Selective enhancement of sensitivity to endothelin-1 despite normal endothelium-dependent relaxation in subcutaneous resistance arteries isolated from patients with Type I diabetes

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ABSTRACT

Type I diabetes mellitus is associated with abnormal vascular function, but few studies have documented its effects on human resistance arteries. This study aimed to determine whether endothelial cell and smooth muscle cell function was impaired in resistance arteries isolated from patients with this condition. Biopsies of subcutaneous gluteal fat were taken from 12 patients with Type I diabetes (age 32.3 ± 1.9 years; duration of diabetes 13.9 ± 2.5 years) and 12 matched controls (age 31.5 ± 2.2 years). Levels of glycosylated haemoglobin were higher (P < 0.0001) in patients (9.38 ± 0.35 %) than in controls (5.48 ± 0.11 %), but most (11 out of 12) patients showed no evidence of microvascular disease. Small resistance arteries were isolated from the biopsies, and isometric responses to vasoconstrictors and vasodilators were measured in a small-vessel myograph. The magnitude and sensitivity of responses to noradrenaline and potassium were not different in diabetic patients compared with controls. In contrast, the sensitivity (pD2; negative logarithm of the concentration of the vasoconstrictor required to produce 50% of the maximum effect), but not the magnitude, of contraction in response to endothelin-1 in vessels from patients (8.87 ± 0.12) was significantly (P < 0.02) greater than in those from controls (8.40 ± 0.13). Endothelium-dependent (acetylcholine, bradykinin, A23187) and -independent (3'-morpholinosydnonimine) relaxation responses were unaltered in patients with Type I diabetes. These results suggest a selective alteration in receptor activity in the endothelium, and contrast strikingly with the considerable evidence of impaired endothelium-dependent relaxation in Type I diabetes. The present study indicates, therefore, that endothelial cell function is largely maintained in resistance arteries from patients with well controlled Type I diabetes. The increased response to endothelin-1 supports the possibility that more significant abnormalities would be evident in patients with severe microvascular complications.

Key words: endothelium, human resistance arteries, Type I diabetes, vasoconstriction, vasorelaxation.

Abbreviations: ACh, acetylcholine; ET-1, endothelin-1; NA, noradrenaline; pD2, negative logarithm of the concentration of the vasoconstrictor required to produce 50% of the maximum effect; PSS, physiological salt solution; KPSS, PSS in which NaCl has been replaced by an equimolar concentration of KCl; SIN-1, 3’-morpholinosydnonimine.

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INTRODUCTION

There is compelling evidence to indicate that the ability of the endothelium to mediate vascular relaxation is impaired in large conduit arteries from patients and animals with Type I diabetes mellitus [1,2]. Similarly, contractile function may also be altered in these vessels, although the nature of this alteration remains controversial. These abnormalities have serious consequences, as impaired function of conduit arteries has been implicated in the increased risk of atheroma in patients with Type I diabetes [2].

A significant proportion of the morbidity and mortality associated with Type I diabetes results from complications such as retinopathy, nephropathy and neuropathy [3]. There is considerable evidence that, as with atheroma, these microvascular complications are the result of vascular dysfunction [4]. There have been relatively few studies of microvascular function in patients with Type I diabetes, however, and consequently both the nature and the causes of any dysfunction remain controversial [5]. It seems unlikely that Type I diabetes would produce the same pathophysiological changes in conduit and resistance arteries, as it is well established that these vessels are functionally distinct. Receptor populations vary in arteries of different anatomical origin [6] and, perhaps more significantly, the factors that contribute to endothelium-dependent relaxation differ in large compared with small vessels. Endothelium-dependent relaxation is mediated almost exclusively by nitric oxide (NO) in conduit arteries [7], whereas the contribution of a putative endothelium-derived hyperpolarizing factor becomes increasingly significant as the diameter of the vessel diminishes [8].

The few studies of vascular function using resistance arteries isolated from either patients with Type I diabetes [9] or animal models of this condition [10] have suggested impaired endothelium-dependent relaxation. Surprisingly, however, the dysfunction detected in human arteries [9] was specific for responses to acetylcholine (ACh), a conclusion that has been challenged by preliminary data from a more recent study [11]. The impact of Type I diabetes on contractile function in resistance arteries is also controversial: contraction of human resistance arteries appeared to be unchanged or impaired in patients with diabetes [9,11], whereas responses to noradrenaline (NA) were enhanced in mesenteric arteries from diabetic rats [10]. The present investigation aimed to clarify the impact of Type I diabetes on resistance artery function by studying both contractile and relaxant responses in resistance arteries taken from patients with this condition. Endothelin-1 (ET-1) was included in the investigation, as this potent vasoconstrictor, which can be released from damaged endothelial cells, has been implicated in the pathogenesis of vascular complications in Type I diabetes [12], but its effects have not been studied previously in resistance arteries from patients with this condition.

METHODS

Subjects

Twelve patients (seven male, five female) with Type I diabetes, and 12 age- and sex-matched healthy controls, with no history of diabetes, were recruited for the study. Patients were selected on the basis that they had no history of cardiovascular disease and were taking no major drugs other than insulin. Controls were recruited from the general population and had no history of cardiovascular disease or diabetes. Six patients and four controls were smokers, and three patients were also taking oral contraceptives. All patients provided written consent, and the study protocol was approved by the Lothian Research Ethics Committee. For each subject, blood pressure was measured three times (sitting, left arm; sitting, right arm; standing, left arm) to obtain mean values for systolic and diastolic pressure. The presence of retinopathy was assessed using dilated pupil ophthalmoscopy, while neuropathy was tested by measuring vibration in the toe. The presence of microalbuminuria was assessed in patients by calculation of the albumin/creatinine ratio.

Preparation of arteries

A biopsy of skin and subcutaneous fat (approx. 2 cm long × 1 cm × 1 cm) was taken from the gluteal region under local anaesthesia (5 ml of 2% lignocaine hydrochloride; Astra, King’s Langley, Herts., U.K.). Resistance arteries were dissected from the biopsy and mounted as ring preparations on two 40 μm stainless steel wires in a small-vessel myograph (J. P. Trading, Aarhus, Denmark). One of these wires was fixed to a movable micrometer, while the other was attached to an isometric force transducer. The vessels were immersed in physiological salt solution [PSS; composition (mM): NaCl, 119; KCl, 4.7; CaCl₂, 2.5; MgSO₄·7H₂O, 1.17; KH₂PO₄, 1.18; NaHCO₃, 25; K₂EDTA, 0.026; d-glucose, 5.5], which was maintained at 37 °C and perfused continuously with 95% O₂/5% CO₂. The length of each vessel segment was measured using a travelling micrometer eyepiece attached to a light microscope. Following an equilibration period (30 min), the length–tension characteristics were determined by subjecting each vessel to incremental stretches and applying the LaPlace equation as described previously [13]. This calculates the internal diameter (l₁₀₀) that the vessel would have in vivo when relaxed and subjected to a pressure of 13.3 kPa (100 mmHg). The vessels were then stretched to their optimum resting setting (0.9l₁₀₀) [10].
independent nitric oxide donor 3
[64x159]«
[64x171]ionophore A23187 (1 nM–3
[64x279]+
[64x279]receptor-dependent, endothelium-dependent calcium
[64x147]l
[64x147]mine (SIN-1; 1 nM–30
[64x231]submaximal concentration of NA (3
[64x243]were obtained following contraction of the artery with a
[64x255]the vascular smooth muscle. Responses to vasodilators
[64x267]cause receptor-independent contraction by depolarizing
[64x399}]K
[150x56]solution (KPSS; [a 125 mM K
[160x147]M). Cumulative
[153x400]+
[153x400]}
[170x103]experiments,

Table 1 Characteristics of control subjects and patients with Type I diabetes

Values are mean ± S.E.M. All values are for 12 observations, except when indicated otherwise by n values quoted in parentheses, and were compared using Student's unpaired t-test.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Diabetic patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.5 ± 2.2</td>
<td>32.3 ± 1.9</td>
<td>0.78</td>
</tr>
<tr>
<td>Duration of Type I diabetes (years)</td>
<td>—</td>
<td>13.9 ± 2.5</td>
<td>—</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>122 ± 3 (10)</td>
<td>121 ± 3</td>
<td>0.78</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79 ± 2 (10)</td>
<td>76 ± 2</td>
<td>0.51</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.85 ± 0.07 (11)</td>
<td>13.84 ± 1.04 (10)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Glycosylated haemoglobin (%)</td>
<td>5.48 ± 0.11</td>
<td>9.38 ± 0.35</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>4.55 ± 0.36 (11)</td>
<td>5.25 ± 0.28</td>
<td>0.13</td>
</tr>
<tr>
<td>Serum triglycerol (mmol/l)</td>
<td>1.17 ± 0.19 (11)</td>
<td>1.72 ± 0.30</td>
<td>0.22</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>75.6 ± 3.6 (11)</td>
<td>68.8 ± 2.4</td>
<td>0.12</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>42.08 ± 0.63</td>
<td>38.4 ± 3.3</td>
<td>0.38</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>3.98 ± 0.34</td>
<td>4.23 ± 0.19</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Protocol
Arterial rings were equilibrated at their optimum resting setting for 30 min, and were then subjected to a standard start procedure. This consisted of five consecutive applications of the vasoconstrictors NA and potassium (K⁺). After each exposure, the artery was washed several times with PSS and the responses were allowed to return to baseline. The first, second and fifth contractions were produced using NA/K⁺ [a 125 mM K⁺ solution (KPSS; made by equimolar substitution of KCl for NaCl in PSS) containing 10 μM NA]. The third contraction was produced using KPSS, while the fourth was obtained using 10 μM NA. This procedure confirmed the viability of each artery, and demonstrated the reproducibility of the vasoconstrictor responses.

Cumulative concentration–response curves were obtained using the receptor-dependent vasoconstrictors NA (1 nM–30 μM) and ET-1 (0.01 nM–0.3 μM) and using elevated K⁺ concentrations (10–125 mM), which cause receptor-independent contraction by depolarizing the vascular smooth muscle. Responses to vasodilators were obtained following contraction of the artery with a submaximal concentration of NA (3 μM). Cumulative concentration–response curves were also obtained for the receptor-dependent, endothelium-dependent agonists ACh (1 nM–30 μM) and bradykinin (0.1 nM–3 μM), the receptor-independent, endothelium-dependent calcium ionophore A23187 (1 nM–3 μM) and the endothelium-independent nitric oxide donor 3’-morpholinosydnonimine (SIN-1; 1 nM–30 μM).

Statistics
All values shown are mean ± S.E.M. for n experiments, where n represents the number of subjects. Contractile responses are expressed in mN/mm, and also as a percentage of the maximum response to the third stimulation with NA/K⁺ (% NA/K⁺). Relaxation is expressed as a percentage of the precontraction with NA. Sensitivity values were obtained by fitting the Hill equation to the data using curve-fitting software (Fig P; Biosoft, Cambridge, U.K.). These are expressed as the negative logarithm of the concentration of the agonist required to produce 50% of the maximum effect (pD₂ for vasoconstrictors; –log IC₅₀ for vasodilators). Comparisons of maximum responses and sensitivities were achieved using Student’s unpaired t-test, and significance was assumed when P < 0.05.

Drugs
All salts were obtained from BDH (Poole, Dorset, U.K.). NA hydrochloride, ACh chloride, bradykinin acetate salt and A23187 free acid were obtained from Sigma (Poole, Dorset, U.K.). ET-1 and SIN-1 were obtained from Alexis (Nottingham, U.K.). Stock solutions (1 mM) were prepared in distilled water, except for ET-1, which was initially dissolved in 50% (v/v) methanol to give a 10 μM stock solution, and A23187, which was initially dissolved in ethanol to give a 0.1 mM stock solution. Subsequent dilutions were made in distilled water, and final bath concentrations of methanol and ethanol did not exceed 1.5% and 3% (v/v) respectively. Stock solutions were frozen as 1 ml aliquots at –20 °C and thawed as required. Any residual solution was discarded at the end of the experiment.

RESULTS
The characteristics of the subjects recruited for this investigation are given in Table 1. Eleven of the patients with diabetes had no history of macrovascular or microvascular complications, nor any evidence of retinopathy or neuropathy. One patient had proliferative retinopathy, but no elevation of the albumin/creatinine...
C. A. McIntyre and others

Figure 1 Cumulative concentration–response curves to the vasoconstrictor agonists (a) ET-1, (b) NA and (c) KCl obtained using arteries from control subjects (■) and patients with Type I diabetes (□).

Values are means ± S.E.M. (n = 12).

Table 2 Maximum contractions of arteries from patients with Type I diabetes and controls in response to NA, potassium (K⁺) and ET-1

Results are expressed as a percentage of the maximum response to NA/K⁺. All values are means ± S.E.M. (n = 12), and were compared using Student’s unpaired t-test.

<table>
<thead>
<tr>
<th>Vasoconstrictor</th>
<th>Controls</th>
<th>Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>115.4 ± 3.2</td>
<td>108.3 ± 2.0</td>
<td>0.09</td>
</tr>
<tr>
<td>K⁺</td>
<td>71.9 ± 6.7</td>
<td>84.1 ± 7.8</td>
<td>0.22</td>
</tr>
<tr>
<td>ET-1</td>
<td>103.7 ± 5.9</td>
<td>104.5 ± 6.03</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Gluteal resistance arteries isolated from patients and controls were of a similar size (mean internal diameter 224 ± 22 μm and 195 ± 9 μm respectively; P = 0.24). All arteries produced concentration-dependent contractions in response to the three vasoconstrictors. The sensitivity (pD₅₀) to ET-1 (Figure 1a) in arteries from patients with diabetes (8.87 ± 0.12) was significantly (P = 0.02) greater than that in arteries from controls (8.40 ± 0.12), but the maximum contractions were similar (3.85 ± 0.66 and 3.39 ± 0.39 mN/mm respectively; P = 0.56). In contrast, sensitivities (pD₅₀ values) of arteries from patients to NA (6.73 ± 0.11) and KPSS (1.50 ± 0.04) were similar to those of arteries from controls [6.98 ± 0.14 (P = 0.19) and 1.47 ± 0.03 (P = 0.55) respectively]. Maximum contractile responses to NA (Figure 1b) and KPSS (Figure 1c) were also similar in patient (4.06 ± 0.71 and 3.26 ± 0.61 mN/mm respectively) and control [2.67 ± 0.47 mN/mm (P = 0.46) and 3.39 ± 0.39 mN/mm (P = 0.56) respectively] arteries. No differences were detected between control and diabetic groups when values for maximum contractions were expressed as a percentage of the maximum contraction in response to NA/K⁺, in order to control for variations in the size of the arterial rings (Table 2).

The four vasodilators used all produced concentration-dependent relaxation in arteries precontracted with a submaximal concentration of NA. Responses to vasodilators in arteries from the three diabetic patients taking oral contraceptives were not different from those obtained in arteries from the rest of the patient group. Arteries from control subjects produced near-maximal relaxation in response to ACh (97.2 ± 1.0%; Figure 2a), bradykinin (94.3 ± 2.2%; n = 8; Figure 2b) and SIN-1 (93.8 ± 4.4%; Figure 2c). Similar responses were produced in arteries from patients with Type I diabetes [95.9 ± 1.8% (P = 0.50), 91.7 ± 2.2% (n = 9) (P = 0.38) and 95.5 ± 3.2% (P = 0.76) respectively]. A23187 produced a smaller relaxation than the other three vasodilators, and did not achieve a definite maximum in the concentration range used (Figure 2d). However, the peak relaxation was similar (P = 0.21) in arteries from patients
**Resistance arteries in diabetes**

**Figure 2** Cumulative concentration–response curves to the vasodilator agonists (a) ACh, (b) bradykinin, (c) SIN-1 and (d) A23187 obtained using arteries from control subjects (■) and patients with Type I diabetes (□). Values are means ± S.E.M. for (a) n = 12, (b) n = 8, (c) n = 8–10, and (d) n = 11–12.

**Table 3** Sensitivity (−log IC₅₀ values) from concentration–response curves obtained to various vasodilatory agonists

<table>
<thead>
<tr>
<th>Vasodilator</th>
<th>Controls</th>
<th>Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACh</td>
<td>7.30 ± 0.09</td>
<td>7.23 ± 0.12</td>
<td>0.63</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>7.69 ± 0.15 (8)</td>
<td>7.95 ± 0.15 (9)</td>
<td>0.29</td>
</tr>
<tr>
<td>A23187</td>
<td>5.96 ± 0.18 (9)</td>
<td>6.10 ± 0.16 (6)</td>
<td>0.61</td>
</tr>
<tr>
<td>SIN-1</td>
<td>5.87 ± 0.21</td>
<td>6.22 ± 0.22</td>
<td>0.26</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This investigation has made two striking observations in resistance arteries from patients with Type I diabetes: (i) a selective enhancement of ET-1-induced contraction, and (ii) normal endothelium-dependent (and endothelium-independent) relaxation. This indication of a limited, selective abnormality in endothelial cell function contrasts directly with the dramatic impairment of endothelium-dependent relaxation generally reported in Type I diabetes. These results indicate that endothelial cell function is largely maintained in subcutaneous resistance arteries from patients with well controlled Type I diabetes.

Damage to the endothelium often results in increased release of ET-1. Consequently, the elevated plasma [14] and tissue [15] concentrations of this peptide in patients suggest that damage to the endothelium is a feature of Type I diabetes. Similarly, urinary concentrations of ET-1 are elevated [16], and its release from resistance arteries is enhanced [17], in diabetic rats, while increased release of ET-1 possibly contributes to the down-regulation of glomerular ET receptors [18]. The precise role of ET-1 in the development of vascular complications, however, remains unclear. Functional data obtained using arteries...
from diabetic rats are contradictory, and there is evidence that the duration of diabetes has a significant impact on both ET-1-mediated contraction and endothelial cell function [12].

The selective enhancement of ET-1-mediated contraction in arteries from patients with Type I diabetes suggests altered function of the ET receptors in the endothelium and/or smooth muscle cells. This contrasts with results from studies using diabetic animals, in which increased ET-1-mediated contraction was just one component of a non-specific enhancement of contractile function, possibly mediated by altered second messenger activity [19,20]. Unaltered responses to NA and KPSS in the present study indicated that vascular remodelling, or a general abnormality in second messenger systems, was not responsible for the increased response to ET-1. Endothelium-derived relaxing factors have a modulatory effect on the ET-1-mediated contraction of human subcutaneous resistance arteries [21]. Consequently, removal of the endothelium results in an increase in sensitivity (but not in maximum contraction) of ~10% [21]. The current investigation suggests that this modulatory function of the endothelium has been partially lost in arteries from patients with Type I diabetes. As the ability of the endothelium to mediate relaxation was not impaired, this may suggest down-regulation of endothelial ET_B receptors. This is strikingly similar to results obtained using resistance arteries from patients with hypertension [22] and normal pressure glaucoma [21]. Alternatively, the enhanced ET-1-mediated contraction may be a consequence of up-regulation of ET_A and/or ET_B receptors on the vascular smooth muscle cells. Further studies would be required to identify the exact mechanism(s) responsible for the enhanced response to ET-1.

Our demonstration of unaltered responses to NA is consistent with data obtained in the isolated forearm [23,24] and in resistance arteries from patients with Type I diabetes [11]. The observation of increased angiotensin II-mediated contraction in the latter study supports the contention that contractile abnormalities detected in these arteries are the result of specific alterations in receptor function. This contrasts directly with a previous investigation of resistance artery function in Type I diabetes, which reported a non-specific decrease in contractile function (using NA, angiotensin II and KPSS). It is possible that this impaired contraction was due to a slightly (but not significantly) lower media/lumen ratio in arteries from the diabetic patients [9].

Endothelial cell dysfunction in animal models of diabetes has been indicated by impaired endothelium-dependent relaxation in conduit and resistance arteries [1]. Similar abnormalities have also been reported in the forearm [23] and brachial arteries [25] of patients with Type I diabetes. These results are challenged, however, by similar investigations which have found responses to endothelium-dependent relaxants to be unchanged [26,27] or even enhanced [28]. The present study used a group of patients with established but generally well controlled diabetes. This compares with a study of conduit arteries in vivo [29] which demonstrated that a similar group of patients [with established diabetes (12 years duration) but no microvascular complications] had both structural and functional abnormalities in the aorta and the radial and carotid arteries. The unaltered responses to receptor-dependent (ACh, bradykinin) and receptor-independent (A23187), endothelium-dependent dilators in the present study demonstrate that endothelium-dependent relaxation was not impaired. Furthermore, the maintained response to SIN-1 indicated that the ability of the vascular smooth muscle to relax in response to exogenous NO was similarly unaffected. These results are consistent with studies in which endothelium-dependent relaxation in the human forearm is only impaired in diabetes if patients also exhibit microalbuminuria [24,26,30]. Furthermore, relaxation in response to NO donors (usually sodium nitroprusside) has been shown repeatedly (although not exclusively [11,24]) to be unaltered in patients with this condition [23,26,27,30]. Therefore it is probable that impaired endothelium-derived NO activity in the microvasculature is restricted to patients with evidence of nephropathy. This would correspond with the demonstration that microvascular permeability is only increased in patients with long-standing Type I diabetes if they also have severe microvascular complications [31].

Our results challenge a previous demonstration that ACh-mediated contraction is selectively impaired in resistance arteries isolated from patients with Type I diabetes [9]. The difference between these studies is unlikely to be due to differences in disease duration in the diabetic groups. The duration of diabetes in the group with impaired ACh-mediated relaxation (18 years [9]) was shorter than that in patients who demonstrated normal responses to this agonist (24 years [11]). In contrast with our study, almost all (nine out of ten) of the individuals in the patient group used by McNally et al. [9] had evidence of retinopathy, possibly indicating that endothelium-dependent relaxation is only altered in patients with both diabetes and more established microvascular disease. Methodological variations are, however, a more likely reason for these discrepant results. In particular, we have found that some (larger) arteries obtained from subcutaneous biopsies fail to relax in response to ACh, but produce a 90–100% relaxation in response to bradykinin [32]. The inadvertent inclusion of a small number of these arteries in the diabetic group could explain both the specific decrease in ACh-mediated relaxation and the variable size and sensitivity of this response reported in the previous study [9].

In conclusion, the present study has demonstrated an enhanced response to ET-1, despite normal endothelium-
dependent relaxation, in subcutaneous resistance arteries from patients with Type I diabetes. This suggests that endothelial cell function is largely intact in these arteries from patients with established, but well controlled, Type I diabetes. The increased response to ET-1 may result from altered ET\(_B\) receptor function on the vascular endothelial cells, and could support the contention that endothelial cell dysfunction is more pronounced in patients with severe microvascular complications. It remains possible that endothelial cell function is altered in resistance arteries in other vascular territories, and also in subcutaneous arteries, from patients with Type I diabetes and associated microvascular complications. Further investigations, such as the recent preliminary report from Malik et al. [11], should confirm the relationship between resistance artery function and the severity of microvascular complications in patients with Type I diabetes.

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