Syndrome X and endothelial dysfunction

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Abstract

Objective: Syndrome X (angina, normal coronary arteriogram and positive exercise test) remains an enigma with unexplained features and apparent conflicts of evidence. The present study addressed whether (i) the Syndrome is characterised by generalised flow-related endothelial dysfunction, (ii) myocardial thallium\textsuperscript{201} defects reflect myocardial or microvascular dysfunction, (iii) endothelial dysfunction and its consequences can be improved by oral l-arginine. Methods: Flow-mediated brachial artery dilatation was measured by ultrasonic \textquoteleft wall-tracking' in 7 Syndrome X patients, further characterised as having thallium\textsuperscript{201} defects and no known cause of endothelial dysfunction, and a normal control group. Syndrome X patients entered a 4-week randomised double-blind placebo-controlled cross-over trial of oral l-arginine (7 g twice daily), with brachial artery studies, exercise tests and technetium\textsuperscript{99} tetrafosmin scans. Results: Flow-mediated dilatation was absent in Syndrome X vs. normal. Stress technetium\textsuperscript{99} tetrafosmin and thallium\textsuperscript{201} scans showed similar defects. Flow-mediated dilatation, symptom-limited exercise duration and peak oxygen consumption (VO\textsubscript{2 max}) were increased but rate-pressure-product (RPP) and radionuclide defects were unchanged after l-arginine vs. placebo. Conclusions: The study supports coronary microvascular rather than myocardial dysfunction and shows loss of flow-mediated dilatation in systemic arteries. Oral l-arginine improved flow-mediated dilatation, exercise capacity and VO\textsubscript{2 max} (by ca. 17%) despite unchanged RPP. The findings support generalised endothelial dysfunction. The arginine effects imply NO-mediated improvement of skeletal muscle perfusion suggesting improved homogeneity of microvascular distribution. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Blood flow; Coronary circulation; Endothelial function; Microcirculation; Nitric oxide; Syndrome

1. Introduction

Syndrome X (angina, normal coronary arteriogram and positive exercise test) [1] remains a controversial subject in respect of its identity, mechanisms, pathogenesis, prevalence and clinical importance. Continuing uncertainties reflect probable differences in patient selection in the published studies, the diagnostic dependence on exclusion of other conditions with which it may co-exist, and interpretative limitations of investigative methods used. A number of studies have provided implicit evidence of coronary microvascular dysfunction [2–7], but whether the angina always reflects myocardial ischaemia is less certain [8–11]. Some recent studies have demonstrated receptor-mediated coronary endothelial dysfunction [12,13] and that pacing and acetylcholine-induced coronary flow responses correlate [14], but whether there is generalised endothelial dysfunction and whether it involves flow-mediated dilatation [15–18] remains to be established. Endothelial dysfunction, moreover, is relatively common, and whether the association is coincidental or causal remains to be confirmed.

We measured brachial artery flow-related dilatation in a group of patients with Syndrome X, defined also as having positive thallium scans and no known cause of endothelial dysfunction, and in a control group of normal subjects.

To test whether the positive thallium\textsuperscript{201} scans might represent abnormalities of myocardial potassium homeo-
stasis rather than of perfusion, as has been suggested [19], exercise scans with thallium$^{201}$ and with technetium$^{99}$ tetrafosmin were compared.

L-arginine supplementation improves endothelial function in some conditions where it is impaired [20–22], but has been shown not measurably to increase endothelium-dependent vasodilatation in normal subjects with normal endothelial function [23]. Parenteral L-arginine has been reported acutely to improve acetylcholine-induced coronary vasodilator responses [24] in Syndrome X, though the evidence is conflicting [25]. The Syndrome X patients were accordingly entered into a placebo-controlled trial of L-arginine, with measurement of flow-mediated dilatation, exercise capacity and radionuclide scans.

2. Methods

2.1. Subjects

Seven Syndrome X patients (aged 51–64 yr, 4 women) with no known cause of endothelial dysfunction were studied (Table 1). Diagnostic criteria were: (i) history of stable effort-related angina (by ≥2 experienced cardiologists), (ii) positive exercise stress test (non-upsloping ST segment >2 mm in chest leads or >1 mm in limb leads; one patient had left bundle branch block [LBBB] – see below, (iii) completely normal coronary angiogram, (iv) reversible exercise-related myocardial thallium$^{201}$ defect, (v) no other cardiovascular disease. Resting electrocardiogram was normal, except in the one man with LBBB, in whom radionuclide scans consistently showed a reversible inferior defect. Chest x-ray and echocardiogram were normal in all patients. None had bronchopulmonary or other serious disease. Exclusion criteria were conditions known to be associated with endothelial dysfunction, ie blood pressure >150/90 mm Hg, present or past active or heavy passive smoking, serum cholesterol >6.5 mmol/l, and serum homocysteine >15 μmol/l (confirmed during the study). All patients continued on stable anti-anginal medication except that nitrovosodilator drugs were stopped for 24 h before each study. One of the 4 post-menopausal women was taking hormone replacement therapy. No alcohol or caffeine-containing beverage was taken during the 24 h before each study.

A control group of 10 normal (normotensive, non-smoking) subjects, matched for age, sex and serum cholesterol, were randomly selected, blind as to their characterisation other than by the features required for matching, from 300 normal subjects in the cumulative databank of patients similarly studied by the same investigators.

2.2. Study design

2.2.1. Syndrome X cf normal subjects

Endothelial function was assessed by measurement of flow-related dilatation of the brachial artery in response to reactive hyperaemia of the hand, using the method established in principle by Celermajer and colleagues [26] and developed for higher resolution measurement by computer-aided `wall-tracking’ [27,28]. As previously described [27,28], brachial artery end-diastolic diameter was measured and averaged over 10 sec periods by high resolution (±3μm) ultrasonic vessel ‘wall-tracking’ (VadirecTM); blood pressure by photoplethysmography (Finapres™) from the middle finger of the ipsilateral arm; and relative blood flow by continuous wave Doppler as the product of mean velocity corrected for Doppler angle and internal brachial artery diameter.

Patients were studied fasting in a temperature-controlled room (21–23°C) following 15 min supine rest. Measurements were made at baseline, during hand hyperaemia at 1 and 2 min after deflation of a wrist cuff inflated to suprasystolic pressure for 5 min, and at 3 min after 400 μg sublingual glyceryl trinitrate (GTN) – protocols developed in preliminary studies with confirmation of reproducibility.
All haemodynamic measurements were confirmed as having returned to baseline 15 min after release of the wrist cuff before administering GTN. The peak increase in end-diastolic internal brachial artery diameter (which occurred at either 1 or 2 min after cuff release) was used as the measure of flow-related dilatation, and the peak flow (averaged over the first 15 s after cuff release) as the measure of hyperaemic flow.

### 2.2.2. L-Arginine study in Syndrome X

The Syndrome X patients were entered into a double-blind randomised placebo-controlled cross-over trial of 4 weeks oral L-arginine. This comprised two 4-week treatment periods with oral L-arginine or matching placebo in randomised order, double-blind, without an intervening washout period. Patients were prescribed 7 g oral L-arginine twice a day (twenty-eight 500 mg coated tablets per day), with food, or the equivalent amount of inactive placebo (lactose) coated tablets. This regime was chosen because it was reported to be well tolerated and to achieve plasma levels approximately twice normal [23].

Each patient was studied at the same time of day (i) 7 days before the start of this trial (Day −7) (for equipment familiarisation and to minimise training effect), (ii) at the start of the study (Day 0), and (iii) and (iv) at the end of each treatment period (Day 28 and Day 56), providing data at baseline (Day 0), after 4 weeks of L-arginine, and after 4 weeks placebo. Investigations were performed in the following order on each study day: (i) clinical assessment (Days 0, 28, 56), including questioning for side effects (Days 28, 56); (ii) venous blood sampling (Days 0, 28, 56); (iii) flow-related brachial artery dilatation (Days −7, 0, 28, 56); (iv) Weber protocol exercise treadmill test with ECG monitoring, measurement of expired gases (Days −7, 0, 28, 56) and technetium(99) tetrafosmin scan (Days 28, 56).

### 2.2.3. Exercise test

Maximal symptom-limited Weber protocol treadmill testing was performed, with continuous 12-lead ECG monitoring, on 3 occasions: Day −7, Day 28 (with technetium(99) tetrafosmin scan), Day 56 (with technetium(99) tetrafosmin scan).

### 2.2.4. Respiratory gas analysis

Breath-by-breath analysis to give minute ventilation (VE), minute O₂ consumption (VO₂) and minute CO₂ production (VCO₂) was carried out using a QMC® Quinton Metabolic Cart, calibrated before each study, as previously described [29]. Inspired and expired oxygen was measured using a Zirconia oxide high temperature furnace sensor, carbon dioxide concentration using an infra-red absorption sensor, and expiratory flow with a pneumotachometer.

### 2.2.5. Radionuclide scans

Thallium⁺²¹ scans were carried out as an entry criterion for the study, and technetium⁹⁹ tetrafosmin scans on Day 28 and Day 56 of the arginine trial, ie on L-arginine and on placebo. Thallium⁺²¹ was injected at peak exercise and scans repeated after redistribution. Technetium⁹⁹ tetrafosmin scans were performed following injections resting and at peak exercise. Conventional short axis, vertical long axis and horizontal long axis slices were displayed and analysed by 2 experienced observers independently and blind to clinical information. The semi-quantitative analysis was carried out from polar plots [30]. Technetium scans on placebo were used to compare with thallium scans, taking advantage of the ethically approved inclusion of technetium scans in the arginine trial protocol.

### 2.2.6. Blood samples and assays

Fasting venous blood was sampled from the antecubital vein before measuring brachial artery responses. Blood was drawn into vials containing EDTA (homocysteine), lithium-heparin (nitrite and nitrate), SSTTM (gel and clot activator) (L-arginine, fasting lipids) and sodium citrate (VWF antigen). Plasma and serum were separated within 1 h by centrifugation at 4400 rpm for 10 min and stored at −70°C until analysis.

### 2.2.7. L-arginine

Serum L-arginine was measured by an ion-exchange amino acid analyser (BIOTRONIK LC5001) using Ninhydrin detection [31].

### 2.2.8. NO₂−—NO₃⁻

Plasma NO₂⁻/NO₃⁻ levels were measured by gas liquid chromatography using electron-capture detection based on the method of Tesch et al. [32].

### 2.2.9. VWF-Ag

Plasma VWF antigen was measured by ELISA based on the method of Cejka [33], with coating antibody A0082 (1/2000 dilution), conjugating antibody P0226 (1,3000 dilution) from DAKO, Denmark and substrate K-Blue from Biosistics Ltd, UK.

### 2.2.10. Homocysteine

Total plasma homocysteine was measured by HPLC using SBD-F (ammonium 7-fluoro-2-oxa-1,3-diazole-4-sulfonate) derivatization based on the method of Ubbink et al. [34,35].

### 2.3. Statistics

Data are given in the text and tables as group mean (SD). The Shapiro–Wilks test was used to test for normality. All data were normal apart from data for hyperaemic blood flow which were consequently logarithm-transformed. Baseline data for Syndrome X and normal controls
were compared using a one-way ANOVA. Data in the Syndrome X arginine trial were compared using ANOVA. A P value < 0.05 was considered significant.

2.4. Ethics

The investigation conforms with the principles outlined in the Declaration of Helsinki. All subjects gave their informed consent to the project which was approved by the Local Ethics Committee (South Glamorgan Health Authority, No. 94/07/69).

3. Results

3.1. Syndrome X cf normal subjects

3.1.1. Patient characteristics

Table 1 shows that the 2 groups were acceptably well-matched. Serum levels of VWF antigen, a marker of endothelial damage, were slightly but not significantly higher in Syndrome X patients than in control subjects or normal laboratory levels. Plasma NO\textsubscript{3}/NO\textsubscript{2} levels were similar in both groups.

3.1.2. Flow-related vasodilatation

This was absent in all Syndrome X patients (Δ diameter = 0.02 [0.09] mm) vs. the normal control group (Δ diameter = 0.12 [0.08] mm, P < 0.05), the difference between the groups being significant (P < 0.001) (Table 2). There was no difference in hyperaemic flow or GTN-induced dilatation between the Syndrome X and control groups.

3.2. L-arginine study in Syndrome X

3.2.1. Adverse effects

The only adverse effects reported were mild diarrhoea reported by two patients, one on L-arginine and one on placebo tablets.

3.2.2. Blood levels

Serum L-arginine levels were ca. 50% (range 0–160%) higher on L-arginine than placebo (Table 3). The wide range in measured levels may reflect differences in pre-sampling dose and in time (1–4 h) to blood sampling, for some patients took their daily dosage of L-arginine not as g b.i.d. (as prescribed) but in divided doses throughout the day. There was no evidence of a carry-over effect between the two treatment periods: mean serum L-arginine was 55% higher when placebo preceded arginine treatment (n = 3) vs. 68% higher when arginine preceded placebo (n = 4). Serum levels of homocysteine, nitrate, nitrite and VWF antigen were unchanged by L-arginine.

3.2.3. Flow-related vasodilatation

L-arginine restored flow-related dilatation (to 0.10 mm

Table 2

<table>
<thead>
<tr>
<th>Syndrome X (n=7)</th>
<th>Normal (n=10)</th>
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</thead>
<tbody>
<tr>
<td><strong>Diameter</strong></td>
<td><strong>Flow</strong></td>
</tr>
<tr>
<td><strong>Baseline (mm)</strong></td>
<td><strong>Baseline (ml min\textsuperscript{-1})</strong></td>
</tr>
<tr>
<td>3.66 ± 0.54</td>
<td>22 ± 16</td>
</tr>
<tr>
<td>3.63 ± 0.57</td>
<td>49 ± 39</td>
</tr>
<tr>
<td>-0.78*</td>
<td>+28 ± 275</td>
</tr>
<tr>
<td>-0.02*</td>
<td>+6 ± 16</td>
</tr>
<tr>
<td>+13.25*</td>
<td>+20 ± 38</td>
</tr>
<tr>
<td>+0.51</td>
<td>+0.12</td>
</tr>
<tr>
<td>3.45 ± 0.58</td>
<td>36 ± 30</td>
</tr>
<tr>
<td>3.57 ± 0.59</td>
<td>36 ± 37</td>
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<tr>
<td>2.34</td>
<td>292</td>
</tr>
<tr>
<td>0.08</td>
<td>8</td>
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<tr>
<td>4.47</td>
<td>77</td>
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<tr>
<td>0.05</td>
<td>0.13</td>
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</table>

Table 3

<table>
<thead>
<tr>
<th>Syndrome X – brachial artery study: L-arginine vs. placebo.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal</strong></td>
</tr>
<tr>
<td>Blood flow (mls/min)</td>
</tr>
<tr>
<td>End-diastolic diameter (mm)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
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<tr>
<td><strong>Hand Hyperemia</strong></td>
</tr>
<tr>
<td>Blood flow (Δ mls/min)</td>
</tr>
<tr>
<td>End-diastolic diameter (mm)</td>
</tr>
<tr>
<td>Δ (mm)</td>
</tr>
<tr>
<td>Δ (%)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
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<tr>
<td><strong>GTN (400μg)</strong></td>
</tr>
<tr>
<td>Blood flow (Δ mls/min)</td>
</tr>
<tr>
<td>end-diastolic diameter (mm)</td>
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<tr>
<td>Δ (mm)</td>
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<tr>
<td>Δ (%)</td>
</tr>
<tr>
<td>systolic BP (mmHg)</td>
</tr>
<tr>
<td>diastolic BP (mmHg)</td>
</tr>
</tbody>
</table>

Mean (SD).

* P < 0.05 vs. placebo.

Δ blood flow and Δ diameter expressed relative to preceding basal values.
New (similar) baseline preceding GTN not shown.
placebo, suggesting a quantitative relationship (though the correlation did not quite achieve significance). The ‘rate-pressure product’ (RPP) (heart rate×systolic blood pressure) at peak exercise was unchanged by L-arginine. Similar radionuclide defects at peak symptom-limited exercise were demonstrated at the same site in each patient on both of the technetium\textsuperscript{99} tetrofosmin scans and the thallium\textsuperscript{201} scan [30]. Peak respiratory exchange ratio \(\left(\frac{VCO_2}{VO_2}\right)\) was <1.0 on every test, indicating that the symptom-limited exercise was not associated with limitation of skeletal muscle perfusion to the point of anaerobic metabolism [29].

4. Discussion

The finding of similar regional defects of myocardial uptake with thallium\textsuperscript{201} and with technetium\textsuperscript{99} tetrofosmin in all cases supports the interpretation of thallium scans in Syndrome X as reflecting regions of relative under-perfusion, rather than primarily myocardial defects of potassium handling as has been suggested [19]. The findings are thus consistent with previous reports in Syndrome X patients using xenon\textsuperscript{133} [36,37] to measure perfusion and with the inference of microvascular dysfunction.

The study showed loss of flow-related brachial artery dilatation in the Syndrome X patients, compared with the matched normal control group, while endothelium-independent GTN responses were unimpaired. Flow-related dilatation is due predominantly to endothelial nitric oxide (NO) activity [38,39] and its loss in disease relates to the NO-mediated component [39]. Endothelial dysfunction, thus measured, demonstrates in particular the loss of physiologically integrative flow-mediated dilatation (previously not found to be impaired in Syndrome X [15–17]), as distinct from endothelial receptor-mediated dilatation with its different cell signalling pathways [18]. One previous similar study [17] found no significant loss of flow-related dilatation but a decrease in hyperaemic flow,

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
 & L-Arginine & Placebo & \(\Delta\%\) \\
\hline
\textbf{Exercise duration (s)} & 536 (317) & 460 (225) & +11 (24) \\
\hline
\textbf{\(\Delta\) Serum L-arginine >40\% (n=4)} & 528 (288) & 416 (145) & +20 (23) \\
\textbf{\(\Delta\) Serum L-arginine <20\% (n=3)} & 548 (421) & 519 (334) & +0 (14) \\
\hline
\textbf{\(\text{VO}_2\text{max} \ (\text{ml kg}^{-1} \text{ min}^{-1})\)} & 15.7 (4.5)* & 13.3 (3.1) & +17 (15) \\
\textbf{Heart rate (min}^{-1}\text{)} & Rest 73 (13) & 74 (11) & \\
& Peak Ex & 105 (26) & 104 (28) \\
\textbf{Mean systolic BP (mmHg)} & Rest 129 (9) & 126 (7) & \\
& Peak Ex & 149 (18) & 149 (16) \\
\textbf{Rate-pressure product (mmHg min}^{-1}\text{)} & Peak Ex 15 851 (5008) & 16 963 (7165) & \\
\hline
\end{tabular}
\caption{Syndrome X exercise test: L-arginine vs. placebo}
\end{table}

\footnote*{\(\Delta\%\) \(P<0.05\) \(vs.\) placebo.}
not apparent in the present study: other metabolic dilator mechanisms generally compensate in this respect for loss of NO activity alone [40,41]. The present study differs from many previous reports in being restricted to patients with confirmatory evidence of microvascular dysfunction from radionuclide scans, thereby avoiding potential dilution of the Syndrome X study group by patients with non-cardiac pain, and to patients with no known cause of endothelial dysfunction – restricting thereby the number of patients available. The finding of endothelial dysfunction, notwithstanding, adds weight to the view that endothelial dysfunction is an intrinsic feature of the syndrome.

Oral L-arginine supplementation restored flow-related dilatation in the brachial artery of these Syndrome X patients. The data suggest that the increase in dilatation and in exercise duration was related to the arginine level measured at the time of study, raising the possibility that it may reflect an acute effect of L-arginine. L-arginine did not increase resting artery diameter or GTN-induced dilatation but only flow-related dilatation, implying that it specifically improved flow-mediated NO production [38,39]. Non-specific dilator effects, as reported with acute high dose parenteral administration [42], are unlikely at the 25-fold lower levels achieved here.

L-Arginine also increased VO_{2max} and the duration of symptom-limited dilatation, confirmed as limited with similar radionuclide defects in every case. The radionuclide defects were unaltered by L-arginine, consistent with the fact that they were measured at the peak of symptom-limited exercise in each case. Changes in the ‘rate-pressure product’ (RPP) at peak exercise provide a measure of changes in cardiac workload. The RPP was unchanged by L-arginine. This suggests that the improvement in exercise duration and VO_{2max} was not attributable to an increase in maximal coronary perfusion such as would enable an increase in cardiac work, but rather to improved skeletal muscle perfusion relative to cardiac workload.

The study provides support for the still debated view that Syndrome X is characterised by endothelial dysfunction. The improvement with L-arginine adds weight to this conclusion. Endothelial dysfunction is shown to affect flow-mediated dilatation and not to be limited to the coronary arteries but generalised. Generalised endothelial dysfunction could account for many of the disparate features of Syndrome X, including systemic [43] and potential cerebral [44] and pulmonary microvascular manifestations [45]. Of particular interest is the experimental evidence that maintenance of microvascular distribution of flow depends on normal flow-mediated NO production [46]. Endothelial dysfunction could thus prejudice tissue perfusion relative to ‘macro-flow’. Conversely, improvement in endothelial function would improve homogeneity of microvascular distribution and tissue perfusion [47]. This could account for the improvement in exercise tolerance and VO_{2max} by L-arginine with unchanged rate-pressure-product, and may be the first recognised clinical demonstration of this phenomenon. Heterogeneity of microvascular flow has been modelled experimentally by coronary microembolization and shown to result in increased adenosine output and resting flow, attributable to local foci of adenosine-mediated ‘steal’, with myocardial ischaemia occurring only with heavier loads of microemboli [48]. This accords with evidence that increased adenosine production can compensate for lack of NO production in increasing flow to meet increased energy consumption [40,41].

Microvascular heterogeneity could thus account for (i) increased resting coronary flow [49,5,7], (ii) enhanced pain perception [50–52] even in the absence of ischaemia, due to local accumulation of adenosine [48] which is an algetic agent [53,54] and which could also lower the threshold to other painful stimuli; (iii) potassium-related ST depression due to opening of K_{ATP} channels by adenosine [55]; (iv) pulmonary microvascular dysfunction as suggested by exercise-related perfusion-ventilation mismatch in the absence of heart failure [45]; (v) the frequent absence of confirmatory evidence of ischaemic changes in cardiac contraction, perfusion or metabolism [8–11,56–58], which may indicate absence of ischaemia or limited investigative resolution and sensitivity for demonstrating widespread small foci of ischaemia; and (vi) the findings of a recent study which, by measuring trans-myocardial intermediary metabolite levels, effectively excluded myocardial ischaemia in most Syndrome X patients during pacing-induced angina with ST depression, but showed that some did develop myocardial ischaemia (JP Bagger, pers. comm.). Myocardial ischaemia may indeed be not an intrinsic feature of the Syndrome but a manifestation of its more severe presentation. An involvement of adenosine in the pathogenesis of Syndrome X has been proposed previously by Maseri and others [59–62].

Insulin resistance, with increased pro-insulin secretion and high triglyceride but low HDL serum levels as in metabolic Syndrome X, has also now been recognised to be a feature of cardiac Syndrome X [63–65]. It too might be a consequence of endothelial dysfunction causing microvascular heterogeneity of skeletal muscle flow, given that glucose uptake can be influenced by insulin-stimulated NO-mediated increase in blood flow [66] which could become locally rate-limiting. Endothelial dysfunction is strongly, albeit probably not universally, associated with insulin resistance in different disease states [47], but whether it directly causes insulin resistance remains controversial [67]. There may be regional and pathological differences in endothelial dysfunction in different conditions. Endothelial dysfunction may moreover be associated with structural microvascular changes [68], though whether this is a feature of Syndrome X remains uncertain [69,6].

The cause of endothelial dysfunction in those Syndrome X patients in whom other causes are excluded, as in the present study, remains to be established. Whether endo-
thelial dysfunction is sufficient cause for Syndrome X or part of a more widespread pathological disorder of unknown aetiology likewise remains to be resolved.

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