Microneurographic Research on Sympathetic Nerve Responses to Environmental Stimuli in Humans

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The sympathetic nervous system plays an important role to maintain the homeostasis of vital functions in humans against environmental stimuli. Sympathetic nerve responses to environmental stimuli in humans have been assessed conventionally using rather indirect methods by analyzing the responses of effector organs or by measuring the changes in plasma norepinephrine level. Meanwhile, the microneurography technique has enabled us to approach the sympathetic nervous system in humans more directly. By applying this technique, it has become possible to investigate how the human sympathetic nervous system responds to different kinds of environmental stimuli. In this paper, the usefulness of microneurography as a research tool in environmental physiology is shown together with a review of microneurographic findings on sympathetic nerve responses to environmental stimuli in humans.

I. Microneurography as a Tool to Investigate Sympathetic Nerve Activity in Humans

Microneurography is an electrophysiological method to record sensory afferent and sympathetic efferent activities from human peripheral nerves in situ [1]. In 1960, Hensel and Boman [2] reported, for the first time, a recording of single afferent fiber discharges from human peripheral nerve in situ using a glass pipette microelectrode. Seven years later, two different groups in Sweden reported recordings of afferent discharges from human peripheral nerve using a metal microelectrode. Knutsson and Widén [3] used a glass-coated platinum–iridium microelectrode to record single afferent nerve activity, while Hagbarth and Vallbo [4] used an epoxy resin–coated tungsten semi-microelectrode to record multi-fiber afferent discharges from human peripheral nerves. The original technique using a tungsten microelectrode reported by Hagbarth and Vallbo has devolved to the microneurography which is used today.

The first recording of multi-fiber sympathetic nerve activity in humans was reported by Hagbarth and Vallbo in 1968 [5]. Since then, microneurography has become to be used in many countries as a tool to investigate sympathetic nerve activity in human subjects in clinical and research fields. Using this technique, postganglionic sympathetic nerve traffic leading to muscles (muscle sympathetic nerve activity; MSNA) and skin (skin sympathetic nerve activity; SSNA) can be recorded separately. It has been made clear that these two sympathetic nerves discharge independently according to regional differentiation [6]. Microneurography is going to be used before, during and after spaceflight in the space shuttle “Neurolab,” to be launched in April 1998, to elucidate how MSNA in astronauts becomes modified by exposure to microgravity in space. For this purpose, microneurography was included for the first time by NASA in medical examinations for the selection of astronauts, who were requested not only to be excellent microneurographers but also to be good subjects for MSNA recording.

1. Microneurography technique to record and identify sympathetic nerve activity from human peripheral nerves

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 of around 1–5 MΩ at 1 kHz, is used to microneurographically record the sympathetic nerve activity from human peripheral nerves. Nerve discharges are recorded as voltage differences between an intra-neurally inserted recording electrode and a reference electrode (surface or needle electrode) placed in the vicinity of the recording electrode. The nerve discharges are fed into a bio-amplifier with a high impedance input and band-pass filtered between 500 and 5,000 Hz. The output of the bio-amplifier should be monitored on a cathode ray oscilloscope with recording, for example, on a thermal array recorder. 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 an analogue or digital data recorder using magnetic tapes or discs with other parameters for later computer analysis (Fig. 1).

All peripheral nerves approachable by the percutaneously inserted tungsten microelectrode can be used for microneurographic recording. Generally median, ulnar, or radial nerves in the upper extremities, and tibial, peroneal or sural nerves in the lower extremities are used for microneurographic recording. In the USA and European countries, the most frequently used nerve for MSNA recording is the peroneal nerve into which the recording electrode is inserted near the fibular head. In Japan, the tibial nerve is most frequently used for sympathetic microneurography. In this case, the recording electrode is inserted through the popliteal fossa (Fig. 1). The double recording of MSNA simultaneously from the tibial and peroneal nerves revealed that MSNAs from these two nerves, which innervate a pair of antagonistic muscles, had almost synchronous and similar discharge burst patterns [7]. On the contrary, SSNA recorded from these two nerves showed different discharge patterns as mentioned later. In rare cases, facial or trigeminal nerves in the face and intercostal nerves can also be used for microneurographic recordings.

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 also be elicited by mechanical stimulation such as tapping, squeezing or stretching the muscle, but not by gentle touching of 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 gentle touching or tapping of 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 these muscle and skin sympathetic nerve activities is based on the following dis-charge 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 (Fig. 2), 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 (Fig. 3), and (3) elicitation with almost constant latency by mental stress and sensory stimuli (sound, pain, electrical stimulation of the peripheral nerve trunk, etc.).

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, simultaneously blocking 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 [8]. (2) The double recording from 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/s [9].

2. Quantitative evaluation of sympathetic nerve activities

Microneurographically recordable sympathetic nerve activity is generally composed of multi-fiber burst distress which can be full-wave rectified and then integrated. Based on integrated traces of neural traffic, MSNA has been evaluated quantitatively as burst rate, which refers to the number of sympathetic bursts per minute. This value is expressed as absolute 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 a 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 number of discharging fibers are modulated under different conditions. The recruited number of discharging fibers
is expressed as the amplitude of the full-wave rectified and integrated traces of the sympathetic nerve activity. Thus, total MSNA is expressed as burst amplitude multiplied by burst rate. This value, which is expressed as an arbitrary unit, is only reliable when the electrode tip is not moved for the duration of the experiment. Under these conditions, total MSNA is the most suitable for evaluation of intra-individual variations of MSNA. A method of quantifying MSNA burst area using frequency domain analysis was proposed not only for evaluation of intra-individual variations but also for inter-individual comparisons [10]. SSNA may be expressed as burst rate, but it seems to be better analyzed as total SSNA, which expresses the total area of the full-wave rectified and integrated SSNA bursts, because of the irregularity in frequency, amplitude and duration of SSNA bursts.

II. Sympathetic Nerve Response to Environmental Stimuli

Microneurography has become a potent research tool in the field of environmental physiology. Using this technique, the changes in MSNA and SSNA have been studied under different environmental conditions [9, 11]. Microneurographic findings on sympathetic nerve response to environmental stimuli in human subjects are reviewed below.

1. Gravitational stimuli

Gravity is always constant on the earth, but gravitational input from the head to the leg (+Gz) in human body can be altered by changing the posture. The value of +Gz is 0 when the subject lies horizontally and becomes 1.0 when the subject stands up. The MSNA recorded from the peroneal nerve was enhanced by changing the posture from a horizontal supine position to sitting, and from sitting to standing [12]. The MSNA recorded from the tibial nerve was increased by head-up tilt from a horizontal supine to an upright posture [13–19] (Fig. 4). In this case, there was a significant positive correlation between the sine function of the tilt angle (gravity component from the head to the leg; +Gz) and the burst rate of MSNA (Fig. 5). There was a significant negative correlation between stroke volume and MSNA burst rate. This finding may indicate that MSNA responds to gravitational stimuli 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. The MSNA response to gravitational stimuli seems to be important in maintaining hemodynamic homeostasis by vasoconstrictive function, increasing peripheral vascular resistance against gravitational stimuli. MSNA was enhanced by lower body negative pressure (LBNP), which had been used to simulate +Gz gravitational stimuli in humans [20–23]. LBPN induces a fluid shift from the upper part of the body to the lower part, which unloaded not only high-pressure (arterial) baroreceptors but also cardiopulmonary low-pressure

Fig. 4. Response of muscle sympathetic nerve activity (tibial nerve) and electrocardiogram to passive head-up tilt. Modified from Iwase et al. [13].
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Fig. 5. Correlation between sine function of tilt angle (+Gz) and burst rate (bursts/min) of muscle sympathetic nerve activity recorded from the tibial nerve. Modified from Iwase et al. [13].

(volume) receptors. The unloading of both high and low-pressure baroreceptors caused by a fluid shift due to gravitational stimuli may be extremely important for the enhancement of vasoconstrictive MSNA. Recent studies have shown that stimulation of the vestibular system enhances MSNA [24]. It is also suggested that afferent input from mechanoreceptors in antigravity muscles can increase orthostatic enhancement of MSNA in humans [25]. Based on these findings, it may also be necessary to consider the role of vestibular and somatosensory systems in relation to MSNA responses to gravitational stimuli.

2. Orthostatic intolerance

Orthostatic intolerance with orthostatic hypotension, with or without syncopal attack, is one of the clinical manifestations of sympathetic disregulation of blood pressure against gravitational stimuli. It was reported that there were two different groups of subjects who suffer from orthostatic intolerance. One was a high responder and the other a low responder of MSNA to gravitational stimuli [26]. In the high MSNA responder group, hypotensive attacks occurred when MSNA responded highly to head-up with tachycardia. In these cases, orthostatic hypotension occurred just after the sudden withdrawal of MSNA associated with marked bradycardia and transient cardiac arrest, which were manifested most frequently at tilt angles of 60–70°. Sudden sympathetic withdrawal just prior to and/or associated with the syncopal attack were reported in vasovagal syncope [27, 28], syncope induced by glossopharyngeal neuralgia [29], and carotid sinus syncope [30, 31]. Progressive withdrawal of MSNA was also reported for vasovagal syncope during LBNP [32]. These findings indicate that a transient vasodilation in muscle due to an absence of vasoconstrictive MSNA may be responsible for syncopal attack in these cases. However, it was reported that neurally-mediated “active” vasodilation should occur during syncope, because the skeletal muscle vasodilation seen during syncope was greater than that caused by sympathetic withdrawal alone [33]. An activation of the vasovagal reflex presumably induced by a strong tachycardia, an excessive increase of MSNA, or both may elicit the sudden inhibition of MSNA. A case of dopamine β-hydroxylase deficiency with a long history of symptoms of orthostatic intolerance presented much higher basal MSNA than age-matched control subjects with appropriate response to head-up tilt [34]. After a 5-month treatment, in this case with L-threo-3,4-dihydroxyphenylserine (L-threo-DOPS), the synthetic precursor of norepinephrine, there was a dramatic clinical improvement with resolution of the orthostatic symptoms and dramatic reduction in MSNA at rest.

In the low MSNA responder group, orthostatic hypotension was associated with poor MSNA response to head-up tilt. Patients of multiple system atrophy or Shy-Drager’s syndrome present this type of orthostatic hypotension. In these cases, MSNA was often not detectable or scarcely discharged in the horizontal supine position, and responded poorly to head-up tilt. The administration of L-threo-DOPS increased MSNA and ameliorated orthostatic hypotension in a case of Shy-Drager syndrome [35]. In 4 cases of peripheral autonomic failure with a protracted history of postural hypotension, MSNA was not detectable in 3 cases and scarcely discharged only in one case under resting conditions. There was no discernible response of MSNA to head-up tilt in all of these cases [34]. It was also reported that MSNA in cases with neurally-mediated syncope had blunted increases to low tilt levels, compared to age and sex-matched controls, followed by a progressive decrease and ultimately complete disappearance [36]. These cases had lower baroreflex sensitivity during tilt. This report challenges the view that generalized sympathetic activation is the precursor of the hemodynamic abnormality underlying neurally mediated syncope.

3. Simulated microgravity

Parabolic flight using a jet airplane is a method to produce short-term (around 20 s) microgravity conditions. During this microgravity, MSNA recorded from the tibial nerve in sitting subjects was transiently suppressed in accordance with the lack of +Gz [37] (Fig.
6). On the contrary, during short-term hypergravity conditions just before and after microgravity, MSNA was enhanced according to the increase of +Gz. The changes in MSNA during parabolic flight were related to changes in intrathoracic and leg fluid volume, which indicate body fluid shift. The MSNA suppression in microgravity was induced by increased intrathoracic fluid volume due to a cephalad fluid shift. These findings indicate that MSNA is enhanced by increased gravitational load on humans, while being suppressed by the lack of +Gz, depending at least in part on the unloading and loading of cardiopulmonary baro- or volume receptors.

Thermoneutral head-out water immersion has also been used to simulate microgravity on the earth. In this condition, buoyancy reduces body weight, and hydrostatic pressure to the lower part of the body induces a cephalad fluid shift, increasing venous return to the heart and the stroke volume. The MSNA recorded from the tibial nerve in standing humans was markedly suppressed by head-out water immersion [38–47]. The suppression of MSNA was proportional to the level of immersion up to the neck, being maximally reduced with immersion to the shoulders or neck (Fig.7). When MSNA was measured in the course of 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 MSNA, while there were significant negative correlations between stroke volume or cardiac output and MSNA [41]. There was no significant correlation between systolic, mean, or diastolic blood pressure and MSNA. 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 increases in the stroke volume and cardiac output due to cephalad fluid shift; thus maintaining hemodynamic homeostasis, cooperating with humoral mechanisms which reduces the secretion of antiuretic hormone (Gauer-Henry reflex). The effects of changes of somatosensory afferent inputs may also be concerned with the suppression of MSNA during water immersion. This problem should be resolved through future study. 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 [39]. This may signify that the role of SSNA in controlling hemodynamic homeostasis against fluid shift is less important than that of MSNA.

Dry immersion is a method to simulate prolonged microgravity conditions. The subject floats on a water-

![Fig. 6. Array display of response in muscle sympathetic nerve activity (tibial nerve) to microgravity induced by parabolic flight. Reprinted from Iwase et al. [37].](image)

![Fig. 7. Response of muscle sympathetic nerve activity (tibial nerve), electrocardiogram, and mean blood pressure to thermoneutral head-out water immersion to the navel and shoulder. Reprinted from Miwa et al. [47].](image)
proof sheet in thermoneutral water. The recording of MSNA before and after 3 d of dry immersion carried out at the Institute of Biomedical Problems, State Scientific Center of Russia, Moscow, showed that MSNA became higher after exposure to simulated microgravity. A subject who presented orthostatic intolerance after 3 d of dry immersion had a high MSNA response to head-up tilt of 60° followed by a sudden orthostatic hypotensive attack (unpublished data). MSNA recorded after 6 d (experiment carried out at the Tsukuba Space Center, National Space Development Agency of Japan in 1996) and 120 d (experiment carried out at the Institute of Biomedical Problems, State Scientific Center of Russia, Moscow in 1997) of head-down (−6°) bedrest to simulate prolonged microgravity, also showed a higher MSNA level than the control value before the bedrest (unpublished data). These findings suggest that MSNA becomes rather higher after exposure to prolonged microgravity. This may signify that post-spaceflight orthostatic intolerance may not be induced by reduced MSNA response to gravitational stimuli, but may depend on an unknown mechanism related to the enhancement of MSNA. More exact information about the role of MSNA in post-spaceflight orthostatic intolerance will be provided by the microneurography experiments using the space shuttle Neurolab, which is to be launched by NASA, in the USA, in April 1998.

4. Altitude stimuli (hypobaric hypoxia)

The MSNA recorded from the peroneal nerve was enhanced by hypoxia induced through the inhalation of low-oxygen gas [48–51]. MSNA recorded from the tibial nerve while sitting increased when the subject was exposed to a hypobaric-hypoxic environment in a low-pressure chamber [52]. When the simulated altitude was elevated stepwise from 0 (sea level) to 7,000 m, the MSNA burst rate increased with altitude. However, there were large variations among individuals in the response of MSNA to hypobaric hypoxia beyond the altitude of 5,000 m. In some subjects, MSNA was transiently reduced beyond the altitude of 6,000 m concomitantly with the appearance of symptoms of high-altitude sickness, including bradycardia, arterial hypotension, nausea, facial pallor or faintness (Fig. 8). In subjects with lowered MSNA response to simulated high altitude, MSNA increased quickly after oxygen inhalation together with the recovery from these clinical symptoms. MSNA measured in healthy sea-level residents after 21 d of residing at 4,300 m was significantly elevated both at rest and during submaximal exercise [53]. This MSNA increase accompanied an increase in arterial norepinephrine levels. This finding indicates that muscle is a major contributor to the increase in plasma norepinephrine levels associated with prolonged altitude exposure. When MSNA and plasma norepinephrine levels were measured simultaneously while the subject inhaled low-oxygen gas, MSNA was increased by the inhalation of gas with oxygen concentrations of 12, 10, and 8%, but there was a discrepancy between MSNA and plasma norepinephrine responses [54, 55]. Under normal atmospheric pressure, MSNA has been reported to correlate with the plasma norepinephrine level [56, 57]. Plasma
norepinephrine was much less influenced by acute hypoxia than MSNA. 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.

With regard to the effects of hypobaric conditions on MSNA, the influence of hypoxemia should also be considered. The MSNA recorded from the peroneal nerve was more enhanced during hypoxemic hypoxia than during isocapnic hypoxia [58]. The minute ventilation and blood pressure increased more during isocapnic hypoxia than during hypoxemic hypoxia [59]. It was suggested that the sympathetic response to hypoxia depends on the interactions between chemoreceptor stimulation and associated hyperventilation. The MSNA increase induced by hypoxia was lowered by baroreflex activation induced with intravenous infusion of phenylephrine [49]. 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 and baroreceptor afferents. Hypoxia potentiated exercise-induced sympathetic neural activation in humans [50]. This may signify that chemoreflex activation by hypoxia can also interact with exercise-induced metaboreflex to increase MSNA. Regarding chemoreflex activation, when the effects of hypoxia and hypercapnia on MSNA were compared, hypercapnia caused a greater increase of MSNA than hypoxia. However, during apnea, hypoxia caused a much greater increase in MSNA than hypercapnia. The inhibitory influence of ventilation on MSNA was greater during hypoxia than hypercapnia [59]. Moreover, the MSNA increase induced by hypercapnia was not reduced by baroreflex activation with phenylephrine [49]. These findings indicate that interactions among baroreflexes, chemoreflexes, metaboreflexes, ventilation and thermal effects, as mentioned below, are important to determine sympathetic nerve responses to altitude stress.

5. Thermal stimuli (ambient temperature)

Changes in ambient temperature particularly influence SSNA. The SSNA recorded from the median nerve was differentiated into vasomotor and sudomotor components based on simultaneous recordings of finger plethysmogram and galvanic skin response in the palm. The vasomotor component of SSNA increased under an ambient temperature of 15°C and was suppressed under an ambient temperature of 43°C. In contrast to this, the sudomotor component of SSNA decreased under a cold environment of 15°C and increased under a hot environment of 43°C. It was reported that SSNA was lowest at a thermoneutral ambient temperature of around 22 to 26°C. Higher than this temperature, the sudomotor component increased, while lower than this temperature, the vasomotor component increased [60]. The sudomotor component of SSNA identified by the simultaneous recording of sweat expulsion by means of the ventilated capsule method was enhanced by raising ambient temperature with an elevation of tympanic temperature [61, 62] (Fig. 9).

One of the problems concerning SSNA is the question whether differences exist between SSNAS leading to glabrous skin, which are dominated by mental sweating, and those leading to hairy skin, dominated by thermal sweating. Simultaneous recording of SSNAS from the median and peroneal nerves during exposure to a cold environment showed a striking similarity of vasomotor bursts with respect to the timing and strength of individual bursts [63]. A similarly strong correlation was also observed among sudomotor bursts recorded simultaneously from the posterior cutaneous antebrachial and superficial radial nerve during exposure to a warm environment. It was suggested that, in the distal glabrous skin areas, thermoregulatory functions were mainly executed via vasoconstrictor fibers whereas sudomotor fibers were brought into action 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. The SSNA in the peroneal nerve innervating hairy skin and that in the tibial nerve innervating plantar
glabrous skin were compared using a technique of double recording under different ambient temperature conditions. SSNA bursts showed nearly synchronized patterns in both nerves; under different ambient temperature conditions, however, there were differences in discharge between the sudomotor and vasconstrictor components of SSNA in both nerves [64]. At an ambient temperature of 34°C, the sudomotor component was high in the peroneal nerve, responsible for thermal sweating, but low in the tibial nerve, while at an ambient temperature of 18°C, the sudomotor component was low in the peroneal nerve but higher in the tibial nerve, presumably related to mental sweating (Fig. 10). These findings may indicate that sudomotor and vasomotor sympathetic activities in the peroneal and tibial nerves are controlled differently under different ambient temperature conditions.

Regarding the possibility that a vasodilator nerve exists in human peripheral nerves, it was demonstrated for the first time that the peroneal nerve contains vasodilator fibers, since intraneural stimulation of superficial peroneal nerve induced vasodilation in innervated skin of a foot which was eliminated by proximal local anesthesia [65]. More recently, it was reported that SSNA recorded from the peroneal nerve, not from the tibial nerve, contains vasodilatory activity which is synchronous with sudomotor nerve activity [66, 67]. This is the first direct evidence that sympathetic outflow in humans contains vasodilatory activity.

It has been shown that not only SSNA but also MSNA is enhanced by heat stimuli [68, 69]. When ambient temperature was changed from 29 to 34°C and then to 40°C, MSNA recorded from the tibial nerve was significantly increased. The increases in MSNA counteracted the lowered blood pressure during heat exposure. MSNA enhancement by heat load was linearly proportional to the rise in core (esophageal) temperature [70]. These findings suggest that heat-induced increases of MSNA may play roles both in thermoregulation and the maintenance of blood pressure against heat exposure.

Regarding MSNA response to low ambient temperature, MSNA was enhanced before the occurrence of shivering concomitantly with blood pressure elevation during exposure to a cold temperature of around 10°C inside a box used for hypothermic surgery [71]. It was suggested that peripheral cold receptors are responsible for MSNA increase in cold environment, which may play a role in thermoregulation. The effects of cold temperature on MSNA and shivering were analyzed using a water blanket. MSNA increased at a low water temperature of 5°C before the occurrence of shivering, showing a positive correlation with diastolic blood pressure and a negative correlation with central (tympanic) temperature [72]. The authors suggested that MSNA enhancement which is responsible for raising blood pressure at low ambient temperature does not depend on baroreflex but may depend on input from central cold receptors. They found that shivering appeared during the period with highly enhanced MSNA, while after having once occurred, shivering showed a suppressive effect on MSNA. The suppressive effect of shivering on MSNA may be due to the muscle-pumping effect of rhythmic involuntary contraction of skeletal muscles to facilitate venous return. The authors concluded that MSNA and shivering may work complementarily for thermogenesis in a cold environment.

6. Local thermal stimuli

The sympathetic nervous system responds not only to ambient temperature but also to local thermal stimuli of the human body. There have been sympathetic nerve activity studies in which the effects of immersing a part of the human body into cold or hot water was observed. The cold pressor test, in which one hand was immersed into ice water for 2 min, enhanced MSNA in the peroneal nerve from 30 s after the onset of immersion [73, 74]. There was no gender difference in MSNA response to the cold pressor test [75]. MSNA responded to the cold pressor test with painful sensation associated with a parallel increase in arterial pressure [76]. MSNA response to the cold pressor test depended on the size of the tissue area exposed to the stimulus, because the immersion of both hands produced a much greater increase in MSNA than the im-
mersion of a single hand [77]. The cold pressor test was considered to be a powerful activator of MSNA associated with blood pressure elevation. The initial effect of the cold pressor test to elevate blood pressure was due to an increase in cardiac output, while the late effect was attributed to increased MSNA [78]. MSNA in the peroneal nerve was also enhanced by immersing the face into water of 20°C for 12 s [79]. This maneuver elicited a “diving reflex” with a marked response in bradycardia. The enhancement of MSNA occurred before the appearance of bradycardia, not depending on baroreflex. These MSNA responses to partial immersion of the human body in cold water are mainly induced by a reflex depending on somatosensory afferent inputs, especially from the skin of the immersed part of the body.

With regard to SSNA response to partial body immersion, the effects of immersion of a hand into cold and hot water have been studied. It was reported that the 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 elicited increased MSNA in the peroneal nerve [74]. SSNA recorded from the median nerve was increased when the contralateral hand of healthy subjects was immersed into ice water and for patients with Raynaud’s phenomenon [80]. In this study, no evidence was found for increased sympathetic activity underlying Raynaud’s phenomenon nor for primary hypersensitivity of the vessels to sympathetic outflow, although there may have been a possible change in the functional relationship between nerve and vessel. The authors suggested that Raynaud’s phenomenon was concerned with some kind of local fault mechanism. This conclusion seems to be contradictory to the finding that, in one case who presented Raynaud’s phenomenon, SSNA increased concomitantly with the appearance of finger pain [81]. One of the reasons for this contradiction may be due to the difference in cold stimuli. The latter’s case was exposed to low ambient (room) temperature of 5°C, while the former cases immersed hands into cold water. It was reported that the immersion of a hand into cold water elicited an increase in SSNA recorded from the median nerve while lowering skin temperature, followed by a decrease in SSNA with the transient elevation of skin temperature [82]. This may suggest that a sympathetic suppressive response is responsible for the mechanism of cold-induced vasodilation (hunting reaction). SSNA recorded from the median nerve also increased concomitantly with transient vasoconstriction by immersion of the hand into hot water of which the temperature was raised by steps of 2°C from 35 or 37 to 41°C every 10 min. A local anesthetic blockade of the median nerve at the site proximal, but not distal to the recording site eliminated the responses of SSNA and finger vasoconstriction. It was 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 [8].

7. Vibration and noise

Vibration and noise are environmental factors which influence sympathetic nerve activity. SSNA recorded from the median nerve in the upper limb significantly increased, with a reduction of the skin blood flow by local vibration of 50 m/s² at 60 Hz applied to the contralateral hand during handgrip of the same hand under a constant grasping power of 2 kg [83, 84]. SSNA also increased, but less by local vibration of 50 m/s² at 120 Hz. SSNA recorded from the tibial nerve in the lower limb was enhanced by local vibration of 100 m/s² at 60 Hz applied to the palm of the hand showing vasoconstriction of the toe and perspiration on the sole of the foot [85] (Fig.11). Regarding the effect of changing stimulus parameters of local vibration to the palm, on SSNA in the tibial nerve, when three different accelerations of 10, 31.2, and 100 m/s², and three different frequencies of 60, 125, and 250 Hz were applied, SSNA increased depending on acceleration when the frequency was constant, while it increased most at the vibratory frequency of 60 Hz and less at the frequency of 125 and 250 Hz when the acceleration was constant [86]. The same kinds of vibratory stimuli to the palm did not increase MSNA recorded from the tibial nerve. It was also reported that local vibration of the upper limb did not increase MSNA recorded from the peroneal nerve in the lower limb [87]. On the contrary, local vibration of 10 m/s² at 60 Hz applied to the palm significantly reduced
MSNA in the tibial nerve [86]. These findings may indicate that local vibration increases SSNA but not MSNA. 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 of the foot. 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. It was demonstrated, using a microneurography technique on humans, that the tuning curve of vibratory sensibility of a single cutaneous mechanoreceptive unit of glabrous skin of the hand had two distinct peaks of threshold at relatively a low frequency of around 30–50 Hz and relatively high frequency of around 150 Hz [88]. It is known from animal experiments that vibratory stimuli with relatively low frequency are mainly perceived by the Meissner corpuscle, while those with relatively high frequency are mainly perceived by the Pacinian corpuscle. These findings may suggest that the vibration-induced sympathetic activation is mediated predominantly by the Meissner corpuscle rather than the Pacinian corpuscle.

SSNA responds strongly to unexpected sudden noise, but it may habituate rather rapidly to repeated noise. It was reported that SSNA responded to tone stimuli in relation to the conscious cognitive process [89]. SSNA recorded from the median nerve did not increase significantly by noise of 100 dB alone, but increased markedly to the combined stimuli of 100 dB noise and local vibration of 50 m/s at 60 Hz applied to the hand [83, 84]. This finding may indicate that expected constant noise does not influence SSNA much, but it may enhance sympathetic outflow to the skin when associated with other kinds of environmental stimuli such as local vibration. In this case, the noise may accelerate vibration-induced enhancement of sympathetic drive to the skin. In cases of vibration-induced white finger, SSNA at rest recorded from the median nerve was higher than that in age- and gender-matched control subjects [90]. But there were no statistically significant differences in SSNA responses to immersion of the contralateral hand into cold water between patients and controls. This finding may suggest that increased vasoconstrictor tone is important as the neural mechanism underlying vibration-induced white finger. The strong enhancement of SSNA induced by combined stimuli of local vibration, noise and low ambient temperature may be responsible for attacks of white finger in these patients [86].

### III. Influence of Aging on Sympathetic Nerve Responses to Environmental Stress

Age is one of the important factors which influence sympathetic nerve responses to environmental stimuli. Microneurographic analysis has revealed that the individual level of MSNA is dependent on the age of the subject. There was a weak positive correlation between the age of subject and burst incidence, signifying the number of bursts per 100 heartbeat of MSNA as recorded from the peroneal nerve while in the supine position [91]. The basal level of MSNA recorded from the tibial nerve expressed as the burst rate while in the supine resting position increased with age. There was a significant positive correlation between the age of subject and burst rate of MSNA at rest in subjects of different ages, ranging from 18 to 76 [15]. An age-dependent increase in MSNA was also reported by other investigators [92–98]. Regarding the mechanism for age-dependent increase in basal MSNA, changes in arterial baroreflex function may not play a crucial role, because there was no significant difference in arterial baroreflex gain for MSNA between younger and older subjects, in contrast to age-dependent reduction in the same reflex gain for heart rate [93, 97]. The elevated MSNA in older adults may be partially related to higher body fat, particularly in the abdominal region [98]. The pressor response to MSNA is delayed and diminished in the elderly [99]. Frequency domain analyses, including fast Fourier transformation and coherence analysis, showed that the coherence between MSNA and blood pressure at 0.1 Hz was lower in the elderly compared to that in young subjects [100]. These findings may indicate that blood pressure response to MSNA is lower in the elderly. A higher level of MSNA in the elderly may play a role to compensate lowered neuro-effector (vascular) responses due to age-related changes in blood vessels or receptors to maintain normal blood pressure. Gender difference was also reported in age-dependent changes in MSNA. A report described that the basal level of MSNA is higher in men than in women both for young and older subjects [94], but another paper reported that this gender difference disappears in the elderly [16] (Fig. 12). The age-related gender difference of MSNA seems to be related to the difference in hormonal secretion, but the detail in the mechanism is unknown.

As mentioned above, the burst rate of MSNA increased linearly with the sine function of the tilt angle (+Gz) during head-up tilt from a horizontally supine
changes in MSNA response to gravitational stimuli.

Regarding the MSNA responses to isocapnic hypoxemia, the magnitude of the absolute increases in MSNA and $\partial$MSNA/$\partial$SaO$_2$ were not significantly different in young and older men; however, because of higher normoxic baseline levels, the percentage increases in burst frequency were smaller in the older men [51]. Although the detail of age-related changes in MSNA has not yet been clarified, it is essentially important to consider the effects of aging when studying sympathetic nerve activities. Further studies are necessary to elucidate the influence of aging on sympathetic nerve responses to environmental stimuli.

IV. Conclusion

Microneurography is an electrophysiological method to record impulse traffic in human peripheral nerve in situ. Using this method, not only sensory afferent nerve activity, but also postganglionic sympathetic effereent outflow leading to muscles (muscle sympathetic nerve activity; MSNA) and the skin (skin sympathetic nerve activity; SSNA) can be recorded directly and separately in human subjects. By applying the microneurography technique, it was revealed that the sympathetic nervous system in humans responds differently to various kinds of environmental stimuli, such as gravity, microgravity, altitude, ambient temperature, local temperature, vibration and noise. MSNA, composed mainly of vasoconstrictor outflow, is particularly important to maintain hemodynamic homeostasis against environmental stimuli. Aging influences MSNA, of which the basal level is elevated with advancing age. SSNA plays an essential role in thermoregulation. SSNA leading to both glabrous and hairy skin is mainly composed of vasoconstrictor and sudomotor activities which respond differently to thermal stimuli. There exist regional differences between SSNA responses to ambient temperature in the nerves innervating hairy and glabrous skin. Vasodilator activity co-works with sudomotor activity only in nerves innervating hairy skin but not in those innervating the glabrous skin.

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