

Relations of Arterial Stiffness With Postural Change in Mean Arterial Pressure in Middle-Aged Adults The Framingham Heart Study

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Abstract—Impaired regulation of blood pressure on standing can lead to adverse outcomes, including falls, syncope, and disorientation. Mean arterial pressure (MAP) typically increases on standing; however, an insufficient increase or a decline in MAP on standing may result in decreased cerebral perfusion. Orthostatic hypotension has been reported in older people with increased arterial stiffness, whereas the association between orthostatic change in MAP and arterial stiffness in young- to middle-aged individuals has not been examined. We analyzed orthostatic blood pressure response and comprehensive hemodynamic data in 3205 participants (1693 [53%] women) in the Framingham Heart Study Third Generation cohort. Participants were predominantly middle aged (mean age: 46±9 years). Arterial stiffness was assessed using carotid–femoral pulse wave velocity, forward pressure wave amplitude, and characteristic impedance of the aorta. Adjusting for standard cardiovascular disease risk factors, orthostatic change in MAP (6.9±7.7 mmHg) was inversely associated with carotid–femoral pulse wave velocity (partial correlation, $r_p = -0.084$; $P < 0.0001$), forward wave amplitude ($r_p = -0.129$; $P < 0.0001$), and characteristic impedance ($r_p = -0.094$; $P < 0.0001$). The negative relation between forward wave amplitude and change in MAP on standing was accentuated in women ($P = 0.002$ for sex interaction). Thus, higher aortic stiffness was associated with a blunted orthostatic increase in MAP, even in middle age. The clinical implications of these findings warrant further study. (*Hypertension*. 2017;69:685-690. DOI: 10.1161/HYPERTENSIONAHA.116.08116.) • [Online Data Supplement](#)

Key Words: arterial pressure ■ blood pressure ■ hypotension, orthostatic ■ pulse wave analysis ■ vascular stiffness

Blood pressure (BP) typically falls initially when changing from a supine to standing position and then stabilizes at a higher mean arterial pressure (MAP) soon after standing when the baroreceptors sense the change in systemic pressure and trigger a compensatory increase in heart rate and peripheral vascular resistance.¹ This orthostatic increase in MAP is necessary to maintain sufficient cerebrovascular perfusion given the change in gravitational potential energy when moving from a supine to standing posture. If there is an insufficient increase in MAP, cerebral vasodilation is required to maintain cerebral perfusion at a constant level. Previous studies have shown that arterial stiffness is associated with short-term orthostatic pressure variability in older adults.^{2,3} Increased vascular stiffness may affect BP homeostasis by diminishing cardiovagal baroreflex sensitivity,⁴⁻⁶ which may blunt orthostatic BP response via limited changes in heart rate or peripheral vasoconstriction.⁷ Arterial stiffness may be assessed via characteristic

impedance (Z_c) or forward pressure wave amplitude, which takes into account both aortic stiffness and peak aortic flow. Additionally, carotid–femoral pulse wave velocity (CFPWV) has emerged as the reference standard measure of aortic stiffness.⁸ Previous studies have shown a positive relation between CFPWV and short-term BP variability in older people,^{2,3,9} but these observations have been largely overlooked in younger adults. The combination of blunted increase in MAP and impaired microvascular reactivity may represent a particularly harmful insult to the brain and may explain recent findings of a relation between stiffness measures and vascular brain injury in young- to middle-aged adults¹⁰ or cognitive impairment in older adults.^{11,12} We hypothesized that higher arterial stiffness, as assessed by CFPWV, Z_c , or forward pressure wave amplitude, is associated with a diminished compensatory increase in MAP on standing in middle-aged individuals and tested this hypothesis in a community-based cohort.

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Methods

Study Sample

Third-generation participants of the Framingham Heart Study were evaluated during their second examination. Participants were predominantly middle aged and of European descent. Satisfactory evaluation of hemodynamic and covariate data was obtained in 3205 of 3411 participants (94%). The Boston University Medical Center Institutional Review Board approved the protocol, and all participants gave written informed consent.

Noninvasive Hemodynamic Data Acquisition and Analysis

Participants were studied in the supine position after resting for \approx 5 minutes. Auscultatory BP was assessed at the level of the brachial artery by using a computer-controlled device that automatically inflated the cuff to a user preset maximum pressure (160 mmHg) and then precisely controlled deflation at 2 mmHg/s. If Korotkoff sounds were detected immediately after cuff inflation, the acquisition was aborted and repeated with maximum cuff pressure increased by 40 mmHg, up to a maximum of 240 mmHg. The device digitized and recorded mean cuff pressure and a cuff microphone channel (12 kHz) throughout the inflation and deflation sequence so that auscultatory BP measurements could be overread at the core laboratory (Cardiovascular Engineering, Inc, Norwood, MA) by analysts who were blinded to participant characteristics. Arterial tonometry was obtained from the brachial, radial, femoral, and carotid arteries using a custom transducer (Cardiovascular Engineering, Inc). Next, 2-dimensional echocardiographic images of the left ventricular outflow tract were obtained from a parasternal long-axis view followed by pulsed Doppler of the left ventricular outflow tract from an apical 5-chamber view. Body surface measurements from suprasternal notch to pulse-recording sites were obtained by using a fiberglass tape measure for carotid, brachial, and radial sites and a caliper for the femoral site.

At the end of the hemodynamic data acquisition, participants were asked to sit up momentarily and then stand. A second BP measurement was taken starting the cuff inflation \approx 2 minutes after standing, meaning that the BP measurement corresponded to a time interval of \approx 2 to 3 minutes after standing. A previous study using continuous BP monitoring in a community-based cohort has shown that BP stabilizes at a new equilibrium value within \approx 20 to 30 seconds after standing and remains stable out to 2 minutes post-standing in the age range of our cohort.¹³ Therefore, change in BP 2 to 3 minutes after standing should provide a robust estimate of change in equilibrium BPs between supine and standing. Changes in BP components were defined as the standing value minus the supine value. Systolic and diastolic BP often have opposite directional responses to standing, whereas MAP, which is the primary contributing factor to mean cerebrovascular perfusion, should increase on standing from a supine position. Thus, we focused our analyses on continuous orthostatic change in MAP as the primary outcome variable.

Tonometry waveforms were signal averaged using the electrocardiographic R-wave as a fiducial point. Average supine systolic and diastolic cuff pressures were used to calibrate peak and trough of the signal-averaged brachial waveform. Diastolic and integrated mean brachial pressures were used to calibrate carotid waveforms.¹⁴ MAP was calculated from the integrated brachial pressure waveform based on tonometry or the oscillometric cuff waveform. CFPWV was calculated, accounting for parallel transmission in the aortic arch and carotid artery, as previously described.¹⁵ Left ventricular outflow tract diameter was measured on echocardiographic images by finding the largest early systolic diameter at a point just proximal to the aortic leaflets. The left ventricular outflow tract Doppler flow velocity waveform was multiplied by outflow tract area to compute aortic volumetric flow. Z_c of the aorta was computed in the time domain by dividing the increase in pressure during early systole by the corresponding increase in volumetric flow.¹⁶ Central pressure and flow waves were separated into their forward and backward components, as previously described.¹⁷

Statistical Analyses

Demographic and hemodynamic characteristics of the sample were tabulated. Given the low prevalence (2.3%) of orthostatic hypotension by the standard definition in this relatively young cohort, we have focused statistical analyses on continuous BP change variables rather than dichotomous variables. We estimated partial correlations of arterial stiffness measures (CFPWV, Z_c , and forward wave amplitude) with orthostatic change in BP variables (systolic, diastolic, mean, and pulse pressure) and heart rate. We adjusted for age, sex, height, body mass index, total cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting glucose, hemoglobin A1c, current smoking, use of medication to treat hypertension or dyslipidemia, prevalent diabetes mellitus, and prevalent cardiovascular disease. To evaluate effect modification by age, sex, and presence of diabetes mellitus in the MAP change on standing, we examined interactions of median age, sex, and presence of diabetes mellitus with aortic stiffness measures in linear regression models that adjusted for risk factors noted above. In a secondary analysis, we included an indicator variable for hypertension (BP \geq 140/90 or treated) in the model. For all analyses, a 2-tailed α value of <0.05 indicated statistical significance.

Results

Characteristics of the sample are summarized in Table 1. The cohort comprised young- to middle-aged adults who were, on average, overweight. Hemodynamic variables are summarized for the full cohort in Table 2 and separately by sex in Table S1 in the [online-only Data Supplement](#). Average supine BP fell within the normotensive range. Standing was associated with substantial increases in diastolic BP, MAP, and heart rate. In contrast, systolic BP increased only modestly, and pulse pressure fell substantially (Table 2). Consistent with the observed fall in pulse pressure, which, at any given level of MAP, will tend to reduce systolic BP and increase diastolic BP, the increase in diastolic BP exceeded the increase in MAP.

Partial correlations of change in BP components and heart rate with CFPWV, Z_c , and forward wave amplitude, adjusted for standard cardiovascular risk factors, are shown in Table 3. Changes in MAP and systolic pressure were inversely related to CFPWV, Z_c , and forward wave amplitude, indicating that

Table 1. Characteristics of the Sample (n=3205)

Variable	Value
Age, y	46 \pm 9
Women, n (%)	1693 (53)
Height, inch	67 \pm 4
Weight, lbs	177 \pm 41
Body mass index, kg/m ²	27.7 \pm 5.4
Fasting glucose, mg/dL	96 \pm 18
Triglycerides, mg/dL	111 \pm 73
Total/HDL cholesterol ratio	3.4 \pm 1.2
Hemoglobin A1c, %	5.5 \pm 0.5
Diabetes mellitus, n (%)	154 (5)
Prevalent cardiovascular disease, n (%)	69 (2)
Treatment for hypertension, n (%)	524 (16)
Treatment for lipid disorder, n (%)	512 (16)
Current smoking, n (%)	370 (12)

Values are mean \pm SD except as noted. HDL indicates high-density lipoprotein.

Table 2. Hemodynamic Variables (n=3205)

Variable	Value
Carotid–femoral pulse wave velocity, m/s	7.1±1.4
–1000/carotid–femoral pulse wave velocity, ms/m	–146±25
Characteristic impedance, dyne·s·cm ^{–5}	194±59
Forward pressure wave, mm Hg	45±11
Supine hemodynamics	
Systolic blood pressure, mm Hg	121±15
Diastolic blood pressure, mm Hg	63±9
Mean arterial pressure, mm Hg	87±11
Pulse pressure, mm Hg	57±12
Heart rate, min ^{–1}	65±10
Systolic ejection period, ms	311±24
Change on standing, median (25th to 75th percentile)	
Systolic blood pressure, mm Hg	2 (–4 to 8)
Diastolic blood pressure, mm Hg	10 (4 to 14)
Mean arterial pressure, mm Hg	7 (2 to 12)
Pulse pressure, mm Hg	–8 (–15 to –1)
Heart rate, min ^{–1}	14 (9 to 20)
Systolic ejection period, ms	–68 (–81 to –55)

Standing blood pressure measurements were taken 2 min after standing.

individuals with stiffer arteries exhibited a smaller increase in MAP on standing. Change in pulse pressure was also negatively related to Z_c and forward wave amplitude. In contrast, change in diastolic pressure had a positive relation with Z_c and forward wave amplitude. Relations between change in heart rate and stiffness measures were modest (forward wave amplitude) or

Table 3. Partial Correlations Among Stiffness and Orthostatic BP Change Variables

Change Variables	Carotid–Femoral Pulse Wave Velocity	Characteristic Impedance	Forward Wave Amplitude
Systolic blood pressure	–0.061	–0.194	–0.247
<i>P</i> value	<0.001	<0.001	<0.001
Diastolic blood pressure	–0.029	0.103	0.116
<i>P</i> value	0.10	<0.001	<0.001
Mean arterial pressure	–0.084	–0.094	–0.129
<i>P</i> value	<0.001	<0.001	<0.001
Pulse pressure	–0.034	–0.256	–0.315
<i>P</i> value	0.053	<0.001	<0.001
Heart rate	–0.005	–0.004	–0.062
<i>P</i> value	0.79	0.83	<0.001

Orthostatic change variables represent standing value minus supine value. Correlations were adjusted for age, sex, height, body mass index, total cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting glucose, hemoglobin A1c, current smoking, use of medication to treat hypertension or dyslipidemia, and prevalent diabetes mellitus or cardiovascular disease.

absent. When we further adjusted models for change in MAP for initial supine MAP, relations between CFPWV and change in MAP on standing became positive ($r_p=0.101$; $P<0.001$), whereas relations of Z_c or forward wave amplitude with change in MAP were no longer significant ($P>0.9$).

A linear regression model of change in MAP on standing, adjusted for age and cardiovascular disease risk factors, revealed a significant interaction between sex and forward wave amplitude ($P=0.002$). To illustrate the sex interaction, the relation between change in MAP on standing and forward wave amplitude was plotted separately by sex (Figure). In addition, estimates for change in MAP in men and women according to sex-specific tertiles of CFPWV are presented. Values represent differences in change in MAP when other covariates in the model were fixed at their mean values. Change in MAP was higher in women ($P<0.0001$), but the increase was progressively blunted in women with higher forward wave amplitude ($P=0.002$ for interaction between sex and forward wave). In addition, the increase in MAP was lower in men or women with higher CFPWV ($P<0.001$).

In light of the propensity for individuals with diabetes mellitus to develop aortic stiffness and orthostatic hypotension, we also assessed for effect modification by the presence of diabetes mellitus. We found a modest accentuation of the negative relations of change in MAP with Z_c (interaction $P=0.02$) and forward wave amplitude (interaction $P=0.05$). Similarly,

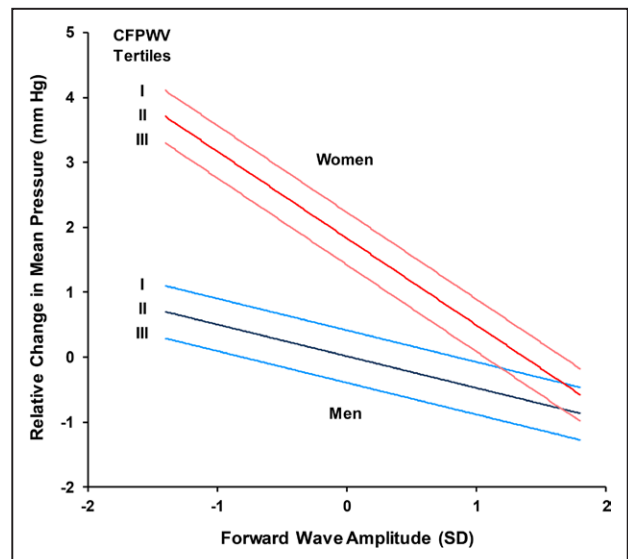


Figure. Orthostatic change in mean arterial pressure (MAP) as a function of forward wave amplitude in groups defined by sex-specific tertiles of carotid–femoral pulse wave velocity (CFPWV). Values represent estimated differences in change in MAP as a function of forward wave amplitude in a model that adjusted for age, sex, height, body mass index, total cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting glucose, hemoglobin A1c, current smoking, use of medication to treat hypertension or dyslipidemia, and prevalent diabetes mellitus or cardiovascular disease. Values for covariates were fixed at the mean value for the cohort, and the range of values plotted correspond to the 5th and 95th percentiles of forward wave amplitude. Women had a greater increase in MAP than men. However, higher stiffness by either measure was associated with a lower increase in MAP on standing; the relation between forward wave amplitude and change in MAP was particularly strong in women. $P<0.0001$ for sex, $P=0.01$ for forward wave, $P=0.002$ for interaction between sex and forward wave, and $P<0.001$ for CFPWV.

we found accentuated negative relations of change in diastolic BP with Z_c (interaction $P=0.005$) and forward wave amplitude (interaction $P<0.001$).

Discussion

We assessed relations of aortic stiffness with the compensatory orthostatic increase in MAP in response to standing in a community-based cohort of middle-aged adults. We report that higher aortic stiffness, assessed as CFPWV, Z_c , or forward wave amplitude, was associated with a blunted increase in MAP on standing from a supine position. The relation between higher forward wave amplitude and lower increase in MAP on standing was accentuated in women and should be interpreted in light of the marked increase in forward wave amplitude that is known to occur after midlife, particularly in women.^{18,19} Relations between aortic stiffness measures and change in heart rate on standing were modest or absent. The observed blunted increase in MAP on standing has important implications for mean perfusion pressure at the level of the brain in an upright individual. If a blunted increase in MAP on standing is combined with blunted cerebral microvascular reactivity in individuals with a stiffened aorta, the combination may contribute to enhanced susceptibility of the brain to adverse effects of aortic stiffening.^{10,20,21}

The negative relation between arterial stiffness measures and orthostatic change in MAP may indicate that the response of strain-sensitive baroreceptors is attenuated in individuals with stiff arteries.³⁻⁶ For example, in older participants of the Rotterdam study, arterial stiffness was shown to be associated with impaired baroreflex sensitivity and orthostatic BP changes.⁶ Furthermore, Okada et al⁴ showed that baroreflex sensitivity was inversely correlated with arterial stiffness among elderly individuals, particularly in older women. However, limited relations between aortic stiffness measures and change in heart rate on standing in the present study suggest that blunted vasoconstriction or accentuated reduction in stroke volume, rather than blunted heart rate response, may contribute more to relations between stiffness and MAP response in our cohort.

To maintain cerebrovascular perfusion pressure on standing from a supine position, MAP must increase in proportion to the change in gravitational potential energy at the level of the brain, which is ≥ 30 cm above the heart (and brachial artery, where BP is measured) when standing. In light of the foregoing, in the absence of a change in MAP at the level of the brachial artery, change in posture will produce a hydrostatic reduction in perfusion pressure at the level of the brain of $\approx \geq 23$ mmHg (30 cm H_2O), depending on height. Individuals who have either a decrease or minimal increase in MAP at the level of the brachial artery on standing may experience a drop in cerebrovascular perfusion, particularly if cerebrovascular vasodilation is impaired and insufficient to counteract the drop in perfusion pressure at the level of the brain. Previous studies have demonstrated inverse relations between aortic stiffness and microvascular reactivity.²² Recently, Rucka et al²³ showed that arterial stiffness contributes to impaired cerebrovascular reactivity in individuals with coronary artery disease. Given the association between arterial stiffness and cerebrovascular structural damage^{24,25} and

impaired cerebrovascular reactivity,^{23,24,26} individuals with stiff arteries may have compounded risk for hypoperfusion because of the combined effects of insufficient increase in MAP and potentially impaired cerebral microvascular vasodilatory response. Thus, a blunted increase in MAP on standing could be an important contributor to relations between arterial stiffness and cognitive impairment, which is a premise that warrants further investigation.

The observation that relations between aortic stiffness measures and change in MAP on standing were reversed (CFPWV) or no longer significant (Z_c , forward wave amplitude) after adjusting for supine MAP may suggest that abnormalities in resting MAP rather than aortic stiffness contributed to the blunted increase in MAP on standing. However, we have previously shown that higher initial aortic stiffness is associated with BP progression and incident hypertension during 7 years of prospective follow-up. In contrast, initial BP was not associated with progression of CFPWV.²⁷ Therefore, adjusting a model examining relations of CFPWV with change in MAP for supine MAP may represent adjusting for a downstream effect of CFPWV. In addition, regardless of whether aortic stiffness contributes to blunted increase in MAP on standing, it is important to note that individuals with stiffer arteries had a smaller increase (or a decrease) in MAP on standing. As noted above, MAP must increase and the cerebral microvasculature must vasodilate to offset the substantial hydrostatic reduction in mean perfusion pressure in the brain when moving from a supine to seated or standing posture. Regardless of mechanism, individuals with a stiffer aorta had a blunted increase in MAP on standing. In light of the known impairment of microvascular reactivity in individuals with a stiffer aorta,^{23,24,26} both mechanisms that contribute to maintenance of cerebral perfusion on standing are impaired, rendering the brain susceptible to episodic relative ischemia in individuals with a stiffened aorta.

Whereas MAP increased, pulse pressure fell substantially on standing in our cohort. Pulse pressure is associated with arterial stiffness and cerebrovascular damage²⁵ and is a known risk factor for adverse cardiovascular events.²⁸⁻³⁰ Our study has shown that moving from a supine to standing position resulted in a lower pulse pressure overall and that the reduction was enhanced in individuals with elevated arterial stiffness. The reduction in pulse pressure on standing may contribute to previously described beneficial effects of increasing the percentage of the workday that is spent standing.^{31,32} However, beneficial effects of standing on pulse pressure may be attenuated in those with stiffer arteries because of the associated blunted increase in MAP on standing. Importantly, differing patterns of change in pulse pressure and MAP on standing produced variable relations of stiffness measures with various BP components. For example, relations of stiffness measures with change in systolic as compared with diastolic BP were comparably robust but opposite in sign (Table 3). As a result, studies of relations between aortic stiffness and BP variability or baroreceptor sensitivity may arrive at discrepant conclusions depending on whether systolic or diastolic BP is examined. The foregoing points require further elucidation.

Our study has limitations that must be considered. Participants rested for 5 minutes before baseline BP measurements; however, it may take >5 minutes of rest for BP to

completely stabilize at a new, lower plateau after lying down, depending on level of activity before the rest period. In addition, we waited only for 2 minutes before initiating the acquisition of standing BP; however, the acquisition takes ≈ 90 to 120 seconds, meaning that the recording corresponds to waiting ≈ 3 minutes between standing and assessment of BP. As a result, we may have under- or overestimated the magnitude of orthostatic change in BP in some individuals. However, we followed a standardized protocol that included use of a digital timer to confirm the time delay between standing and taking the upright BP. Additionally, given that we focused on changes in MAP at a fixed interval after standing, early transient changes in BP after standing may have been missed. Finally, the cohort consisted primarily of young- to middle-aged adult participants of European descent, so results may not be generalizable to other ages, races, or ethnicities.

Perspectives

Impaired regulation of BP on standing can result in adverse effects such as dizziness, confusion, or fainting because of insufficient cerebral perfusion. MAP assessed at the level of the heart must rise on standing to maintain cerebral perfusion in response to a change in gravitational potential energy and hydrostatic perfusion pressure at the level of the brain. In our young- to middle-aged cohort, those with greater arterial stiffness experienced a blunted increase in MAP on standing. Interventions that reduce arterial stiffness may improve regulation of MAP and in turn minimize potential adverse effects on cerebral perfusion. Future studies are needed that examine relations between arterial stiffness, cerebrovascular reactivity, and brain structure and function and that assess effects of interventions that reduce stiffness on orthostatic change in MAP.

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Novelty and Significance

What Is New?

- The association of arterial stiffness and the change in mean arterial pressure (MAP) on standing has not been examined previously in a large community-based cohort of young to middle-aged adults. Individual with a stiffer aorta exhibited a blunted increase in MAP on standing.

What Is Relevant?

- On standing, the combination of an increase in MAP and dilation of intracerebral arterioles contributes to maintain sufficient cerebrovascular perfusion. Aortic stiffness is associated with the blunting of both responses, potentially leading to episodic reductions in cerebral perfusion in individuals with a stiff aorta.

Summary

Higher aortic stiffness, assessed by various measures, is associated with a blunted orthostatic increase in MAP that may be associated with a reduction in cerebrovascular perfusion pressure. In light of previous studies demonstrating blunted reactivity of small vessels in individuals with higher aortic stiffness, blunted orthostatic increase in MAP in association with higher aortic stiffness may contribute to known associations between aortic stiffness and cerebrovascular disease.

Relations of Arterial Stiffness With Postural Change in Mean Arterial Pressure in Middle-Aged Adults: The Framingham Heart Study

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Supplemental Data for:

Relations of arterial stiffness with postural change in mean arterial pressure in middle-aged adults: The Framingham Heart Study

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Supplemental Table S1. Hemodynamic variables by sex.

Variable	Men	Women
Carotid-femoral pulse wave velocity, m/s	7.5 ± 1.5	6.8 ± 1.3
-1/Carotid-femoral pulse wave velocity, ms/m	-139 ± 24	-153 ± 25
Characteristic impedance, dyne*s*cm ⁻⁵	181 ± 55	204 ± 60
Forward pressure wave, mm Hg	47 ± 11	44 ± 11
Supine hemodynamics, mean ± SD		
Systolic blood pressure, mm Hg	125 ± 13	117 ± 15
Diastolic blood pressure, mm Hg	65 ± 9	62 ± 9
Mean arterial pressure, mm Hg	89 ± 10	85 ± 11
Pulse pressure, mm Hg	59 ± 11	55 ± 12
Heart rate, min ⁻¹	63 ± 10	66 ± 10
Systolic ejection period, ms	307 ± 23	315 ± 24
Change upon standing, median (25 th , 75 th percentile)		
Systolic blood pressure, mm Hg	3 (-4, 8)	2 (-4, 8)
Diastolic blood pressure, mm Hg	9 (4, 14)	10 (5, 14)
Mean arterial pressure, mm Hg	6 (1, 11)	8 (3, 13)
Pulse pressure, mm Hg	-8 (-15, 0)	-8 (-15, -2)
Heart rate, min ⁻¹	14 (9, 20)	14 (9, 21)
Systolic ejection period, ms	-65 (-78, -53)	-70 (-84, -57)