Impairment of Thermoregulatory Control of Skin Sympathetic Nerve Traffic in the Elderly

Guido Grassi, MD; Gino Seravalle, MD; Carlo Turri, MD; Giovanni Bertinieri, MD; Raffaella Dell’Oro, MD; Giuseppe Mancia, MD

Background—Human aging is characterized by a marked increase in muscle sympathetic nerve traffic (MSNA). No information exists, however, on the effects of aging on skin sympathetic nerve traffic (SSNA) and on its reflex modulation by thermoregulatory mechanisms.

Methods and Results—In 13 young, 11 middle-aged, and 12 elderly healthy subjects, we measured arterial blood pressure (Finapres), skin temperature (thermocouples), and resting MSNA and SSNA (microneurography). Measurements also included the SSNA responses to (1) an acute increase and reduction (±8°C) in room temperature, each lasting 45 minutes and (2) an acoustic stimulus capable to trigger an emotional arousal. Although resting MSNA was progressively and significantly (P<0.05) increased from young to middle-aged and elderly groups, SSNA was significantly (P<0.05) reduced in the latter compared with the former 2 groups. Cold exposure induced a SSNA increase that was significantly (P<0.01) smaller in the elderly than in young and in middle-aged subjects. Conversely, heat exposure induced a SSNA reduction that was significantly (P<0.05) smaller in elderly than in young and middle-aged subjects. Compared with SSNA in young individuals, the SSNA change from cold to warm temperature was reduced by 61% in the elderly group. This was not the case, however, for the SSNA responses to the arousal stimulus, which were superimposable in the 3 groups.

Conclusions—These data provide the first demonstration of a dichotomy in the MSNA and SSNA responses to aging. They also show that aging markedly impairs thermoregulatory control of SSNA and that this impairment might participate at the age-related SSNA decrease. (Circulation. 2003;108:729-735.)

Key Words: aging ■ nervous system ■ nervous system, sympathetic ■ reflex

Studies performed via microneurographic recording of efferent postganglionic sympathetic nerve traffic have shown that sympathetic activation represents a hallmark of several cardiovascular and noncardiovascular diseases, including congestive heart failure, essential hypertension, obesity, and liver cirrhosis. They have also shown, however, that this neuroadrenergic activation does not uniformly affect the whole cardiovascular system. For example, although sympathetic neural outflow to the skeletal muscle vascular districts is markedly increased in all the above-mentioned diseases, neuroadrenergic drive to skin circulation remains similar to that seen in age-matched healthy controls. Whether this is the case also in conditions physiologically characterized by a marked increase in muscle sympathetic neural outflow has never been investigated, and it is therefore unknown whether the muscle–skin sympathetic dichotomy occurs only in diseases or represents an inherent feature of the sympathetic pattern of cardiovascular modulation.

In the present study, we recorded efferent postganglionic sympathetic nerve traffic to muscle and skin vascular districts in young, middle-aged, and elderly healthy individuals based on the evidence that aging is characterized by a steep progressive increase in sympathetic activity. Because control of skin sympathetic neural outflow has been shown to depend on both thermoregulatory and central emotional influences, the present study was also designed to examine whether possible age-related differences in muscle and skin sympathetic activity depend on alterations in the mechanisms modulating nerve traffic to the latter district.

Methods
The present study included 44 male healthy subjects with ages ranging from 18 to 81 years. Because of an inability to obtain adequate and stable muscle and skin sympathetic nerve traffic recordings (see below), however, the study was successfully completed in 36 subjects, who were classified, according to their age values, as young (n=13; age range, 18 to 29 years), middle-aged (n=11; age range, 38 to 51 years), and elderly (n=12; age range, 65 to 81 years). They were selected for the study if (1) blood pressure (BP) values were <140/90 mm Hg (systolic/diastolic) in the young and middle-aged group and <160/90 mm Hg in the elderly group at repeated

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sphygmomanometric measurements performed over 2 visits; (2) body mass index (body weight in kilograms divided by the square of the height in meters) was <25 kg/m²; and (3) there was no historical, clinical, or laboratory evidence of congestive heart failure, myocardial infarction, renal insufficiency, cardiac arrhythmias, diabetes, endocrinological disorders, or other cardiovascular or noncardiovascular diseases known to affect sympathetic function and thermoregulatory control. All subjects were in sinus rhythm, had normal echocardiographic images and values, were under no drug treatment, and had no smoking habit or history of excessive alcohol consumption.

Although young subjects were recruited from the student population of our university, middle-aged and elderly individuals belonged to a group of subjects seen in the outpatient clinic of our hospital for periodical routine examinations. Young and middle-aged subjects were physically untrained, and elderly subjects were in good physical and mental condition and able to attend to the usual daily-life activities of retired people. All subjects gave their informed consent to the study, the protocol of which was approved by the Ethics Committee of our Institution.

Measurements
BP was measured by (1) a mercury sphygmomanometer taking the first and fifth Korotkoff sound to identify systolic and diastolic values, respectively, and (2) a finger photoplethysmographic device (Finapres, Ohmeda 2300) capable of providing accurate and reproducible beat-to-beat systolic and diastolic values. Heart rate was continuously monitored by a phototachometer triggered by the R wave of an EKG lead. Respiration rate was monitored by a strain-gauge pneumograph positioned at mid-chest level. Skinfold thickness was measured with Harpenden calipers at the biceps, triceps, and subcapular sites, averaging the data to obtain a mean value. Skin temperature was recorded at 4 sites from uncovered thermocouples, and weighted mean skin temperature was calculated. Multiunit recordings of efferent postganglionic sympathetic nerve traffic to skeletal muscle (muscle sympathetic nerve activity [MSNA]) or skin (skin sympathetic nerve activity [SSNA]) areas were obtained through a tungsten microelectrode inserted into the right or left peroneal nerve, as previously described. The nerve signal was amplified 70,000×, fed through a bandpass filter (700 to 2000 Hz), and integrated with a custom nerve traffic analyzer (Bioengineering Department, University of Iowa). Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronic), and recorded with BP, heart rate, and respiratory rate on thermic paper by an ink polygraph (Gould 3800, Gould Instruments).

The muscle or skin nature of sympathetic nerve traffic was assessed by the criteria detailed in previous studies. Neurograms were accepted only if (1) they did not show simultaneous SSNA and MSNA activity and (2) the signal-to-noise ratio was >3. MSNA was quantified either as bursts per minute or as bursts per 100 heart beats, and SSNA was quantified as bursts per minute and as total burst area per minute (expressed in arbitrary units). The latter resulted from one half of the product of burst duration (expressed in milliseconds) and burst magnitude (expressed in arbitrary units) times the number of bursts per minute. The SSNA response to an acoustic stimulus (see below) was quantified in a different fashion because the short-lasting nature (5 seconds) of the stimulus only allowed a single burst to be obtained. Comparison thus had to be made between the area of this burst and the average area of the bursts over the 5 minutes preceding the stimulus, irrespective of the bursts frequency.

Protocol and Data Analysis
All the studies were performed in the same seasonal period, i.e., between the end of September and late March. Subjects were brought to a semidark quiet room in the morning after a light breakfast and between the end of September and late March. Subjects were brought to a semidark quiet room in the morning after a light breakfast and respiration rate on thermic paper by an ink polygraph (Bioengineering Department, University of Iowa). Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronic), and recorded with BP, heart rate, and respiratory rate on thermic paper by an ink polygraph (Gould 3800, Gould Instruments).

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The MSNA and SSNA values were, respectively, directly and inversely related to thermoregulatory influences. The delivery of the stimulus was not anticipated by the subject. Although the MSNA/SSNA recording sequence was not randomized, changes in environmental temperature were randomized so that half of the subjects were first exposed to the reduction, the other half first to the increase.

Data were analyzed by a single observer unaware of the study design and subjects’ age to obtain average values for every minute throughout the recording. Data from the 15-minute normothermic control periods (one for MSNA and two for SSNA) were averaged.

The effects of thermal challenge on skin temperature and SSNA were evaluated by taking into account the absolute values (averaged every 3 minutes) before and during the stimulus delivery and the recovery time. Values from individual subjects were averaged for each age group and expressed as mean±SEM. The differences in mean values between groups were assessed by 2-way ANOVA. The Student t test for unpaired observations was used to locate the statistical significance of the differences, following Bonferroni correction for multiple comparisons. MSNA and SSNA values and subjects’ age were also analyzed as linear correlations. A value of P=0.05 was taken as the level of statistical significance.

Results
The Table shows the demographic, anthropometric, and hemodynamic data in the 3 groups of subjects. Young, middle-aged, and elderly individuals displayed almost superimposable body weight, body mass index, heart rate, respiration rate, and skin temperature; (2) after 3 sphygmomanometric BP measurements, the microelectrode was inserted into the peroneal nerve to obtain MSNA, which was recorded together with finger BP, heart rate, and respiration rate for 15 minutes; (3) the microelectrode was then repositioned in the peroneal nerve fascicles to obtain SSNA, which was also recorded together with finger BP, heart rate, respiration rate, and skin temperature for 15 minutes at a constant room temperature of 23°C and a relative humidity of 60%; (4) the SSNA and the other above-mentioned variables were continuously monitored for 45 minutes during a reduction in room temperature to 15°C; (5) the room temperature was restored to 23°C, and all variables were continuously recorded for 45 minutes; (6) after a 15-minute control period at 23°C, all variables were again recorded for 45 minutes during an increase in room temperature to 31°C. Reductions and increases in room temperature were obtained via a room air conditioning system capable to cause 1°C change in 2 minutes and maintain thereafter the selected temperature; (7) step 5 was repeated; (8) all variables were again recorded for a 5-minute period at a room temperature of 23°C; and (9) a 5-second acoustic signal provided by an alarm clock was delivered to obtain a SSNA response unrelated to thermoregulatory influences. The delivery of the study was as follows: (1) the subject was dressed in light cotton clothing, placed supine, and fitted with devices to measure sphygmomanometric BP, finger BP, heart rate, respiration rate, and skin temperature; (2) after 3 sphygmomanometric BP measurements, the microelectrode was inserted into the peroneal nerve to obtain MSNA, which was recorded together with finger BP, heart rate, and respiration rate for 15 minutes; (3) the microelectrode was then repositioned in the peroneal nerve fascicles to obtain SSNA, which was also recorded together with finger BP, heart rate, respiration rate, and skin temperature for 15 minutes at a constant room temperature of 23°C and a relative humidity of 60%; (4) the SSNA and the other above-mentioned variables were continuously monitored for 45 minutes during a reduction in room temperature to 15°C; (5) the room temperature was restored to 23°C, and all variables were continuously recorded for 45 minutes; (6) after a 15-minute control period at 23°C, all variables were again recorded for 45 minutes during an increase in room temperature to 31°C. Reductions and increases in room temperature were obtained via a room air conditioning system capable to cause 1°C change in 2 minutes and maintain thereafter the selected temperature; (7) step 5 was repeated; (8) all variables were again recorded for a 5-minute period at a room temperature of 23°C; and (9) a 5-second acoustic signal provided by an alarm clock was delivered to obtain a SSNA response unrelated to thermoregulatory influences. The delivery of the stimulus was not anticipated by the subject. Although the MSNA/SSNA recording sequence was not randomized, changes in environmental temperature were randomized so that half of the subjects were first exposed to the reduction, the other half first to the increase.

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unchanged respiration rate, but it caused a progressive and marked increase in SSNA, when expressed both as number of bursts and as total burst area per minute. Heat exposure also did not affect BP, heart rate (data not shown), and respiration rate, but it caused a progressive marked decrease in SSNA, when expressed both as number of bursts and as total burst area per minute (Figure 3). In both instances, the SSNA changes went “pari passu” with the changes in skin temperature. All variables returned to control when original environmental temperature was restored.

Figures 2 and 3 also show that in the elderly group skin temperature changes were superimposable to those seen in the other 2 groups, whereas the SSNA responses, although qualitatively similar, were quantitatively much smaller, this being the case when the data were expressed not only as number of bursts per minute but also as total burst area per minute. That is, when skin temperature was decreased, SSNA increased much less in the elderly, achieving absolute values that at the end of the thermal stimulus were significantly greater than those of the other 2 groups. The overall magnitude of the change in SSNA from cold to heat was reduced by 61% (bursts per minute) and 64% (burst area) in the elderly compared with the young group. Figure 4 shows the data obtained before and after delivery of an acoustic stimulus. Before the stimulus, the average burst area was similar in the 3 age groups, the elderly showing, as expected, a lower resting sympathetic burst rate. The acoustic stimulus caused a marked increase in the burst area that was similar in the 3 groups.

Discussion

Confirming previous reports by our group and others, the present findings show that MSNA undergoes a progressive and marked increase from young to middle-aged and elderly subjects. They also show that, in contrast, SSNA undergoes a progressive and marked reduction. Thus, the different behavior of MSNA and SSNA is not limited to diseases, but it involves physiological conditions such as aging, in which the MSNA-SSNA dichotomy is even more evident. This implies that sympathetic activation is commonly characterized by a regional distribution. For aging, this is probably not limited to skeletal muscle and skin circulation because previous studies in the elderly have shown norepinephrine spillover rate to be increased in the heart but unchanged in the kidney compared with the rate in young individuals.

It is generally believed that the increase in MSNA associated with aging depends on an age-related impairment of baropulmonary and cardiopulmonary reflexes on which MSNA mainly depends. The present study, however, sheds light on the mechanisms that may be responsible for the concomitant age-related SSNA inhibition. In line with previous findings, in all individuals acute changes in environmental temperature triggered modifications in sympathetic outflow to skin districts. The SSNA responses, however, were markedly less pronounced in subjects age ≥65 years than in young or middle-aged individuals. This was not owing to the fact that in the elderly changes in environmental temperature did not effectively stimulate cutaneous thermoreceptors because (1) skin temperature was similarly modified by the thermal challenge in all age groups, and (2) skinfold thickness, although significantly greater in the elderly than in young subjects, displayed similar values in middle-aged and old individuals, in whom the SSNA responses to temperature changes were markedly different. Furthermore, the lower baseline SSNA was not responsible because in the elderly (1) the reduction in SSNA induced by

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**Table 1: Demographic, Anthropometric, and Hemodynamic Data in the 3 Groups of Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (n=13)</th>
<th>Middle-Aged (n=11)</th>
<th>Elderly (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>23.8±1.8</td>
<td>46.2±1.9†</td>
<td>71.6±2.2‡†‡</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>75.3±2.2</td>
<td>76.2±2.4</td>
<td>76.8±2.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.7±0.8</td>
<td>22.9±0.9</td>
<td>23.0±0.9</td>
</tr>
<tr>
<td>Sphygmonometric blood pressure (S/D), mm Hg</td>
<td>132.4±2.4/76.1±2.1</td>
<td>136.2±2.6/78.3±2.3</td>
<td>148.7±2.9†/80.5±2.5</td>
</tr>
<tr>
<td>Beat-to-beat blood pressure (S/D), mm Hg</td>
<td>129.7±2.5/74.8±2.2</td>
<td>133.7±2.8/76.9±2.4</td>
<td>145.4±3.1/78.5±2.5</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70.5±1.9</td>
<td>68.7±2.1</td>
<td>71.8±2.0</td>
</tr>
<tr>
<td>Respiration rate, breaths/min</td>
<td>19.7±0.7</td>
<td>20.5±0.9</td>
<td>20.4±0.8</td>
</tr>
<tr>
<td>Skinfold thickness, mm</td>
<td>9.03±0.9</td>
<td>9.65±1.1</td>
<td>10.5±1.2</td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>33.1±0.4</td>
<td>32.8±0.5</td>
<td>32.4±0.5</td>
</tr>
</tbody>
</table>

Data are shown as mean±SEM. Sphygmonometric blood pressure values are the average of 3 measurements. S indicates systolic blood pressure; D, diastolic blood pressure.

*P<0.05, †P<0.01, middle-aged and elderly subjects vs young subjects.

‡P<0.05 compared with middle-aged subjects.
heat and the increase in SSNA induced by cold exposure were both strikingly compromised, and (2) in both circumstances, absolute sympathetic activity values were different from the other groups. This allows us to conclude that aging is characterized by an impairment of the SSNA responses to thermal challenges. This impairment is likely to be specific for thermoregulatory control of neural sympathetic outflow to cutaneous circulation because the SSNA response to an acoustically elicited arousal, ie, the other important modulator of SSNA, was indistinguishable in the 3 age groups.

The present study does not clarify where in the reflex arch (afferent signal from cutaneous thermoreceptors, central integration at hypothalamic level, efferent sympathetic response) the age-related alteration in the autonomic thermoregulatory process occurs. The observation that in the elderly the SSNA response to arousal is preserved, however, rules out any major responsibility

Figure 2. Effects of cold exposure on absolute skin temperature (skin T, top); SSNA, expressed as bursts per minute (Bs/min; middle); and total burst area per minute (bottom) in young (○), middle-aged (□), and elderly (●) subjects. Numbers at bottom are values of respiration rate (Resp Rate) expressed as breaths per min. Data are mean ± SEM for the control normothermic period (control), during cold exposure (stimulus), and at the restoration of baseline temperature (recovery). A.u. indicates arbitrary units. *P<0.05, **P<0.01 elderly vs young subjects, †P<0.05, ††P<0.01 elderly vs middle-aged subjects.
of efferent sympathetic neurons. Interestingly, Frank et al.\textsuperscript{27} have recently reported an age-related decrease in plasma norepinephrine response to core cooling, suggesting that afferent and central alterations may both be involved.

In middle-aged subjects, both SSNA and SSNA responses to the thermal challenge were only slightly and not significantly reduced compared with those seen in the younger group. Thus, thermoregulatory control of SSNA may undergo little alterations in middle-aged subjects and only shows a substantial impairment when subjects’ age is clearly advanced. This is not the rule for all aspects of autonomic drive, however. For example, reflex control of MSNA by cardiopulmonary receptors (ie, a reflex importantly participating at BP and blood volume homeostasis)\textsuperscript{25} shows a clearcut impairment already in middle-aged individuals, a further marked deterioration characterizing the elderlies.\textsuperscript{28} There thus seems

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Effects of heat exposure on absolute skin temperature (Skin T, top); SSNA, expressed as bursts per minute (Bs/min; middle), and total burst area per minute (bottom) in young (-), middle-aged (○), and elderly (•) subjects. Numbers at bottom are values of respiration rate (Resp Rate) expressed as breaths per minute. Data are mean ± SEM for the control normothermic period (control), during heat exposure (stimulus), and at the restoration of baseline temperature (recovery). A.u. indicates arbitrary units. *P<0.05, **P<0.01 elderly vs young subjects, †P<0.05 elderly vs middle-aged subjects.}
\end{figure}
to be a certain degree of heterogeneity as far as the impairment of autonomic functions with aging is concerned, the delayed impairment of that involved in thermoregulation possibly reflecting the crucial importance its preservation has for body homeostasis.

Our study has 2 limitations and a pathophysiological implication. The first limitation is that SSNA was recorded in 1 district only. However, it is unlikely that in other skin districts the SSNA behavior is substantially different, because several studies have shown SSNA to be similar when recorded at different skin nerve sites. The second limitation is that the multiunit approach we used for SSNA recording does not allow to discriminate between sympathetic influences to blood vessels and sweat glands. Evidence is available that both sudomotor and vasomotor fibers fire in thermo-neutral environments so that either types could have been affected by heat and cold exposure. However, sudomotor fiber activity is increased by heat and reduced by cold, whereas the changes in overall SSNA we recorded were in the opposite direction, suggesting a net prevalence of the vasomotor fiber component with firing that is reduced by heat and increased by cold. Further studies using single fiber nerve traffic recording will be needed, however, to provide quantitative data on this issue.

The pathophysiological implication concerns the mechanisms responsible for the impaired thermoregulatory ability known to characterize the elderly. It is unlikely that these results originated from a subclinical polyneuropathic state because in our elderly patients (1) average values of signal-to-noise ratio of SSNA recordings were not significantly different between the 3 groups, and (2) there was no significant relationship between these values and resting SSNA. It is thus more likely that these results are part of an age-related and more generalized impairment in body homeostasis. Evidence has been obtained that aging is accompanied by a reduced responsiveness of skin vessels to adrenergic neurotransmitters, possibly because of a downregulation of α-adrenoceptors. Our findings, however, provide the first evidence that SSNA modulation by thermal stimuli is impaired as well and that multiple neural mechanisms, including those above the more peripheral ones, participate.

References
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