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Brachial artery pulse pressure and common carotid artery diameter: mutually independent associations with mortality in subjects with a recent history of impaired glucose tolerance

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Abstract

Background Decreased large artery function, as reflected by increased brachial artery pulse pressure and increased carotid artery diameter and stiffness, may contribute to the increased mortality risk that is observed in subjects with impaired glucose tolerance. We therefore investigated the association between brachial artery pulse pressure and carotid artery diameter and stiffness, which are estimates of central artery stiffness and arterial remodelling, respectively, and mortality in subjects with a recent history of impaired glucose tolerance.

Design A prospective, population-based cohort study. We measured brachial artery pulse pressure by oscillometric blood pressure measurements, and common carotid artery diameter and distensibility and compliance coefficients by ultrasound in 140 subjects with a recent history of impaired glucose tolerance. During a median 6·6-year follow-up, 16 subjects died.

Results Brachial artery pulse pressure and common carotid artery diameter were positively related to all-cause mortality [hazard ratios per standard deviation, 1·7 (1·2–2·5) and 2·1 (1·3–3·3), respectively]. Results were similar after adjustment for gender, age, waist-to-hip ratio, body mass index, total cholesterol concentration, pre-existent cardiovascular disease, and hypertension, and after additional mutual adjustment. Common carotid artery distensibility and compliance coefficients were not statistically significantly associated with mortality.

Conclusions Among subjects with a recent history of impaired glucose tolerance, brachial artery pulse pressure and common carotid artery diameter are independently associated with mortality risk. Stiffness of the central arteries may explain the association between pulse pressure and mortality risk. The association between carotid diameter and mortality risk is more likely to reflect arterial remodelling in response to atherosclerosis than that in response to increased local stiffness.

Keywords common carotid artery diameter, common carotid artery stiffness, impaired glucose tolerance, mortality, pulse pressure.
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Introduction

Cardiovascular risk factors cluster in subjects with impaired glucose tolerance or type 2 diabetes mellitus [1,2], which results in a risk of cardiovascular disease that is considerably higher than that in subjects with normal glucose tolerance [1,3]. This clustering of cardiovascular risk factors is thought to induce adverse changes in arterial structure and function, which then predispose to clinical atherothrombotic disease.

In subjects with normal glucose tolerance, a large brachial artery pulse pressure [4–10] and an enlarged carotid artery diameter are associated with an adverse cardiovascular prognosis [11], suggesting that these alterations in arterial function and structure are relevant to the pathogenesis of clinical atherothrombotic disease. More specifically, brachial artery pulse pressure is thought to reflect stiffness of the central arteries, and enlarged carotid artery diameter is one of the manifestations of arterial remodelling (i.e. a change in structural and functional arterial properties through time due to exposure to an adverse metabolic and/or biophysical environment) [12]. Indeed, increased central arterial stiffness is associated with increased cardiac afterload [13,14] and decreased coronary artery filling pressure [15], which may explain the association of brachial artery pulse pressure with mortality [4–10]. In turn, at least two processes may be involved in arterial diameter enlargement due to remodelling and may explain the association of a large arterial diameter with mortality [11]. First, diameter enlargement occurs in atherosclerosis, either locally, in order to maintain free lumen area in arterial segments in which intima-media thickness is increased [16] (a sign of atherosclerosis in progress) or in which an atherosclerotic plaque is present [17], or as part of a more generalized phenomenon [16]. Second, arterial diameter enlargement often occurs hand in hand with an increase in local stiffness [18–20], possibly to maintain local compliance (i.e. the capacity of the artery to buffer pulsatile blood flow [21]).

In subjects with impaired glucose tolerance, arterial stiffness is increased as compared to subjects with normal glucose tolerance [22]. In addition, carotid arterial diameter enlargement occurs in relation to blood pressure level and plasma glucose concentration, suggesting arterial remodelling [19]. However, it is not known whether these estimates of altered arterial function and structure are associated with an adverse prognosis in subjects with impaired glucose tolerance. Because, as explained above, arterial remodelling may be related to increased local arterial stiffness, it is conceivable that increased arterial stiffness and arterial remodelling affect prognosis through the same pathway, and are therefore not independently associated with an adverse prognosis.

To study these issues, we measured brachial artery pulse pressure and common carotid artery diameter and stiffness in 140 subjects with a recent history of impaired glucose tolerance, and investigated whether these estimates of arterial function and structure were associated with risk of mortality during a 6·6-year follow-up.

Methods

Study population and overall design

The present study comprises part of the Hoorn Study, a population-based cohort study of diabetes and cardiovascular disease in which 2484 Caucasian men and women born between 1914 and 1940 participated. The study population, research design, laboratory methods and anthropometric measurements have been described in detail previously [19,23,24]. In brief, an age-, gender- and glucose-tolerance-stratified sample of 708 subjects was invited for additional extensive investigations; 631 subjects (89%) agreed and participated in the follow-up of the study. Of these 631, 224 had impaired glucose tolerance according to the average of two oral glucose tolerance tests (1985 WHO criteria [25]), in which samples were taken in the fasting state (between 08·30 h and 09·30 h after a 10-h fast) and 120 min after a 75-g glucose load [25]. Of the subjects with impaired glucose tolerance, 140 (63%) agreed to undergo ultrasonography of the common carotid artery combined with blood pressure measurements, which took place 2·3 years (median 25–75%: 2·0–2·7 years; between January and October 1993) after the diagnosis of impaired glucose tolerance. (Two more follow-up common carotid artery examinations were conducted and have been described elsewhere [19].) We obtained metabolic and anthropometric measurements 6·0 weeks (median; 25–75%: 4–13 weeks) before the common carotid artery examination. We shall refer to these 1993 measurements as 'baseline'. Subjects were then followed until January 2000 (median follow-up duration 6·6 years; interquartile range: 6·6–6·7). Dates of death were extracted from the population register of the city of Hoorn or from the population registers of the cities to which the subjects had moved.

Measurement of common carotid artery diameter

Common carotid artery diameter was determined using an ultrasound system (Ultramark IV, ATL, Bothell, WA) in combination with a vessel wall movement detector system [26] (Wall Track System, Neurodata, Bilthoven, the Netherlands). All subjects refrained from smoking or consuming caffeine for at least 4 h before the examination. Measurements were carried out by a single experienced ultrasound technician in a quiet room after the subjects had rested for 15 min in the supine position. After localization of the common carotid artery, a cross-section was selected for diameter measurement approximately 10 mm proximal to the carotid bulb. Sites with mural atherosclerotic plaques were avoided. Each recording lasted 4 s; this enabled continuous recording of the arterial

diameter for several heart beats. Recordings were ECG-triggered to maximizing the number of heart beats in this period and were repeated if the diastolic diameter or the difference between systolic and diastolic diameter (distension; see below) showed a standard deviation of more than 10%.

Blood pressure measurement

The systolic, mean and diastolic blood pressures were recorded at the level of the left brachial artery at 5-min intervals using an oscillometric blood pressure measuring device (Col, in press-Mate BP-8800, Colin, Komaki-City, Japan). Pulse pressure was defined as systolic minus diastolic blood pressure. The mean of all blood pressure measurements during the actual ultrasonography (median: 3) was used in the statistical analyses. Subjects were regarded as hypertensive if their systolic blood pressure was ≥ 160 mmHg, if their diastolic blood pressure was ≥ 95 mmHg and/or if they used antihypertensive medication.

Definition of arterial properties

Common carotid artery diameter (in mm) was defined as mean diastolic diameter of three recordings, common carotid artery distension (in μm) as mean difference between systolic and diastolic diameters. The distensibility coefficient was calculated as [(2 $\times$ distension)/(diameter $\times$ pulse pressure $\times$ 0·1333)] (in Pa^{-1}), and the cross-sectional compliance coefficient as ($\pi \times$ diameter) $\times$ [distension/(266·6 $\times$ pulse pressure)] (in mm^2 kPa^{-1}) [20,27,28]. Pulse pressure was not calculated from common carotid, but from brachial artery blood pressure, which has been shown to provide a relatively good approximation [19,27]. The distensibility and the compliance coefficients are indices of elasticity and therefore inversely related to stiffness. The distensibility coefficient describes intrinsic vessel wall stiffness, while the compliance coefficient is a measure of the capacity of the vessel to buffer the pulsatile blood flow.

Reproducibility

The intrameasurement variability (coefficient of variation) in the three ultrasound recordings of one measurement of the carotid diameter was 1·0%. The variability between two measurements conducted on the same day by the same observer (coefficient of variation) was 1·5% for the diameter, 4·2% for the distensibility coefficient and 2·1% for the compliance coefficient.

Statistical analysis

Data were expressed as mean (standard deviation) or as median (interquartile range), the latter for variables without a normal distribution. Student's *t*-test was used to examine differences between drop-outs and participants, and between those who died and those who did not. Variables without a normal distribution were logarithmically transformed before they were entered in Student's *t*-test (but in the tables their untransformed values are shown). The Mann–Whitney test was used for variables without a normal distribution after logarithmic transformation. The χ^2 test was used for comparing gender, smoking habits, glucose tolerance category, pre-existent cardiovascular disease and hypertensive status between groups. Cox's proportional hazards regression analysis was used to investigate the association of clinical, biochemical and haemodynamic variables with mortality, focusing on brachial artery pulse pressure and common carotid artery diameter, distensibility coefficient and compliance coefficient as key independent variables. We employed four models. In the first model, no adjustments were made (univariate). In the second model, adjustments were made for age and sex. In the third model, we added independent variables that were univariately associated with mortality with $P < 0{\cdot}10$, except that we did not adjust the association between pulse pressure and mortality for systolic blood pressure or the presence of hypertension, because these variables are closely related to pulse pressure. Instead, we did analyses without and with adjustment for mean arterial pressure, the latter to obtain an estimate of the association between pulse pressure (i.e. arterial stiffness) and mortality independent of the increase in stiffness due to increased blood pressure *per se* [29]. In the fourth model, adjustments were made only for carotid artery diameter (in analyses that focused on brachial pulse pressure) or for brachial pulse pressure (in analyses that focused on carotid artery diameter), in order to investigate whether any association between brachial artery pulse pressure and mortality was mediated through carotid diameter (assumed to reflect arterial remodelling), and whether any association between carotid artery diameter and mortality was mediated through brachial artery pulse pressure (assumed to reflect central arterial stiffness). (Adjustments for brachial artery pulse pressure or for common carotid artery diameter were not possible in analyses with carotid artery distensibility or compliance coefficients as key independent variables, as these were calculated using pulse pressure and diameter.) Results of Cox's regression analyses are shown per standard deviation of the independent variable.

Probability values $< 0{\cdot}05$ were considered to be statistically significant. SPSS (SPSS for Windows, version 9·0, SPSS Inc., Chicago, IL) was used for all analyses.

Results

Patient characteristics

Table 1 shows the baseline clinical characteristics of the

Table 1 Baseline characteristics among 140 subjects with a recent history of impaired glucose tolerance, according to prognosis

	Survived ($n = 124$)	Died ($n = 16$)	P
n (men/women)	52/72	9/7	0·28
Age (years)	65·5 (59·5–71·8)	74·4 (63·7–76·2)	0·01
Cigarette smoking (yes/no)	67/57	5/11	0·09
Fasting serum glucose (mmol L^{-1})	6·5 ± 0·8	6·5 ± 0·6	0·83
2 h postload serum glucose (mmol L^{-1})*	9·9 ± 2·6	10·6 ± 2·3	0·31
Fasting serum insulin (pmol L^{-1})	74·3 (47·2–121·5)	96·4 (69·1–158·5)	0·17
HbA_{1c} (%)	5·7 ± 0·6	5·8 ± 0·5	0·79
NGT/IGT/type 2 DM/unknown^{-1}† (n)	19/63/40/2	3/5/7/1	0·40
Waist-to-hip ratio	0·90 ± 0·08	0·95 ± 0·12	0·03
Body mass index (kg m^{-2})	27·7 ± 3·5	29·3 ± 3·2	0·09
Total cholesterol (mmol L^{-1})	6·5 ± 1·3	5·8 ± 1·0	0·02
LDL-cholesterol (mmol L^{-1})	4·6 ± 1·2	4·1 ± 1·0)	0·14
HDL-cholesterol (mmol L^{-1})	1·11 (0·96–1·33)	1·10 (0·94–1·24)	0·72
Triglycerides (mmol L^{-1})	1·7 (1·3–2·5)	1·6 (1·3–2·3)	0·38
Pre-existent cardiovascular disease‡ (yes/no)	17/107	5/11	0·07
Hypertensive§ (yes/no)	43/81	10/6	0·03
Systolic blood pressure (mmHg)	143 ± 21	154 ± 25	0·05
Mean arterial pressure (mmHg)	103 ± 14	108 ± 16	0·13
Diastolic blood pressure (mmHg)	79 ± 11	80 ± 11	0·82
Heart rate (beats min^{-1})	69 ± 12	72 ± 16	0·41
Pulse pressure (mmHg)	63 ± 13	74 ± 18	0·003
Common carotid artery properties			
Diameter (mm)	6·92 ± 0·73	7·57 ± 0·91	0·001
Distensibility coefficient (Pa^{-1})	11·4 ± 3·8	10·3 ± 5·0	0·30
Compliance coefficient (mm^2 kPa^{-1})	0·43 ± 0·17	0·47 ± 0·27	0·46

Continuous variables are expressed as mean ± SD or as median (interquartile range).

*Two hours after a 75-g glucose load following overnight fasting; † according to the 1985 WHO criteria for glucose tolerance [25]; ‡ self-reported peripheral arterial disease, stroke, transient ischaemic attack, angina pectoris, myocardial infarction, coronary bypass grafting or angioplasty, and/or abnormal resting electrocardiogram (Minnesota codes 1–1 or 1–2)); § systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg and/or using antihypertensive medication.

NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

study population. Participants ($n = 140$) had higher fasting and postload glucose levels at the time of diagnosis of impaired glucose tolerance than did those who did not participate [$n = 84$; 6·1 ± 0·7 vs. 5·9 ± 0·6 ($P = 0·02$) and 9·3 ± 1·5 vs. 8·7 ± 0·8 mmol L^{-1} ($P < 0·001$), respectively (mean ± SD)], while blood pressure, lipid levels and other clinical data were not different (data not shown).

During the course of the follow-up 16 subjects died. At baseline, those who died, as compared to survivors, were 5·3 years older ($P = 0·01$), had a lower total cholesterol concentration (difference 0·7 mmol L^{-1}; $P = 0·02$), but had a higher pulse pressure (difference 11 mmHg; $P = 0·003$), and a 0·65-mm larger carotid artery diameter ($P = 0·001$; Table 1). Baseline carotid artery distensibility and compliance coefficients did not differ significantly between those who died and those who survived (Table 1).

Determinants of mortality

In univariate analyses, variables significantly associated with mortality risk were age, waist-to-hip ratio, total serum cholesterol concentration (negatively), the presence of hypertension, systolic blood pressure, brachial artery pulse pressure and common carotid artery diameter (Table 2, model 1). After adjustment for age and gender, variables significantly associated with mortality risk were total cholesterol (negatively), the presence of hypertension, pulse pressure and common carotid artery diameter (Table 2, model 2).

In multivariate analyses with brachial artery pulse pressure as key independent variable, further adjustment for waist-to-hip ratio, body mass index, total cholesterol concentration and pre-existent cardiovascular disease (Table 3, model 3a), and mean arterial pressure (Table 3, model 3b) did not materially change the point estimate of the association between pulse pressure and mortality, which was also the case after separate adjustment for these variables. Additional adjustment for smoking in model 3 also had no major effect on the association (data not shown). Adjustment for carotid artery diameter only (Table 3, model 4) somewhat lowered the point estimate of the association between pulse pressure and mortality, which was not materially altered after further adjustment for age and sex (data not shown).

Table 2 Determinants of mortality during a 6·6-year follow-up among 140 subjects with a recent history of impaired glucose tolerance

	Hazard ratio (95% CI) Model 1	*P*	Hazard ratio (95% CI) Model 2	*P*
Gender (0 = male, 1 = female)	0·8 (0·5–1·2)	0·26	0·7 (0·4–1·1)	0·11
Age	**2·1 (1·2–3·9)**	**0·01**	**2·3 (1·3–4·3)**	**0·01**
Cigarette smoking (0 = no, 1 = yes)	0·6 (0·4–1·1)	0·11	0·6 (0·3–1·0)	0·06
Fasting serum glucose	1·0 (0·6–1·6)	0·88	0·9 (0·5–1·6)	0·73
2 h postload serum glucose	1·2 (0·8–1·9)	0·33	1·2 (0·7–2·0)	0·49
Fasting serum insulin	1·3 (0·9–2·0)	0·20	1·2 (0·7–1·8)	0·52
HbA_{1c} (%)	1·1 (0·7–1·7)	0·80	1·0 (0·6–1·6)	0·91
Glucose tolerance category*	1·2 (0·7–2·0)	0·58	1·0 (0·6–1·7)	0·90
Waist-to-hip ratio	**1·6 (1·03–2·6)**	**0·04**	1·4 (0·8–2·2)	0·21
Body mass index	1·5 (0·9–2·0)	0·096	1·6 (1·0–2·5)	0·07
Total cholesterol	**0·6 (0·3–0·9)**	**0·02**	**0·6 (0·3–0·95)**	**0·03**
LDL-cholesterol	0·7 (0·4–1·1)	0·16	0·7 (0·4–1·1)	0·11
HDL-cholesterol	0·9 (0·5–1·5)	0·63	1·0 (0·6–1·7)	0·99
Triglycerides	0·7 (0·4–1·4)	0·31	0·8 (0·4–1·6)	0·46
Pre-existent cardiovascular disease (0 = no, 1 = yes)	1·4 (0·9–2·0)	0·09	1·3 (0·9–2·0)	0·13
Hypertensive (0 = no, 1 = yes)	**1·7 (1·02–2·8)**	**0·04**	**1·8 (1·04–2·9)**	**0·03**
Systolic blood pressure	**1·5 (1·004–2·2)**	**0·048**	1·5 (0·9–2·4)	0·09
Mean arterial pressure	1·4 (0·9–2·2)	0·12	1·4 (0·8–2·2)	0·21
Diastolic blood pressure	1·1 (0·7–1·7)	0·78	1·1 (0·6–1·9)	0·76
Heart rate	1·2 (0·8–2·0)	0·39	1·2 (0·8–2·0)	0·36
Pulse pressure†	**1·7 (1·2–2·5)**	**0·004**	**1·6 (1·1–2·5)**	**0·02**
Common carotid artery properties:				
Diameter‡	**2·1 (1·3–3·3)**	**0·002**	**2·0 (1·3–3·3)**	**0·004**
Distensibility coefficient	0·8 (0·4–1·3)	0·30	0·9 (0·5–1·7)	0·72
Compliance coefficient	1·2 (0·8–1·9)	0·45	1·5 (0·9–2·4)	0·21

Results of proportional hazards regression analyses are shown as hazard ratios and 95% confidence intervals per standard deviation of the independent variables. P, probability value. Adjustments: model 1: none (univariate); model 2: for age and gender. Associations with $P < 0·05$ are shown in boldface.

*According to the 1985 WHO criteria for glucose tolerance [25] (0, normal glucose tolerance; 1, impaired glucose tolerance; 2, type 2 diabetes mellitus).

† standard deviation, 14 mmHg.

‡ standard deviation, 0·78 mm.

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

In multivariate analyses with carotid artery diameter as key independent variable, further adjustment for waist-to-hip ratio, body mass index, total cholesterol concentration and pre-existing cardiovascular disease (Table 3, model 3a), and mean arterial pressure (Table 3, model 3b) somewhat lowered the point estimate of the association between carotid diameter and mortality. We then separately entered each of the variables of model 3 into model 2 and found that total cholesterol concentration, body mass index, waist-to-hip ratio, mean arterial pressure and pre-existent cardiovascular disease (from largest to smallest magnitude of the effect) all contributed to the result of model 3. In addition, we adjusted model 3b for systolic blood pressure or the presence of hypertension instead of mean arterial pressure, but this gave similar results. Additional adjustment for cigarette smoking somewhat increased the point estimate of the association between carotid artery diameter and mortality (model 3a: hazard ratio, 2·1 (1·3–3·5); model 3b: hazard ratio, 2·0 (1·2–3·4)). Adjustment for pulse pressure only (Table 3, model 4) somewhat lowered the point estimate of the association between carotid diameter and mortality, which was not materially altered after further adjustment for age and sex (data not shown).

After adjustment for the same variables as in the pulse pressure or diameter analyses, neither the carotid distensibility coefficient nor the carotid compliance coefficient were statistically significantly associated with mortality (data not shown).

Discussion

We determined brachial artery pulse pressure and common carotid artery diameter and stiffness in 140 middle-aged and elderly subjects with a recent history of impaired glucose tolerance, and assessed the associations of these indices of vascular function and structure with risk of mortality during 6·6 years of follow-up. There were four main findings. First, a higher brachial artery pulse pressure at baseline (thought to reflect central arterial stiffness) was associated with an increased mortality risk [hazard ratio

Table 3 Brachial artery pulse pressure and common carotid artery diameter as determinants of mortality during a 6·6-year follow-up among 140 subjects with a recent history of impaired glucose tolerance

Independent variable	Model	Hazard ratio	*P*
Brachial artery pulse pressure	1	1·7 (1·2–2·5)	0·004
	2	1·6 (1·1–2·5)	0·02
	3a	1·6 (1·1–2·6)	0·03
	3b	1·6 (0·9–3·1)	0·14
	4	1·4 (0·9–2·1)	0·10
Common carotid artery diameter	1	2·1 (1·3–3·3)	0·002
	2	2·0 (1·3–3·3)	0·004
	3a	1·8 (1·1–2·8)	0·02
	3b	1·7 (1·05–2·7)	0·03
	4	1·8 (1·1–2·9)	0·03

Results of proportional hazards regression analyses are shown as hazard ratios and 95% confidence intervals per standard deviation of the independent variables. *P*, probability value. Adjustments: model 1: none (univariate); model 2: for age and sex; model 3a: as in model 2 plus for waist-to-hip ratio, body mass index, total cholesterol, and presence of pre-existent cardiovascular disease; model 3b: as in model 3a plus for mean arterial pressure; model 4: adjusted only for diameter (in pulse pressure analyses) or for pulse pressure (in diameter analyses).

per standard deviation of pulse pressure (14 mmHg), 1·7 (1·2–2·5)]. Second, a larger common carotid artery diameter at baseline (thought to reflect arterial remodelling) was also associated with an increased mortality risk [hazard ratio per standard deviation of diameter (0·78 mm), 2·1 (1·3–3·3)]. Third, these associations were largely independent of each other, which suggests that the pathways linking pulse pressure and carotid diameter to mortality differ to an important extent. Fourth, carotid artery distensibility and compliance coefficients, which are commonly used as measures of local arterial stiffness, were not significantly associated with mortality risk. We also found negative associations between, on the one hand, total cholesterol concentration and (self-reported) cigarette smoking and, on the other, mortality. However, since low-density lipoprotein cholesterol concentration, more directly linked to disturbance of lipid metabolism than total cholesterol concentration, was not associated with mortality, this argues against an actual negative association of a disturbed lipid metabolism with mortality. Intrinsic imprecision of self-reported smoking habits may have played a role in our findings with regard to cigarette smoking. Taken together, our main results suggest that both central arterial stiffness and arterial remodelling, as far as they are reflected by brachial artery pulse pressure and carotid artery diameter, respectively, may be relevant to understanding the increased cardiovascular mortality risk in subjects with impaired glucose tolerance (and, by extension, in patients with type 2 diabetes), and that the pathway linking carotid arterial remodelling to mortality is more likely to involve a response to atherosclerosis than to arterial stiffening.

Brachial artery pulse pressure was a determinant of mortality in individuals with a recent history of impaired glucose tolerance after adjustment for age and sex, which is consistent with reports linking pulse pressure with cardiovascular mortality [4–8] in the general population. The association between pulse pressure and mortality was no longer significant after further adjustment for multiple cardiovascular risk factors including mean arterial pressure (Table 3), but it should be noted that this may, in part, be caused by overadjustment as increased pulse pressure may be an intermediary in the pathway linking cardiovascular risk factors with mortality. Increased brachial artery pulse pressure is a sign of stiffening of arteries involved in buffering the pulsatile blood flow [4–10], i.e. the aorta, in particular the ascending aorta and the aortic arch [30], but also the abdominal aorta and its proximal elastic branches. Stiffening of these arteries not only decreases their buffering capacity; it is also responsible for an increased pressure load imposed upon the left ventricle caused by an earlier return of reflected pulse waves [13]. Both phenomena cause central blood pressure to increase during systole and to decrease during diastole. The former is associated with increased cardiac afterload [13,14], the latter with decreased coronary artery filling pressure [15], and these mechanisms may explain the association between brachial artery pulse pressure and increased risk of mortality.

Carotid artery diameter was also positively associated with mortality risk after adjustment for age and sex. Further adjustment for other cardiovascular risk factors somewhat diminished the risk estimate, but it remained statistically significant (Table 3, model 3), and, for reasons similar to those noted above for pulse pressure, this risk estimate may be somewhat overadjusted. It may at first seem surprising that a *larger* carotid diameter should be associated with *increased* mortality risk. Pathophysiologically, diameter enlargement may represent active remodelling of the vascular wall associated with local or more generalized atherosclerosis [16,17], a process in which enzymatic breakdown of extracellular matrix on the one hand and smooth muscle cell proliferation on the other are combined in a well-programmed reorganization [31]. Alternatively or additionally, it may reflect structural damage to cellular and extracellular matrix elements associated with increased local arterial stiffness [14,16,18,19]. An example of the latter is that advanced glycation end products, whose formation is stimulated under conditions of hyperglycaemia, may cross-link elastin fibres resulting in increased susceptibility to rupture of elastic lamellae, increased local stiffness and a larger diameter [32]. Although a definite distinction between these two processes as the underlying factor of diameter enlargement may not be possible, our data do not support increased local arterial stiffness as the most likely one. First and foremost, carotid artery distensibility (and compliance) coefficient, which directly reflect local stiffness, were not significantly associated with mortality risk (Table 2). Second, the associations of brachial pulse pressure and carotid artery diameter on the one hand and mortality on the other were largely independent of each other, suggesting the presence of distinct underlying mechanisms. If, as

seems likely, increased central arterial stiffness explains why increased brachial artery pulse pressure is associated with an adverse prognosis, then it follows that increased arterial stiffness is a less likely explanation for the association between carotid artery diameter and mortality risk. We therefore favour the interpretation that carotid artery diameter enlargement may be a response to the atherosclerotic process and that this may explain its association with mortality. Such diameter enlargement can occur as a response to local atherosclerosis [17], or as a more generalized phenomenon in response to atherosclerosis elsewhere [16]. We cannot distinguish between these possibilities, because, although we avoided measuring diameter at sites with mural atherosclerotic plaques, we did not obtain an estimate of intima-media thickness as a measure of local incipient atherosclerosis.

Regardless of their pathophysiological interpretation, our data suggest that measurement of carotid arterial diameter (and possibly also of brachial artery pulse pressure) in subjects with impaired glucose tolerance may be useful to obtain an estimate of mortality risk that is more precise than that based on the measurement of conventional risk factors alone, and may thus have additional value. This may be clinically useful, because it can help to individualize decisions on the treatment of, for example, hypercholesterolaemia or hypertension.

The limitations of our study must be considered. Our study was too small to analyse associations with cardiovascular instead of all-cause mortality. We were also unable to establish definitively whether the association between pulse pressure and mortality remained statistically significant after adjustment for risk factors other than age and sex. Drop-out from the impaired glucose tolerance cohort before the ultrasound measurements ($n = 84$) [19] may have caused bias, as these subjects had a slightly more impaired glucose homeostasis than did those who participated. However, it is unlikely that the associations that we found would have been different in the drop-outs as compared to the participants, as glucose levels, either fasting or postload, were not significantly associated with mortality in any of the analyses. A strength of our design was that we investigated a population-based sample of individuals with impaired glucose tolerance [19], a condition that is known to be prevalent among the middle-aged and elderly and to be associated with an increased risk of mortality compared to the normal glucose-tolerant state [3]. It is not clear, however, whether our findings can be generalized to individuals with type 2 diabetes or with normal glucose tolerance.

In conclusion, the results of our study show that, among middle-aged and elderly subjects with a recent history of impaired glucose tolerance, brachial artery pulse pressure and common carotid artery diameter were positively associated with risk of mortality during 6·6 years of follow-up. These findings suggest that increased central arterial stiffness (reflected by brachial artery pulse pressure) and arterial remodelling (reflected by carotid diameter enlargement) are part of the pathophysiology of clinical atherothrombotic disease in individuals with impaired glucose tolerance.

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