Both endothelium-dependent and endothelium-independent function is impaired in patients with angina pectoris and normal coronary angiograms

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Background The aim of this study was to investigate both endothelium-dependent and endothelium-independent vasodilatation in syndrome X patients. Recently selective impairment of endothelium-dependent function has been reported in a small number of syndrome X patients. However, other investigators have reported impaired endothelium-independent function.

Methods We infused the endothelium-independent vasodilators papaverine and glyceryl trinitrate, and endothelium-dependent vasodilator acetylcholine in the left coronary artery of 35 patients with syndrome X and in 17 control subjects (atypical chest pain, negative exercise test, and normal coronary angiograms). Coronary blood flow was measured with an intracoronary Doppler catheter positioned in the proximal left anterior descending coronary artery, and the artery diameter was assessed using quantitative coronary angiography.

Results The mean increase in coronary blood flow in response to a 12mg dose of papaverine was significantly less in the syndrome X group (185 ± 74% vs 411 ± 59%, \( P<0.001 \)). The increase in coronary blood flow in response to acetylcholine, at doses of 1, 3, 10, and 30 \( \mu \)g.min\(^{-1}\), was also significantly lower in the syndrome X group (12 ± 3, 41 ± 33, 57 ± 68, and 124 ± 87% \( P<0.001 \)) as compared to the control group (76 ± 49, 214 ± 116, 355 ± 115, and 361 ± 74%).

Conclusion These findings demonstrate that both endothelium-dependent and endothelium-independent dilation of the coronary microvasculature is impaired in syndrome X.

Key Words: Syndrome X, endothelial function, papaverine, acetylcholine, coronary blood flow.

Introduction

Many patients undergo coronary angiography each year for investigation of chest pain believed to be due to coronary artery disease. However, 10% to 30% of such patients are found to have normal coronary arteries on angiography. The term syndrome X was first used by Kemp in his editorial comment accompanying an article by Arbogast and Bourassa, in which these authors compared the features of a group of patients with angina and angiographically normal coronary arteries (Group X) with those of a group of patients with angina and coronary artery stenoses. Subsequently, the term has become a label for patients with normal coronary angiograms who present with typical exertional angina pectoris. The term syndrome X is now widely used, particularly in European centres, to define patients with symptoms of typical angina pectoris, positive exercise test (≥0.1 mV of ST segment depression) and normal coronary angiograms. The exclusion of extracardiac and known cardiac causes of chest pain with normal coronary arteries, such as left ventricular hypertrophy, systemic hypertension, valvular heart disease, and cardiomyopathy is usually required for the diagnosis of syndrome X.

The spectrum of current controversy regarding the pathophysiology of syndrome X is wide and seems to include all aspects of the disease. An impaired coronary flow reserve in syndrome X was first reported by Opherk et al. This was subsequently confirmed by several investigators using different techniques. A reduced coronary reserve in conjunction with the...
presence of angina and electrocardiographic changes closes the loop of classical ischaemic cascade and this has been used to support the presence of myocardial ischaemia in syndrome X.

A functional abnormality of the coronary microcirculation has been proposed to explain these observations. Recently, Egashira et al. [1] have proposed that a selective dysfunction of the coronary microvascular endothelium may be responsible for the impairment of coronary flow responses and myocardial ischaemia during stress. They studied the responses of coronary blood flow to the endothelium-dependent vasodilator acetylcholine and endothelium-independent vasodilators isosorbide dinitrate and papaverine in nine syndrome X patients and 10 controls (patients with atypical chest pain, normal exercise test, and normal coronary angiograms). Syndrome X patients had smaller increases in coronary blood flow than the control patients in response to graded doses of intracoronary acetylcholine, despite having similar changes in the diameters of the epicardial coronary arteries. The responses of coronary blood flow to isosorbide dinitrate and papaverine were similar in the two groups. However, the number of patients studied has been small. We have previously demonstrated an impaired coronary flow reserve in response to papaverine in a larger study of 53 syndrome X patients suggesting the presence of endothelium-independent dysfunction in these patients [1]. The aim of this study was to investigate both endothelium-dependent and endothelium-independent coronary blood flow responses in a larger study of different syndrome X patients to see if a selective dysfunction of coronary microvascular endothelium truly exists.

**Method**

**Study patients**

Coronary blood flow responses were studied in 35 patients with syndrome X and 17 control patients.

**Syndrome X group**

There were 16 males and 19 females. All patients gave a history of chest pain typical of angina pectoris and had a positive exercise electrocardiogram. The exercise test was said to be positive if there was at least 1 mm of horizontal or downward sloping ST segment depression at 80 ms after the J point. The left ventricle and the coronary arteries were completely normal on angiography and this was confirmed by two independent observers. There was no evidence of epicardial coronary artery spasm. Patients with hypertension, diabetes mellitus, and valvular heart disease or left ventricular hypertrophy were excluded from the study. All patients had continued to have chest pain despite reassurances after their initial cardiac catheter and were taking anti-anginal medications. None were taking hormone-replacement therapy.

**Control group**

There were eight males and nine females. All patients had atypical chest pain, normal exercise test, and completely normal coronary arteries on angiography without coronary spasm. These patients were investigated following recurrent hospital admissions due to chest pain which was classified as atypical of angina by the referring physician. In all patients, the coronary angiograms were reviewed prior to the study by two independent observers and only patients with completely normal coronary arteries were included in the study. Patients with hypertension, diabetes mellitus, valvular heart disease or left ventricular hypertrophy were excluded from the study. None were taking hormone-replacement therapy.

**Blood analysis**

Patients' blood was analysed for full blood count, serum urea and electrolytes, and fasting lipids on the morning of their cardiac catheter study.

**Echocardiography**

Echocardiographic assessment was performed in all patients. Cross-sectional and M mode assessment of the left ventricular posterior wall and septal thickness was made. Patients with a diastolic septal or posterior wall thickness of more than 11 mm were excluded from the study to minimize any effect of left ventricular hypertrophy on coronary blood flow measurements.

**Catheterization protocol**

Patients were fasted overnight for their cardiac catheterization. All cardiac medications had been stopped for 48 h. Patients were premedicated with diazepam 10 mg intravenously. A size 8F angioplasty guide catheter was positioned at the left coronary ostium. Coronary angiography was performed by the Judkins technique through the right femoral artery in all patients. Coronary injections were performed manually with up to 8 ml of intracoronary radio-opaque contrast medium (Niopam). Cine film recordings were performed in multiple projections. The proximal left anterior descending coronary artery was centred for optimal viewing after the initial angiograms had been obtained. To eliminate vasoactive effects of the contrast medium at least 10 min were allowed to lapse before the coronary blood flow study.

Heparin sodium, 10,000 units, was then given intravenously. A size 8F angioplasty guide catheter was positioned at the left coronary ostium. Through this, a 0.014 inch guide wire was advanced into the distal part of the left anterior descending coronary artery. Using a monorail technique, a size 3-6F 20 Mega Hertz Doppler-tipped catheter (Schneider, U.K.) was then advanced over the guide wire and positioned in the proximal segment of the left anterior descending coronary artery. The Doppler catheter was then connected to a Millar velocimeter (Model MDV-20, Millar Instruments, Houston, Texas, U.S.A.). The Doppler catheter and the range-gate of the velocimeter were adjusted to obtain good quality phasic and mean coronary blood flow velocity signals. These signals were recorded on a
Mingograf recorder (Siemens-Elema, Sweden). Baseline mean resting and phasic coronary blood flow velocity were then recorded. This technique of coronary blood flow velocity measurements has been extensively validated and described in detail[13,14]. The following infusions were then given in a random order: a bolus injection of 12 mg papaverine, saline infusion of 0.5 ml.min⁻¹ for 2 min, and acetylcholine (0.5 ml.min⁻¹) at doses of 1, 3, 10, and 30 µg.min⁻¹ for 2 min at each dose. A 200 µg dose of glyceryl trinitrate (50 µg.ml⁻¹) was infused over a 1 min period at the end. We used a 12 mg dose of papaverine in this study as we have shown previously that this dose produces maximal hyperaemia in all patients[11]. At least 5 min were allowed to elapse in between infusions to allow the coronary diameter and coronary blood flow velocity changes to return to baseline. Coronary angiography of the LAD was performed before and 2 min after the administration of each agent.

Quantitative measurements
Coronary angiograms were recorded on 35-mm cinefilm (50 frames. s⁻¹) with a cineangiographic system (Siemens, Germany). Quantitative measurements of the left anterior descending coronary artery diameter in diastole, 2 mm from the tip of the Doppler catheter, were performed using digital electronic callipers (Sandhill Scientific Inc). This method has been used previously to assess the arterial diameter of coronary vessels and has been described in detail[11,15-18].

Ethical approval
The study was approved by the Huntingdon Health Authority Ethical Committee. Full informed consent was obtained from all patients prior to the study.

Coronary blood flow calculations
Coronary blood flow velocity was recorded at rest and after each infusion. The Doppler velocity recordings were corrected for changes in the arterial cross-sectional area to provide an estimate of volumetric flow. Estimates of coronary blood flow (Q) were made from measurements of mean coronary flow velocity (V) and vessel cross-sectional area (CSA):

\[ Q = V \times CSA \]

Cross-sectional area was calculated by the following equation:

\[ CSA = \pi r^2 \]

where \( r \) = coronary artery radius as determined by quantitative analysis of the angiograms obtained in the preselected views. To obtain an estimate of coronary blood flow at rest (in ml.min⁻¹), the resting cross-sectional area of the coronary artery (in m²) was multiplied by the mean coronary blood flow velocity (in cm.s⁻¹) and by 60 s. The increases in coronary blood flow were expressed as the percent increase from baseline.

Statistical analysis
Values are given as mean ± SD. Analysis of variance for repeated measures followed by Bonferroni’s multiple-comparison test was used for comparing serial changes in the arterial pressure, heart rate, arterial diameter, and coronary blood flow. Student’s t-test were used to compare paired or unpaired data. Differences were considered to be significant at the \( P<0.05 \) level.

Results
Patient variables are shown in Table 1. The echocardiographic measurements are shown in Table 2. There were
Table 3  Haemodynamic changes in response to infusions in the syndrome X group

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Before infusion</th>
<th>After infusion</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR  )</td>
<td>SBP (mmHg)</td>
</tr>
<tr>
<td>Papaverine</td>
<td>72±13</td>
<td>131±18</td>
</tr>
<tr>
<td>GTN</td>
<td>75±15</td>
<td>127±19</td>
</tr>
<tr>
<td>Ach 1 μg.min⁻¹</td>
<td>73±12</td>
<td>132±17</td>
</tr>
<tr>
<td>Ach 3 μg.min⁻¹</td>
<td>75±15</td>
<td>128±19</td>
</tr>
<tr>
<td>Ach 10 μg.min⁻¹</td>
<td>73±12</td>
<td>132±16</td>
</tr>
<tr>
<td>Ach 30 μg.min⁻¹</td>
<td>76±14</td>
<td>128±19</td>
</tr>
</tbody>
</table>

Values are given as mean±SD. Ach = acetylcholine; GTN = glyceryl trinitrate; HR = heart rate (beats . min⁻¹); RPP = rate pressure product (systolic pressure x heart rate); SBP = systolic blood pressure (mmHg).

Table 4  Haemodynamic changes in response to infusions in the control group

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Before infusion</th>
<th>After infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR  )</td>
<td>SBP (mmHg)</td>
</tr>
<tr>
<td>Papaverine</td>
<td>74±12</td>
<td>128±12</td>
</tr>
<tr>
<td>GTN</td>
<td>74±10</td>
<td>125±14</td>
</tr>
<tr>
<td>Ach 1 μg.min⁻¹</td>
<td>75±12</td>
<td>128±12</td>
</tr>
<tr>
<td>Ach 3 μg.min⁻¹</td>
<td>76±12</td>
<td>126±14</td>
</tr>
<tr>
<td>Ach 10 μg.min⁻¹</td>
<td>75±12</td>
<td>127±16</td>
</tr>
<tr>
<td>Ach 30 μg.min⁻¹</td>
<td>74±11</td>
<td>126±14</td>
</tr>
</tbody>
</table>

Values are given as mean±SD. Ach = acetylcholine; GTN = glyceryl trinitrate; HR = heart rate (beats . min⁻¹); RPP = rate pressure product (systolic pressure x heart rate); SBP = systolic blood pressure (mmHg).

Systemic haemodynamics

The haemodynamic changes in response to the infusions are shown in Tables 3 and 4. There was no significant change in the resting heart rate or systolic pressure as a result of the infusions.

Changes in the LAD diameter (Fig. 1)

An intracoronary infusion of saline did not change the arterial diameter significantly. A 12 mg dose of papaverine and a 200 μg dose of glyceryl trinitrate caused comparable increases in diameter in both groups (P=ns). The administration of acetylcholine produced a biphasic response in both groups. The diameter increased significantly after the infusion of acetylcholine at a dose of 10 μg . min⁻¹ (P<0.01) and decreased after a dose of 30 μg . min⁻¹ (P<0.01). There was no significant difference between the two groups as regards percent changes in the arterial diameter induced by the acetylcholine infusions. There was no significant difference between males and females.

Changes in coronary blood flow (Fig. 2)

The infusion of saline did not alter the coronary blood flow significantly. The percent increase in coronary blood flow by glyceryl trinitrate was lower in the syndrome X patients as compared to controls. However, this was not statistically significant. The percent increase in coronary blood flow in response to papaverine was significantly lower in the syndrome X group (P<0.001). The administration of graded doses of acetylcholine produced a dose-dependent increase in coronary blood flow in both groups. However, this increase in coronary blood flow in the syndrome X group was significantly lower than that in the control group at all doses. There was no significant difference between males and females.

Discussion

Our study has demonstrated a significant impairment of increase in coronary blood flow in response to papaverine and graded doses of acetylcholine in syndrome X patients as compared to controls. The response to intracoronary nitrate was also lower in the syndrome X group, but this did not reach statistical significance. These findings suggest that both endothelium-dependent vasodilatation and endothelium-independent vasodilation of resistance coronary vessels is impaired in syndrome X patients.
Figure 1 Mean changes (%) in the diameter of the proximal left anterior descending coronary artery (LAD). Bars indicate standard deviation. Ach 1 = acetylcholine 1 µg.min⁻¹; Ach 3 = acetylcholine 3 µg.min⁻¹; Ach 10 = acetylcholine 10 µg.min⁻¹; Ach 30 = acetylcholine 30 µg.min⁻¹; Nitr = glyceryl trinitrate; Pap = papaverine; Sal = saline. There was no significant difference between the two groups. = syndrome X; = controls.

Figure 2 Mean increases (%) in coronary blood flow in control subjects (■) and syndrome X patients (□). *P<0.05, **P<0.001. Bars indicate standard deviation. Ach 1 = acetylcholine 1 µg.min⁻¹; Ach 3 = acetylcholine 3 µg.min⁻¹; Ach 10 = acetylcholine 10 µg.min⁻¹; Ach 30 = acetylcholine 30 µg.min⁻¹; Nitr = glyceryl trinitrate; Pap = papaverine; Sal = saline.
Endothelium-dependent function and acetylcholine

Acetylcholine relaxes blood vessels by means of muscarinic receptors that stimulate the synthesis and release of endothelium-derived relaxing factor\(^\text{[19]}\). Endothelin derived relaxing factor is identical to nitric oxide or very closely related to it\(^\text{[20,21]}\). That this vasodilatation is mediated by endothelium derived relaxing factor is supported by the observation that methylene blue (an agent thought to inactivate endothelin derived relaxing factor in part by generation of superoxide free radicals\(^\text{[22]}\), and L-arginine analogues (which inhibit the synthesis of nitric oxide) can block acetylcholine-induced vasodilatation\(^\text{[23,24]}\). Nitric oxide activates soluble guanylyl cyclase, increasing the levels of cytoplasmic cyclic 3',5'-guanosine monophosphate (GMP) and thereby reducing calcium flux and causing vascular relaxation\(^\text{[25-27]}\). Nitrates cause endothelium-independent vasodilatation through the same effector pathway by providing an inorganic source of nitric oxide\(^\text{[28]}\). Papaverine is a smooth muscle relaxant and vasodilator. It is an alkaloid devoid of narcotic properties. The main pharmacological action of papaverine is that of a vasodilator acting on the smooth muscle of the arterioles and capillaries of all vascular beds\(^\text{[29]}\). This activity is related predominantly to the inhibition of cyclic adenosine 3',5'-monophosphate (AMP) phosphodiesterase but has also been shown to inhibit the function of cyclic GMP phosphodiesterase\(^\text{[30]}\). As a consequence of phosphodiesterase inhibition, the myocardial cyclic AMP levels rise substantially. Elevation of cyclic AMP appears to act not by reducing levels of cytosolic free calcium but by stimulating phosphorylation of myosin light chain kinase and thus decreasing the calcium sensitivity of the contractile proteins\(^\text{[31]}\).

Acetylcholine infusions induced a biphasic response in both groups of patients in our study. As shown by other studies\(^\text{[22,23,25]}\), lower doses of acetylcholine induced vasodilatation, but a high dose caused vasoconstriction. This suggests that the endothelium-dependent vasodilatation of large coronary arteries in response to acetylcholine at low doses is not impaired in syndrome X and that the observed attenuated increase in coronary blood flow in these patients does not result from excessive vasoconstriction of the large coronary arteries.

Acetylcholine has a dual effect on the vascular smooth muscle. It causes relaxation which is strictly dependent on the presence of an intact and normally functioning endothelium. It also causes vasoconstriction which results from stimulation of specific muscarinic receptors located on smooth muscle cells. The net resulting coronary vasomotor response depends on the balance between these two opposing effects. Therefore, an impaired response to acetylcholine may be due to impaired endothelium-dependent vasodilatation, an enhanced smooth muscle cell muscarinic receptor response, altered signal transduction properties, or reduced production, release or diffusion of endothelium derived relaxing factor. Acetylcholine-mediated endothelium-derived vasoconstrictor substance has also been described\(^\text{[36,37]}\). It has also been shown that acetylcholine released from cholinergic nerves causes prejunctional inhibition of noradrenaline release from sympathetic nerve terminals resulting in vasodilatation\(^\text{[38]}\). Therefore, several mechanisms may co-exist. Our study does not allow us to determine the precise location of the defect in the nitric oxide system that leads to abnormal endothelium-dependent vascular relaxation. Further studies of endothelial function are needed to further elucidate the mechanisms of the impaired response of coronary blood flow to acetylcholine in syndrome X patients. The use of agents such as substance P (which does not act directly on the smooth muscle and is an endothelium-dependent vasodilator that stimulates the release of vasoactive factors from the endothelial cells by acting on its own tachykinin receptor distinct from the muscarinic receptor) or the nitric oxide precursor L-arginine (which enhances endothelial vasodilator function) would allow further assessment of the underlying mechanisms.

Papaverine and endothelium

The mechanism of action of papaverine is not dependent upon the endothelium. The results from this study support our previous observation that coronary flow reserve in response to papaverine is impaired in syndrome X\(^\text{[11]}\). The reduced flow response to papaverine in the syndrome X group seems to exclude the possibility that impaired flow responses could be related solely to a specific abnormality of endothelium-dependent function. An impaired response to both papaverine and acetylcholine may indicate a primary abnormality of vascular smooth muscle responsiveness. The observation that response to glycerol trinitrate was not significantly different between the two groups suggests that the impaired responses of the resistance vessels are not a consequence of a nonspecific defect in the responsiveness of the vascular smooth muscle. However, we cannot entirely exclude the possibility of a nonspecific defect in the responsiveness of the vascular smooth muscle as our observations are based on a single dose of glyceryl trinitrate and other doses of glyceryl trinitrate may have different effects.

It is possible that the impaired coronary vasodilatation was selective only for papaverine and not for other endothelium-independent agonists. However, we did not examine the responses to agents other than nitrates (e.g. adenosine). It is also possible that coronary vasomotor responses to both endothelium-dependent and endothelium-independent agonists may be affected in a hierarchical fashion in syndrome X and the impaired flow response to papaverine in this study may perhaps be related, in part, to a more severe vasomotor dysfunction in patients in our study as compared to previous studies.
All our patients were taking anti-anginal medications for their symptoms. However, all medications were stopped a minimum of 48 h prior to the study and it is unlikely that residual drug effects could have had a significant effect on the findings.

**Comparison with other studies**

The changes observed in coronary blood flow and arterial diameter in response to nitrates and graded dose acetylcholine infusion in our study are similar to the changes seen in Egashira et al.'s study. The changes observed in arterial diameter in response to papaverine are also similar. However, the response to papaverine is clearly impaired in our study suggesting impaired responsiveness of the coronary microcirculation in syndrome X patients as compared to controls. Egashira et al.'s study only studied those syndrome X patients in whom an intracoronary infusion of 10 mg of papaverine evoked myocardial production of lactate. They suggested that the net lactate production in response to papaverine indicates that myocardial ischaemia resulted from inhomogeneous myocardial perfusion. The production of lactate, however, suggests that myocardial ischaemia results from a microvascular abnormality not dependent on the endothelium and the patients they studied have endothelial-independent dysfunction as well as the endothelium-dependent dysfunction suggested by the limited response of coronary blood flow to acetylcholine.

It is clear from our previous study that there is a great scatter in the coronary flow reserve values with some syndrome X patients having a high flow reserve. Several studies in humans have shown that the coronary flow reserve values obtained in response to papaverine, using the same technique as our study, average 4.7 ± 0.2 with a range of 3.7 to 8.3. It is interesting to note that, in Egashira et al.'s study, six of the nine (67%) syndrome X patients studied had a coronary flow reserve < 3.5 in response to a hyperaemic dose of papaverine as compared to only three of the 10 (30%) control subjects. The difficulties of conducting coronary flow studies in syndrome X due the heterogeneous nature of this syndrome have been highlighted before. Studies which investigate small numbers of patients may include syndrome X patients who have a normal coronary flow reserve and control patients with a negative exercise test may indeed include patients who have an impaired coronary flow reserve.

Motz et al. studied the responses of coronary blood flow to acetylcholine and the largely endothelium-independent vasodilator dipyridamole in 23 patients with angina and normal coronary arteries. In eight patients the response to acetylcholine was less than the response to dipyridamole, suggesting defective endothelium-dependent vasodilatation. In six patients coronary blood flow increased significantly after both acetylcholine and dipyridamole. However, in six patients, neither acetylcholine nor dipyridamole caused a significant increase in coronary flow. However, as they had not studied the response of nitrates in their study, the results suggested that the vasodilatation was impaired due to a defect in the vascular smooth muscle or due to impairment of both endothelium-independent function. The results from our study suggest that the latter may be the case. Also, their study had included many patients with hypertension and diabetes mellitus, which are known in impair endothelium-dependent vasodilatation. The more uniform results in our study and Egashira et al.'s study may be due to the strict selection of study patients.

Vrints et al., have demonstrated that patients with angina and normal coronary arteries had a loss of endothelium-dependent vasodilatation of the large coronary arteries with acetylcholine. This is different to the observation in our and Egashira et al.'s study and may be related to the different populations studied and due to the differences in the dose of acetylcholine.

**Conclusion**

It is now generally believed that syndrome X almost certainly encompasses several pathophysiological disease entities. Coronary flow reserve studies have demonstrated an impaired flow response to pacing stress and to pharmacological vasodilatation. The fact that these abnormalities have been demonstrated by several different methodologies further strengthens the conclusion that an abnormal flow reserve does exist. We have demonstrated an impaired endothelium-dependent vasodilator response to acetylcholine as well as an impaired endothelium-independent vasodilator response to papaverine. This suggests a dynamic abnormality of the coronary microcirculation in syndrome X patients which may contribute to the altered regulation of myocardial perfusion in these patients. However, it is also clear that other patients with chest pain and normal coronary arteries do not have any evidence of an abnormal coronary flow reserve suggesting that syndrome X, even if defined by the ECG response to exercise, probably consists of more than one distinct pathophysiological entity. Therefore, it would be unreasonable to ascribe the angina in all syndrome X patients to an abnormal vasodilator response. This suggest that other factors must also be important. An abnormal pain perception, a significant reduction in coronary blood flow on oesophageal acid stimulation, a significant reduction in coronary blood flow on hyperventilation with and without epicardial coronary constriction, a heightened sympathetic tone, and insulin resistance have all been reported in syndrome X and highlight the heterogeneous nature of this syndrome.

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References


