Increased augmentation index and systolic stress in type 1 diabetes mellitus

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Summary

Type 1 diabetes mellitus is associated with endothelial dysfunction and increased arterial stiffness, both of which may contribute to the excess cardiovascular mortality in such patients. Arterial stiffening increases pulse wave velocity and wave reflection, which augments central systolic pressure and stress. Using the non-invasive technique of pulse wave analysis, we investigated aortic augmentation and central pressure in 35 patients with type 1 diabetes and 35 matched controls. Peripheral pulse waveforms were recorded from the radial artery. Central aortic waveforms were then generated, and augmentation index (AIx), ascending aortic pressure and tension time index (TTI), a measure of systolic load, were calculated. Peripheral and central blood pressure did not differ between the two groups. AIx was significantly elevated in the diabetic patients compared with controls (7.1 ± 1.6% vs. 0.4 ± 2.0%; p = 0.01), as was the TTI (2307 ± 51 mmHg.s.min⁻¹ vs. 2010 ± 61 mmHg.s.min⁻¹; p < 0.001). Estimated pulse wave velocity was also higher in the diabetic group. Type 1 diabetes is associated with an increased AIx and rate of wave travel, indicating enhanced wave reflection and increased systemic arterial stiffness, and elevation of the TTI. Such haemodynamic effects may contribute to the increased left ventricular mass and risk of cardiovascular disease associated with type 1 diabetes mellitus.

Introduction

The single most common cause of death amongst diabetic patients is atherosclerotic cardiovascular disease.¹ ² The risk of developing specific complications of diabetes mellitus (e.g. retinopathy, nephropathy, neuropathy) is clearly associated with the degree and duration of hyperglycaemia, but the relationship between diabetes and macrovascular disease is poorly understood.¹ Indeed, intensive glycaemic control does not reduce cardiovascular mortality in patients with either type 1 or type 2 diabetes mellitus.³ ⁴ Why diabetes should promote atherogenesis remains unclear, although this may be related to the association of diabetes with other risk factors including hyperlipidaemia and hypertension in the ‘metabolic syndrome’.⁵

Increased arterial stiffness is a feature of both type 1 and 2 diabetes, and can be detected using a variety of techniques.⁶ It occurs early in the course of diabetes and is not related to the presence of atheroma.⁷ ⁸ Indeed, disruption of normal endothelial function may be partly responsible for arterial stiffening in diabetes.⁹ Mounting evidence suggests that arterial stiffness is not only an important additional and independent risk factor for cardiovascular...
disease, but that it may also have a role in the process of atherosclerosis itself.\textsuperscript{6,9} Therefore, assessment of arterial stiffness may improve risk stratification.

Current methods of assessing arterial stiffness, such as measurement of pulse wave velocity (PWV) or the use of ultrasound-derived indices, only provide information about compliance within a specific artery or arterial segment, and tend to be time-consuming and/or operator-dependent.\textsuperscript{10} However, the technique of pulse wave analysis (PWA) provides information about systemic arterial stiffness. Previously, PWA was limited to peripheral pressure waveforms,\textsuperscript{11} but further development of the technique by O'Rourke and colleagues has made non-invasive analysis of central pressure waves possible.\textsuperscript{12} From these waveforms central arterial pressure—and various other haemodynamic parameters including augmentation index (AIX) and the tension time index (TTI), a measure of systolic stress and, therefore, of left ventricular workload—can also be determined. The aim of the present study was to test the hypothesis that type 1 diabetes is associated with increased systemic arterial stiffness and elevated central systolic stress, in a group of otherwise healthy younger adults with diabetes and normal peripheral blood pressure.

\section*{Methods}

\subsection*{Patients}

Thirty-five patients who had had type 1 diabetes for a minimum of 10 years were recruited from the local adult diabetic clinic at the Western General Hospital, Edinburgh. Concurrently, non-diabetic controls were recruited from a community database of volunteers held at the Western General Hospital and selected such that, as a group, their distribution of age, sex and weight closely matched the patient group. Approval for the study was obtained from the local Research Ethics Committee, and informed consent obtained from each participant. The investigation conformed to the principles outlined in the Declaration of Helsinki. All subjects were free from clinical evidence of cardiovascular disease at entry, and all diabetic subjects were receiving insulin at the time of the study. Subjects with clear evidence of hypertension (blood pressure $>160/100$ mmHg) or hypercholesterolaemia (total serum cholesterol $>6.5$ mmol/l), or those receiving any medication other than insulin, were excluded. Cigarette smokers were allowed to participate.

\subsection*{Peripheral blood pressure measurement}

Blood pressure was recorded in duplicate in the dominant arm using a validated oscillometric technique (HEM-705CP; Omron).\textsuperscript{13} Values were reported as the mean of the two readings, and peripheral mean arterial pressure was calculated as the diastolic pressure plus one-third of the pulse pressure.

\subsection*{Pulse wave analysis}

Central pressure waveforms were derived and analysed using the technique of PWA (SCOR; PWV Medical), as previously described.\textsuperscript{14} In brief, a high-fidelity micromanometer (SPC-301; Millar Instruments) was used, by experienced operators (DFR), to flatten, but not occlude, the radial artery of the dominant arm using gentle pressure with the wrist slightly extended and supported on a pillow. Data were collected directly into a portable microcomputer and, after 20 sequential waveforms had been acquired, an averaged peripheral waveform, and a corresponding central waveform, were generated. Recordings were excluded if the systolic or diastolic variability of the waveforms exceeded 5\%, or the amplitude of the waveform, a measure of the quality of the tracing, was $<100$ mV. The central waveform was then analysed using the system software to determine AIX, central pressure, ejection duration, the timing of wave reflection and heart rate. AIX represents the difference between the first and second peaks of the central pressure waveform, in systole, expressed as a percentage of the pulse pressure, and is a measure of systemic arterial stiffness and wave reflection (Figure 1). The TTI, the area under the systolic portion of the pressure waveform per min (the systolic pressure-time integral), an index of systolic stress, and the diastolic pressure-time integral were also determined (Figure 1).\textsuperscript{15,16} From these variables the subendocardial viability index (diastolic pressure-time integral divided by TTI) was calculated.\textsuperscript{17} This provides a useful measure of the relationship between subepicardial and subendocardial blood flow, and thus the potential for myocardial ischaemia.\textsuperscript{18} Ejection duration was calculated as the time from the foot of the pressure wave to the incisura. The aortic pulse wave velocity was estimated by calculating the time between the foot of the pressure wave and the inflection point, which provides a measure of the timing of the reflected wave, as described previously.\textsuperscript{19,20} All measurements were made in duplicate.

\subsection*{Protocol}

Diabetic patients were studied whilst attending a late-afternoon diabetic clinic at the Western General Hospital, and controls were studied in the Clinical Research Centre. All were subject to an identical protocol. After 5 min seated rest in a quiet room, brachial artery pressure was determined and then
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A further two had evidence of background retinopathy and one evidence of proliferative retinopathy alone. Serum triglycerides and glucose were significantly elevated in the diabetic group compared with the control group. However, total serum cholesterol did not differ significantly between the two groups (Table 1).

The peripheral systolic pressure did not differ significantly between diabetic patients (126 ± 2 mmHg; 95% CI 98–153 mmHg) and controls (123 ± 2 mmHg; 95% CI 97–150 mmHg). Peripheral diastolic pressure was also similar between the two groups: diabetics 77 ± 2 mmHg (95% CI 59–95 mmHg), controls 77 ± 1 mmHg (95% CI 64–90 mmHg). Table 2 summarizes the results of the study, and Figure 2 shows representative ascending aortic waveforms, determined by PWA, from the two groups. Ascending aortic pressure, assessed by PWA, was not significantly different between the two groups, and neither was the ratio of peripheral to central pulse pressure. However, AIx, heart rate, and TTI were significantly higher amongst the diabetic patients compared with controls, and ejection duration and subendocardial viability index significantly lower. There was no difference in the diastolic pressure time integral between the two groups. In addition, the reflected pressure wave returned to the ascending aorta significantly earlier in the diabetic subjects compared with controls.

To investigate the factors influencing AIx in the diabetic patients, a multiple regression model was constructed with AIx as the dependent variable. Duration of diabetes, height, sex, heart rate, peripheral mean arterial pressure, HbA1c, and serum triglycerides were entered into the model. Age was not included, due to the close relationship between age and duration of diabetes, and the relatively small number of subjects used to generate the model. Duration of diabetes, short stature, low heart rate and serum triglycerides correlated positively with AIx, but there was no significant association between the other variables and AIx (Table 3). The regression model accounted for 57% of the variance in AIx between the diabetic subjects.

Results

Thirty-five patients with type 1 diabetes, aged 30 ± 7 years (mean ± SD, range 19–45), and 35 controls, aged 30 ± 8 years (mean ± SD, range 18–50), were entered into the study. There was no significant difference in age, sex, height, weight, BMI, or the number of smokers between the two groups (Table 1). Amongst the diabetic group, the average HbA1c was 8.8 ± 0.2% (reference range 5.0–6.5%) and duration of diabetes was 18 ± 1 years (range 10–32). One diabetic patient had microalbuminuria and proliferative retinopathy, a further two had evidence of background retinopathy and one evidence of proliferative retinopathy alone. Serum triglycerides and glucose were significantly elevated in the diabetic group compared with the control group. However, total serum cholesterol did not differ significantly between the two groups (Table 1).

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Discussion

Our main finding, using analysis of the derived central pressure waveform, was that AIx and TTI were elevated in the diabetic group compared with controls. AIx provides a measure of the contribution made by the reflected wave to ascending aortic pressure. However, since the amplitude and velocity of the reflected wave are dependent upon arterial stiffness, AIx also acts as a measure of
Table 1  Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Male (n)</th>
<th>Age (years)</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>Smokers (n)</th>
<th>PSBP (mmHg)</th>
<th>PDBP (mmHg)</th>
<th>PMAP (mmHg)</th>
<th>PPP (mmHg)</th>
<th>TC (mmol/l)</th>
<th>TG (mmol/l)</th>
<th>Glucose (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>35</td>
<td>14</td>
<td>30 ± 1</td>
<td>1.74 ± 0.02</td>
<td>75.0 ± 2.0</td>
<td>24.7 ± 0.6</td>
<td>8</td>
<td>123 ± 2</td>
<td>77 ± 1</td>
<td>93 ± 1</td>
<td>46 ± 2</td>
<td>4.5 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>4.4 ± 0.1</td>
</tr>
<tr>
<td>DM</td>
<td>35</td>
<td>14</td>
<td>30 ± 1</td>
<td>1.71 ± 0.02</td>
<td>72.3 ± 2.2</td>
<td>24.5 ± 0.5</td>
<td>8</td>
<td>126 ± 2</td>
<td>77 ± 2</td>
<td>94 ± 2</td>
<td>49 ± 2</td>
<td>4.5 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>8.3 ± 0.9</td>
</tr>
</tbody>
</table>

All values are means ± SEM. *p < 0.05, **p < 0.001 compared with controls. Unless otherwise stated p > 0.05. DM, diabetic subjects; BMI, body mass index; PSBP, peripheral systolic blood pressure; PDBP, peripheral diastolic blood pressure; PMAP, peripheral mean arterial pressure; PPP, peripheral pulse pressure; TC, total cholesterol; TG, triglycerides.

Table 2  Haemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Alx (%), TTI (mmHg.s.min⁻¹), DPTI (mmHg.s.min⁻¹), SVI (%), HR (min⁻¹), CSBP (mmHg), CDBP (mmHg), CPP (mmHg), PPP:CPR (ratio), ED (ms), TR (ms)</th>
</tr>
</thead>
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<tr>
<td>Controls</td>
<td>0.4 ± 2.0, 2010 ± 61, 3273 ± 56, 167 ± 5, 73 ± 2, 107 ± 2, 79 ± 1, 28 ± 1, 1.7 ± 0.1, 298 ± 5, 155 ± 3</td>
</tr>
<tr>
<td>DM</td>
<td>7.1 ± 1.6, 2307 ± 51, 3295 ± 76, 145 ± 5, 82 ± 2, 110 ± 2, 80 ± 2, 30 ± 1, 1.6 ± 0.1, 277 ± 4, 142 ± 2</td>
</tr>
<tr>
<td>p</td>
<td>0.011, &lt;0.001, 0.8, 0.003, 0.003, 0.3, 0.8, 0.1, 0.5, 0.001, 0.003</td>
</tr>
</tbody>
</table>

All values are means ± SEM. p values were determined using unpaired 2-tailed Student’s t-tests. Alx, augmentation index; TTI, tension time index; DPTI, diastolic pressure time integral; SVI, subendocardial viability index; CSBP, central systolic blood pressure; CDBP, central diastolic blood pressure; CPP, central pulse pressure; PPP, peripheral pulse pressure; ED, ejection duration; TR, timing of the reflected pressure wave.
Figure 2. Representative ascending aortic waveforms. Note the prominence of the second systolic peak in the diabetic group, compared with the control group.

Table 3  Regression analysis for the diabetic subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Regression coefficient ± SE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Years</td>
<td>1.2 ± 2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height</td>
<td>m</td>
<td>-29.5 ± 21.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate</td>
<td>bpm</td>
<td>-3.0 ± 0.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>mmol/l</td>
<td>1.7 ± 0.9</td>
<td>0.049</td>
</tr>
<tr>
<td>PMAP</td>
<td>mmHg</td>
<td>-</td>
<td>0.4</td>
</tr>
<tr>
<td>HbA1c</td>
<td>%</td>
<td>-</td>
<td>0.8</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

Multiple regression analysis for the diabetic subjects (n = 35), with Ax as the dependent variable. R^2 value for the model = 0.566, p < 0.001. PMAP, peripheral mean arterial pressure.

...systemic arterial stiffness. To evaluate large-artery stiffness more directly, we also calculated the timing of the reflected pressure wave, which, as previously described, provides an estimate of the aortic PWV and thus aortic stiffness. In keeping with the higher Ax, the reflected pressure wave returned to the ascending aorta sooner in the diabetic subjects, indicating a higher PWV. Taken together, these data imply enhanced wave reflection and increased systemic arterial stiffness in patients with type 1 diabetes mellitus.

A number of variables are known to influence Ax. Indeed, Ax is positively correlated with age and blood pressure, and inversely correlated with height. However, in the present study the two study groups were well matched for age, sex ratio, height, weight and serum cholesterol. Peripheral mean arterial pressure did not differ significantly between the two groups and is, therefore, unlikely to account for the increased Ax of the diabetic group. Ax is also inversely related to heart rate and, as expected, in the present study resting heart rate was higher in the diabetic patients, confirming previous data. Nevertheless, this is not a confounding factor, because such a difference would tend to decrease, rather than increase, Ax, leading to a relative underestimate of arterial stiffness in the diabetic group. Indeed, correcting for the difference in heart rate, using our own data, increases the observed difference in Ax from 6.7% to 10.5%; implying that, if anything, we may have underestimated arterial stiffness amongst subjects with type 1 diabetes.

Despite having a higher Ax, the diabetic subjects did not have a higher central systolic or pulse pressure. Indeed, pressure amplification (the ratio of peripheral to central pulse pressure) did not differ between the two groups. The most likely explanation for this is the relatively young age of the subjects studied and the small sample size. The average Ax in our control group was 0.4%, in keeping with the low mean age of 30 ± 1 years and, in such a relatively young group, arterial stiffening, despite increasing wave reflection and Ax, will not initially increase systolic pressure, although it will alter the shape of the central pressure waveform. However, the TTI was higher in the diabetic group, indicating a larger area under the systolic portion of the pressure-time waveform (systolic pulse-time integral) and, therefore, increased systolic stress. Similar findings have been reported previously and may be explained by both increased arterial stiffness and a higher resting heart rate in the diabetic subjects. Interestingly, TTI appears to be a better predictor of left ventricular hypertrophy than peripheral ambulatory blood pressure and therefore, increased systolic load, resulting, in part, from systemic arterial stiffening may help explain the higher left ventricular mass reported in normotensive type 1 diabetic subjects. However, since we did not assess left
ventricular mass in the present study we cannot directly confirm this.

In contrast, the diastolic pressure-time integral did not differ between the two study groups. This may be explained by a higher average heart rate in the diabetic subjects leading to an increased number of diastolic filling periods per minute, but a decrease in the absolute duration of each one, resulting in no overall change in diastolic pressure-time integral. As a consequence of these haemodynamic alterations, subendocardial viability index was reduced in the diabetic subjects, indicating a greater propensity to myocardial ischaemia.\(^{18}\) Importantly, as in the present study, such haemodynamic changes may not necessarily result in a raised peripheral systolic pressure. This re-emphasizes the importance of assessment of the central waveform.

Our results support previous studies, using peripheral PWA, which demonstrated increased arterial stiffness in patients with type 1 diabetes,\(^{34,35}\) and indicate that similar abnormalities occur in the central waveform. Brooks et al.\(^{27}\) have also reported an increase in AIx in patients with type 1 diabetes compared with a control group, but this difference was only apparent after adjustment for various confounding factors, and, unlike in our study, the two groups were not well-matched for key baseline characteristics known to influence AIx such as height and peripheral blood pressure.

Arterial stiffening has been demonstrated in association with type 1 diabetes by a variety of other methods, including ultrasound.\(^{9}\) Some, but not all studies, have suggested a correlation between arterial stiffness and the degree of glycaemic control, as assessed by HbA\(_{1c}\).\(^{36}\) However, in the present study there was no significant correlation between HbA\(_{1c}\) and AIx in the multiple regression analysis performed for the diabetic group. More recently, the Edinburgh Artery Study Group reported a close relationship between the prevalence of peripheral vascular disease in diabetic patients, and both systolic blood pressure and serum triglycerides.\(^{37}\) Although we were unable to demonstrate any correlation between AIx and peripheral blood pressure in those individuals with diabetes, there was a significant association with serum triglycerides. We deliberately excluded individuals with clinical evidence of macrovascular disease (including peripheral vascular disease), or other cardiovascular risk factors, apart from cigarette smoking, and elected to study a relatively young cohort, which makes it unlikely that atherosclerosis per se explains the increased arterial stiffness in our diabetic group. Indeed, previous studies have reported arterial stiffening in children with diabetes,\(^{11,35,38}\) and in healthy subjects with a family history of diabetes.\(^{39}\)

Stiffening of the arterial tree, whether due to ageing, diabetes or other cardiovascular risk factors, has important haemodynamic consequences, including an increase in the TTI, a predisposition to left ventricular hypertrophy, reduced shear stress, and ultimately a widening of the pulse pressure.\(^{40}\) Such changes occur because of an alteration in the shape of the pressure waveform, and augmentation of central systolic pressure and stress, as shown in the current study. The importance of arterial stiffness is emphasized by the correlation between arterial stiffness and the degree of coronary artery disease at angiography,\(^{41}\) and recent data indicating that pulse pressure, a surrogate marker of arterial stiffness,\(^{42}\) and aortic PWV\(^{43,44}\) are both important independent predictors of cardiovascular events.

In summary, we have confirmed earlier observations that arterial stiffness is increased in patients with type 1 diabetes who do not have clinical evidence of atheromatous disease. In addition, we have extended these earlier findings by demonstrating that systolic stress is increased amongst type 1 diabetic patients compared with matched controls. Increased systolic stress may explain the raised left ventricular mass reported in normotensive subjects with type 1 diabetes mellitus, and contribute to the excess mortality associated with this condition. PWA is to be included in the ASCOT Study,\(^{45}\) a trial of different antihypertensive regimens, the SEARCH Study, which will address the desirable degree of cholesterol reduction, and the European FIELD study of insulin treatment in type 2 diabetes. These studies will address the importance of arterial stiffness as a predictor of risk, and provide data about the effect of treatment on stiffness and outcome. However, at present, no studies are planned to assess the importance of arterial stiffness as a risk predictor in patients with type 1 diabetes mellitus. Clearly, the available evidence would suggest that such a trial is required.

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**References**


