J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis

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Summary

The J-shaped relation between diastolic blood pressure and mortality from coronary heart disease continues to provoke controversy. We examined the association between diastolic blood pressure and progression of aortic atherosclerosis in a population-based cohort of 855 women, aged 45–64 years at baseline. The women were examined radiographically for calcified deposits in the abdominal aorta, which have been shown to reflect intimal atherosclerosis.

After 9 years of follow-up, slight progression of atherosclerosis was noted in 19% of women and substantial progression in 16%. The age-adjusted relative risk of substantial atherosclerotic progression in women with a decrease in diastolic pressure of 10 mm Hg or more was 2·5 (95% CI 1·3–5·6), compared with the reference group of women who had a smaller decrease or no change. The excess risk in this group was confined to women whose increase in pulse pressure was above the median (3·9 [1·5–9·9] vs 1·1 [0·3–4·2] in women with an increase in pulse pressure below the median). The relative risks for women with rises in diastolic pressure of 1–9 mm Hg and 10 mm Hg or more were 2·2 (1·1–4·3) and 3·5 (1·6–8·0), respectively.

These findings suggest that a decline in diastolic blood pressure indicates vessel wall stiffening associated with atherosclerotic progression. They support the hypothesis that in low-risk subjects progression of atherosclerosis may be accompanied by a decrease in diastolic blood pressure rather than the opposing idea that low diastolic blood pressure precipitates the occurrence of atherosclerotic events.

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Introduction

The continuing debate about the cause of the J-shaped relation between diastolic blood pressure and death from coronary heart disease has been mainly based on two ideas. One hypothesis is that low diastolic blood pressure increases the risk of death in ischaemic heart disease by compromising coronary blood flow.[1] A second hypothesis attributes the J-curve to a subgroup of subjects whose diastolic blood pressure is low because of deteriorating health.[2] Sleight[3] raised another possible explanation for the J-curve. He suggested that subjects with stiffer arteries have wide pulse pressures and artifactually lowered diastolic blood pressure, and that the stiffer arteries are likely to be associated with excess mortality. Stiffening of the aorta is the main determinant of a wide pulse pressure and is often seen in association with atherosclerosis.[4] Previous studies have shown that aortic atherosclerosis reflects general atherosclerosis and predicts symptomatic cardiovascular disease at various sites.[5-8] Widespread atherosclerosis may therefore be the link between stiffening of the large arteries, accompanied by a fall in diastolic blood pressure, and excess mortality from coronary heart disease. We have tried to find support for Sleight's hypothesis by testing whether progression of aortic atherosclerosis, as detected by radiography, is associated with a decline in diastolic blood pressure. The study was carried out in a population-based cohort of 855 middle-aged and elderly women who were followed up for 9 years.

Subjects and methods

Between 1975 and 1978, a population-based study on risk factors for chronic diseases was carried out in the Dutch town of Zoetermeer. All inhabitants of two districts of the town aged 5 years or older were invited for a medical examination. In 1985, all female participants aged 45–64 years at baseline were invited for a follow-up examination to investigate osteoporotic fractures and some cardiovascular risk factors.[9] Of the 1167 women invited, 71 had died and 87 had moved away during the follow-up period. 855 (85%) of the remaining women were re-examined. The mean duration of follow-up was 8·9 (SD 0·8) years.

Aortic atherosclerosis was diagnosed by radiographic detection of calcific deposits in the abdominal aorta.[10] At each examination, lateral abdominal films (T12-S1) were made from a fixed distance with the subject seated. Baseline and follow-up films were examined in pairs. We judged that calcifications were present in the abdominal aorta when linear densities were seen in an area parallel and anterior to the lumbar spine (L1–L4). Baseline and follow-up extent of atherosclerosis was scored according to the length of the involved area (≤1 cm, 2–5 cm, 6–10 cm, >10 cm). In the analysis we combined the first two classes as mild and the third and fourth classes as advanced atherosclerosis.

Progression of atherosclerosis was defined as the appearance of new calcifications or enlargement of the calcified area present at baseline. The extent of change was scored on a three-point scale:

	Baseline	Follow-up
Mean (SD)		
Age (yr)	53 3 (5 7)	62 2 (5 8)
Height (m)	1 63 (0 06)	1 62 (0 06)
Weight (kg)	67 6 (9 8)	69 0 (10 6)
Quetelet's index (kg/m²)	25 5 (3·5)	26 3 (3 9)
Systolic blood pressure (mm Hg)	134 (19)	145 (21)
Diastolic blood pressure (mm Hg)	83 (11)	82 (10)
Serum cholesterol (mmol/L)	6 2 (1 1)	7 2 (1 2)
Percentage		
Current smokers	34	25
Former smokers	15	24
Diabetes mellitus	1	2
Postmenopausal	65	99
Aortic atherosclerosis	22	43
History of cardiovascular disease	2	4

Table 1: **Baseline and follow-up characteristics of 855 subjects**

1 was the appearance of one or more new small streaks at least 1 cm long, or a small increase in length of the involved area (1–2 cm); 2 was the appearance of several larger streaks over the anterior or posterior wall, or a moderate increase in length of the involved area (up to 5 cm); and 3 was an increase in length of the involved area of more than 5 cm. We describe the first category as slight atherosclerotic progression and the second and third categories, which were combined because of small numbers, as substantial atherosclerotic progression. No subject showed a decrease in extent of atherosclerosis.

All films were examined by two independent observers without knowledge of the subjects' risk-factor status. Observers were aware of the date of the radiographs. When the inter-observer difference was qualitative (present versus absent) or when the difference in severity grades for atherosclerotic extent or change was more than one, the observers reviewed the films together to reach consensus. The percentage of agreement for atherosclerotic progression was 0·75 and the weighted kappa statistic 0·77, with weights taken as the squared distance between categories. The reproducibility of whether atherosclerosis was present was assessed by independent readings of pairs of radiographs taken within a maximum period of 6 months. The percentage of agreement was 0·71 and the weighted kappa statistic 0·92.

To validate further our detection method, the radiographic grading (no, mild, or advanced atherosclerosis) was compared with the extent of calcification assessed by computed tomography (CT). Three 10 mm thick slices were imaged through the midplanes of the lumbar vertebrae L1 to L3. The appearance was classified as no calcification, calcification on one image, and calcification on two or three images. Independent readings were done for 56 unselected elderly subjects; aortic calcifications were detected by radiography in 32. The percentage of agreement was 0·70 and the weighted kappa statistic 0·75. In all but 1 subject, calcifications detected by radiography were shown to be located in the vessel on the corresponding CT images.

At baseline and follow-up, blood pressure was measured on the left arm by means of a random zero sphygmomanometer with the subject seated. The mean of two readings was used in the analysis. Measurements of other risk factors have been described.[10] Subjects were asked to bring all drugs used at the time of investigation to the research centre, where the treatments were noted.

For the analysis of blood pressure change, we excluded women with missing data on atherosclerotic change (59), blood pressure at baseline (6), or blood pressure at follow-up (2), women receiving antihypertensive medication at baseline (184) or follow-up (228), and women who reported a history of a major cardiovascular event at baseline (15) or follow-up (32). The total excluded for one or more reasons was 345, so 510 women were available for this analysis. For the analysis of baseline blood pressure, women receiving antihypertensive medication at follow-up were not excluded, which resulted in 603 women for that analysis.

The risk of atherosclerotic progression was estimated in four categories of blood pressure change. Inspection of the data showed that the nadir of the association between change in diastolic blood pressure and substantial atherosclerotic progression was in the second category, which was therefore used as the reference group. For change in systolic blood pressure the lowest category was used as reference. Four categories of baseline diastolic blood pressure were made with cutoffs of 75, 85, and 95 mm Hg. The second category (75–84 mm Hg) was used as reference. We carried out polytomous logistic regression analysis with the PR module of the BMDP statistical package.[11] The model specified regression coefficients for the effects of blood pressure on risks of distinct grades of atherosclerosis. The odds ratios derived from logistic regression analysis were used as an approximation of relative risk.

Results

Aortic atherosclerosis was present at baseline in 22% of women (table 1). At follow-up, slight and substantial atherosclerotic progression were observed in 19% and 16% of women, respectively. The average changes in systolic and diastolic blood pressure among women not on antihypertensive medication at baseline or follow-up were 10 (16) mm Hg and 0 (9) mm Hg, respectively.

Baseline blood pressure and progression of atherosclerosis

There was no relation between baseline diastolic blood pressure and slight progression of atherosclerosis (table 2). However, for substantial progression of atherosclerosis, both the lowest category of baseline blood pressure and the highest two categories had significant excess risks compared with the reference group. For systolic blood pressure, there was a significant excess risk of atherosclerotic progression only in the highest category.

Change in blood pressure and progression of atherosclerosis

We detected a weak linear association between change in diastolic blood pressure and slight progression of atherosclerosis (figure, table 3). However, the relation between change in diastolic blood pressure and risk of

	Diastolic blood pressure (mm Hg)				Systolic blood pressure (mm Hg)			
	<75 (n=174)	75–84 (n=215)	85–94 (n=135)	≥95 (n=79)	<120 (n=150)	120–139 (n=268)	140–159 (n=140)	≥160 (n=45)
Slight atherosclerotic progression								
No of cases	33	44	27	16	25	53	32	10
Relative risk (95% CI)*	1 0 (0 6–1 8)	1 0‡	1 0 (0 6–1 7)	1 1 (0 5–2 1)	1 0‡	1 1 (0 6–1 8)	1 3 (0 7–2 3)	1 6 (0 6–3 9)
Relative risk (95% CI)†	0 9 (0 5–1 5)	1 0‡	1 0 (0 5–1 8)	1 0 (0 5–2 1)	1 0‡	1 4 (0 8–2 5)	1 4 (0 7–2 8)	2 2 (0 8–5 9)
Substantial atherosclerotic progression								
No of cases	27	18	26	14	15	31	24	15
Relative risk (95% CI)*	2 1 (1 1–4 0)	1 0‡	2 3 (1 2–4 5)	2 2 (1 0–4 9)	1 0‡	1 0 (0 5–2 0)	1 6 (0 8–3 3)	4 0 (1 6–9 7)
Relative risk (95% CI)†	1 9 (1 0–3 9)	1 0‡	2 3 (1 1–4 7)	2 2 (1 0–5 3)	1 0‡	1 3 (0 6–2 6)	1 9 (0 9–4 2)	5 1 (1 8–14 0)

*Adjusted for age. †Adjusted for age, serum cholesterol, Quetelet's index, smoking status, diabetes mellitus, menopausal status, and duration of follow-up. ‡Reference category

Table 2: **Relative risk of atherosclerotic progression by category of baseline blood pressure (n = 603)**
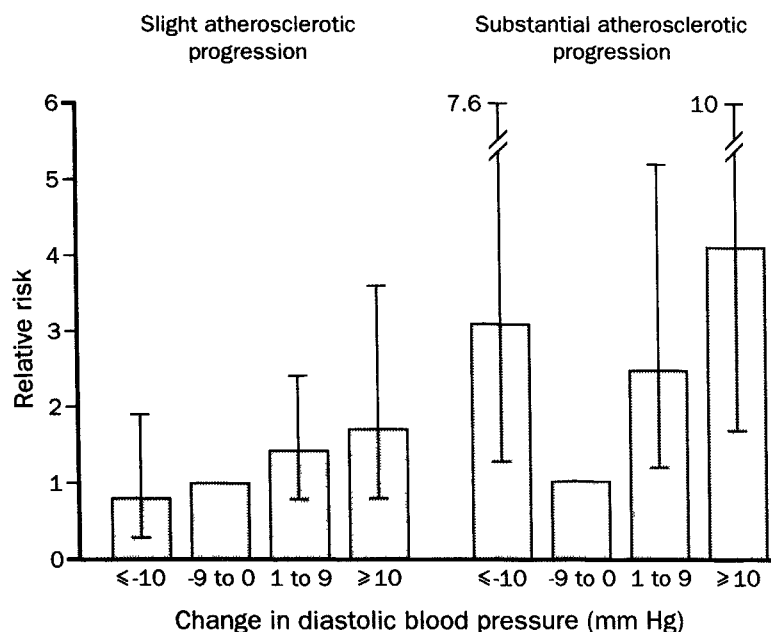
Figure: Relative risk of slight and substantial atherosclerotic progression by change in diastolic blood pressure during follow-up

Relative risk adjusted for age and other cardiovascular risk factors.

substantial progression was again non-linear—both women who had large decreases and women who had increases in blood pressure had excess risks of substantial progression. When the group with a decrease in diastolic blood pressure of 10 mm Hg or more (n = 65) was divided at the median change in pulse pressure (9 mm Hg), the age-adjusted relative risk of substantial progression was 3·9 (1·5–9·9) for those above the median and 1·1 (0·3–4·2) for those below, compared with the reference group. There was a positive relation between change in systolic blood pressure and substantial atherosclerotic progression, but risk estimates were of borderline significance (table 3).

Blood pressure at follow-up and presence of atherosclerosis

The age-adjusted relative risk of advanced atherosclerosis compared with the reference group (75–84 mm Hg) was 1·6 (0·8–3·0) for the lowest blood pressure category (<75 mm Hg), 1·7 (0·9–3·1) for 85–94 mm Hg, and 3·7 (1·6–8·7) for more than 95 mm Hg. The association was also examined among women on antihypertensive medication at follow-up (n = 203). 53 of these women had advanced atherosclerosis. For comparison, the corresponding age-adjusted relative risks of presence of advanced atherosclerosis in this group were 3·1 (0·9–11·0), 1·9 (0·8–4·7), and 1·5 (0·5–5·0).

Discussion

In this population-based prospective follow-up study, we observed a J-shaped relation between change in diastolic blood pressure and substantial progression of aortic atherosclerosis. Both women with a large decrease in diastolic blood pressure and those with a rise were at increased risk of progression.

Before we can interpret these findings, we must establish the validity of radiographic assessment of aortic calcification for the diagnosis of atherosclerosis. Comparison with CT assessments showed that calcifications detected by radiography were located in the vessel. Hyman and Epstein[12] reported that necropsy samples from 20 subjects with aortic calcifications detected by radiography showed pathologically demonstrable atherosclerosis in all; among 31 subjects with no calcification in the aorta detected by radiography, atherosclerosis was found at necropsy in 5, which suggests that false-negative classification occurs. Misclassification in our study, however, would be independent of blood pressure status; the observed associations may therefore underestimate the true effects.

A decrease in diastolic blood pressure as a consequence of stiffening of the large arteries, as implied by Sleight's hypothesis, was discussed many years ago.[4,13] Our results suggest that substantial progression of atherosclerosis in the aorta is associated with these changes. We suggest that at least part of the J-curve relation between diastolic blood pressure and cardiovascular mortality can be attributed to the decline in diastolic blood pressure as a consequence of stiffening of the large arteries. We propose that the latter is associated with widespread atherosclerosis, which in itself leads to an increased risk of cardiovascular disease.[5-8]

We cannot conclude from this study whether atherosclerosis results in vessel wall stiffness or whether vessel wall stiffness, or a wide pulse pressure, accelerates the process of atherosclerosis. If the latter were true, however, we would expect to find a J-shaped relation between change in diastolic blood pressure and slight progression of atherosclerosis. We found no such relation. This result supports the view that atherosclerosis, when present to a sufficient degree, contributes to vessel wall stiffness. The excess risk of atherosclerotic progression in women with low baseline diastolic blood pressures may reflect the presence of a hardened, atherosclerotic vessel wall likely to show atherosclerotic progression during follow-up. It is not likely that the observed associations are caused by confounding factors, because any such factor would need to have a J-shaped relation with diastolic (but not systolic) blood pressure or with atherosclerosis.

	Change in diastolic blood pressure (mm Hg)				Change in systolic blood pressure (mm Hg)			
	≤ −10 (n=65)	−9 to 0 (n=203)	1 to 9 (n=169)	≥10 (n=73)	≤0 (n=144)	1–9 (n=103)	10–19 (n=141)	≥20 (n=122)
Slight atherosclerotic progression								
No of cases	10	39	35	14	28	19	31	20
Relative risk (95% CI)*	0 8 (0 4–1 8)	1 0‡	1 3 (0 7–2 1)	1 4 (0 7–2 9)	1 0‡	1 0 (0 5–2 0)	1 3 (0 7–2 4)	0 8 (0 4–1 6)
Relative risk (95% CI)†	0 8 (0 3–1 9)	1 0‡	1 4 (0 8–2 4)	1 7 (0 8–3 6)	1 0‡	1 1 (0 6–2 3)	1 6 (0 8–3 1)	1 0 (0 5–2 2)
Substantial atherosclerotic progression								
No of cases	12	17	21	14	12	13	20	19
Relative risk (95% CI)*	2 5 (1 3–5 6)	1 0‡	2 2 (1 1–4 3)	3 5 (1 6–8 0)	1 0‡	1 7 (0 8–4 0)	2 2 (1 0–4 7)	2 0 (0 9–4 3)
Relative risk (95% CI)†	3 1 (1 3–7 6)	1 0‡	2 5 (1 2–5 2)	4 1 (1 7–10 0)	1 0‡	1 7 (0 7–4 1)	2 2 (1 0–5 0)	1·9 (0 8–4 5)

*Adjusted for age. †Adjusted for age, change in serum cholesterol, change in body weight, smoking status, diabetes mellitus, menopausal status, and duration of follow-up.
‡Reference category.

Table 3: Relative risk of atherosclerotic progression by category of blood pressure change (n = 510)

Cruickshank found no J-curve for the relation between diastolic blood pressure and death from myocardial infarction among treated hypertensive patients with wide pulse pressures.[14] This finding is not incompatible with Sleight's hypothesis; he expected subjects who had low diastolic and wide pulse pressures to have excess mortality compared with those who had normal pulse pressures.[3] This would reflect an artifactual lowering of diastolic blood pressure, accompanying widening of the pulse pressure, in subjects with stiffer arteries. Our finding that the excess risk of substantial atherosclerotic progression in the lowest category of diastolic blood pressure change was confined to women in the top half of the pulse-pressure change distribution also supports this notion.

The J-curve has been observed for the absolute value of diastolic blood pressure and for change during intervention in patients taking placebo or active treatment in randomised trials.[15] We examined the relation between diastolic blood pressure and extent of atherosclerosis among subjects who reported use of antihypertensive medication at follow-up. Though numbers were small, we found the highest risk of advanced atherosclerosis among women who had the lowest diastolic blood pressures. This finding suggests that in subjects treated for hypertension, as in untreated subjects, vessel wall stiffening associated with atherosclerosis may account for at least part of the J-curve. Some studies found that the J-curve was present only among a subgroup of subjects with coronary heart disease.[1,16] Another mechanism may be acting in high-risk subjects. Cruickshank attributed the excess risks in this subgroup to compromised coronary blood flow at lower diastolic blood pressures.[1]

Studies in elderly populations have shown increased cardiovascular risks at low systolic and diastolic blood pressures.[17,18] Extension of the follow-up period in the EPESE study[17] eliminated the excess risk associated with low systolic pressure, but only partly diminished that associated with low diastolic pressure. Pre-existing disease, associated with early excess risk of mortality, is thus not the only underlying mechanism of the J-curve in the elderly. The J-curve has not been observed in most prospective follow-up studies in middle-aged subjects.[19] Because vessel wall stiffening is an ageing phenomenon, it may not contribute to manifest cardiovascular disease in middle age. The finding of a J-curve in middle-aged hypertensive patients may be explained by the earlier age at development of vessel wall stiffness in hypertension.[20]

No previous population-based follow-up study has examined the association between change in diastolic blood pressure and risk of cardiovascular disease in detail. Our results show that in later life both increases and falls in diastolic blood pressure are associated with an excess risk of atherosclerosis. Change in diastolic blood pressure may

therefore be a better predictor of cardiovascular disease than absolute blood pressure value, which results from both recent changes and life-long experience.

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