Sex Differences in Age-Related Stiffening of the Aorta in Subjects With Type 2 Diabetes

Lorenita De Angelis, Sandrine C. Millasseau, Andrew Smith, GianCarlo Viberti, Richard H. Jones, James M. Ritter, Philip J. Chowienczyk

Abstract—Hypertension and type 2 diabetes are associated with increased aortic pulse wave velocity (PWV), a measure of aortic stiffness and a powerful risk factor for cardiovascular events. The association of hypertension with type 2 diabetes may obscure the degree to which diabetes rather than hypertension contributes to an elevated PWV. The objective of this study was to determine whether the presence of type 2 diabetes is associated with an elevated PWV compared with nondiabetic subjects matched for mean arterial blood pressure. PWV was determined by measuring carotid to femoral transit time using applanation tonometry in 186 subjects (104 women) with (n=93) and without (n=93) type 2 diabetes. Diabetic and nondiabetic subjects were matched for age and mean arterial pressure (to ±5 years and 5 mm Hg, respectively). PWV was strongly correlated with age and mean arterial blood pressure (R=0.59 and 0.29 respectively, each P<0.0001). PWV increased significantly more with age in women with diabetes (slope of regression line±SE: 0.19±0.03 m·s⁻¹·year⁻¹) than in nondiabetic women (0.08±0.02 m·s⁻¹·year⁻¹, P<0.01 for difference). In men, however, the age-related increase in PWV was similar in diabetic (0.15±0.03 m·s⁻¹·year⁻¹) and nondiabetic subjects (0.13±0.03 m·s⁻¹·year⁻¹, P=NS). The interaction of diabetic status with age and with sex was significant (P=0.01). Type 2 diabetes is associated with a greater age-related stiffening of the aorta in women compared with men, and this is not explained by hypertension. (Hypertension. 2004;44:67-71.)

Key Words: aorta ■ diabetes ■ elasticity ■ hypertension

Type 2 diabetes is associated with high mortality and morbidity due to coronary artery disease and other atherosclerotic disease. Of the established risk factors for coronary artery disease, hypertension is more prevalent in type 2 diabetes. Its importance is underlined by the findings of the UK Prospective Diabetes Study, which showed a 34% reduction in events because of macrovascular disease (myocardial infarction, sudden death, stroke, and peripheral vascular disease) in the group assigned strict blood pressure reduction in events because of macrovascular disease (myocardial infarction, sudden death, stroke, and peripheral vascular disease) in the group assigned strict blood pressure control (mean blood pressure: 144/82 mm Hg) compared with the group assigned to less strict control (154/87 mm Hg). However, hypertension and other established risk factors do not completely account for the excess mortality in type 2 diabetes. Type 2 diabetes negates the protective effects of female sex and confers greater relative risk in women compared with men. A number of studies have identified abnormalities of arterial stiffness in subjects with diabetes, and it has recently been recognized that aortic stiffness measured by pulse wave velocity (PWV) is highly predictive of cardiovascular mortality in subjects with type 2 diabetes. Aortic PWV also predicts cardiovascular mortality in nondiabetic hypertensive subjects. The importance of PWV may relate both to its association with atherosclerotic changes within the vascular wall and to adverse hemodynamic effects including increased pulse pressure and left ventricular afterload and impaired coronary perfusion. In both nondiabetic and diabetic subjects PWV is strongly associated with age and blood pressure. In patients with type 1 diabetes, PWV is higher (compared with nondiabetic controls) in women but not in men. Because of the high prevalence of hypertension in type 2 diabetes, it is not certain to what degree diabetes per se contributes to an elevated PWV or whether associated hypertension accounts for the elevated PWV observed in subjects with diabetes. The purpose of the present study was to examine whether the presence of type 2 diabetes is associated with an elevated aortic PWV compared with nondiabetic subjects matched for age and mean arterial blood pressure (MAP) and to examine any sex differences in PWV.

Methods

The study was approved by the Research Ethics Committee of Guy’s and St Thomas’ Hospital, and all subjects gave written informed consent. Subjects were consecutively recruited from the Diabetic Clinic at Guy’s and St Thomas’ Hospital, London, and control nondiabetic subjects were recruited over the same time period from the Hypertension Clinic and from the local community. Diabetes was
defined according to the American Diabetes Association criteria (fasting plasma glucose >7 mmol/L or use of hypoglycemic medication). The majority of subjects with diabetes (57/93, 61%) were hypertensive as defined by the International Society of Hypertension (antihypertensive treatment or blood pressure >140 mm Hg systolic and/or >90 mm Hg diastolic on >2 occasions). Patients with clinical evidence of coronary artery disease, cerebrovascular disease, peripheral vascular disease, or renal impairment (creatinine >140 μmol/L) were excluded. Diabetic and nondiabetic subjects were matched for age (to ±5 years) and MAP to ±5 mm Hg. Subject characteristics are tabulated in the Table. Blood pressure was measured in triplicate by mercury sphygmomanometer after 15 minutes supine. MAP was calculated as diastolic blood pressure plus one third pulse pressure. Aortic PWV was determined from carotid and femoral pressure waveforms obtained noninvasively by applanation tonometry (Millar tonometer, Millar Instruments) using the SphygmoCor system (Atcor). Waveforms were referenced to a concurrently recorded ECG and carotid to femoral transit time (ΔT) was computed from the foot to foot time difference between carotid and femoral waveforms. The distance between the surface markings of the sternal notch and femoral artery was used to estimate the path length between the carotid and femoral arteries (L), and PWV computed as L/ΔT. The within-subject standard deviation of PWV assessed using this method in our laboratory is 0.5 m·s⁻¹.

Statistical Analysis

Results are summarized as means±SE. Univariate and multivariate regression analysis was used to confirm associations between PWV and age and between PWV and blood pressure and to explore the relation with other risk factors. A generalized linear model (GLM, SPSS, version 11.0) was used to examine the interaction of diabetic status with age and sex. MAP rather than systolic blood pressure or pulse pressure was used as the covariate in these models, because MAP determines mean transmural pressure. Studies in isolated arteries and in vivo in peripheral arteries suggest that mean transmural pressure is the main determinant of PWV, whereas systolic blood pressure and pulse pressure are influenced as a result of increased aortic stiffness. P<0.05 was taken as statistically significant, and all tests were 2-tailed.

Results

As a result of the study design, subjects with and without diabetes were similar with respect to age and MAP. They were also similar with respect to body mass index (BMI), total cholesterol, systolic and diastolic blood pressure, and pulse pressure. PWV was strongly positively correlated with age, mean blood pressure, systolic blood pressure, and pulse pressure (R=0.59, 0.29, 0.46, and 0.51 respectively, each P<0.0001). PWV was not significantly correlated with BMI, total cholesterol, triglycerides, HDL cholesterol (in a subset of 112 of the subjects in whom HDL was available), or smoking; there was no difference between PWV in subjects treated with different classes of antihypertensive drugs, even

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diabetic</th>
<th>Nondiabetic</th>
<th>Diabetic</th>
<th>Nondiabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53±11</td>
<td>55±12</td>
<td>57±12</td>
<td>56±12</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>31±5</td>
<td>30±6</td>
<td>32±5</td>
<td>30±7</td>
</tr>
<tr>
<td>Smokers</td>
<td>5</td>
<td>7</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.7±2.2</td>
<td>–</td>
<td>8.3±2.0</td>
<td>–</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>8±7</td>
<td>–</td>
<td>8±5</td>
<td>–</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.9±1.3</td>
<td>5.1±0.9</td>
<td>5.0±1.0</td>
<td>5.3±0.9</td>
</tr>
<tr>
<td>Triglycerides, mmol/L*</td>
<td>1.9 (1.1–2.2)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.4 (1.0–2.0)</td>
<td>0.9 (0.7–1.5)</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L†</td>
<td>1.2±0.3</td>
<td>1.7±0.2</td>
<td>1.3±0.2</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>140±22</td>
<td>141±18</td>
<td>141±20</td>
<td>138±18</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>83±8</td>
<td>84±10</td>
<td>80±8</td>
<td>82±9</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>102±11</td>
<td>103±10</td>
<td>100±10</td>
<td>101±10</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>57±18</td>
<td>58±16</td>
<td>61±17</td>
<td>56±16</td>
</tr>
</tbody>
</table>

Drug treatment

<table>
<thead>
<tr>
<th></th>
<th>Sulphonylureas, %</th>
<th>Metformin, %</th>
<th>Insulin, %</th>
<th>ACE-inhibitors/ARB, %</th>
<th>β-Blockers, %</th>
<th>Calcium-channel blockers, %</th>
<th>α-Blockers, %</th>
<th>Diuretics, %</th>
<th>Statins, %</th>
<th>HRT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>38</td>
<td>–</td>
<td>31</td>
<td>41</td>
<td>8</td>
<td>15</td>
<td>10</td>
<td>18</td>
<td>13</td>
<td>–</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>41</td>
<td>23</td>
<td>26</td>
<td>14</td>
<td>42</td>
<td>22</td>
<td>9</td>
</tr>
</tbody>
</table>

Data are means±SD.

ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HRT, hormone replacement therapy.

*Values are medians (interquartile range).
†Measured in a subset of 112 subjects.
when corrected for age and blood pressure. In a multivariate model, age, MAP, and diabetic status were independently correlated with PWV (each $P < 0.0001$) but other risk factors were not. There was a significant interaction between diabetic status and sex ($P = 0.01$) such that the increased PWV in diabetic subjects was because of increased PWV in women with diabetes (Figure 1). This sex difference in the impact of diabetes on PWV was further attributable to differences in the age-related increase in PWV (Figure 2). In men, PWV was similar in diabetic and nondiabetic subjects and increased with age to similar degree in subjects with and without diabetes (slope of regression line $\pm SE$: $0.15 \pm 0.03$ m $\cdot$ s$^{-1}$ $\cdot$ year$^{-1}$ versus $0.13 \pm 0.03$ m $\cdot$ s$^{-1}$ $\cdot$ year$^{-1}$, $P = NS$ for difference in slope of regression lines). In women, PWV was significantly greater and increased significantly more with age in subjects with diabetes compared with subjects without diabetes ($0.19 \pm 0.03$ m $\cdot$ s$^{-1}$ $\cdot$ year$^{-1}$ versus $0.08 \pm 0.02$ m $\cdot$ s$^{-1}$ $\cdot$ year$^{-1}$, $P < 0.01$ for difference in slope of regression lines). The difference between the slopes of the regression lines relating PWV to age in subjects with and without diabetes was greater in women than in men ($P = 0.01$). In women but not in men with diabetes, PWV was significantly correlated with duration of diabetes ($P < 0.0001$) and, in combination with age and MAP, this accounted for 64% of the variability in PWV. These conclusions regarding the difference in the relationship of PWV to age in women with and without diabetes were not altered when PWV was corrected for total cholesterol, triglycerides, HDL cholesterol, smoking, and antihypertensive drug treatment. Pulse pressure was significantly correlated with PWV ($R = 0.46$ and $R = 0.56$, for subjects with and without diabetes respectively, each $P < 0.0001$, Figure 3), but the relationship between pulse pressure and age was similar in all groups (Figure 2).

Discussion

Aortic PWV has been reported as elevated in subjects with type 2 diabetes compared with nondiabetic subjects. However, because of the high prevalence of hypertension associated with type 2 diabetes, it is difficult to be certain to what degree diabetes rather than hypertension contributes to the elevated PWV seen in subjects with type 2 diabetes. The main findings of the present study are that, when subjects are matched for blood pressure: (1) PWV is similar in men with and without type 2 diabetes; (2) the age-related increase in PWV is similar in men with and without diabetes; whereas (3) PWV is greater in women with diabetes compared with women without diabetes and (4) the age-related increase in PWV is greater in diabetic than in nondiabetic women. Thus, in men, the presence of type 2 diabetes is not necessarily responsible for an increase in PWV over and above that due to concomitant hypertension, but, in women, type 2 diabetes is associated with an accelerated age-related increase in PWV above that expected from the level of blood pressure. These findings are consistent with the observation that, in nondiabetic subjects, stiffness of the common carotid artery is
correlated with insulin resistance in women but not in men.\textsuperscript{26} In the ARIC study, the correlation of glucose and insulin with stiffness of the carotid artery also tended to be higher in women than in men.\textsuperscript{27} Our findings are also consistent with observations in type 1 diabetes where stiffness of the common carotid artery and aorta is increased in women but not in men and there is a correlation with the duration of diabetes.\textsuperscript{21,28} The similarity of PWV in men with and without diabetes but with similar blood pressure suggests that, in men with diabetes, hypertension is the major contributor to increased PWV. The presence of diabetes imposes a greater risk of cardiovascular events in women compared with men.,\textsuperscript{3–7} and the present results are consistent with increased relative risk in women compared with men with diabetes.

Our study did not address possible mechanisms by which diabetes could accelerate age-related stiffening of the aorta in women but not in men. Estrogen affects connective tissue structure through a variety of mechanisms,\textsuperscript{29} and, in postmenopausal women, hormone replacement therapy is associated with reduced arterial stiffness in nondiabetic postmenopausal women\textsuperscript{30,31} but not in postmenopausal women with diabetes.\textsuperscript{32} It is, therefore, possible that diabetes reverses or negates beneficial effects of estrogen on aortic stiffness. Changes in the type or structure of elastin and/or collagen, particularly the formation of cross links through nonenzymatic glycosylation of proteins\textsuperscript{33} could also have a role. Although no relationship was found in our study between glycemic control as reflected by HbA1c levels and aortic PWV we found a strong independent relation between PWV and duration of diabetes in women. It is unlikely that metabolic factors other than diabetes played a role in determining the present findings. We found no significant relationship of PWV with total cholesterol, triglycerides, or HDL-cholesterol. Although positive and negative associations of aortic stiffness with cholesterol have been reported using different methods,\textsuperscript{34} most studies using PWV have shown no correlation with total cholesterol.\textsuperscript{17,18,34} A notable exception is in young subjects with familial hypercholesterolaemia, where a negative correlation has been observed.\textsuperscript{35} The present findings are in line with a recent large population-based study (n=993) by Amar et al.\textsuperscript{36} These investigators found no significant relationship between PWV and total cholesterol in untreated subjects and only a weak relationship with apolipoprotein B in subjects treated for cardiovascular risk factors. Furthermore, no correlation was seen between PWV and the various components of the metabolic syndrome, including BMI, fasting glucose, insulin, triglycerides, and HDL-cholesterol. The lack of correlation of PWV with smoking in the present study is also consistent with previous findings.\textsuperscript{36,37}

The importance of PWV is thought to relate not only to its association with structural changes within the vascular wall but also to adverse hemodynamic effects. These include an increase in systolic blood pressure and pulse pressure and, hence, an increase in dynamic left ventricular load. Brachial artery pulse pressure is more closely predictive of mortality than systolic or diastolic blood pressure in older patients in the Framingham cohort\textsuperscript{38} and in patients with type 2 diabetes.\textsuperscript{39} In the present study, brachial systolic blood pressure and brachial pulse pressure were similar in all subject groups, yet PWV was higher in women with diabetes compared with nondiabetic control women. This implies that brachial pulse pressure has limitations as a measure of aortic stiffness and may not detect the accelerated age-related increase in aortic stiffness seen in women with type 2 diabetes. Brachial pulse pressure does not necessarily equate to central pulse pressure (because of peripheral amplification\textsuperscript{16}), and it is possible that central pulse pressure is more closely related to PWV. Peripheral amplification is, however, less marked in older subjects\textsuperscript{40} and therefore the similarity of brachial pulse pressure in older diabetic and nondiabetic women suggests that central blood pressure is unlikely to differ between these groups in our study. Factors other than aortic stiffness, such as stroke volume and peripheral resistance, influence pulse pressure\textsuperscript{24} and may account for the limited correlation that we observed between pulse pressure and PWV. This accounted for only 26% of the variability in pulse pressure and is compatible with a disassociation between effects of aging on PWV and pulse pressure. An elevated PWV in women with diabetes may be associated with adverse hemodynamic effects other than increased pulse pressure such as earlier return of pressure wave reflection. This will alter the profile of the aortic pressure waveform and hence may adversely affect coronary hemodynamics, particularly coronary perfusion pressure.

Our study had a number of limitations. The limited sample size and the fact that 28% of diabetic subjects were treated with insulin means that the results cannot be generalized to all subjects with diabetes. We cannot exclude a type II error with respect to a small difference between PWV (or the slope of the PWV versus age relationship) in men with and without diabetes but this would not influence the positive findings with respect to the gender difference. It is possible that differences in the distribution of antihypertensive drugs may have influenced the results. However, we found no difference between PWV with respect to groups treated with different drugs, and previous studies have demonstrated no significant difference in long-term effects of different classes of antihypertensive drugs.\textsuperscript{41} Finally, the operator was not blind to diabetic status, introducing the theoretical possibility of bias. Measurements of PWV were, however, performed using an automatic system minimizing this possibility. In conclusion, in subjects with type 2 diabetes on treatment, diabetes is associated with a greater age-related stiffening of the aorta in women compared with men and this is not explained by hypertension.

References


Sex Differences in Age-Related Stiffening of the Aorta in Subjects With Type 2 Diabetes
Lorenita De Angelis, Sandrine C. Millasseau, Andrew Smith, GianCarlo Viberti, Richard H.
Jones, James M. Ritter and Philip J. Chowienczyk

Hypertension. 2004;44:67-71; originally published online May 17, 2004;
doi: 10.1161/01.HYP.0000130482.81883.fd
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/44/1/67

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/