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## Age-Related Changes in Muscle Sympathetic Nerve Activity in Essential Hypertension

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Toshiyoshi Matsukawa, and Masao Ishii

To investigate the pathophysiological role of the sympathetic nervous system in essential hypertension, this study recorded the muscle sympathetic nerve activity (MSNA) of the tibial nerve and examined the age-related changes in patients with essential hypertension and in normotensive persons. There were 43 normotensive subjects (16–69 years old) and 63 patients with essential hypertension (18–67 years old) in the study. The MSNA at rest, recorded by microneurography, was evaluated by burst rate (bursts/min), burst incidence (bursts/100 heart beats), and spike frequency (spikes/min). The MSNA recording showed a high reproducibility with a correlation coefficient of 0.86 ( $p < 0.01$ ) in repeated studies. The MSNA was significantly greater in the hypertensive patients than in the normotensive subjects, irrespective of activity units ( $p < 0.01$ ), and this finding was consistent in the young (30 years old or less), middle-aged (31–50 years old), and old groups (51 years old or more). Furthermore, MSNA showed a significant positive correlation with age both in the normotensive subjects ( $r = 0.43$ ,  $p < 0.01$  for burst rate;  $r = 0.49$ ,  $p < 0.01$  for burst incidence; and  $r = 0.50$ ,  $p < 0.01$  for spike frequency) and in the hypertensive patients ( $r = 0.40$ ,  $p < 0.01$  for burst rate;  $r = 0.44$ ,  $p < 0.01$  for burst incidence; and  $r = 0.40$ ,  $p < 0.01$  for spike frequency). Although there was a significant positive correlation between plasma norepinephrine concentration and MSNA in the hypertensive patients and the normotensive subjects, the difference in plasma norepinephrine concentration between the two groups was not significant at any age level. These results indicate that sympathetic nerve activity is increased in patients with essential hypertension at any age level and plays a long-term role in the development and maintenance of blood pressure elevation. (*Hypertension* 1989;13:870–877)

An increase in sympathetic nerve activity is considered to be an important factor in the pathogenesis of essential hypertension. Direct evidence supporting this proposition, however, is still insufficient, especially in humans. The results of many previous studies that have investigated the role of the sympathetic nervous system in hypertension by measuring the plasma concentrations of catecholamines have been conflicting; plasma norepinephrine concentration has been shown to be elevated in patients with essential hypertension compared with normotensive subjects in some studies<sup>1–3</sup> but not significantly different between patients with essential hypertension and normotensive subjects in other studies.<sup>4,5</sup> With

regard to the age-related changes in plasma concentration of norepinephrine, the results have also been conflicting; plasma norepinephrine concentration has been observed to increase with advancing age in both hypertensive patients and normotensive subjects,<sup>6,7</sup> only in normotensive subjects,<sup>4,5</sup> only in hypertensive patients,<sup>8,9</sup> or in neither.<sup>10,11</sup> Although the plasma concentration of norepinephrine could be an index of overall sympathetic nerve activity, its pathophysiological implication needs to be evaluated with care because it is determined by reuptake into the nerve endings, metabolic degradation, and binding to neuronal and non-neuronal tissue, in addition to the secretion and spillover from the nerve endings.<sup>12,13</sup>

Recently, a method to record the activity of sympathetic nerves contained in the nerve bundles innervating the skeletal muscle in humans has been developed.<sup>14</sup> Recording sympathetic nerve activity with such a method is considered to be a better approach than measuring circulating norepinephrine to evaluate sympathetic nerve activity. To investigate the pathophysiological role of the sympathetic nervous system in essential hypertension,

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this study recorded the muscle sympathetic nerve activity (MSNA) of the tibial nerve and examined its age-related changes in patients with essential hypertension and in normotensive persons.

### Subjects and Methods

There were 43 normotensive subjects (32 male and 11 female), ranging in age from 16 to 69 years old, and 63 patients with uncomplicated essential hypertension (48 male and 15 female), ranging in age from 18 to 67 years old. The hypertensive patients were in stage I or II according to the World Health Organization classification with sitting blood pressure of 160/95 mm Hg or more on three different occasions. The hypertensive patients were not treated with any antihypertensive agents for at least 2 weeks before the study. Secondary hypertension was excluded by thorough examinations, including radiological and endocrinologic studies.

The subjects were instructed to take 7–10 g salt/day and to use a portable device<sup>15</sup> or salt titrator tape<sup>16</sup> for urine sampling. They were asked to refrain from smoking, alcohol, coffee, and sedative agents for at least 14 hours before the study. Informed consent was obtained from each subject after the purpose and procedure of the study were explained in detail.

### Study Protocol

The study was performed on subjects who had been supine on a table for 30–60 minutes. When the MSNA of the tibial nerve was recorded, as will be discussed later, the subjects were kept prone, and a tungsten microelectrode was inserted into the tibial nerve at the popliteal fossa. Brachial arterial pressure was noninvasively measured using an automatic sphygmomanometer (1846SX, Critikon, Tampa, Florida). Also, a finger plethysmograph manometer, which was developed in our laboratory,<sup>17</sup> was applied to the middle finger to continuously record arterial pulse waves. The difference between finger arterial pressure and brachial arterial pressure was adjusted by intermittently comparing the finger and the brachial arterial pressures. Heart rate was also monitored electrocardiographically (Figure 1).

Thirty or 40 minutes after insertion of the electrode, venous blood samples were obtained from the antecubital vein for measuring the plasma concentration of norepinephrine; then the recording of MSNA was started. Recording of MSNA was carried out for 30–60 minutes. To examine the reproducibility of the MSNA recording, the study with the protocol was repeated in five of the normotensive subjects and in 12 of the hypertensive patients with intervals of 3–20 days.

### Recording of Muscle Sympathetic Nerve Activity

To record MSNA, a tungsten microelectrode, 200  $\mu\text{m}$  in shaft diameter, with an uninsulated tapered tip of 1–5  $\mu\text{m}$  (No. 25-05-1, Federick Haer & Co., Brunswick, Maine) was inserted manually through

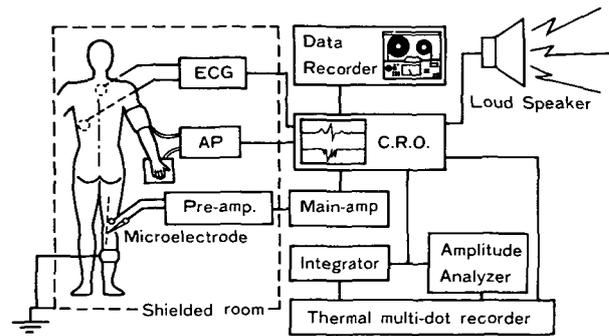


FIGURE 1. Schematic drawing of recording and analyzing system of muscle sympathetic nerve activity (MSNA). Subject was kept in prone position in sealed room. Tungsten microelectrode was inserted through skin to tibial nerve at popliteal fossa. Nerve activities were amplified through preamplifiers and a main amplifier (Pre-amp and Main-amp). Characteristic nerve activities could be detected with loudspeaker and cathode ray oscilloscope (C.R.O.). Arterial pressure (AP) was measured by finger plethysmograph manometer and an automatic sphygmomanometer at middle finger and brachial artery, respectively. These data were recorded on magnetic tapes, played back for analysis with an integrator and an amplitude analyzer, and printed out with a thermal multidot recorder.

the skin into a bundle of muscle nerve fibers of the tibial nerve at the popliteal fossa. The impedance of the electrode was about 10  $\text{M}\Omega$ . Spike potentials, amplified with a preamplifier and a main amplifier (DPA-22 and DPA-200, Diamedical, Tokyo, Japan), were monitored with an oscilloscope (VC-10, Nihonkohden, Tokyo, Japan) and a loudspeaker and recorded continuously on magnetic tapes that were later played back to analyze the MSNA (Figure 1). The recorded MSNA was passed through an integrator (Integrator 1333, San-ei, Tokyo, Japan) with a time constant of 100 msec to obtain the mean voltage of MSNA<sup>14</sup> or through an amplitude analyzer (DSE-335P, Diamedical, Tokyo, Japan) to convert individual spikes into uniform pulses.<sup>18–21</sup> The low-level control of the window discriminator was routinely set to filter the background noise level. The spikes that crossed the set at a low level generated normalized voltage steps, which were integrated to determine the number of spikes. A system for the recording and analyzing of MSNA is also illustrated in Figure 1.

The intensities of the MSNA were evaluated by measuring the number of sympathetic bursts per minute (burst rate),<sup>22–26</sup> the number of bursts per 100 heart beats (burst incidence),<sup>22–26</sup> and the number of spikes per minute (spike frequency).<sup>18–21</sup> When MSNA, arterial pressure, and heart rate became stable, the baseline levels of MSNA were sampled for 15–30 minutes. Then, the neural firings were identified as MSNA when the following criteria were fulfilled<sup>14, 18–20, 24</sup>: 1) Weak electrical stimulation (1–3 V, 0.2 msec, 1 Hz) of the tibial nerve

## CARDIOVASCULAR AND SYMPATHETIC RESPONSES TO TRIMETHAPHAN

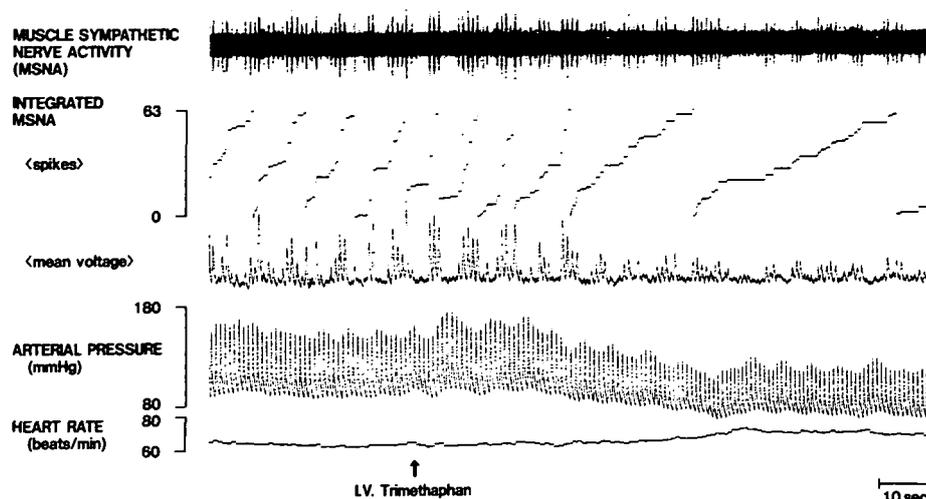


FIGURE 2. An example of the recording of muscle sympathetic nerve activity (MSNA) and arterial pressure before and after intravenous administration of 0.05 mg/kg trimethaphan. The nerve discharges and spikes diminished immediately after trimethaphan injection.

through the electrode elicited involuntary muscle contraction but not paresthesias. 2) Tapping or stretching the muscle and tendon supplied by the impaled fascicle of the tibial nerve elicited afferent mechanoreceptor discharges, whereas stroking the skin in the distribution of the tibial nerve did not evoke afferent discharges. 3) Spikes revealed characteristic pulse-synchronous spontaneous discharges during phase II and phase III of a Valsalva maneuver. 4) The spikes were remarkably diminished by ganglion blockade trimethaphan (Figure 2). If these criteria for acceptable recording of MSNA were not satisfied or if the recorded MSNA showed lability or poor signal-to-noise ratios, the recordings were discarded. It was possible to maintain stable recording of the MSNA with a good signal-to-noise ratio for 1–2 hours once such a characteristic sympathetic discharge was found.

#### Measurements of Plasma Concentration of Norepinephrine

Venous blood samples obtained from the antecubital vein were collected into prechilled tubes contain-

ing EDTA disodium salt (1 mg/ml), immediately centrifuged at 4° C, and stored at –80° C until use. The plasma concentration of norepinephrine was determined according to the trihydroxyindol method using high-pressure liquid chromatography (HLC-825CA, Toyo Soda, Tokyo, Japan), as previously described.<sup>27</sup> Coefficients of variation were 6.0% for intra-assay variation and 11.7% for interassay variation.

#### Statistics

Measured variables were expressed as mean  $\pm$  SEM. Group differences were assessed by Student's *t* test or two-way analysis of variance. Correlation coefficients between two parameters were calculated by least-squares linear regression analysis. Values of  $p < 0.05$  were considered significant.

#### Results

##### Main Clinical Findings of Subjects

Table 1 shows the number, age, systolic and diastolic arterial pressures, and heart rate of the normotensive subjects and hypertensive patients,

TABLE 1. Age, Systolic and Diastolic Arterial Pressure, and Heart Rate in Normotensive and Hypertensive Subjects in Three Age Groups

	<i>n</i>	Age (yr)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Heart rate (beats/min)
<i>Young groups (<math>\leq 30</math> yr)</i>					
Normotensive	18	22.6 $\pm$ 0.8	126.1 $\pm$ 2.6	71.3 $\pm$ 2.2	67.7 $\pm$ 1.9
Hypertensive	16	22.3 $\pm$ 0.9	150.5 $\pm$ 3.4*	98.8 $\pm$ 2.6*	75.5 $\pm$ 1.9†
<i>Middle-aged groups (31–50 yr)</i>					
Normotensive	15	42.5 $\pm$ 1.7	130.4 $\pm$ 2.7	80.3 $\pm$ 1.4	71.5 $\pm$ 2.4
Hypertensive	27	41.6 $\pm$ 0.9	161.1 $\pm$ 3.4*	102.2 $\pm$ 2.0*	72.0 $\pm$ 1.7
<i>Older groups (&gt;51 yr)</i>					
Normotensive	10	57.0 $\pm$ 1.7	128.3 $\pm$ 3.2	74.1 $\pm$ 2.6	67.0 $\pm$ 1.9
Hypertensive	20	58.5 $\pm$ 0.9	169.8 $\pm$ 4.3*	99.0 $\pm$ 2.0*	67.8 $\pm$ 2.3

Data are mean  $\pm$  SEM. BP, blood pressure.  
\* $p < 0.01$ , † $p < 0.05$  vs. normotensive subjects.

who were each divided into three age groups: the young group (30 years old or less), middle-aged group (31–50 years old), and older group (51 years or more). Arterial pressure and heart rate values were obtained at the start of MSNA recording. Systolic and diastolic arterial pressure were significantly higher in the hypertensive patients in each age group, and heart rate was greater in the young hypertensive patients than in the young normotensive subjects.

Systolic, but not diastolic, arterial pressure was significantly correlated with age in the hypertensive patients ( $r=0.46, p<0.01$ ). However, there was no definite relation between systolic or diastolic arterial pressure and age in the normotensive subjects. Heart rate was not correlated with age in either group.

*Reproducibility of Muscle Sympathetic Nerve Activity*

The recording of MSNA was repeated in five normotensive subjects and 12 hypertensive patients under the same protocol with intervals of 3–20 days. As represented in Figure 3, there was a significant positive correlation between the first and the second measurements of the MSNA expressed in terms of burst rates or spike frequencies. This relation was maintained when MSNA was expressed in terms of burst number per 100 heart beats ( $r=0.84, p<0.01$ ).

*Muscle Sympathetic Nerve Activity in Normotensive Subjects and Hypertensive Patients and Its Age-Related Changes*

MSNA was significantly increased in all hypertensive patients compared with all normotensive subjects, irrespective of the expressions of the activity (Table 2). This finding was consistent when MSNA was analyzed for the three age groups (Table 2).

When the relation between MSNA and age was analyzed, a significant positive correlation between the two variables was found, no matter what unit of activity was used for MSNA (Figure 4). Figure 5 shows representative recordings in a young normotensive male whose arterial pressure was 120/62 mm Hg and a normotensive male in the older group whose arterial pressure was 136/70 mm Hg. Sym-

pathetic nerve bursts and the integrated voltage steps of spikes appear to be increased in the subject in the older group compared with the young subject.

*Relation Between Muscle Sympathetic Nerve Activity and Plasma Concentration of Norepinephrine*

No significant difference in the plasma concentration of norepinephrine between the normotensive subjects and hypertensive patients was observed when analyzed for all the participants. However, the plasma norepinephrine concentration tended to be higher in the young hypertensive patients than in the young normotensive control subjects (Table 3). The plasma concentration of norepinephrine was significantly correlated with age in the normotensive subjects ( $r=0.58, p<0.01$ ) but not in the hypertensive patients ( $r=0.18, NS$ ).

The plasma concentration of norepinephrine was significantly correlated with MSNA both in the normotensive subjects ( $r=0.60, p<0.01$  for burst rate of MSNA;  $r=0.56, p<0.01$  for burst incidence; and  $r=0.54, p<0.01$  for spike frequency) and in the hypertensive patients ( $r=0.40, p<0.01$  for burst rate;  $r=0.42, p<0.01$  for burst incidence; and  $r=0.40, p<0.01$  for spike frequency).

**Discussion**

It is known that a recorded MSNA often shows large interindividual variations, and that noise signals, which usually accompany the recording, make quantitative analysis of MSNA difficult.<sup>26,28</sup> Thus, we set the window discriminator so as to cut off background noise signals, integrated the spikes that crossed the set level, and expressed MSNA in terms of burst rate, burst incidence, and spike frequency to determine the frequency and magnitude of sympathetic bursts. If the recording of MSNA showed instability or poor signal-to-noise ratios, the recording was discarded from the study. Careful procedure and analysis for the MSNA recording seem to have been the reason for the nearly satisfactory reproducibility of the recording of MSNA in the present study.

In the present study, the MSNA at rest was greater in the hypertensive patients than in the

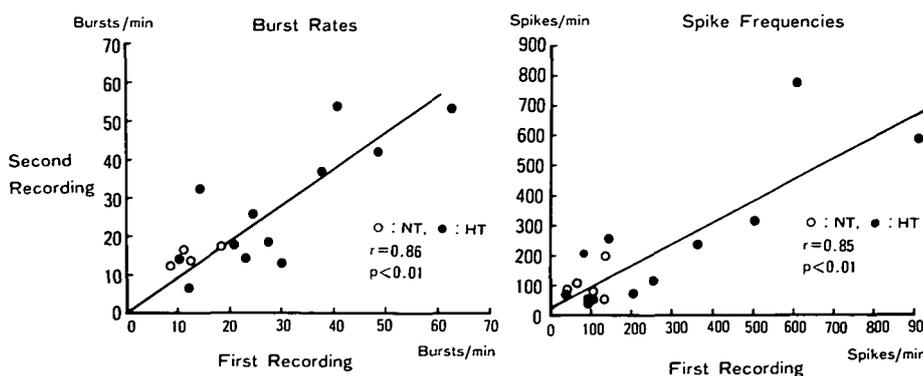


FIGURE 3. Plots of reproducibility of muscle sympathetic nerve activity (MSNA) repeated in five normotensive subjects and 12 hypertensive patients in intervals of 3–20 days. There was a significant positive correlation between the first and the second measurements of the MSNA expressed in terms of burst rate (left) or spike frequency (right).

**TABLE 2. Muscle Sympathetic Nerve Activities Expressed in Terms of Burst Rate, Burst Incidence, and Spike Frequency in Normotensive and Hypertensive Subjects in Three Age Groups and in All Subjects**

	Burst rate (bursts/min)	Burst incidence (bursts/100 heart beats)	Spike frequency (spikes/min)
<i>Young groups (≤30 yr)</i>			
Normotensive	17.5±1.5	25.4±1.9	108.9±14.3
Hypertensive	23.5±2.2*	34.8±3.1*	175.4±20.9*
<i>Middle-aged groups (31–50 yr)</i>			
Normotensive	18.1±1.6	27.1±2.6	139.3±17.1
Hypertensive	28.6±2.4†	43.7±4.1†	219.3±26.9†
<i>Older groups (&gt;51 yr)</i>			
Normotensive	27.5±4.0	44.3±7.0	251.0±50.2
Hypertensive	39.4±3.6†	62.6±4.9†	397.5±59.8†
<i>All subjects</i>			
Normotensive	20.1±1.6	30.4±2.5	152.6±16.6
Hypertensive	30.7±1.9†	47.4±2.8†	264.7±25.5†

Data are mean±SEM.

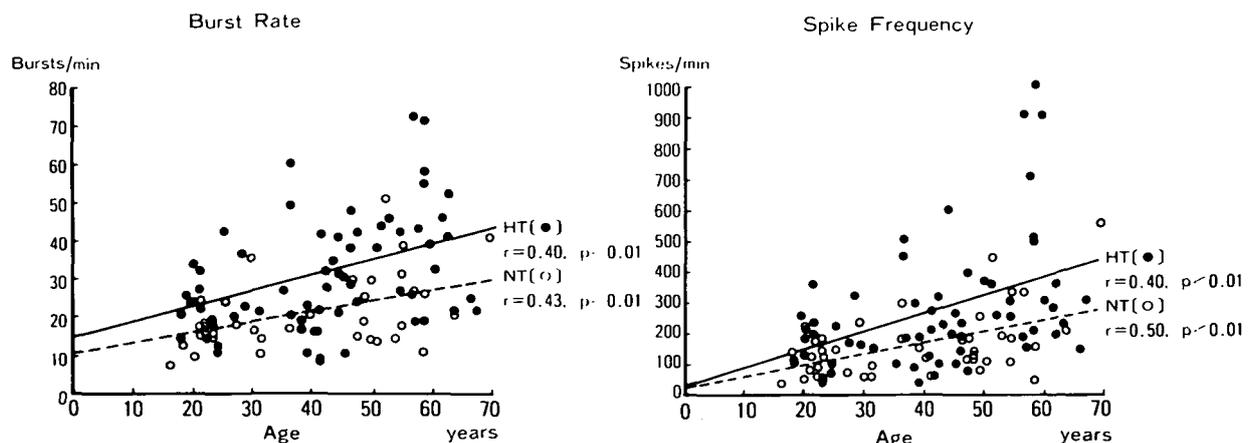
\* $p < 0.05$ , † $p < 0.01$  vs. normotensive subjects.

normotensive subjects, and this finding was consistent for the young, middle-aged, and older groups. Mörlin and coworkers<sup>22</sup> reported that, although MSNA was increased in 18 patients with essential hypertension compared with 20 normotensive subjects, the difference disappeared when MSNA was age-adjusted. Although the exact reason for the difference in results between their study and ours is not clear, the differences in the number of subjects and selected nerves or posture for recording seem to be the reason. We recorded MSNA at the tibial nerve of prone subjects, whereas they used the peroneal nerve of supine subjects. The MSNA signals may be different depending on what organs or muscle the selected nerve bundles innervate.<sup>29</sup> Although the reason for the difference in results remains to be clarified by further investigation, the results of our study suggest that sympathetic nerve activity is increased in patients with essential hypertension.

The exact mechanism of the increased resting MSNA in patients with essential hypertension is

still controversial. However, there have been some possible interpretations proposed. The first interpretation may be the involvement of the central nervous system.<sup>30–33</sup> In experimental hypertension models, such as spontaneously hypertensive rats, the tissue concentration of norepinephrine has been shown to be reduced in the A<sub>1</sub> and A<sub>2</sub> areas or nucleus tractus solitarius of the medulla oblongata in the early stage of hypertension.<sup>34</sup> Increased  $\alpha_1$ -receptor density or decreased  $\alpha_2$ -receptor density in the central nervous system have also been reported in these types of experimental hypertension.<sup>35</sup> These changes in the central nervous system may result in an elevation of the peripheral sympathetic nerve activity. We recently reported that the MSNA response to cold pressor stimuli was augmented in adolescent borderline hypertensive patients.<sup>20</sup> This evidence may also suggest impaired central regulation of MSNA in hypertensive patients.

The second interpretation is related to the reduced baroreceptor reflex sensitivity in hypertensive patients. Reduced baroreceptor reflex sensitivities



**FIGURE 4.** Plots of relation between muscle sympathetic nerve activity (MSNA) and age in normotensive (NT) or hypertensive (HT) participants when MSNA was expressed in burst rate (left) or spike frequency (right).

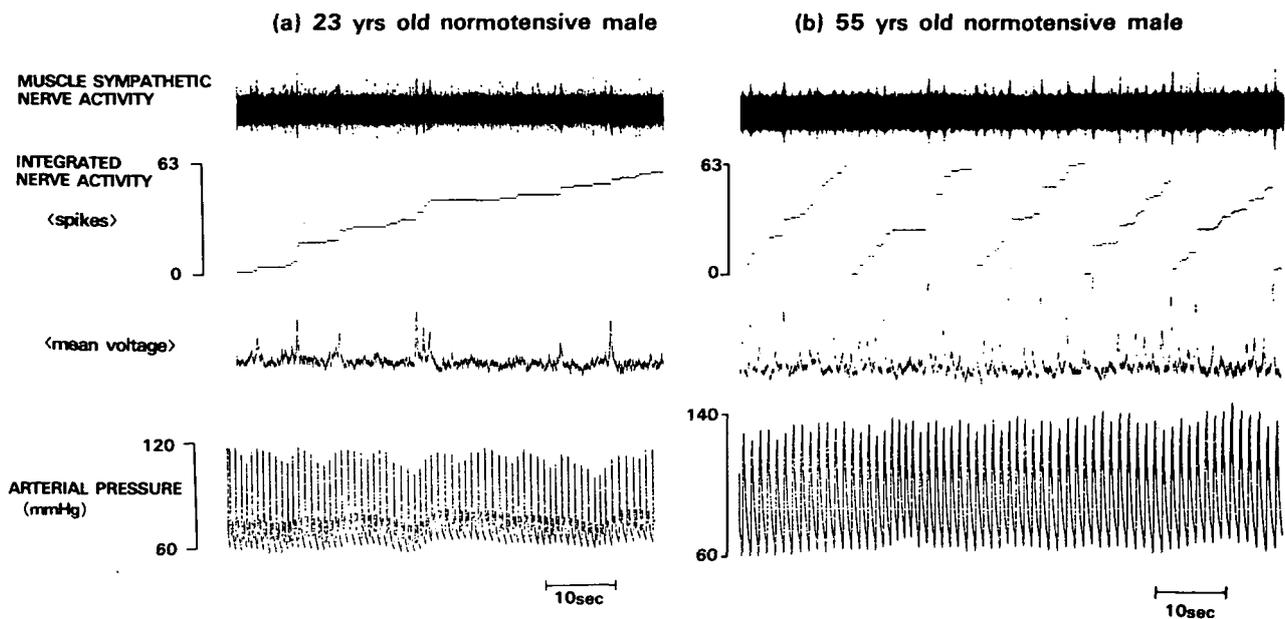


FIGURE 5. Representative recordings of the nerve discharge, integrated activities, sympathetic burst, and arterial pressure in a 23-year-old normotensive male (left) and a 55-year-old normotensive male (right).

have often been demonstrated in experimental hypertension<sup>30,31,36</sup> or clinical hypertension.<sup>37,38</sup> Our recent studies have demonstrated that the reduction in MSNA in response to phenylephrine infusion is blunted in adolescent borderline and established hypertensive patients compared with normotensive control subjects.<sup>21</sup> Taken together, it seems possible that both reduction in sympathoinhibition and augmentation in sympathoactivation are involved in the elevated levels of MSNA in hypertensive patients.

In the present study, the MSNA at rest was observed to increase with advancing age both in the normotensive subjects and the hypertensive patients. This finding is consistent with a study by Mörlin et al<sup>22</sup> and Wallin and Sundlöf.<sup>25</sup> The exact mechanism of the age-related increases in MSNA are con-

jectural. One possible interpretation may be reduced baroreceptor reflex sensitivity with age. The baroreceptor reflex sensitivity has been repeatedly reported to be reduced with aging in animals<sup>39</sup> and humans.<sup>37</sup> Reduced baroreceptor reflex sensitivity, which may result from anatomic changes in the receptors or decreased arterial wall compliance secondary to aging, possibly increases sympathetic nerve activity.

Another possible interpretation is related to the central nervous system itself. Previous studies have demonstrated that the elevation of circulating norepinephrine in response to sympathoactivating stimuli is enhanced in the aged.<sup>40</sup> Furthermore, previous experimental studies have shown that activation of arterial chemoreceptors by hypoxemia is a potent stimulus to sympathetic nerve activity.<sup>41</sup> It has been reported that aged people often have hypoxemia.<sup>42</sup> It is, however, uncertain as to whether hypoxemia played a significant role in the age-related changes in MSNA in this study because the oxygen content of the arterial blood samples was not measured.

In our study, as long as the sympathetic nerve activity was examined in terms of MSNA, it was suggested that the sympathetic nerve activity was increased in patients with essential hypertension compared with normotensive control subjects in each age group. These findings contrast with the report by Esler et al<sup>3</sup> in which kinetic studies with tritiated norepinephrine were positive in younger hypertensive patients (less than 40 years old) but not in older patients (more than 60 years old); the findings are also at variance with the review by Goldstein,<sup>12</sup> who observed that virtually all studies of young, established hypertensive patients were positive with respect to plasma norepinephrine. Although the reason for the differences in results between the present study and theirs is not known,

TABLE 3. Plasma Norepinephrine Concentration at Rest in Normotensive and Hypertensive Subjects in Three Age Groups and in All Subjects

Group	Plasma norepinephrine concentration (pg/ml)
<i>Young groups (≤30 yr)</i>	
Normotensive	155.9±14.0
Hypertensive	189.7±14.2*
<i>Middle-aged groups (31–50 yr)</i>	
Normotensive	200.4±17.5
Hypertensive	238.8±25.1
<i>Older groups (&gt;51 yr)</i>	
Normotensive	251.7±27.9
Hypertensive	230.4±14.5
<i>All subjects</i>	
Normotensive	197.4±13.8
Hypertensive	229.4±14.8

Data are mean±SEM.

\* $p < 0.1$  vs. normotensive subjects.

the difference in age grouping, the severity of hypertension of the subjects, or the methods of the study may be involved. In the present study, however, the plasma concentration of norepinephrine was significantly correlated with MSNA in both the hypertensive patients and the normotensive subjects and tended to be higher in the young hypertensive patients than in the control subjects. Accordingly, the findings of the present study do not seem to contradict the concept that sympathetic nerve activity is increased in young hypertensive patients and plays an important role in initiation of blood pressure elevation in essential hypertension.<sup>3,12</sup>

It is well known that the circulating level of norepinephrine is determined not only by the spillover of the transmitter from sympathetic nerve terminals but also by metabolic degradation, uptake into nonneural tissue, and urinary excretion.<sup>12,13</sup> These complicated processes of secretion, metabolism, and excretion of norepinephrine may have obscured the difference in circulating norepinephrine between the normotensive subjects and hypertensive patients and its age-related change in the hypertensive patients as observed in the present study.

In summary, MSNA of the tibial nerve, which may directly reflect sympathetic nerve activity, was increased in patients with essential hypertension compared with age-matched normotensive subjects. Furthermore, the MSNA was significantly correlated with age in both the normotensive subjects and the hypertensive patients. These results obtained in the present study suggest that, although the exact mechanism remains to be elucidated, an increase in sympathetic nerve activity plays an important role in the elevation of blood pressure in essential hypertension.

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