Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood pressure changes in older adults: The Rotterdam Study

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Objective **Arterial stiffness may be involved in the impairment of the arterial baroreflex. In the present study the associations between arterial stiffness and cardiovagal baroreflex sensitivity (BRS) and between BRS and postural blood pressure (BP) changes were investigated within the framework of the Rotterdam Study.**

Methods **Arterial stiffness was determined by aortic pulse wave velocity and the carotid distensibility coefficient. Continuous recording of the R–R interval and finger BP was performed with the subject resting supine, and BRS was estimated from the spontaneous changes in systolic BP and corresponding interbeat intervals. Measures of aortic stiffness or carotid distensibility and BRS were available in 2490 and 2083 subjects, respectively. The association between arterial stiffness and ln BRS was investigated by multivariate linear regression analysis and then by analysis of covariance, comparing BRS by quartiles of arterial stiffness.**

Results **The mean age of the subjects was 71.7 ± 6.6 (41.7% men). Aortic stiffness was negatively associated [β = −0.029; 95% confidence interval (CI): −0.040, −0.019] and the carotid distensibility coefficient positively associated with BRS (β = 0.017; 95% CI: 0.010, 0.024). An orthostatic decrease in systolic BP was absent in 1609 subjects, between 1 and 10 mmHg in 502 and >10 mmHg in 269 subjects, with corresponding mean values (95% CI) of ln BRS of 1.47 (1.44–1.51), 1.43 (1.37–1.49) and 1.36 (1.28–1.44) ms/mmHg (test for trend *P*<0.019). An orthostatic decrease in diastolic BP was absent in 1123 subjects, 1–10 mmHg in 1057 and >10 mmHg in 209 subjects, with corresponding mean values of ln BRS of 1.49 (1.45–1.53), 1.41 (1.37–1.45) and 1.45 (1.36–1.54) ms/mmHg (*P*<0.04).**

Conclusion **In a large population of older subjects, arterial stiffness appears to be an independent determinant of impaired BRS. Within the same population, impaired BRS was associated with orthostatic BP changes. *J Hypertens* 25:1421–1426 © 2007 Lippincott Williams & Wilkins.**

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Introduction

The arterial baroreflex has an essential role in the short-term regulation of blood pressure by adapting heart rate, stroke volume and vascular tone to changes in pressure [1,2]. Baroreflex sensitivity (BRS) decreases with age [3–5] and it has been suggested that arterial stiffening in the barosensitive regions of the carotid artery and aorta is involved in this age-related decrease in BRS, by limiting the stretch and relaxation of the baroreceptors in response to changes in blood pressure. In addition, conditions such as hypertension and diabetes mellitus, which are more prevalent in the elderly, may contribute as well [6,7]. Previous studies have found an association between arterial stiffness and BRS [8–11]. However, these studies were relatively small [8,9] or performed in specific categories of patients [10,11], therefore, the generalizability of the results in other populations remains uncertain. In a previous study [12], we showed a high prevalence of orthostatic hypotension in subjects with stiffer arteries, and hypothesized that this might be due to impaired sensitivity of the arterial baroreflex. In the present study, performed in a large population of older adults, we first investigated whether arterial stiffness, measured by two methods, i.e. the carotid–femoral pulse wave velocity (PWV) and the carotid distensibility, is associated with impaired cardiovagal BRS. Second, we investigated the

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possible association between cardiovagal BRS and postural blood pressure changes.

Methods

Study population

This study was conducted within the framework of the Rotterdam Study, an ongoing, prospective, population-based cohort study, comprising 7983 men and women aged 55 years and over and living in Ommoord, a suburb of Rotterdam, The Netherlands. The rationale and design of the Rotterdam Study have been described elsewhere [13]. The overall aim of the Rotterdam Study is to investigate the incidence and determinants of chronic disabling diseases. The third examination phase took place from 1997 until 1999. During this phase, measurements of cardiovascular risk factors, atherosclerosis, arterial stiffness and BRS were conducted. Subjects in nursing homes did not visit the research centre and were not invited for these measurements. The Medical Ethics Committee of Erasmus Medical Center approved the study and written consent was obtained from all participants.

Cardiovascular risk factors

Information on cardiovascular risk factors was collected during the third follow-up examination. Data on drug use and smoking habits were obtained during the home interview. Body mass index [weight (kg)/height^2 (m^2)] was calculated. Serum total cholesterol and high-density lipoprotein (HDL) cholesterol values were determined by an automated enzymatic procedure (Boehringer Mannheim System, Mannheim, Germany). Diabetes mellitus was defined as the use of blood glucose-lowering medication and/or a fasting serum glucose level equal to or greater than 7.0 mmol/l [14].

Blood pressure measurements

Systolic (first Korotkoff phase) and diastolic (fifth Korotkoff phase) blood pressure levels were measured twice on the right arm using a random-zero sphygmomanometer, with the patient in the supine position after 5 min rest. The mean of the two blood pressure values was used in the analyses. Orthostatic hypotension was defined as a decline in systolic blood pressure of $\geq$20 mmHg and/or a decline in diastolic blood pressure of $\geq$10 mmHg within 3 min of standing [15].

Measurement of atherosclerosis

Ultrasonography of both carotid arteries was performed with a 7.5-MHz linear-array transducer and a duplex scanner (ATL UltraMark IV, Bothell, Washington, USA). Common carotid intima–media thickness (IMT) was determined as previously described [16]. The maximum common carotid IMT was determined as the average of the maximum IMT of near- and far-wall measurements over a length of 1 cm, and the average of left and right maximum common carotid IMTs was computed.

Measures of arterial stiffness

Aortic stiffness

Carotid–femoral PWV, a measure of aortic stiffness, was calculated with the subjects in the supine position. PWV was assessed with an automatic device (Complior; Artech Medicla, Pantin, France) [17] that measures the time delay between the rapid upstroke of the feet of simultaneously recorded pulse waves in the carotid and the femoral artery. The distance between the recording sites in the carotid and the femoral artery (the carotid artery and the groin) was measured with a tape over the surface of the body. PWV was calculated as the ratio of the distance and the foot-to-foot time delay and expressed in metres per second.

Carotid stiffness

Common carotid distensibility was assessed with the subjects in the supine position, the head tilted slightly to the contralateral side for the measurement in the common carotid artery. The vessel wall motion of the right common carotid artery was measured by means of a duplex scanner (ATL Ultramark IV, operating frequency 7.5 MHz) connected to a vessel wall movement detector system. The details of this technique have been described elsewhere [18]. After 5 min rest, a region at 1.5 cm proximal to the origin of the bulb of the carotid artery was identified using B-mode ultrasound. The displacement of the arterial walls was obtained by processing the radio frequency signals originating from two selected sample volumes positioned over the anterior and posterior walls. The end-diastolic diameter (D), the absolute stroke change in diameter during systole (ΔD), and the relative stroke change in diameter (ΔD/D) were computed as the mean of four cardiac cycles of three successive recordings. The cross-sectional arterial wall distensibility coefficient (DC) was calculated according to the following equation: (distensibility coefficient = $2\Delta D/(D \times \text{pulse pressure})$ (MPa^{-1}) [19].

Cardiovagal baroreflex function assessment

Systemic haemodynamic function was assessed non-invasively using the Finapres (TNO Instruments, Amsterdam, The Netherlands). The Finapres measures continuous beat-to-beat blood and interbeat interval (IBI). Baroreflex sensitivity was calculated as previously described [20]. This method calculates the cross-correlation between 10-s systolic blood pressure (SBP) series and 10-s IBI series delayed 0–5 s. The delay giving the highest correlation is selected if significant at a pre-set level ($P = 0.01$). Then the regression slope is recorded as one BRS value. Subsequently, the process is repeated for series of SBP and IBI samples 1 s later. A recording of at least 10 min was taken with the patient in the supine position to assess resting BRS. The finger cuff was placed on the middle finger of the left hand. All data were subsequently downloaded to a PC-based analysis program, allowing averaging of the results over defined

time periods and display of the variables as percentage change from baseline. All analyses are averaged over a period of at least 300 heartbeats.

Population for the analysis

Of the 4024 subjects who underwent the physical examination of the third phase of the Rotterdam Study, aortic stiffness measured as PWV was measured in 3550 subjects, whereas common carotid distensibility was measured in 3098 subjects. BRS was measured in 2577 subjects. Missing information on measures of arterial stiffness and BRS was entirely due to logistic reasons. Finally, information on aortic stiffness, BRS and orthostatic hypotension was available in 2400 subjects, of these, information on carotid distensibility was available in 2083 subjects.

Statistical analysis

The association between BRS and measures of arterial stiffness was first investigated by linear regression analysis (with PWV and DC as the independent variables in two different models) and then by analysis of covariance, where mean values of ln BRS were compared across quartiles of levels of arterial stiffness. BRS was logarithmically transformed because of its skewed distribution. Cut-off points for quartiles of PWV were 11.3 m/s, 13.1 m/s and 15.2 m/s, whereas cut-off points for quartiles of DC were 7.5, 10.1 and 13.2 (MPa^{-1}). Models were adjusted for age, gender, mean arterial pressure and heart rate, and additionally for body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, smoking status and use of antihypertensive medications. In the third model we added measures of carotid IMT. Furthermore, we performed analysis of covariance whereby mean values and corresponding 95% confidence intervals (CIs) of ln BRS were compared across categories of changes of blood pressure levels due to orthostatic challenge (no decrease of blood pressure was the reference category). These analyses were adjusted first for age, gender and baseline blood pressure levels; secondly, other known cardiovascular risk factors were added into the model. Finally, we compared, with analysis of covariance, mean values and corresponding 95% CIs of changes of heart rate across categories of changes of blood pressure levels during orthostatic challenge. These analyses were adjusted for age, gender and mean heart rate in the supine position. Analysis of covariance adjusted for age and gender was performed to investigate differences of the ln BRS, PWV and DC in subjects with and without orthostatic hypotension.

Results

Baseline characteristics of the population are shown in Table 1. Mean age of the study population was 71.7 ± 6.6 years and 41.7% were men. Mean PWV was 13.4 ± 3 m/s whereas the mean DC was $10.6 \pm 4.3\,MPa^{-1}$. The mean value of ln BRS was 1.45 ± 0.64 ms/mmHg. After adjustment for age, gender, mean arterial pressure and heart rate, PWV was negatively (coefficient $\beta = -0.032$; 95% CI: −0.042, −0.023) associated with ln BRS, whereas DC was positively associated with ln BRS ($\beta = 0.020$; 95% CI: 0.014, 0.027). Estimates remained significant after adjustment for cardiovascular risk factors and after additional adjustment for carotid IMT (Table 2). In adjusted models, mean values and 95% CIs of ln BRS by quartiles of aortic stiffness were 1.58 (1.53–1.64), 1.48 (1.43–1.53), 1.43 (1.38–1.47) and 1.33 (1.27–1.38) ms/mmHg, respectively (test for trend $P < 0.001$) (Fig. 1). Corresponding mean values of ln BRS by quartiles of carotid distensibility were 1.40 (1.34–1.46), 1.41 (1.36–1.47), 1.47 (1.41–1.51) and 1.56 (1.51–1.62) ms/mmHg, respectively (test for trend $P = 0.001$) (Fig. 2). There was no orthostatic decrease in systolic blood pressure in 1609 subjects; in 502 subjects the decrease was between 1 and 10 mmHg and in 269 subjects the decrease was ≥10 mmHg (Fig. 3). In adjusted models, corresponding mean values of BRS and 95% CI in these groups of subjects were 1.47 (1.44–1.51) ms/mmHg, 1.43 (1.37–1.49) ms/mmHg, and 1.36 (1.28–1.44) ms/mmHg, respectively (test for trend $P < 0.019$). There was no orthostatic decrease in diastolic blood pressure in 1123 subjects; in 1057 subjects the decrease was between 1 and 10 mmHg and in 209 subjects the decrease was ≥10 mmHg (Fig. 4).

Table 1 Baseline characteristics of the population ($n = 2400$)

Men (%)	41.7
Age (years)	71.7 ± 6.6
Mean arterial pressure (mmHg)	106.7 ± 12.6
Heart rate (bpm)	74.3 ± 11.7
Diabetes mellitus (%)	6.6
Body mass index (kg/m^2)	26.8 ± 3.8
Current smokers (%)	14.9
Total cholesterol (mmol/l)	5.8 ± 0.9
HDL-cholesterol (mmol/l)	1.38 ± 0.38
Intima–media thickness (mm)	0.86 ± 0.14
Orthostatic hypotension (%)	18.7
Pulse wave velocity (m/s)	13.4 ± 3
Distensibility coefficient (MPa^{-1})[a]	10.6 ± 4.3
ln cardiovagal baroreflex sensitivity (ms/mmHg)	1.45 ± 0.64

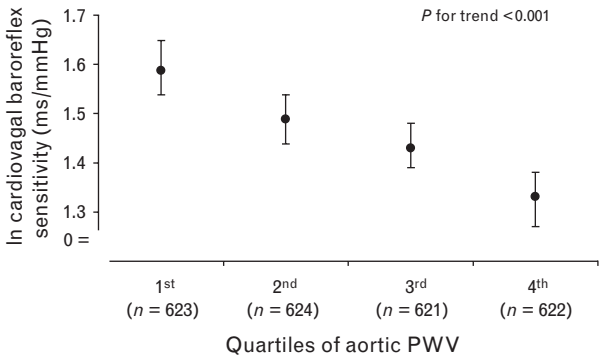
HDL, high-density lipoprotein. Values are means ± SD for continuous variables and percentages for dichotomous variables. [a]Data available for 2083 subjects.

Table 2 Multiple linear regression (β) coefficients and 95% confidence intervals (CI) describing the association between measures of arterial stiffness (independent variable) and ln cardiovagal baroreflex sensitivity (dependent variable)

	Aortic stiffness (m/s) β (95% CI)	Carotid distensibility (MPa^{-1}) β (95% CI)
Model 1	−0.032 (−0.042, −0.023)	0.020 (0.014, 0.027)
Model 2	−0.030 (−0.041, −0.021)	0.018 (0.011, 0.025)
Model 3	−0.029 (−0.040, −0.019)	0.017 (0.010, 0.024)

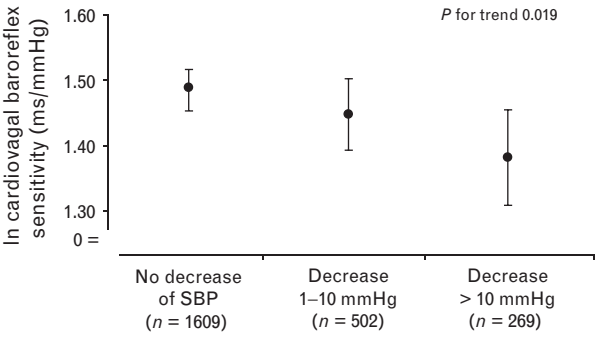
Model 1: Adjusted for age, gender, mean arterial pressure and heart rate. Model 2: model 1 + body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, smoking and use of antihypertensive medication. Model 3: model 2 + carotid intima–media thickness.

Fig. 1



Points represent mean values of cardiovagal baroreflex sensitivity; lines represent 95% confidence intervals. Means are adjusted for age, gender, mean arterial pressure, heart rate, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, smoking, use of antihypertensive medication and carotid intima–media thickness. PWV, pulse wave velocity.

Fig. 3



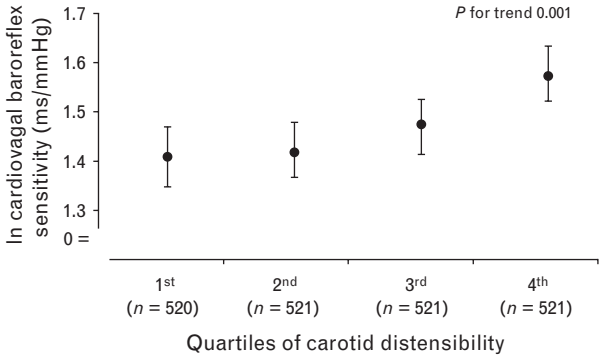
Points represent mean values of cardiovagal baroreflex sensitivity; lines represent 95% confidence intervals. Means are adjusted for age, gender, mean arterial pressure, heart rate, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, smoking, use of antihypertensive medication, carotid intima–media thickness and supine systolic blood pressure. SBP, systolic blood pressure.

Corresponding mean values of BRS and 95% CI in these groups of subjects were 1.49 (1.45–1.53) ms/mmHg, 1.41 (1.37–1.45) ms/mmHg, and 1.45 (1.36–1.54) ms/mmHg, respectively (test for trend $P < 0.035$). Mean heart rate did not change significantly during orthostatic challenge in categories of postural blood pressure changes, being 8.5, 8.1, 9.1 bpm across categories of systolic blood pressure changes and 7, 8.9, 9.1 bpm across categories of diastolic blood pressure changes. Orthostatic hypotension was present in 18.7% of the subjects; the ln BRS in subjects with and without orthostatic hypotension did not differ significantly, being 1.44 (1.41–1.47) and 1.48 (1.42–1.54) ms/mmHg, respectively ($P = 0.22$). The PWV and the DC were significantly different in subjects with and without orthostatic hypotension, being 13.4 (13.2–13.5) and 13.8 (13.5–13.9) m/s ($P = 0.02$) and 10.7 (10.5–10.9) and 10.3 (9.9–10.7) MPa^{-1} ($P = 0.05$), respectively.

Discussion

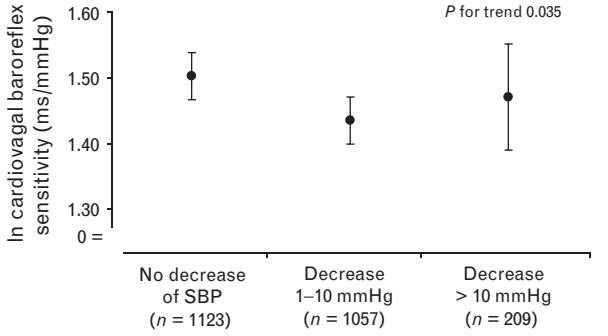
In this large population study performed in older subjects, we investigated the relation between arterial stiffness and cardiac BRS and tested the hypothesis that impaired BRS associates with postural blood pressure changes. The main findings of our study can be summarized as follows: arterial stiffness, measured as aortic stiffness and carotid distensibility, is associated with impaired cardiovagal BRS; this association is independent of cardiovascular risk factors and atherosclerosis; and impaired cardiovagal BRS associates with postural

Fig. 2



Points represent mean values of cardiovagal baroreflex sensitivity; lines represent 95% confidence intervals. Means are adjusted for age, gender, mean arterial pressure, heart rate, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, smoking, use of antihypertensive medication and carotid intima–media thickness.

Fig. 4



Points represent mean values of cardiovagal baroreflex sensitivity; lines represent 95% confidence intervals. Means are adjusted for age, gender, mean arterial pressure, heart rate, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, smoking, use of antihypertensive medication, carotid intima–media thickness and supine diastolic blood pressure. SBP, systolic blood pressure.

decreases of systolic and diastolic blood pressure but not with orthostatic hypotension.

Previous studies have shown an association between arterial stiffness and the decrease of BRS in healthy men [8,9], in patients with acute ischaemic stroke and in chronic haemodialysis patients [11]. Other investigators found that levels of systolic blood pressure were associated with a low baroreflex gain in healthy elderly subjects, but no association between carotid stiffness and BRS could be established [21]. However, these studies were relatively small [21], only men were included [8,9]; or they were conducted in specific categories of patients [10,11], making the generalizability of these findings questionable.

Several mechanisms may underlie the association between arterial stiffness and impaired cardiovagal BRS. Changes in arterial pressure result in changes in transmural stretch within the aorta and the carotid arteries, activating or deactivating the baroreceptors located within the arterial wall. The stretch-sensitive baroreceptors are not only sensitive to absolute changes in arterial pressure, but also to the rate of pressure change [22]. The stiffness of the carotid arteries and the aorta, in which the arterial baroreceptors are located, may affect the stretch-sensitive receptors and hence BRS, because higher pressure thresholds and/or a more intense pressure change to distend the arterial wall are required [6,23]. In addition to structural vascular changes, functional mechanisms may contribute to alter baroreflex responses. Baroreceptor activation is modulated by the activity of potassium channels and the sodium–potassium pump, by paracrine factors such as prostacyclin [24], by oxygen free-radicals [25], and by platelet aggregation [26]. Endothelial dysfunction, which is strongly related to arterial stiffness [27], impairs the release of prostacyclin, and enhances the formation of oxygen free-radicals and platelet aggregation [28], and in this way may contribute to the impairment of BRS associated with vascular stiffness.

Impaired BRS has been found to be associated with hypertension [6], diabetes mellitus [7] and carotid atherosclerosis [29,30], conditions involved in the development of arterial stiffness [31]. In our study, the association between arterial stiffness and impaired cardiovagal BRS remained significant after adjustments for various cardiovascular risk factors and carotid intima–media thickness, suggesting that arterial stiffness itself is involved in the impairment of cardiovagal BRS.

We found that subjects with low cardiovagal BRS had a more pronounced decrease of blood pressure during orthostatic challenge, whereas no association was found between impaired cardiovagal BRS and orthostatic hypotension. The immediate haemodynamic response to orthostatic challenge is complex and involves baroreflex-mediated changes of the venous and arterial part of the circulation, apart from the baroreflex-mediated changes in heart rate and stroke volume. With regard to the maintenance of blood pressure during orthostatic challenge, baroreflex-mediated increase in vasomotor tone in the elderly is more critical than the increase of heart rate [32]. To what extent the BRS, as assessed in the present study, reliably reflects the baroreflex-mediated change in vasomotor tone is uncertain. In this regard it should be also taken into account that the chronotropic responsiveness of the heart to changes in sympathetic and parasympathetic tone decreases with age [33]. This could have further impaired the usefulness of cardiovagal BRS as a measure of overall BRS, and possibly provides an explanation for the absent association between impaired BRS and orthostatic hypotension in our study.

The present study may have some other limitations. First, the cross-sectional design may limit the ability to infer a causal relationship between measures of aortic stiffness and cardiovagal BRS. Second, measurements of arterial stiffness and cardiovagal BRS were not available for all participants; but since this was primarily due to logistic reasons and hence random, we believe that this will not have biased our results.

In conclusion, this is the first large, population-based study, showing that aortic and carotid stiffness are associated with impaired cardiovagal BRS in older subjects, implying that the changes in transmural pressure necessary to activate the arterial baroreceptors are likely to be affected by arterial stiffness. Moreover, we found impaired cardiovagal BRS to be associated with a postural decrease of both systolic and diastolic blood pressure but not with orthostatic hypotension.

Acknowledgement

There are no conflicts of interest.

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