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Age-Related Influences of Leg Vein Filling and Emptying on Blood Volume Redistribution and Sympathetic Reflex during Lower Body Negative Pressure in Humans

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Abstract: To test the hypothesis that leg vein filling and emptying functions could be impaired with advancing age, which would produce less blood volume redistribution toward the lower body and smaller sympathetic reflex response during mild gravitational stress, 9 young and 10 elderly healthy males were exposed to a lower body negative pressure (LBNP) of 15 mmHg. Venous occlusion plethysmography was used to determine the functions of the leg veins. We found that the baseline venous distensibility index (VDI) was lower (0.057 ± 0.004 vs. $0.048 \pm 0.003\ \mathrm{ml \cdot 100\ ml^{-1} \cdot mmHg^{-1}}$, young vs. elderly; $p<0.05$), and half-emptying time ($T_{1/2}$) was shorter (1.6 ± 0.1 vs. 1.3 ± 0.1 s, young vs. elderly; $p<0.05$) in the elderly. At 15 mmHg-LBNP, VDI was decreased and $T_{1/2}$ was shortened significantly in the young group, but only slightly in the elderly group. Neither blood pressure nor heart rate changed significantly in either group. The reduction in peripheral venous pressure, which was recorded from the left antecubital vein at the cubital fossa, was less in the elderly, indicating a smaller decrease in central blood volume during LBNP; however, the enhancement of muscle sympathetic nerve activity was nearly the same as that in the young. We conclude that leg vein filling and emptying functions are impaired in elderly people, producing less blood pooling in the legs and smaller reduction in peripheral venous pressure during LBNP; the maintained sympathetic reflex response might be attributable to the well-preserved baroreflex function control of sympathetic outflow to the muscle in the elderly. [Japanese Journal of Physiology, 52, 77–84, 2002]

Key words: venous distensibility index, half-emptying time, muscle sympathetic nerve activity, gravitational stress.

In aged people, decreases in stroke volume and cardiac output during orthostatic challenge were found to be reduced [1–3]. Although the exact mechanisms have not been well clarified, it is supposed that the stiffness of the vessels is greater in the elderly, blunting venous pooling in the legs and reducing the drop in central blood volume in an upright position [4].

Olsen *et al.* [5] observed that baseline leg venous compliance was smaller, and the capacitance response in the legs to lower body negative pressure (LBNP) was lower in elderly people. They proposed that the decreased leg venous compliance with advancing age and the concomitant reduction in capacitance response during LBNP could have implications for both the sympathetic reflex and the cardiovascular responses during acute hypovolemic circulatory stress, which might be diminished in aged people. Their recent study suggested that the attenuated cardiovascular responsiveness found in the elderly during orthostasis seemed to be caused by a reduction in leg capacitance response and a concomitant smaller central hypovolemic stimulus rather than a reduced efficiency of the reflex response [6]. However, no work has been done to investigate simultaneously the venous system,

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the sympathetic reflex, or the cardiovascular responsiveness in aged people during gravitational stress.

The present study was performed to test the hypothesis that leg vein filling and emptying functions could be impaired with advancing age, which would cause less blood volume redistribution toward the lower body and smaller sympathetic reflex response during mild gravitational stress produced by LBNP of 15 mmHg in healthy humans. We chose a mild gravitational stress because we wanted to mainly unload the cardiopulmonary baroreceptors instead of the arterial baroreceptors without changing the discharge of the arterial baroreceptors.

The venous distensibility index (VDI) and half-emptying time ($T_{1/2}$) were used as vein filling and emptying parameters, respectively [7]. VDI indicates the stiffness of an elastic vein and is described quantitatively in terms of the relationship between its distending pressure and its volume, which is one of the properties of veins specific to individuals in supine positions and not a function of time. $T_{1/2}$ is the time that takes for half the leg blood volume to return to the central part of the body, whose properties are quite transient, and a function of time. These two physiological variables are greatly involved in the process of regulating cardiac performance and systemic arterial pressure [8, 9]. Sympathetic reflex response was directly recorded as the muscle sympathetic nerve activity (MSNA) by a microneurographic technique.

In the present study, we aimed to clarify (1) how advancing age affects baseline VDI and $T_{1/2}$ in a resting supine position, and (2) how the changes in VDI and $T_{1/2}$ influence the blood volume redistribution and MSNA response to 15 mmHg-LBNP in the elderly.

METHODS

Subjects. Nine young and 10 elderly healthy nonobese men, aged 31 ± 1 (mean$\pm$SE) and 69 ± 1 years, weighing 66 ± 2 and 55 ± 2 kg (body fat $<20\%$ of body weight), 174 ± 2 and 160 ± 1 cm tall, respectively, participated in this study. None had a history of cardiovascular disease, kidney disease, diabetes, venous insufficiency, or other diseases and were on no medication at the time of the study. All had abstained from alcohol and caffeine use for 24 h before the procedure, and all reported no recent use of tobacco or other pharmacological agents. The subjects were informed of the purpose and the procedures used in the study and gave their consent to participate in the experiment. The present study was conducted under the guidelines proposed by the Japan Microneurography Society and was approved by the Human Research Committee of the Research Institute of Environmental Medicine, Nagoya University.

Experimental protocol and procedures. The experimental protocols were performed in the morning or at noon 1 h after a light meal and normal hydration. All experiments were carried out with the subject supine, dressed in shorts without shirt, and in a room with an ambient temperature of 24–26°C. VDI, $T_{1/2}$, and calf blood flow (CBF, $\text{ml}\cdot100\,\text{ml}^{-1}\cdot\text{min}^{-1}$) were measured by mercury-infused silastic strain gauge venous occlusion plethysmography (Hokanson EC5R plethysmograph, Hokanson, Bellevue, WA, USA). Calf vascular resistance (CVR, unit) was calculated from the ratio of mean arterial pressure (MAP, mmHg) to CBF. MSNA was recorded microneurographically from the left tibial nerve at the popliteal fossa. The heart rate (HR, $\text{beats}\cdot\text{min}^{-1}$) obtained from electrocardiogram (ECG) and blood pressure (BP, mmHg) waves obtained by tonometry (model BP-508S, Nippon Colin, Komaki, Japan) were simultaneously recorded. Peripheral venous pressure (PVP, mmHg) was measured from a 20-gauge catheter placed in a large antecubital vein of the left arm at the cubital fossa, through a transducer kit (Baxter, Tokyo, Japan), and connected to a pressure amplifier (model AP-641G, Nihon Kohden, Tokyo, Japan). Because of the limitation of our facilities, we could not apply LBNP to the subject and record MSNA on the right lateral decubitus position; therefore PVP was measured in the supine posture. We suppose that the CHANGE in PVP during LBNP should be the same as that measured from the right lateral decubitus position. As changes in PVP were observed to be parallel to changes in central venous pressure [10], we selected PVP to evaluate the reduction in central blood volume during LBNP.

After the subjects rested for >30 min, the control data of VDI, $T_{1/2}$, HR, BP, PVP, MSNA, and CBF were recorded. LBNP of 15 mmHg was applied for 12 min, and VDI and $T_{1/2}$ were measured from the 6th min of LBNP. The lower body chamber pressure was then returned to 0 mmHg for recovery. The recovery period lasted for 6 min. All variables were monitored throughout the procedures and stored on a digital audio tape recorder (model PC216Ax, 16-channel, double-speed, Sony Precision Technology, Tokyo, Japan) for later analysis.

Lower body negative pressure (LBNP). The LBNP facility affiliated with the Space Medicine Center, Research Institute of Environmental Medicine, Nagoya University, was employed for the study. LBNP was applied distally to the subject's iliac crest by sealing the subject within a customized pressure box at the level of the iliac crest. Pressure was regulated within the LBNP chamber by controlling valves that adjusted the vacuum into the chamber with the help of a computer using a closed-loop servomechanism. The pressure applied was read via a pressure transducer connected to the inside of the chamber.

Venous occlusion plethysmography measurements and calculations. For all measurements, the subject relaxed in the supine position with his right leg elevated 3–5 cm above the heart level. The right heel was supported by a cushion. A mercury-in-silastic strain gauge was placed at the maximal circumference of the right calf. A contoured 22 cm wide thigh cuff was positioned around the proximal right thigh. The subject was informed of the importance of muscle relaxation during the testing period. In this investigation, the foot blood circulation was not excluded. The occlusion cuff pressure used in this study was relative to the outside of the negative pressure chamber.

Figure 1 shows how leg vein filling and emptying were measured. In the supine position, the vein in an elevated leg is collapsed, so the early phase of expansion of the vein involves no actual stretching of the elastic material in its wall, and a small change in distending (transmural) pressure merely changes the geometry of the vein. Once the vein has assumed a circular cross section, subsequent increases in its transmural pressure are opposed by the development of increased tension in the wall, and stiff collagen fibers must be stretched to increase the volume [11]. It was observed that when the transmural pressure was increased over 18 mmHg, the vein had a circular cross section either in young or in older healthy subjects [5]. Therefore in the present study we applied a low counterpressure of 20 mmHg to equalize the circular cross section of the vein before measurement. After a control baseline was obtained, the occlusion cuff was inflated quickly to 20 mmHg for 1 min, and a small curve with a steeply ascending beginning followed by a plateau was observed. The cuff pressure was then rapidly increased to 50 mmHg, and a similar curve appeared with a larger range of a steeply ascending beginning, followed by another plateau as a result of arterial inflow without venous outflow. It has been found that in the resting supine position, especially for an elevated leg, the venous pressure in the leg vein does not exceed the atrium level (5 mmHg) [12]; thus 50 mmHg of cuff pressure can completely block the venous return. After a venous stasis period, the cuff pressure was abruptly released to 0 mmHg. The criteria for deflating the cuff here were (1) the calf circumference increment had reached its maximum, and (2) the curve had reached a plateau. In our measurement, a 50 mmHg cuff inflation for venous occlusion was maintained for 2 min. After cuff deflation, the curve dropped quickly and became slower until it reached the previously noted baseline.

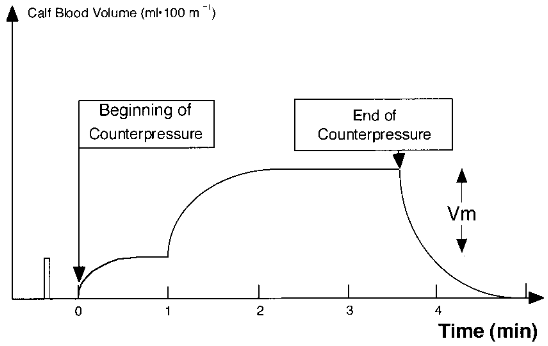

Fig. 1. Illustration of plethysmographic curve. Changes in leg vein filling and emptying followed an application of counterpressure. ΔV_{max}20, percent change in calf volume at the counterpressure of 20 mmHg; ΔV_{max}50, percent change in calf volume at the counterpressure of 50 mmHg; ΔV_m, percent change in the maximum venous emptying volume. VDI was calculated from the ratio of $[\Delta V_{max}50-\Delta V_{max}20]$ to [50−20]. $T_{1/2}$, half-emptying time, which was the time calculated from the end of the counterpressure to half of ΔV_m.

VDI was calculated from the equation of $\Delta V/\Delta P=[\Delta V_{max}50-\Delta V_{max}20]\cdot[50-20]^{-1}$, where ΔV_{max}50 was the percent change in calf blood volume at 50 mmHg counterpressure and ΔV_{max}20 was the percent change in calf blood volume at 20 mmHg counterpressure. The applied cuff pressure was taken as the transmural pressure [13]. Since the capacitance response is usually terminated within about 3 min [14], transcapillary fluid filtration was ignored in the present study. VDI was expressed as [ml blood]$\cdot$[100 ml tissue]$^{-1}\cdot$mmHg^{-1}. $T_{1/2}$ was the time measured from the end of the counterpressure to half maximum venous outflow (emptying) volume ($\Delta V_m/2$).

For measuring CBF, the occlusion cuff was inflated quickly to 50 mmHg to stop blood from leaving the measurement site but not hinder the arterial inflow. After 5 s inflation, the cuff was then deflated for a 25 s interval. The calf swelling because of the arterial inflow and the rate of blood flow were determined by measuring the rate of increase in volume. The inflow rate was determined by a line drawn on the recorded output tangent to the first few pulses following cuff inflation. The slope of this line was defined as the rate of volume change that was caused by arterial inflow. The flow rate was expressed as volume change per unit time, such as [ml of blood flow]$\cdot$[100 ml tissue]$^{-1}\cdot$min^{-1}. The measurement was repeated 8 times in each stage and the mean value was obtained.

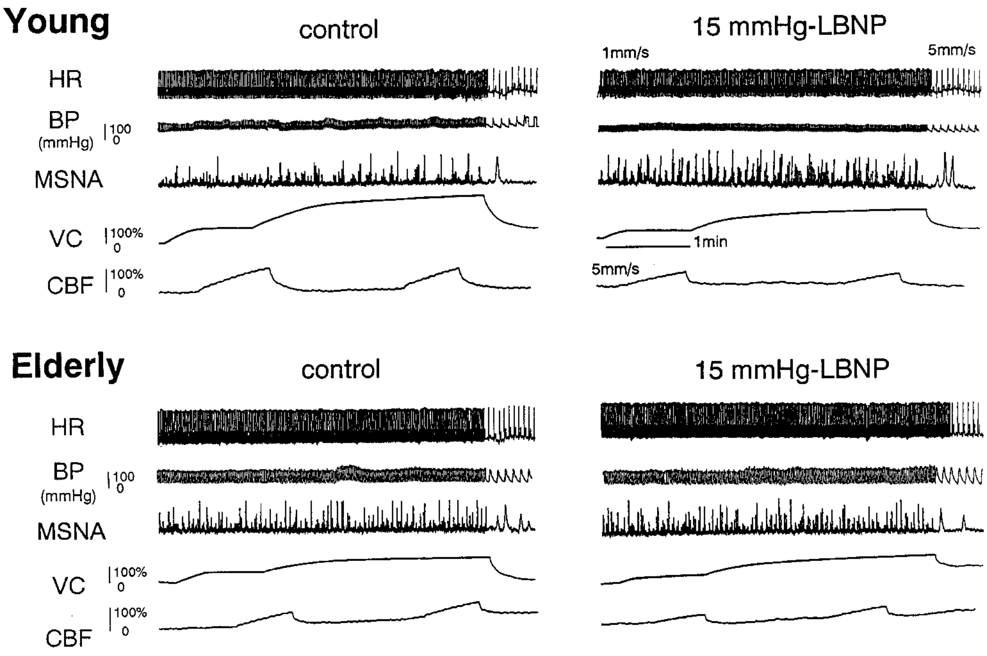

Fig. 2. Original tracings of electrocardiogram (HR), blood pressure (BP), integrated muscle sympathetic nerve activity (MSNA), venous curve (VC), and calf blood flow (CBF) at control and 15 mmHg lower body negative pressure (LBNP) in one young and one elderly subject.

Recording of MSNA. MSNA was recorded from the left tibial nerve at the popliteal fossa by a microneurographic technique by the use of a tungsten microelectrode with a tip diameter of $\sim 1\ \mu\mathrm{m}$ and an electrode impedance of $2\text{–}5\ \mathrm{M}\Omega$ (model 26-05-1, Frederic Haer, Bowdoinham, ME, USA). Nerve signals were fed through a high-input impedance preamplifier with a 500–5,000 Hz band-pass filter. MSNA was then full-wave rectified and integrated with a time constant of 0.1 s. The identification of MSNA was based on the presence of the following discharge characteristics described elsewhere [15]: (1) pulse-synchronous and rhythmic efferent burst discharges; (2) afferent activity evoked by tapping of the appropriate muscle but not in response to a gentle touch; (3) modulation by respiration; and (4) enhancement by maneuvers increasing intrathoracic pressure, such as the Valsalva maneuver.

Statistical analysis. An unpaired t-test was used to test the differences of subjects' characteristics in the young and elderly groups. We employed a two-way factorial ANOVA to determine the effects of aging on leg vein filling and emptying characters, MSNA and cardiovascular responses to LBNP. Session (young vs. elderly) and period (control vs. 15 mmHg-LBNP) were set as the main factors. Post hoc comparisons were performed by Fisher's test. $p<0.05$ was considered statistically significant. All analyses were conducted with a computerized statistical analysis system (StatView J-4.5, Power PC Version, 1992-98, Abacus Concepts).

RESULTS

Complete data were obtained in all experiments. Figure 2 shows the original tracings of the electrocardiogram, BP, and integrated MSNA, along with the venous occlusion curve and CBF, in one young and one elderly subject at resting control and 15 mmHg-LBNP. Baseline MSNA and the shape of the venous occlusion curve were different in two subjects. During 15 mmHg-LBNP, MSNA was enhanced in both subjects; the venous occlusion curve changed markedly in the young, but did not alter in the elderly.

Baseline VDI was smaller (0.057 ± 0.004 vs. $0.048\pm0.003\ \mathrm{ml}\cdot 100\ \mathrm{ml}^{-1}\cdot\mathrm{min}^{-1}$, young vs. elderly; $p<0.05$), and $T_{1/2}$ was shorter (1.6 ± 0.1 vs. 1.3 ± 0.1 s, young vs. elderly; $p<0.05$) in the elderly group. In response to 15 mmHg-LBNP, VDI was decreased significantly in the young group (by 19.3%, $p<0.01$), and nearly not changed in the elderly group (by 2.1%, Fig. 3A); $T_{1/2}$ was shortened in all subjects, but was pronounced in the young (Fig. 3B).

Cardiovascular and MSNA variables at rest and during 15 mmHg-LBNP are presented in Table 1. Baseline HR was not different between the groups, and resting MAP tended to be higher in the elderly ($p=0.067$). Resting CBF and CVR were not significantly different between the young and elderly subjects. Baseline MSNA, as assessed in bursts per min, was significantly higher in the elderly group ($p<0.05$).

In response to 15 mmHg-LBNP, neither HR nor MAP changed markedly in any subject (Fig. 4A, B). The reduction in PVP (ΔPVP) during LBNP was less in the elderly compared with that in the young (-2.5 ± 0.7 vs. -1.5 ± 0.4 mmHg, young vs. elderly; $p<0.05$, Fig. 4C). Although the absolute MSNA burst rate was higher in the elderly at 15 mmHg-LBNP (Table 1), the increment of MSNA (ΔMSNA) was not different between two groups (9 ± 3 vs. 7 ± 2 bursts $\cdot$ min^{-1}, young vs. elderly; $p>0.05$, Fig. 4D), indicating that the enhanced MSNA responses were nearly the same in the young and elderly. Similarly, the decrease in CBF and the increase in CVR during LBNP were not significantly different between two groups.

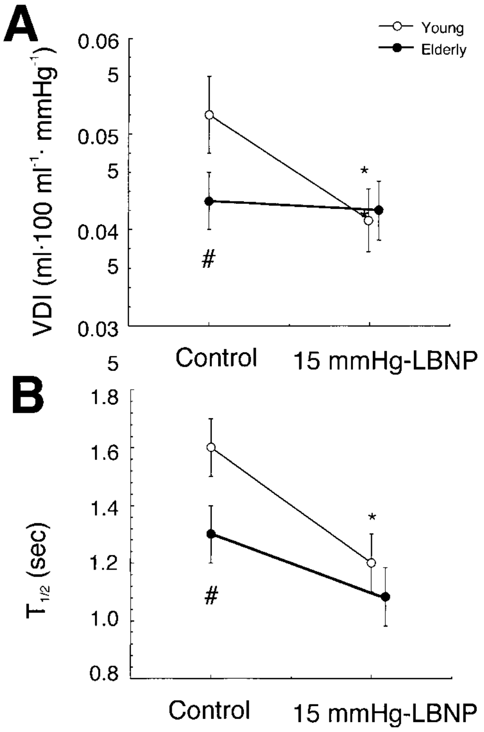

Fig. 3. Responses of leg vein filling and emptying to lower body negative pressure (LBNP). Each curve represents averaged group data [means±SE, $n=9$ subjects in the young group (○); and $n=10$ subjects in the elderly group (●)] of venous distensibility index (VDI, **A**) and half-emptying time ($T_{1/2}$, **B**) in response to 15 mmHg-LBNP. $^{*}p<0.05$ vs. the control; $^{**}p<0.01$ vs. the control; $^{\#}p<0.05$ vs. the young group.

DISCUSSION

The major findings from the present study were that (1) baseline VDI was smaller and $T_{1/2}$ was shorter; (2) changes in VDI and $T_{1/2}$ were less in the elderly subjects at 15 mmHg-LBNP; and (3) the reduction in PVP was less, but the enhancement in MSNA was similar in the elderly compared with the young during LBNP.

Possible mechanisms for the impaired leg venous functions in the elderly. We found that the baseline VDI was smaller in the elderly, indicating a reduction in venous distensibility. It is known that the visco-elasticity of the peripheral venous wall decreases with advancing age [16] because the collagen/elastin ratio has been found to be higher and the venous wall has been observed to be thicker in aged people [17], and these changes parallel the changes in the arterial wall [18]. As elastic tissue is decreased and collagen content in the smooth muscle is increased in aged people, these two factors can stiffen the venous wall and reduce the venous distensibility.

It is suggested that the leg venous compliance is smaller when a large muscle mass is providing structural support to limit the expansion of the veins [19]. Muscle mass is decreased with advancing age because of muscle atrophy. This can increase the leg venous compliance and the venous distensibility. However, the characteristics of the skeletal muscle surrounding the veins are supposed to be a major factor in leg venous compliance [19]. The skeletal muscle tone may affect the venous distension or the capacity of veins to store more blood [7]. The tone is higher in elderly people because of an increment of collagen content in the skeletal muscle. Thus the muscular elasticity should be lower in the elderly [20], which may restrict the distensibility of the veins. On the other hand, muscle atrophy might influence the vascular bed in the

Table 1. Cardiovascular and vasomotor responses to LBNP in the young and elderly subjects.

	HR	MAP	PVP	CBF	CVR	MSNA
Control						
Young ($n=9$)	71±2	87±2	1.3±2.1	3.7±0.5	23.7±4.5	21±4
Elderly ($n=10$)	67±2	95±3	1.2±1.2	3.4±0.3	27.6±5.5	$32\pm3^{\#}$
15 mmHg-LBNP						
Young ($n=9$)	72±3	82±2	$-1.2\pm2.0^{*}$	$3.0\pm0.4^{*}$	$27.1\pm4.9^{*}$	$30\pm5^{*}$
Elderly ($n=10$)	69±2	89±3	$-0.3\pm1.3^{*}$	$2.9\pm0.2^{*}$	$31.7\pm5.3^{*}$	$39\pm3^{*,\#}$

Values are means±SE. LBNP, lower body negative pressure; HR (beats $\cdot$ min^{-1}), heart rate; MAP (mmHg), mean arterial pressure; PVP (mmHg), peripheral venous pressure; CBF (ml $\cdot$ 100 ml^{-1} $\cdot$ min^{-1}), calf blood flow; CVR (unit), calf vascular resistance; MSNA (bursts $\cdot$ min^{-1}), muscle sympathetic nerve activity. $^{*}p<0.05$ vs. the control; $^{\#}p<0.05$ vs. the young group.

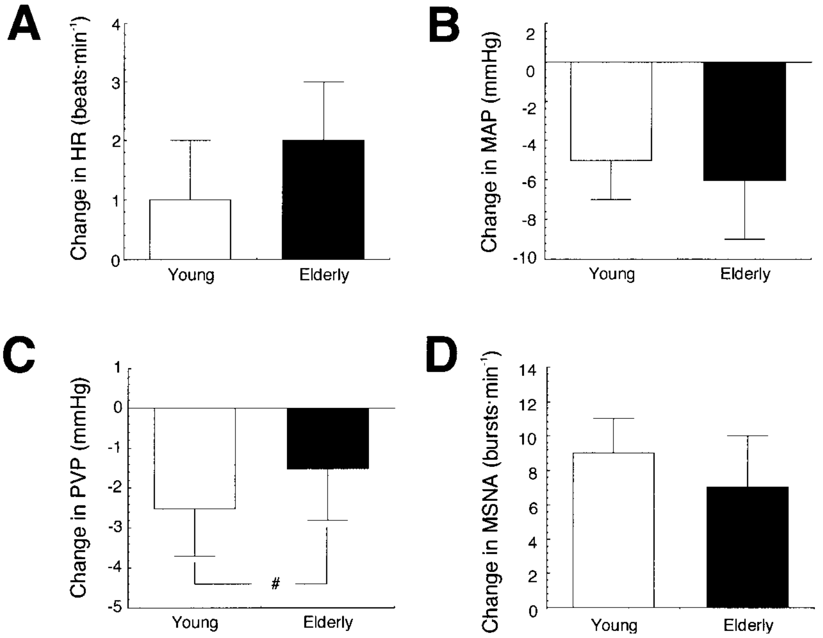

Fig. 4. Changes in heart rate (A), mean arterial pressure (B), peripheral venous pressure (C), and muscle sympathetic nerve activity (D) before and during the application of 15 mmHg in young (□) and elderly (■) subjects. Bars are mean±SE, $^{\#}p<0.05$.

muscles. It is very likely that the changed vascular bed in the elderly would affect VDI, but we did not have direct evidence to support this notion in the present study. Further investigations are necessary.

Moreover, the decreased VDI may be related to a higher baseline level of MSNA in the elderly. It is suggested that the lower venous capacitance in aged people might be due to a higher baseline sympathetic tone [21]. Therefore the smaller baseline VDI is not only derived from the structural changes, but it also related to the functional changes of the vessels with advancing age.

$T_{1/2}$ is the venous emptying parameter, reflecting the active behavior of venous walls and their resistance to blood flow [22]. It represents how quick venous blood returns to the central part of the body during postural changes in humans. Therefore a change in $T_{1/2}$ may largely influence the venous return and the central blood volume. Venous emptying seems to be proportional to filling. The possible mechanisms for the shorter baseline $T_{1/2}$ in the elderly might also be related to the factors mentioned above.

The reduced baseline VDI and $T_{1/2}$ should have resulted in a centralized blood volume at the resting supine position in the elderly, which might have increased the loading of the cardiopulmonary baroreceptors. It is unlikely, however, because the absolute central blood volume in the elderly could have been the same or even lower than in the young, since dehydration usually occurs with advancing age [23, 24]. This notion was supported by our observation that baseline PVP was not different between the groups. Moreover, there was no evidence of vasodilation occurring in the elderly because baseline MSNA was significantly higher in these subjects. Thus it is quite unlikely that a loading of the cardiopulmonary baroreceptors is larger in elderly people in supine rest. In the present study, we couldn't know the absolute values of blood pooling in the thorax and legs; what we could know was the relative changes of these values. Further investigations are necessary to solve this issue.

Influences of leg vein filling and emptying on blood volume redistribution and sympathetic reflex response with age. During 15 mmHg-LBNP, VDI was decreased and $T_{1/2}$ was shortened significantly in the young, but only slightly in the elderly. The decrease in VDI, indicating a reduction in the distensibility of the leg veins, could restrict much blood pooling in the legs during LBNP. It was found that the transmission of externally applied pressure produced by LBNP to the underlying tissue was almost identical in the young and elderly [5]; therefore the reduction in visco-elastic properties of the veins as well as the increased stiffness of the surrounding skeletal muscles with age may account for the smaller leg vein filling and emptying responses in the elderly. The main difference from the study by Olsen *et al.* was that they employed a strong level of LBNP (22, 44 and 59 mmHg), but ours was 15 mmHg because we did not like to induce the arterial blood pressure change during the study.

The smaller change in VDI during LBNP in the elderly could result in a reduction in blood volume redistribution toward the lower body and cause a smaller decrease in PVP, and thereby less unloading of the cardiopulmonary baroreceptors, including probably the arterial baroreceptors to some extent. Because the increments in MSNA responses were nearly the same in both groups despite a reduced blood volume redistribution toward the lower body in the elderly, we would suppose that the sympathetic reflex response is well maintained in elderly subjects. Recent studies have shown that the cardiopulmonary and/or integrated sympathetic baroreflexes were preserved or even augmented with advancing age [25, 26]. Our results were consistent with these studies, but different from one that reported an impaired ARTERIAL baroreflex function for both heart rate and sympathetic nerve activity in the elderly [27]. The reasons for this difference were not clear, but probably include (1) the mean age of the elderly group was 75 years in that study, but it was 69 years in ours; (2) they applied Valsalva's maneuver, but we applied LBNP to the subjects; and (3) they reported the ARTERIAL baroreflex function, and we discussed the cardiopulmonary baroreflexes.

On the other hand, because the functions of baroreflex control of sympathetic outflow to the muscles were well preserved or even augmented with advancing age [25, 26], the attenuated responsiveness of leg veins to gravitational stress in the elderly might have some physiological relevance for the maintenance of cardiovascular homeostasis. Because baseline MSNA was high in the elderly, the attenuated leg venous responses could avoid a much higher MSNA enhancement in these subjects.

Unexpectedly, the decrease in calf blood flow and the increase in calf vascular resistance during LBNP were not significantly different between the two groups in the present investigation. Previous studies have shown that the sensitivity and/or concentration of α- and β-adrenergic receptors in end organs are reduced with advancing age, resulting in an attenuated vasoconstrictor responsiveness in the elderly [28–30]. Because the decreased visco-elasticity of the peripheral venous wall has been found to be parallel to the changes in the arterial wall in aged people [18], it is very unlikely that the arterial part has no obvious changes in the elderly. It is possible, however, that the vasoconstrictor responsiveness in the splanchnic vascular bed rather than in the muscular and/or cutaneous vascular beds attenuates with advancing age. If so, the responses of calf blood flow and calf vascular resistance could have not been changed markedly in the elderly group in the present study. The other possibility is an intensity of loading. This issue was discussed previously between Ng *et al.* [31] and ourselves [32] that the weak–moderate load intensity does not necessarily cause the differences.

In conclusion, we found in the present study that leg vein filling and emptying functions were impaired with advancing age, which resulted in less blood volume redistribution toward the lower body during mild gravitational stress; however, MSNA responses were not different between the young and elderly subjects. It is suggested that although aging can diminish the functions of the venous system, the sympathetic reflex response is well preserved in aged people.

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