. A local anesthetic blockade of the median nerve at the site proximal, but not distal, to the recording site abolished the responses of SSNA and finger blood flow to immersion of the hand into the hot bath. The authors concluded that heat-induced vasoconstriction exactly opposite to hunting reaction was evoked reflexly, largely through increased sympathetic outflow to the resistance vessels of the finger.

Sympathetic nerve responses to local vibration

Vibratory stimulus is the most important factor in the pathophysiological mechanism of VWF. Naito[42] reported that SSNA recorded from the median nerve in the upper limb was

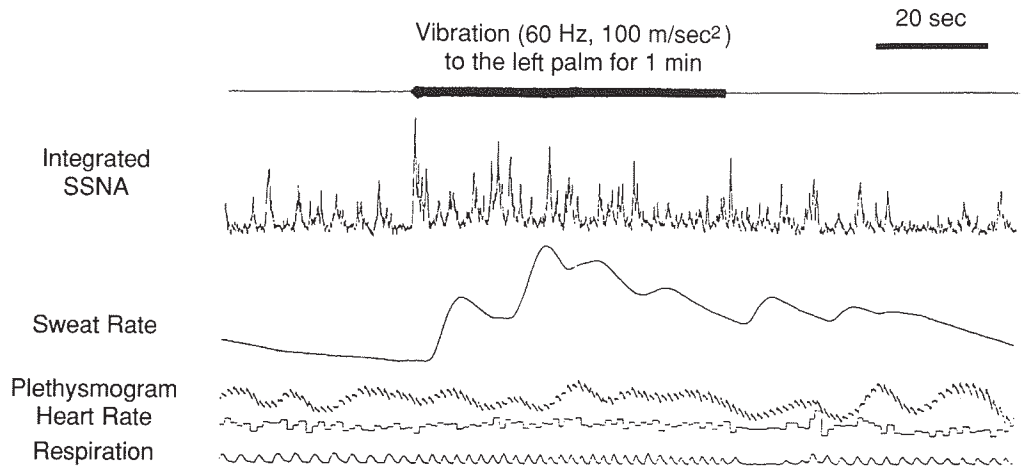

Fig. 4. Response of SSNA to local vibration
Local vibration of 60 Hz with the acceleration of 100 m/sec² to the left palm for 1 min elicits an increase of SSNA recorded from the right tibial nerve concomitantly with an increase of sweat rate. (Modified from Sakakibara et al. 1990[43])

significantly increased, with a reduction of the skin blood flow by local vibration of 50 m/s^2 at 60 Hz applied to the contralateral hand during the grip of the same hand under a constant grasping power of 2 kg. The SSNA was also increased but less by local vibration of 50 m/s^2 at 120 Hz. Sakakibara et al.[43] reported that SSNA recorded from the tibial nerve in the lower limb was enhanced with vasoconstriction of the toe and perspiration on the sole of the foot by local vibration of 100 m/s^2 at 60 Hz applied to the palm of the hand (Fig. 4). Takeuchi[44] also found that local vibration of the palm induced an increase in SSNA recorded from the tibial nerve with a reduction in skin blood flow in the toe. He analyzed how the difference in acceleration and frequency of local vibration to the palm influences the SSNA response recorded from the tibial nerve. As the parameter of local vibration, he used three different accelerations of 10, 31.2 and 100 m/s^2 with the constant frequency of 60 Hz, and three different frequencies of 60, 125 and 250 Hz with the constant acceleration of 100 m/s^2. When the frequency was constant, SSNA increased depending on the acceleration (Fig. 5). When the acceleration was constant, SSNA increased most at the vibratory frequency of 60 Hz and less at the frequency of 125 and 250 Hz

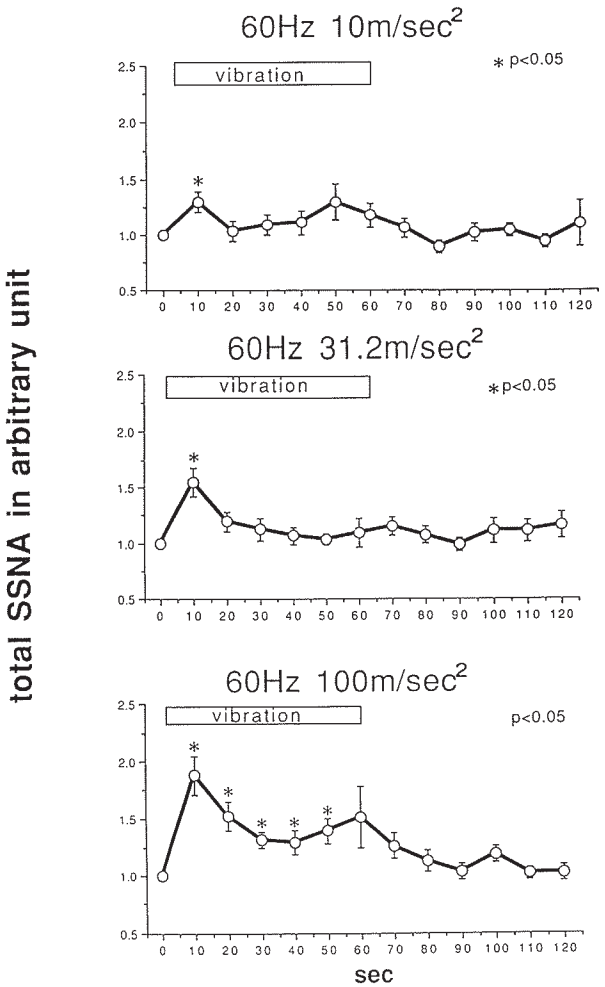

Fig. 5. Response of SSNA to local vibration with different stimulus acceleration
Local vibration of 60 Hz to the left palm for 1 min elicits an increase of SSNA recorded from the tibial nerve depending on the stimulus acceleration. (Takeuchi[44])

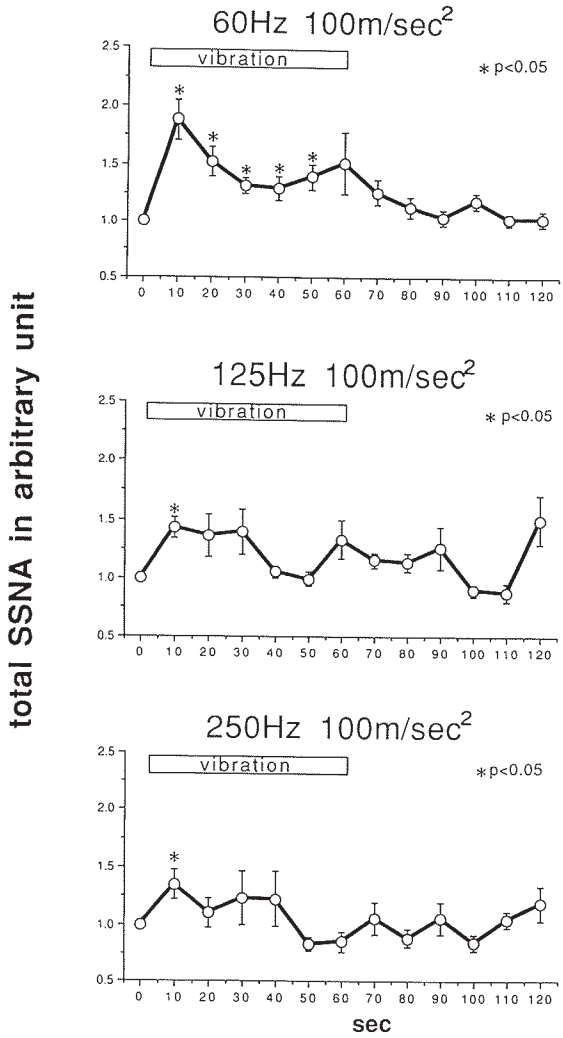

Fig. 6. Response of SSNA to local vibration with different stimulus frequency
Local vibration with constant acceleration to the left palm for 1 min elicits the maximum increase of SSNA recorded from the right tibial nerve at the vibratory frequency of 60 Hz. (Takeuchi[44])

(Fig. 6). Takeuchi investigated also the effect of the same kinds of vibratory stimuli on MSNA recorded from the tibial nerve, but he did not find any increase in MSNA. On the contrary, he found a significant decrease of MSNA in the tibial nerve induced by local vibration of 10 m/s^2 at 60 Hz applied to the palm. Mark et al.[45] also reported that local vibration of the upper limb did not increase MSNA recorded from the peroneal nerve in the lower limb.

These findings may indicate that local vibration increases SSNA but not MSNA. The local vibration to the hand increases SSNA not only in the upper limb but also in the lower limb to reduce skin blood flow and increase perspiration on the sole. The vibration-induced activation of SSNA seems to be acceleration-dependent when the vibratory frequency is constant. Regarding vibratory frequency, 60 Hz vibration seems to be most effective to induce SSNA increase. Mano and Miyaoka[46] demonstrated microneurographicaly in humans that vibratory stimuli to the

palm with a relatively low frequency around 30 — 50 Hz were mainly perceived by Meissner corpuscle, while those with relatively high frequency around 150 Hz or more were mainly perceived by Pacinian corpuscle. Based on this finding, it may be presumed that the vibration-induced sympathetic activation is mediated predominantly by Meissner corpuscle rather than Pacinian corpuscle.

Sympathetic nerve responses to noise

SSNA is characterized to respond to various sensory stimuli including tactile and pain stimuli to the skin, electrical stimulation of the sensory nerve, light and sound stimuli depending on the mechanism of somato-sympathetic reflex. SSNA also responds strongly to unexpected sudden noise, but it may habituate rather rapidly to repeated noise. Naito[42] analyzed the SSNA response in the median nerve when the subject was exposed to noise of 57 dB(A) and 100 dB(A). She found no response to 57 dB(A) noise and a significant increase of SSNA only at the initial phase of 100 dB noise stimuli. The same author found a pronounced increase of SSNA to combined stimuli of 100 dB noise and local vibration of 50 m/sec^2 at 60 Hz applied to the hand and noise. This finding may indicate that although expected constant noise does not influence SSNA much, it may enhance sympathetic drive to the skin when associated with other kinds of environmental stimuli such as local vibration.

Sympathetic nerve responses to static exercise (handgrip)

The handgrip exercise may be also important for the mechanism of VWF. The effect of hand gripping has been particularly studied on MSNA, since the exercise has strong influences on systemic blood pressure. MSNA recorded from the tibial or peroneal nerve in the lower limb was enhanced by hand gripping depending on the duration and intensity of the exercise. Saito et al.[47] reported that this MSNA enhancement was related to subjective fatigue sensation of the contracting muscle. Mark et al.[45] reported that the MSNA enhancement during hand gripping persisted after the discontinuance of the exercise, when the blood supply to the contracting muscle was occluded. They also found that the vibratory stimuli to the muscle mechanoreceptors in resting arm did not increase MSNA recorded from the peroneal nerve. Victor et al.[48] reported based on their study using microneurography and ^{31}P-NMR spectrometry that MSNA enhancement during static exercise was related to a reduction of intracellular pH in the contracting muscle. From these findings it has been speculated that MSNA is enhanced during exercise by a reflex mechanism depending on afferent inputs from muscle metaboreceptors (chemoreceptors) which are stimulated by muscle metabolites. With regard to SSNA response to handgrip, Saito et al.[49] reported that SSNA recorded simultaneously with MSNA from bilateral tibial nerves was also enhanced by hand gripping but mainly at the initial phase of the exercise, in contrast to time-dependent increase of MSNA (Fig. 7). This may signify that SSNA may not be enhanced by afferent input from muscle metaboreceptors, which increases depending on the duration of the exercise.

INFLUENCE OF AGING ON SYMPATHETIC NERVE RESPONSES TO ENVIRONMENT

Age is one of the important factors which influence autonomic responses to environment. Microneurographic analysis has revealed that the individual level of MSNA is dependent on the age of the subject. Sundlöf and Wallin[50] reported that there was a weak positive correlation between the age of the subject and the burst incidence signifying the number of bursts per 100

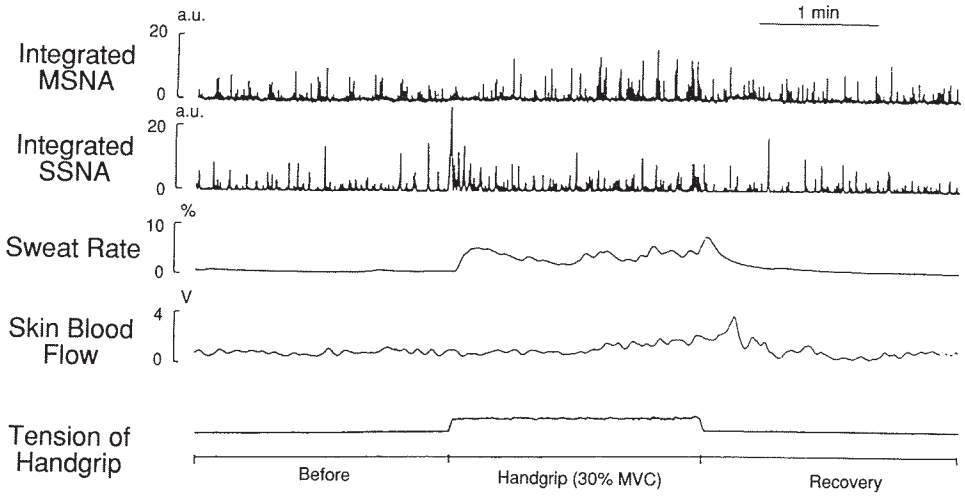

Fig. 7. Response of MSNA and SSNA to handgrip exercise
Handgrip exercise with a tension at 30% of maximum voluntary contraction elicits an increase in both MSNA and SSNA recorded simultaneously from the bilateral tibial nerves, concomitantly with an increase in sweat rate in the sole.

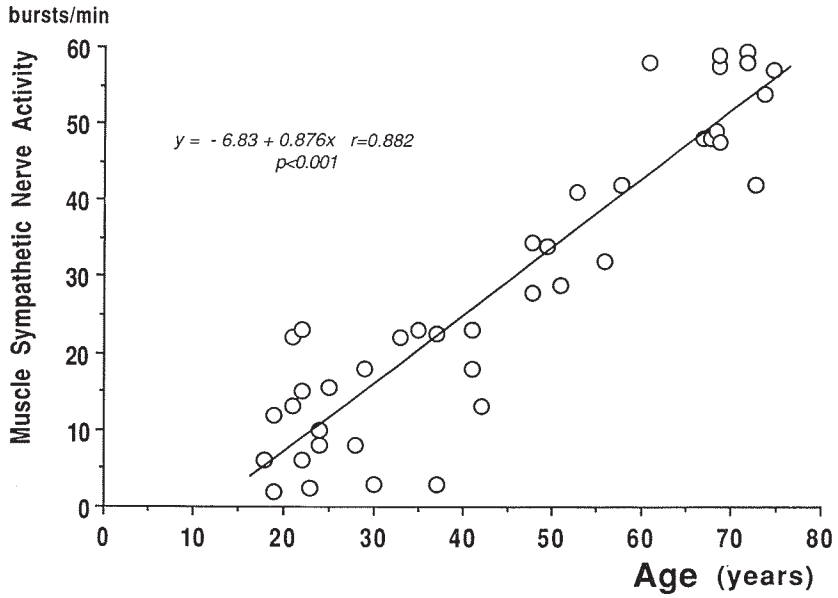

Fig. 8. Correlation between age and basal level of MSNA
The basal level (bursts/min at rest) of MSNA recorded from the tibial nerve increases with age. There exists a significant positive correlation between the age of the subject (abscissa) and the basal level of MSNA (ordinate).

heart beats of MSNA as recorded from the peroneal nerve while in a supine position. Iwase et al.[2,3] and Mano et al.[4] studied systematically the effects of aging on MSNA recorded from the tibial nerve while in a supine resting condition and during head-up tilting, in subjects of different ages ranging from 18 to 75. They found that the basal level of MSNA expressed as the burst rate, while in a supine resting position increased with age. There was a significant positive correlation between the age of the subject and the burst rate of MSNA at rest (Fig. 8). During head-up tilting from a horizontally supine position (0°) to an upright position (90°), the burst rate of MSNA increased linearly with the sine function of the tilt angle (+Gz). There was no significant difference between the age and the MSNA burst rate during upright standing. Consequently, the change in MSNA burst rate during tilting from 0° to 90° was reduced by aging because of a higher resting activity at 0°. There was a significant negative correlation between the age of the subject and the change in MSNA burst rate induced by head-up tilting.

On the other hand, the suppressive response of MSNA to weightlessness simulated by thermoneutral head-out water immersion was less prominent in the older subjects than in the younger ones.[5,6] There was a significant negative correlation between the age of the subject and suppression rate of MSNA during head-out immersion.[6] One of the causes of age-dependent changes in MSNA may be age-dependent changes in baroreceptor functions. Although the details of the mechanisms of age-dependent changes in MSNA have not yet been clarified, it may be important to consider the effects of aging when studying sympathetic responses to environments.

The influence of aging on sympathetic nerve responses to other kinds of environmental stimuli, including somoto-sympathetic reflexes, should be studied in the near future.

SYMPATHETIC NERVE MECHANISM OF VIBRATION-INDUCED WHITE FINGER

VWF is related to complex autonomic dysfunctions. Among sympathetic nerve responses to the environment mentioned above, the response to local vibration is the most important factor in the pathophysiological mechanisms of VWF. Microneurographic analysis has revealed that local vibration to the palm increases SSNA not only in the upper limb but also in the lower limb.[43,44] This may signify that local vibration of the palm can enhance overall sympathetic drive to the skin in the human body. As the result of enhanced sympathetic drive, vasoconstriction may occur not only in the hand but also in the foot to induce not only white finger but also white toe. Vibration-induced SSNA response may depend on the somoto-sympathetic reflex. Vibratory frequency of 60 Hz was the most effective to induce SSNA response. Somatic afferent informations of local vibration to the skin at the frequency of 60 Hz may be mediated mainly by skin mechanoreceptive unit of Meissner corpuscle, because this cutaneous mechanoreceptor is most sensitive to 60 Hz vibration.[45] Noise is one of the factors considered to be responsible for VWF. Expected constant noise does not seem to be important for the sympathetic enhancement, but the combined stimuli of noise and local vibration can accelerate vibration-induced enhancement of sympathetic drive to the skin.[42]

Another important factor for VWF is cold stress which enhances sympathetic drives to the skin and muscle. Cold-induced enhancement of sympathetic drive depends partly on the somato-sympathetic reflex, in which the somatic afferent input may be mediated by skin cold nociceptors. The enhancement of SSNA induces skin vasoconstriction and white finger, while the enhancement of MSNA may induce an elevation of the systemic blood pressure. The effect of hand grip exercise may be also related to the mechanism of VWF. This kind of exercise

enhances not only MSNA by somato-sympathetic reflex depending on afferent input from muscle metaboreceptors,[47] but also SSNA.[49] In this case also, the enhancement of MSNA elevates systemic blood pressure and that of SSNA induces skin vasoconstriction. VWF may be related to complex mechanisms including excessive somato-sympathetic reflexes induced by vibration, cold stress and hand grip exercise.

Gravitational stress may also have some roles for the sympathetic mechanisms of VWF. Since chain saw operators work principally in the standing or sitting position, they are exposed to +Gz gravitational stress. MSNA is enhanced by baroreflex mechanism depending on +Gz gravitational input. The gravity-dependent enhancement of MSNA may also influence the above-mentioned vibration/cold/exercise-induced somato-sympathetic reflex related to VWF. Aging is also one of the important factors influencing the sympathetic nerve response to environment. For example, aging elevates the basal level of MSNA, but reduces its response to gravitational stress. The effect of aging on SSNA or somato-sympathetic reflexes has not been so far studied systematically, but it may be indispensable to consider the influence of aging on the sympathetic nerve mechanism of VWF.

CONCLUSION

The sympathetic nervous system in humans responds differently to various kinds of environmental stimuli, such as gravity, altitude, ambient temperature, local temperature, local vibration or exercise. Aging is an important factor influencing sympathetic nerve responses to environment. Complex autonomic dysfunctions, including sympathetic nerve responses to local vibration, noise, cold stimuli and handgrip exercise with excessive somoto-sympathetic reflexes, may be responsible for the underlying mechanisms of vibration-induced white finger.

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