Delayed and diminished pressor response to muscle sympathetic nerve activity in the elderly

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Sugiyama, Yoshiki, Toshiyoshi Matsukawa, A. S. M. Shamsuzzaman, Hisashi Okada, Takemasa Watanabe, and Tadaaki Mano. Delayed and diminished pressor response to muscle sympathetic nerve activity in the elderly. *J. Appl. Physiol.* 80(3): 869–875, 1996.—We studied the effects of aging on α-receptor-mediated vasoconstrictive responses to sympathetic nerve activity in 16 healthy aged [75.8 ± 2.7 (SE) yr] and young men (33.8 ± 2.0 yr). Muscle sympathetic nerve activity (MSNA), heart rate, and blood pressure were analyzed during slow respiration (0.1 Hz). Peak amplitude and phase were calculated from a cosine function fitted with 0.1 Hz by using the least squares method. The latency of the pressor response to MSNA, defined as lag time from the peak of MSNA to diastolic blood pressure, was significantly longer in the aged than the young group (7.1 ± 0.3 vs. 5.4 ± 0.4 s; $P < 0.01$). The extent of pressor response to MSNA, defined as diastolic blood pressure rise in response to increase in total MSNA, was significantly lower in the aged than the young group (0.038 ± 0.006 vs. 0.099 ± 0.024 mmHg/unit, $P < 0.001$). These results suggest that α-receptor-mediated vasoconstrictive responses to MSNA may be attenuated in the elderly.

maximum entropy method; end-organ responsiveness; human

THE AUTONOMIC REGULATION of the cardiovascular system is affected with advancing age. This regulation depends not only on neural activity, which may reflect the amount of neurotransmitter, but also on the responsiveness of its receptors. It has been postulated that sympathetic nerve activity, which is assessed by plasma catecholamine concentrations (20, 21) or by direct intraneural recording of postganglionic sympathetic nerve activity to skeletal muscle (4, 11, 17, 24), increases with aging. The responsiveness of the heart to catecholamines is described to be diminished with increasing age (10, 11). However, there have been few systematic studies examining the effects of aging on α-receptor-mediated responsiveness of blood vessels to sympathetic activity (2, 5), which is thought to have greater importance in blood pressure regulation.

Microneurography has enabled direct observation of sympathetic nerve activity leading to skeletal muscle (MSNA) in human subjects (15), which is the activity of postganglionic efferent nerves innervating the vasculature in skeletal muscles. MSNA has a vasoconstrictive effect via α-receptors and plays a major role in blood pressure control by increasing peripheral vascular resistance. Increases in MSNA cause elevation in blood pressure, whereas decreases in MSNA are followed by a blood pressure drop (24). In turn, increased afferent activity from arterial baroreceptors causes a reduction in MSNA, whereas decreased afferent activity brings about an enhancement of MSNA through negative-feedback mechanisms including arterial baroreceptors (6, 24). In view of the time relationship between MSNA and blood pressure waveforms, we can determine both the vasoconstrictive effect of MSNA and the baroreceptor-MSNA reflex. In this study, we measured the latency and extent of the pressor response in systemic blood pressure to MSNA in the elderly compared with those in the young as a control group to elucidate the effects of aging on α-receptor-mediated responsiveness of blood vessels.

MATERIALS AND METHODS

Subjects. The subjects were eight aged men, aged 71–80 yr [75.8 ± 2.7 (SE) yr], and eight young men, aged 28–44 yr (33.8 ± 2.0 yr). Medical history and physical examinations, including resting and maximal exercise electrocardiograms, were normal. None of the subjects was taking medication that might affect cardiovascular function. None was obese; their body weight ranged from −14 to +15% of ideal body weight as assessed by body mass index, and their body fat ranged from 16.3 to 28.5% from the sum of two gender-specific skinfolds. Their body weight and body fat showed no significant difference between the two groups. Although physical activity and energy expenditure were not measured, the activities of their daily lives were not impaired. The study was approved by the Human Research Committee of the Research Institute of Environmental Medicine of Nagoya University and was conducted in accordance with the guidelines of the Japan Microneurography Society. Each subject gave his consent to participate in the study after a detailed explanation of the procedure.

Experiments. The subjects fasted overnight from 9:00 P.M. on the previous day. The subjects lay on a bed in the supine position in an air-conditioned room with the temperature controlled between 25 and 27°C. A tungsten microelectrode with a shaft diameter of 100 μm and an impedance of 2–5 MΩ (model 26-05-1, Federick Haer, Brunswick, ME) was inserted percutaneously without anesthesia into the muscle nerve fascicles of the tibial nerve at the popliteal fossa. MSNA was identified on the basis of the criteria described elsewhere (15, 16). The nerve signals were fed into a high-input impedance preamplifier (model DAM-6A, W-P Instruments, New Haven, CT) and monitored on an oscilloscope (model 5113, Tektronix, Beaverton, OR) after band-pass filtering between 500 and 5,000 Hz (model E-3201A, NF, Yokohama, Japan). We simultaneously observed the respiration curve and electrocardiogram (ECG) recorded by a hyperventilation detector (model MZE-6100, Nihon Kohden, Tokyo, Japan) and blood pressure waveform recorded by mass-compensatory photoplethysmography (Finapres 2300, Ohmeda, Louisville, CO). After >30 min of supine rest, subjects breathed slowly for 200 s at a frequency of 0.1 Hz, with 5 s for inspiration and 5 s for expiration in accordance with a metronome. All data were

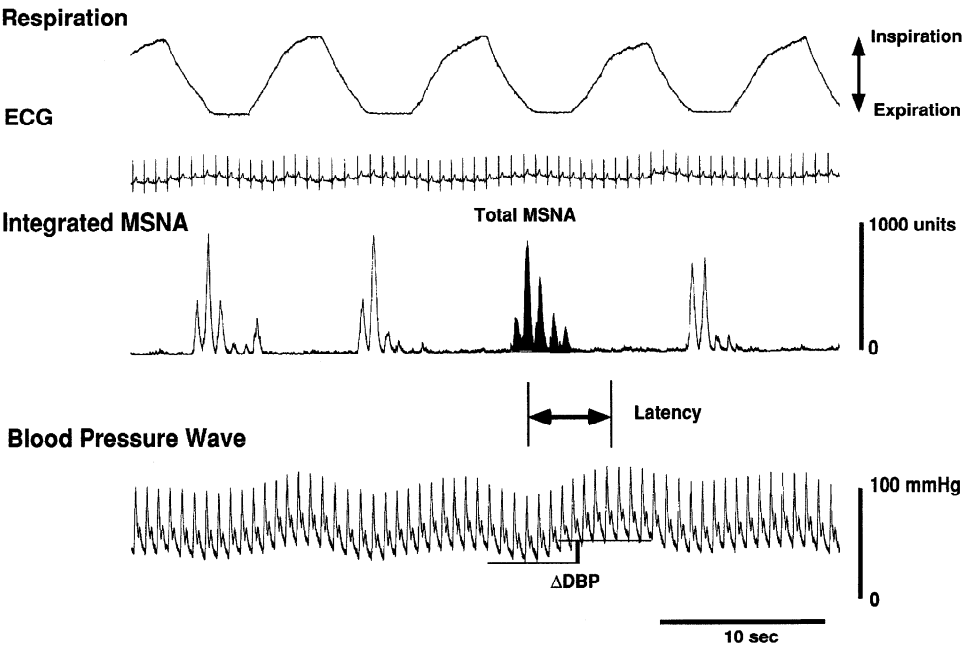

Fig. 1. Tracing of respiration curve, ECG, integrated muscle sympathetic nerve activity (MSNA), and blood pressure from 1 subject. MSNA was assessed quantitatively by measuring burst area from baseline, as indicated by shaded area. Maximum amplitude in integrated MSNA trace of each subject was fixed at 1,000 units. Latency of pressor response to MSNA was defined as lag time from peak phase of MSNA to that of diastolic blood pressure (DBP), which was obtained from variables of fitted cosine functions. Extent of pressor response to MSNA was defined as increase in amplitude of DBP (ΔDBP), which was obtained from variables of fitted cosine functions, divided by total MSNA as quantified in burst area.

stored on an FM magnetic tape recorder (model KS-616U, Sony Magnescale, Tokyo, Japan).

Data analysis. MSNA, ECG, and blood pressure waveforms were played back from the FM tape. MSNA was full-wave rectified and fed through a resistance-capacitance integrating circuit with a time constant of 0.1 s to obtain the integrated MSNA as a trace of mean voltage neurogram. The mean voltage neurogram of MSNA was displayed together with the ECG on a pen recorder (RECTI-HORIZ, NEC San-ei, Tokyo, Japan). Sympathetic bursts were identified by inspecting the mean voltage neurogram and are expressed as bursts per minute (burst rate). In accordance with previous studies, burst rate was used to compare resting MSNA between groups. Simultaneously, the ECG and blood pressure waveforms as well as the integrated MSNA trace were off-line digitized at 200 Hz through an analog-to-digital converter (model ADX-98E, Canopus, Kobe, Japan) on a personal computer (model PC9801DA, NEC, Tokyo, Japan). Each R-wave peak was detected on the ECG with a fast-peak detection algorithm, and consecutive instantaneous heart rates were calculated with temporal positions of R-wave peaks. Likewise, systolic and diastolic blood pressures with their temporal positions were also determined by detecting the peak and minimum, respectively, on the blood pressure waveform beat by beat. The beat-to-beat data of each variable were interpolated by cubic spline function and resampled at a frequency of 1 Hz. MSNA was also assessed quantitatively by measuring burst area from baseline every second to obtain time-series data for further analysis. The maximum amplitude in the integrated MSNA trace from each subject was fixed as 1,000 units, and the total MSNA was expressed in units per second.

Spectral analysis using the maximum entropy method (19) (MemCalc2000, Suwa Trust, Tokyo, Japan) was applied to the time-series data of each variable. Fast Fourier transform and autoregressive method are widely used for spectral analysis. However, these methods have some weakness such as poor resolution due to the effect of window functions and the small value of lag, respectively. Contrary to this, the maximum entropy method is considered to overcome these disadvantages and to have a comparably high degree of resolution despite a limited data length. After a confirmation of the existence of short-term fluctuation at a frequency of 0.1 Hz, a cosine function at the same frequency was fitted by means of the least-squares method (19). Peak phase and peak amplitude were obtained from each variable of the fitted cosine functions. We defined the latency of pressor response to MSNA as the lag time from the peak phase of MSNA to that of diastolic blood pressure. Likewise, we also defined the extent

Table 1. *Age, resting values of blood pressure, heart rate, and muscle sympathetic nerve activity, peak amplitudes and peak phases of cosine function fitted to each variable and pressor response to muscle sympathetic nerve activity*

	Young	Aged
Age, yr	33.8 ± 2.0	75.8 ± 2.7†
Resting		
SBP, mmHg	124.2 ± 3.9	134.6 ± 4.3
DBP, mmHg	66.2 ± 2.7	70.7 ± 1.0
HR, beats/min	60.9 ± 2.2	56.4 ± 2.2
MSNA, bursts/min	25.7 ± 2.5	40.6 ± 1.7†
MSNA, units·s·min^{-1}	2,752 ± 160	4,880 ± 517†
Peak amplitude of fitted cosine function		
SBP, mmHg	4.33 ± 1.07	7.85 ± 1.59
DBP, mmHg	3.16 ± 0.34	3.31 ± 0.48
HR, beats/min	4.37 ± 1.40	2.68 ± 1.39†
MSNA, units·s·s^{-1}	37.9 ± 5.4	85.8 ± 9.0†
Peak phase of fitted cosine function		
SBP, s	6.1 ± 0.4	7.5 ± 0.3†
DBP, s	5.4 ± 0.4	7.1 ± 0.3†
HR, s	3.6 ± 0.3	4.8 ± 0.4
Pressor response to MSNA		
Latency (MSNA − DBP), s	5.4 ± 0.4	7.1 ± 0.3†
Extent of pressor response to MSNA (ΔDBP/MSNA), mmHg·s·units^{-1}	0.099 ± 0.024	0.038 ± 0.006†

Values are means ± SE for 8 subjects in each group. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity; MSNA − DBP, lag time from the peak phase of MSNA to that of DBP; ΔDBP/MSNA, increase in amplitude of DBP vs. total MSNA. Peak phases are expressed as lag time from the peak of MSNA. †$P < 0.05$ vs. young.

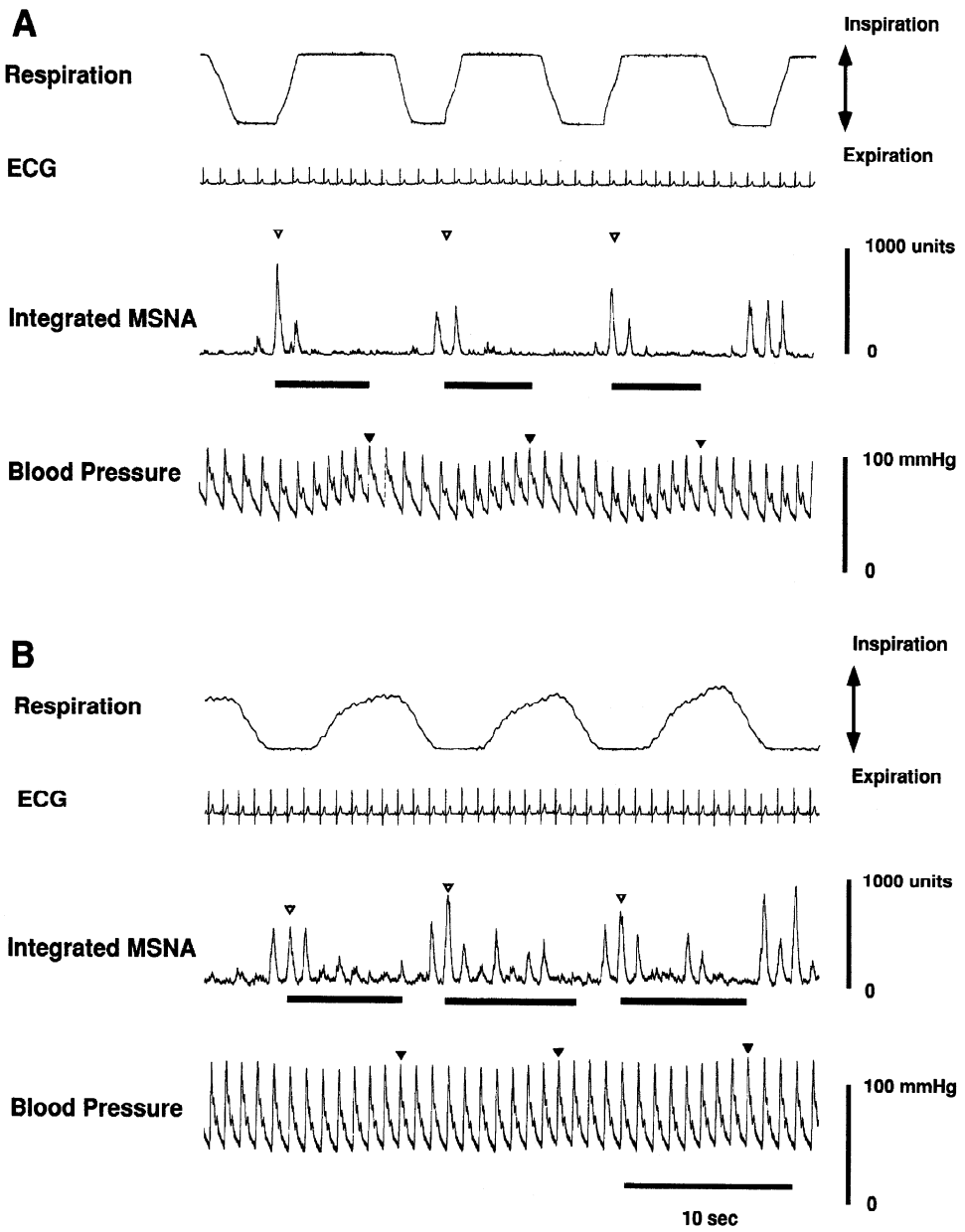

Fig. 2. Typical example of changes in pneumogram, ECG, integrated MSNA trace, and blood pressure waveforms in 1 young subject (38 yr; *A*) and in 1 aged subject (80 yr; *B*). ▽, Temporal positions of peaks of both integrated MSNA trace; ▼, temporal positions of peaks of blood pressure. Bars, vascular latency, which was obtained from cosine function.

of pressor response to MSNA as the increase in amplitude of diastolic blood pressure vs. total MSNA as quantified in the burst area, as shown in Fig. 1.

Values are expressed as means ± SE. The differences in means were analyzed by Student's *t*-test and were considered to be significant when P values were < 0.05.

RESULTS

Resting values. Subject profiles and results are summarized in Table 1. The resting systolic and diastolic blood pressure tended to be higher in the aged group than in the young group (systolic blood pressure, $P = 0.08$; diastolic blood pressure, $P = 0.13$). The resting heart rate showed no significant difference in these two groups. The resting MSNA, as assessed in bursts per minute and units per second per minute, was significantly higher in the aged group than in the young group.

Spectral analysis. Typical examples of changes in respiration curve, ECG, integrated MSNA trace, and blood pressure waveforms are shown for one of the young subjects and for one of the aged subjects (Fig. 2). Slow respiration at a frequency of 0.1 Hz induced rhythmic and grouped discharges of MSNA at the same frequency. Instantaneous heart rate and systolic and diastolic blood pressures were also entrained and showed consistent fluctuation at a frequency of 0.1 Hz. In some subjects, slower fluctuations with a cycle duration ranging between 60 and 140 s were superimposed on the short-term fluctuation at 0.1 Hz.

Cosine fitting. A cosine curve at a frequency of 0.1 Hz gave a good fit to each observed variable (Fig. 3). The peak amplitudes as calculated from the fitted cosine functions of systolic and diastolic blood pressures, heart rate, and MSNA are shown in Table 1. The peak

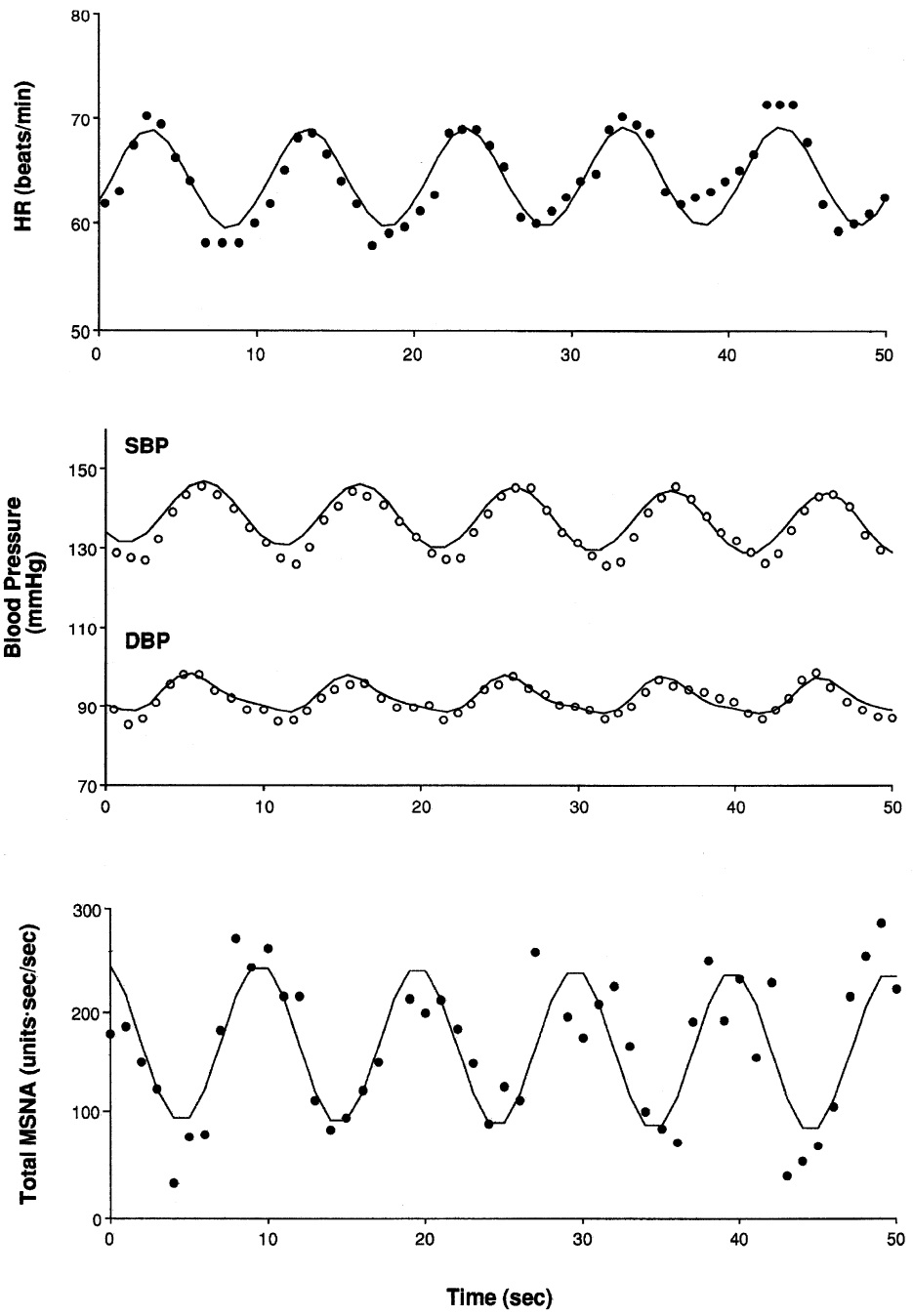

Fig. 3. Cosine curve at frequency of 0.1 Hz fitted to observed heart rate (HR), systolic blood pressure (SBP), DBP, and MSNA data in 1 subject.

amplitudes of systolic and diastolic blood pressure were not significantly different between the aged group and the young group. The mean peak amplitude of heart rate in the aged group was significantly lower than that in the young group. The MSNA as assessed in burst area in the aged group was significantly higher than that in the young group. The time lags of peaks of systolic and diastolic blood pressure and the heart rate from the peak of MSNA are shown in Table 1. Peak phases of systolic and diastolic blood pressure in the aged group were significantly prolonged compared with those in the young group. The mean peak phase of heart rate in the aged group tended to be delayed relative to that in the young group ($P = 0.08$).

Pressor response. The latency of pressor response to MSNA was translated into the time lag of the peak of diastolic blood pressure from the peak of MSNA. The latency was significantly prolonged in the aged group compared with the young group (Fig. 4). The pressor response in diastolic blood pressure to MSNA was significantly lower in the aged group than in the young group (Fig. 4).

Blood pressure-MSNA relationships. The peak of MSNA preceded the bottom of diastolic blood pressure fluctuation, and the lag time was longer in the aged group than in the young group (2.07 ± 0.31 vs. 0.4 ± 0.35 s). The changes in total MSNA in response to the diastolic blood pressure fluctuation were higher in the

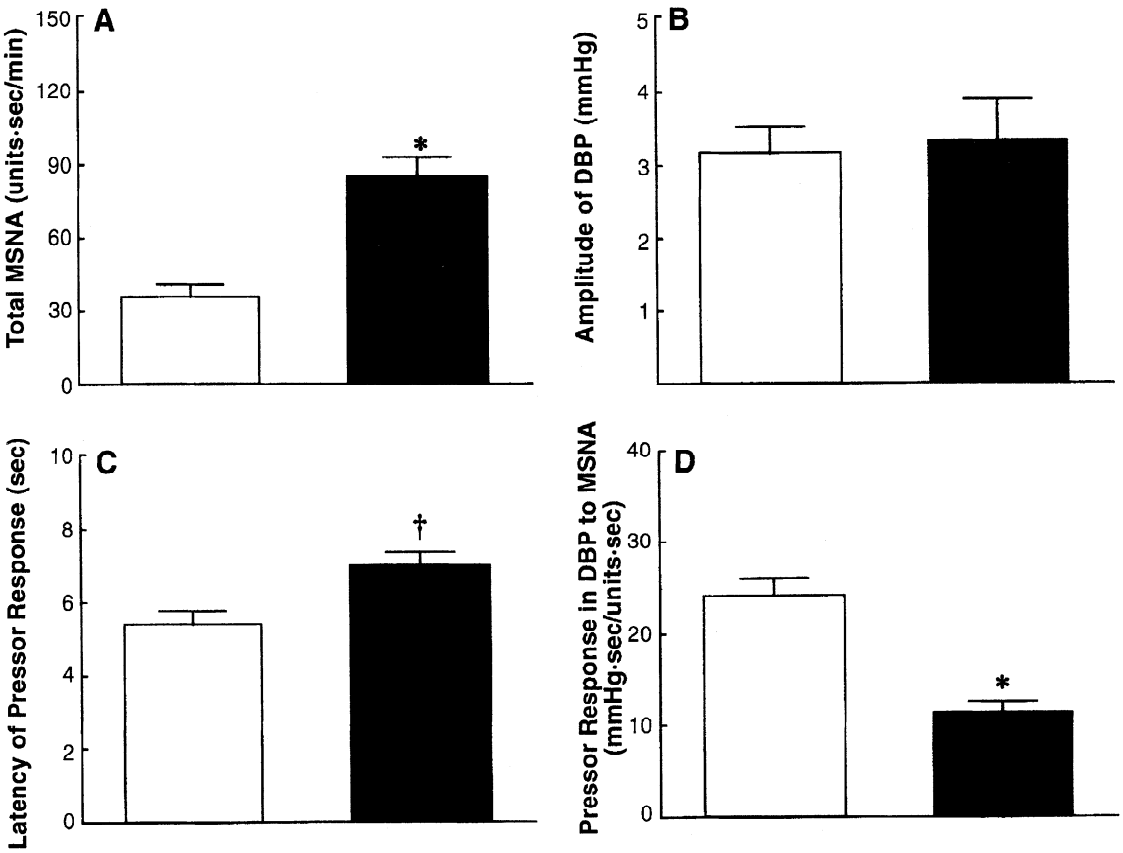

Fig. 4. Comparisons between aged (solid bars) and young (open bars) groups of total MSNA during slow respiration as measured in burst area (total MSNA; *A*), amplitude of DBP (*B*), latency of pressor response (*C*), and extent of pressor response to MSNA (*D*). Latency of pressor response was significantly prolonged in aged group compared with young group. Extent of pressor response was significantly diminished in aged group relative to that in young group despite higher MSNA. Values are means ± SE. $*P < 0.001$ vs. young group. $\dagger P < 0.01$ vs. young group.

aged group than in the young group (31.7 ± 5.9 vs. 12.6 ± 1.6 units/mmHg).

DISCUSSION

We studied the effect of aging on the α-receptor-mediated pressor response to sympathetic nerve activity by assessing the succeeding changes in systemic blood pressure after MSNA. Vascular tone in skeletal muscles is neurally regulated by MSNA and plays an important role in maintenance of peripheral vascular resistance. In the aged group, the pressor response to sympathetic vasomotor outflow was significantly diminished and delayed compared with the young group.

MSNA has a vasoconstrictive effect in the vasculature of the skeletal muscles via α-receptors. Wallin and Nerhed (30) studied the transient changes in blood pressure after a peak of MSNA by using a signal-averaging technique in human subjects. In this study, we used cosine fitting with spectral analysis instead of the signal-averaging technique because the signal-averaging technique possibly fails to assess the latency of pressor response due to high burst rate in the elderly.

Under natural breathing, there are low- and high-frequency oscillations in short-term fluctuations of the heart rate and blood pressure variabilities (1). Low-frequency oscillation from 0.04 to 0.15 Hz is in the range of Mayer's rhythm. High-frequency oscillation in the range between 0.15 and 0.4 Hz depends on the respiratory rate. In this study, subjects were asked to breathe slowly at a frequency of 0.1 Hz. We expected induction of a single short-term fluctuation by controlling respiratory rate at a frequency of 0.1 Hz to allow easy analysis of the time relationship between MSNA and blood pressure. We chose the frequency of 0.1 Hz as the respiratory rate because low-frequency oscillation from 0.04 to 0.15 Hz is thought to be derived from a slow temporal response of the α-adrenergic effector mechanism (14). All variables were indeed entrained into a frequency of 0.1 Hz. In some subjects, components slower than 0.04 Hz appeared in blood pressure and the heart rate. The cycle duration ranged between 60 and 140 s (0.02 to 0.007 Hz), which is referred to as the 1-min wave (9, 10).

Slow respiration may provoke changes in intrathoracic pressure and thereby result in stimulation of cardiopulmonary baroreceptors. Nonhypotensive lower body negative pressure studies suggested that afferent activity from the cardiopulmonary baroreceptors may also affect MSNA discharges (23, 29) mediated by the nucleus tractus solitarii in the medulla oblongata (6, 24). Changes in MSNA induced by slow respiration via cardiopulmonary baroreceptors evoke subsequent

changes in blood pressure. To analyze the time relationship of blood pressure vs. MSNA, we applied cosine fitting to the variables by using the least-squares method after deciding the main frequency by means of spectral analysis (19). A cosine function gave a good fit to all observed variables. Thus peak phases and amplitudes can be obtained from the variables of the fitted cosine functions. The latency from the peak of MSNA to the peak of diastolic blood pressure was 5.4 s in the young group and was consistent with the results reported by Wallin and Nerhed (30). In the aged group, the latency of pressor response to MSNA was 7.1 s on average and was significantly prolonged compared with that in the young group. In addition to the delayed response of blood pressure to MSNA, the aged group showed a diminished response to MSNA compared with the young group.

Blood pressure or sympathetic nerve activity regulation has been reported to be impaired (21, 22) or exaggerated (20) in the elderly. However, recent works have indicated appropriate blood pressure regulation in the elderly in response to various perturbations despite the modification of the autonomic regulation of the cardiovascular system (3, 18, 25, 26). Previous studies focusing on the baroreflex sensitivity revealed attenuated baroreceptor-heart rate reflex sensitivity in the elderly (4, 8, 21, 22). End-organ responsiveness of the heart to catecholamines and β-adrenergic agonists or antagonists have been reported to be diminished with aging (12, 13). In the present study, elderly subjects showed normal resting blood pressure and the amplitudes of systolic and diastolic blood pressure were not different from the young group, suggesting appropriate blood pressure regulation at rest in the elderly despite the high MSNA values and the increased latency and decreased extent of pressor response to MSNA. Thus the delayed and diminished pressor response to MSNA may not be detrimental but may contribute to maintain blood pressure stable.

The pressor response to sympathetic nerve activity is thought to be affected by baroreflex function, β-adrenergic responsiveness of the heart (the heart rate response), and α-adrenergic-receptor-mediated vascular responsiveness to sympathetic nerve activity. The attenuated baroreflex-mediated buffering effect on blood pressure can conversely cause an enhanced pressor response in the elderly. On the other hand, the pressor response to sympathetic nerve activity was diminished in the elderly despite the attenuated baroreflex function (8, 22). Thus the cardiac and vascular responsiveness to sympathetic nerve activity are suggested to cause the diminished pressor response in the elderly. Wallin and Nerhed (30) reported that the transient increase in blood pressure, occurring on average 5.5 s after the MSNA burst, is due to the combined effects of cardioacceleration and peripheral vasoconstriction. Because sympathetic control of peripheral vascular resistance is thought to be more important in blood pressure regulation than in control of the heart, a reduced α-adrenergic-receptor-mediated vascular response is suggested to contribute mainly to the diminished pressor response in the elderly. Moreover, the peak amplitude of heart rate was significantly lower and the peak phase of heart rate from the peak of MSNA tended to be prolonged in the elderly subjects. Therefore, heart rate may be an important variable contributing to the attenuated pressor response seen in the elderly individuals.

The exact mechanisms responsible for the delayed and diminished vascular response in the aged group are unknown, but there are some possibilities, including reduced vascular compliance due to arteriosclerosis, impaired reuptake of norepinephrine resulting in less effective release of norepinephrine, and a decrease in number of α-receptors in vascular smooth muscles. Previous reports have suggested an altered myogenic responsiveness, resulting in reduced contractile strength of vascular smooth muscles to stimuli such as catecholamines with advancing age (7, 27). Another possibility is downregulation of α-receptors in vascular smooth muscles. MSNA increases significantly with advancing age in the supine resting position (4, 11, 17, 24). High plasma catecholamine levels in aged individuals (20, 21) may reflect increased norepinephrine release at the sympathetic nerve terminals (28). The cause of the observed age-dependent increases in both MSNA and plasma catecholamine levels has not yet been fully clarified. High concentrations of plasma norepinephrine at the sympathetic nerve terminals may provoke downregulation of α-receptors in vascular smooth muscles.

In conclusion, the α-receptor-mediated pressor response to sympathetic nerve activity may be attenuated in the elderly.

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