Aortic Pulse-Wave Velocity and Its Relationship to Mortality in Diabetes and Glucose Intolerance
An Integrated Index of Vascular Function?

Kennedy Cruickshank, MB, MD; Lisa Riste, PhD; Simon G. Anderson, PhD; John S. Wright, PhD; Graham Dunn, PhD; Ray G. Gosling, PhD

Background—Arterial distensibility measures, generally from pulse-wave velocity (PWV), are widely used with little knowledge of relationships to patient outcome. We tested whether aortic PWV predicts cardiovascular and all-cause mortality in type 2 diabetes and glucose-tolerance–tested (GTT) multiethnic population samples.

Methods and Results—Participants were randomly sampled from (1) a type 2 diabetes outpatient clinic and (2) primary care population registers, from which nondiabetic control subjects were given a GTT. Brachial blood pressures and Doppler-derived aortic PWV were measured. Mortality data over 10 years’ follow-up were obtained. At any level of systolic blood pressure (SBP), aortic PWV was greater in subjects with diabetes than in controls. Mortality risk doubled in subjects with diabetes (hazard ratio 2.34, 95% CI 1.5 to 3.74) and in those with glucose intolerance (2.12, 95% CI 1.11 to 4.0) compared with controls. For all groups combined, age, sex, and SBP predicted mortality; the addition of PWV independently predicted all-cause and cardiovascular mortality (hazard ratio 1.08, 95% CI 1.03 to 1.14 for each 1 m/s increase) but displaced SBP. Glucose tolerance status and smoking were other independent contributors, with African-Caribbeans experiencing reduced mortality risk (hazard ratio 0.41, 95% CI 0.25 to 0.69).

Conclusions—Aortic PWV is a powerful independent predictor of mortality in both diabetes and GTT population samples. In displacing SBP as a prognostic factor, aortic PWV is probably further along the causal pathway for arterial disease and may represent a useful integrated index of vascular status and hence cardiovascular risk. (Circulation. 2002;106:2085-2090.)

Key Words: blood flow ■ vasculature ■ diabetes mellitus ■ mortality

The achievement of a successful reduction in morbidity and mortality by treating hypertension has been a major success of modern medicine.1,2 The continuous relationship of blood pressure (BP) to outcomes suggests that divisions of BP into “normal” or “high” are arbitrary. Randomized trials in uncomplicated hypertension show BP treatment still only reduces absolute risk by 1% to 2%, so that 10 to 20 people require treatment for 5 years to prevent 1 cardiovascular event.2

In type 2 diabetes, risk is 2- to 4-fold higher than without diabetes at any level of standard risk factors,3 and the absolute benefit from treating high BP is greater.4 The imprecision in estimating risk from BP alone and its dependence on the quality of the vascular tree focus attention on how best to measure that quality noninvasively.5 Ultrasound methods from the 1960s and 1970s6 allow valid, repeatable detection of structure, such as carotid intimal-medial thickness, and function via flow and pressure-related waveforms, from which vascular distensibility is derived. Central and peripheral measurement methods are now used7-10 with newer tonometric methods for the radial artery.5,11

We assessed whether pulse-wave velocity (PWV) along the descending aorta, from which distensibility or compliance is derived,7,12 contributes to vascular risk. We examined whether for given levels of BP in people with and without type 2 diabetes, those whose aortas were stiffer (less distensible) would be at greater risk of mortality. Our secondary hypothesis was that PWV might represent an integrated index of vascular structure and function, on and through which other standard risk factors might operate (e.g., high BP, lipid disturbances, and glycation), all cumulative over a lifetime.
TABLE 1. PWV and BP by Ethnic Group and Glucose Tolerance Status

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Known Diabetes (n=178)</th>
<th>Community Controls (n=54)</th>
<th>Known Diabetes (n=127)</th>
<th>Community Controls (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.4 (61.2–63.5)</td>
<td>61.9 (60.4–63.4)</td>
<td>58.1 (56.6–59.5)</td>
<td>60.5 (58.9–62.1)</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>5.8 (4.8–6.9)</td>
<td>...</td>
<td>8.0 (6.6–9.4)</td>
<td>...</td>
</tr>
<tr>
<td>% Current smokers</td>
<td>25.8 (19.4–32.2)</td>
<td>37.0 (24.1–49.9)</td>
<td>18.1 (11.4–24.8)</td>
<td>16.2 (7.8–24.6)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>146.9 (143.5–150.4)</td>
<td>136.3 (130.8–141.8)</td>
<td>141.4 (137.5–145.3)</td>
<td>139.7 (134.0–145.3)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78.8 (77.1–80.4)</td>
<td>77.3 (74.7–79.9)</td>
<td>78.0 (76.2–79.8)</td>
<td>78.6 (75.9–81.4)</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>12.0 (11.4–12.5)</td>
<td>10.1 (9.5–10.7)</td>
<td>11.6 (10.9–12.2)</td>
<td>10.5 (9.7–11.2)</td>
</tr>
</tbody>
</table>

Values are means (95% CI). *Combined type 2 clinic and community cases.

Methods

Participants
Lists of patients with type 2 diabetes who were attending the outpatient clinic (Dr R.F. Mahler) at Northwick Park Hospital, northwest London, between 1986 and 1990 and whose records were kept on computer databases were randomly sampled each week (Dr R. Greenwood). Those sampled, representative of all those attending, were invited for detailed measurement of their aortic PWV and BP, as described previously. No blood samples were taken. The response rate was 77%. Participants fasted for a 75-g glucose tolerance test (GTT), classified by World Health Organization 1985 and 1999 criteria. In the second hour, twice in a 1-week period, PWV was measured. Those with either impaired fasting glucose, impaired glucose tolerance, or new diabetes were termed glucose intolerant. Those normoglycemic at 2 hours were the comparison (control) group. Those with either impaired fasting glucose, impaired glucose tolerance, or new diabetes were termed glucose intolerant. Those normoglycemic at 2 hours were the comparison (control) group. Those with known type 2 diabetes (n=17) were not subjected to glucose challenge.

The Northwick Park and Central Middlesex Hospital committees granted ethical permission for all baseline measurements and mortality follow-up.

Aortic PWV
PWV measurement (2 observers, 80% by JSW) used 2 continuous-wave Doppler probes. One was clamped at the base of the left side of the neck to insonate the root of the left subclavian artery to obtain a stable aortic arch flow waveform. The other insonated the abdominal aorta, above its bifurcation, to obtain a stable distal aortic waveform. This maximized vessel length for the waveforms while minimizing reflection artifacts from smaller resistance-vessel beds. Participants were supine for >5 minutes before recording. Signals from the foot of the proximal to the foot of the distal waveform generated transit times over the measured cutaneous distance (sternoclavicular notch to distal probe), giving PWV (in meters per second). Recordings were averaged over 45 to 120 cardiac cycles that included, yet were buffered against, sinus arrhythmias and respiratory rate variations. Typical transit times were 27±4.5 ms, generated when the foot of the systolic upstroke was clearly defined from each probe, with a summary value, indicated by computer-generated histogram of the individual transit times. In a repeatability study, PWV measurements at 1 and 3 months did not differ significantly from those assessed at baseline (−0.02 [95% CI −0.06 to 0.03] m/s and 0.03 [95% CI −0.03 to 0.09] m/s, respectively).
Three brachial BP measurements were taken before and 3 after the PWV with a random zero sphygmomanometer and large cuff when appropriate (>33 cm). The average of the last 2 BPs of each set was used. ECGs were graded by Minnesota coding, with only “definite” criteria for ischemic heart disease (IHD) used here.
Follow-up was via tagging of death certificates at the Office of National Statistics, United Kingdom. Their 3-monthly reports recorded dates of deaths or emigration, with censoring at December 31, 2000.
Analysis used the Intercooled Stata version 7 program for ANOVA or χ² squared test, mortality analyses with person-months of follow-up, and multivariate Cox proportional hazard models. Model numbers varied depending on the variables included, with any missing values causing the participant to be dropped from the model. Hazard ratios from these models are expressed as a percentage increase or decrease in risk per unit of the relevant variable.

Results
Of 397 patients with known diabetes, 60% were men, and 45% were African-Caribbean or Gujerati (Table 1). Total mean age was 60 (95% CI 59 to 61) years. Mean systolic but not diastolic BP and aortic PWV rose progressively with declining glucose tolerance. Nine percent of those with known diabetes and 2% of normoglycemics had definite IHD.
In diabetes, PWV rose progressively with age at 0.22 (95% CI 0.18 to 0.26) m/s per year and with systolic BP at 0.09 (0.08 to 0.1) m/s per mm Hg (Figure 1a). In controls who took GTTs, the rise in PWV with systolic pressure was similar (0.075, 0.06 to 0.09; Figure 1b). For any level of systolic pressure, particularly 140 mm Hg and more for those with diabetes, some people had higher PWV (stiffer aortas) than others. Between 140 and 160 mm Hg, 17% with diabetes had PWV ≥15 m/s compared with only 2% of controls (χ² 6.9, P<0.01).
A Kaplan-Meier survival plot (adjusted to age 60 years) by GTT status (Figure 2) showed progressively poorer survival with declining status: at 10 years, survival was 90% in controls, 85% in those with glucose intolerance, and only 70% in those with known diabetes.
Overall follow-up was 10.7 years (12.7 [12.6 to 12.8] years for survivors and 6.9 [6.4 to 7.3] years for those who died). More men (42%) died than women (33%). Those with diabetes who died were significantly older, smoked more, and had PWVs 2.6 m/s faster and mean systolic pressures 10-mm Hg higher than those who survived (Table 2). Total duration of diabetes (baseline plus survival time) was 14.3.
13.0 to 15.6) years at death but 18.2 (17.4 to 19.1) years in survivors. Risk factors were higher in those without diabetes who died than in those who remained alive. When survival status was superimposed on the plot of PWV against systolic pressure (Figure 3), those who died had higher baseline PWVs on average for any level of baseline systolic pressure.

The first Cox proportional model was for those with diabetes only (n = 394), of whom 179 (45.1%) died. Including only age (8% [95% CI 6% to 11%] increase in risk per year), sex (women 45% [95% CI 41% to 77%] less risk of mortality), and systolic pressure (4% [95% CI 1% to 7%] increase per 5 mm Hg) without PWV, all were independent significant predictors of both all-cause and cardiovascular mortality. When PWV was added, age and sex remained independently significant, systolic pressure was displaced and not significant (P > 0.1), but PWV was highly predictive (hazard ratio 1.08 [95% CI 1.03 to 1.14] for each 1 m/s increase). Diabetes duration and BP treatment status were not significant contributors. Substitution of pulse (systolic minus diastolic) pressure also had no impact.

Among glucose intolerant and normoglycemic groups (n = 174), there were 40 deaths (23%). Again, if sex, age, and systolic pressure were entered, only age and pressure were significant. Addition of PWV again displaced systolic pressure.

The final model combined those with diabetes and controls (n = 565). Age, PWV, GTT category, smoking status, and sex (women had 34% less risk) were independent significant predictors of total mortality (Table 3). Substitution of pulse for systolic pressure again had no impact. Minnesota coding for definite IHD was not an independent contributor. African-Caribbean origin was independently associated with lower total (59%, 95% CI 31% to 75%) and cardiovascular (84%, 95% CI 56% to 94%) mortality because of less IHD (6%) than in Europeans or Gujaratis (31%). Total mortality for Gujaratis was also less than for Europeans (32%, 95% CI 6% to 51%).

**Discussion**

These results illustrate for the first time the prognostic value of PWV in type 2 diabetes compared with a community-based control population of defined glucose tolerance status. Random sampling ensured participants should be representative of both type 2 diabetes clinic attenders and the controls of their respective ethnic communities.13
Arterial functional status potentially indicates prognosis in people with and without diabetes. Early methods suggested PWV was faster in type 2 diabetes than in controls.\(^{14,15}\) As in the present study’s baseline data,\(^16\) others reported worse aortic compliance or distensibility in type 2 diabetes than in controls in smaller clinical studies.\(^{17,18}\) Structural indices such as carotid intima-media thickness also show excess disease in those with diabetes.

### TABLE 2. Baseline Clinical Characteristics of the Subjects by Glucose Tolerance and Survival Status

<table>
<thead>
<tr>
<th></th>
<th>Known Diabetes* (n=397)</th>
<th>Glucose Intolerant† (n=55)</th>
<th>Normal Glucose Tolerance (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alive (n=218)</td>
<td>Died (n=179)</td>
<td>Alive (n=37)</td>
</tr>
<tr>
<td>Age, y, mean (95% CI)</td>
<td>57.5 (56.6–58.5)</td>
<td>63.8 (62.6–65.0)</td>
<td>57.7 (55.2–60.2)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male§</td>
<td>120 (50.2)</td>
<td>119 (49.8)</td>
<td>16 (61.5)</td>
</tr>
<tr>
<td>Female</td>
<td>98 (62)</td>
<td>60 (38)</td>
<td>21 (72.4)</td>
</tr>
<tr>
<td>Ethnic group, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White European</td>
<td>81 (46)</td>
<td>97 (54)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Gujarati</td>
<td>76 (60)</td>
<td>51 (40)</td>
<td>20 (63)</td>
</tr>
<tr>
<td>African-Caribbean</td>
<td>41 (75)</td>
<td>14 (25)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (54)</td>
<td>17 (46)</td>
<td>...</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>116 (63)</td>
<td>68 (37)</td>
<td>30 (75)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>54 (48)</td>
<td>58 (52)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>33 (41)</td>
<td>47 (59)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>...</td>
<td>...</td>
<td>27.5 (26.4–28.6)</td>
</tr>
<tr>
<td>Duration of diabetes, y, mean (95% CI)</td>
<td>5.7 (4.9–6.6)</td>
<td>7.8 (6.6–9.0)</td>
<td>...</td>
</tr>
<tr>
<td>Duration of follow-up, y, mean (95% CI)</td>
<td>12.6 (12.4–12.7)</td>
<td>6.6 (6.1–7.1)</td>
<td>13.1 (12.9–13.2)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>140 (137–144)</td>
<td>150 (147–154)</td>
<td>136 (130–143)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>78 (77–80)</td>
<td>79 (77–81)</td>
<td>79 (76–83)</td>
</tr>
<tr>
<td>BP treated, n (%)</td>
<td>59 (27.1)</td>
<td>59 (31.8)</td>
<td>12 (32.4)</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>10.4 (10.0–10.8)</td>
<td>13.0 (12.4–13.6)</td>
<td>9.8 (9.1–10.5)</td>
</tr>
<tr>
<td>IHD on Minnesota coding, n (%)</td>
<td>4 (2.8)</td>
<td>21 (15.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Includes 17 community controls with known Type 2 diabetes.
†Includes categories of impaired fasting and impaired glucose tolerance and newly detected diabetes.
ANOVA, alive vs died: §P<0.0001; †P<0.05; ||P<0.01.
Progressive atheromatous disease, including declining aortic elastin quality and content, \(^{23}\) leads to increasing aortic stiffness, detectable as increasing PWV, which together define arterial aging. Notable is the decline in arterial wall quality over a lifetime; the propensity to arterial disease may be initiated in utero. \(^{12,24}\) This long-term perspective includes tracking of BP (and likely PWV) throughout childhood, together with other risk factors. \(^{22}\) Tracking indicates the average tendency for individuals to stay in or close to the original centiles of a risk factor when first measured, whether soon after birth, in childhood, or as an adult. Intergenerational (not necessarily genetic) transfer of risk also seems to occur, \(^{25}\) although clearly some genetic predisposition is established, as in Marfan syndrome. Our results are compatible with glycosylated protein end products \(^{26}\) related to mild hyperglycemia likely promoting arterial stiffness well before an individual meets current criteria of overt diabetes. This is shown by the progressive increase in PWV at baseline between GT categories (Table 2), distinguishing those who died from the survivors. However, glycation alone is unlikely to be a full explanation, because PWV was only marginally different at 10.6 (95% CI 10 to 11), 9.9 (95% CI 9 to 11), and 9.7 (95% CI 9.3 to 10.1) m/s in those still alive with diabetes, glucose intolerance, and normoglycemia, respectively. Glucose tolerance category remained highly significant in the final Cox model (Table 3). These participants likely remain at risk of increased morbidity, not measured here, and mortality over longer follow-up. Detailed characterization of complications and metabolic status (e.g., retinopathy and glycosylated hemoglobin) in diabetes was not possible at baseline. Causes of death in such patients are generally vascular, and independently of age and known diabetes duration, aortic PWV still emerged from this relatively large sample as a powerful independent indicator of risk.

A final point that may surprise North American readers is that African-Caribbean participants had a better overall outcome than other groups. Despite frequent high BP and excess diabetes in African-Caribbeans in Britain, \(^{13,27}\) such a pattern reflects exactly that reported for 20 years in national morbidity \(^{28}\) and mortality statistics in people with \(^{29}\) or without \(^{30}\) diabetes and is similar to that in Caribbean migrants to the United States. \(^{31}\) However, the picture may well change with increasing smoking and dietary fat along with decreasing fruit and vegetable intakes in younger African-Caribbeans in Britain. \(^{32}\) Our data refer only to people of Caribbean origin, and African descent and not to people of direct West African origin, whose dietary and cultural background are quite different. \(^{33}\) These issues are discussed elsewhere. \(^{34}\)

In conclusion, the results suggest that PWV is a powerful independent predictor of later mortality across the entire spectrum of glucose tolerance, with or without overt type 2 diabetes. That PWV displaced systolic BP from the list of other independent risk factors also suggests that it reflects a final common pathway on which BP and other risk factors operate across all ethnic groups. For given levels of BP, some people have stiffer arteries than others. Because PWV measurement is simple and relatively inexpensive, PWV may become a useful clinical method for assessing vascular and general risk of mortality.
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References
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