Combined Endothelin Receptor Blockade Evokes Enhanced Vasodilatation in Patients With Atherosclerosis

Felix Böhm, Gunvor Ahlborg, Bo-Lennart Johansson, Lars-Olof Hansson, John Pernow

Abstract—Endothelin (ET)-1 causes vasoconstriction via ET_A and ET_B receptors located on vascular smooth muscle cells and vasodilatation via ET_B receptors on endothelial cells. Studies in vitro indicate an upregulation of ET_B receptors in atherosclerosis. The present study investigated the vascular effects evoked by endogenous ET-1 in atherosclerotic patients. Forearm blood flow (FBF) was measured with venous occlusion plethysmography in 10 patients with atherosclerosis and in 10 healthy control subjects during intra-arterial infusion of selective ET receptor antagonists. The ET_B receptor antagonist BQ788 evoked a significant increase in FBF (31±13%) in the patients, whereas a 20±9% reduction was observed in the control subjects. The ET_A receptor antagonist BQ123 combined with BQ788 evoked a marked increase in FBF (102±25%) in the patients compared with no effect in the control subjects (−3±9%, P<0.001 versus patients). The ET_B receptor antagonist BQ123 increased FBF to a similar degree in patients (39±11%) as in control subjects (41±11%). The increase in FBF evoked by selective ET_A receptor blockade was significantly (P<0.05) less than that evoked by combined ET_A/ET_B receptor blockade in the atherosclerotic patients. These observations suggest an enhanced ET-1–mediated vascular tone in atherosclerotic patients, which is at least partly due to increased ET_B-mediated vasodilatation.

Key Words: endothelin receptors regional blood flow atherosclerosis

The endothelins (ETs) are a family of peptides with potent and characteristically long-lasting vasoconstrictor and vasopressor actions. ET-1 is the major isoform in the cardiovascular system and is produced in endothelial cells. The functional effects of ET-1 are mediated by 2 distinct receptor subtypes, the ET_A and the ET_B receptors. The ET_A receptor is expressed on vascular smooth muscle cells (VSMCs), and its activation by ET-1 leads to vasoconstriction. ET_B receptors are present on VSMCs and on endothelial cells. Activation of VSMC ET_B receptors results in vasoconstriction, whereas activation of the ET_B receptor results in vasodilatation via the release of NO. Thus, the net result depends on the receptor localization that predominates. Local administration of the selective ET_A receptor antagonist BQ123 resulted in forearm vasodilatation in healthy subjects. The selective ET_B receptor antagonist BQ788, on the other hand, induced reduction in forearm blood flow (FBF). Combined administration of the 2 antagonists resulted in vasodilatation, a response indicating that ET-1 contributes to vascular tone via the ET_A receptor and that this constrictor tone, to a minor degree, is counteracted by the ET_B receptor.

It has been speculated that ET-1 plays a part in the pathophysiology of several cardiovascular disorders, including atherosclerosis. There is enhanced expression of ET-1 in VSMCs and macrophages of human atherosclerotic plaques. Although the ET_A receptor seems to be the major receptor mediating vasoconstriction in healthy humans, the situation may be different in atherosclerosis. Binding studies in vitro suggest that ET_B receptors are upregulated in the atherosclerotic human coronary artery. Furthermore, accumulation of foam cells and T lymphocytes in human atherosclerotic lesions may modulate a switch of ET receptor subtypes from ET_A to ET_B in VSMCs, suggesting that ET_B receptors may play a more important role in atherosclerotic vessels. Little is known about the functional consequences of altered ET receptor expression in atherosclerosis. We recently demonstrated more pronounced vasoconstriction to ET_B receptor stimulation in patients with atherosclerosis than in healthy control subjects. However, the importance of endogenous ET-1 in blood flow regulation via the different ET receptors in atherosclerotic patients has, so far, not been investigated.

Therefore, the present study was undertaken to test the hypothesis that the vasodilatory response to combined ET_A and ET_B receptor inhibition in patients with atherosclerosis is enhanced compared with that seen after selective ET_A receptor inhibition and compared with that seen in healthy subjects. We evaluated the response to selective ET_A receptor blockade, selective ET_B receptor blockade, and combined ET_A and ET_B receptor blockade in the forearms of patients with atherosclerosis and healthy control subjects.
The investigations were performed with the subjects in the supine position in a quiet laboratory with controlled temperature. The investigations were performed with the subjects in the supine position in a quiet laboratory with controlled temperature.

None of the control subjects was on any medication. Acetylsalicylic acid was withheld for at least 4 half-lives before the protocol. The doses of BQ788 and BQ123 were based on a

Methods

Subjects

The present study included 2 different experimental protocols. Each protocol was performed on 2 different occasions in random order on 10 male patients with atherosclerosis and on 10 healthy male control subjects. Nine of the patients and 8 of the control subjects participated in both protocols. Some basal characteristics of the study population are presented in Table 1. The patients had symptoms of intermittent claudication, with significant atherosclerotic lesions and flow obstructions in the large arteries of the legs as determined by ultrasound scanning and/or angiography. All patients also had coronary artery disease (angina pectoris that had required coronary revascularization or previous myocardial infarction). None of the patients had any history of congestive heart failure or diabetes mellitus. Two of the patients were treated hypertensives, but there was no difference in blood pressure between patients and control subjects. None of the control subjects had any evidence of significant stenotic lesions or flow obstructions in the brachial artery as determined by ultrasound scanning. The patients were on regular medication with antihypertensive, without history of cardiovascular disease, and with normal ankle/brachial pressure index and pulse curves in the dorsalis pedis artery.

TABLE 1. Basal Characteristics of Patients With Atherosclerosis and Healthy Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Patients (N=11)</th>
<th>Control Subjects (N=12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±3</td>
<td>63±2</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79±4</td>
<td>83±4</td>
<td>NS</td>
</tr>
<tr>
<td>Forearm circumference, cm</td>
<td>27.0±0.4</td>
<td>27.2±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Length, m</td>
<td>1.74±0.02</td>
<td>1.77±0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, weight/length$^2$</td>
<td>26±1</td>
<td>26±1</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.9±0.3</td>
<td>5.3±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.2±0.3</td>
<td>3.2±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.0±0.04</td>
<td>1.3±0.07</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.8±0.2</td>
<td>1.8±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>4.1±0.3</td>
<td>3.0±0.1</td>
<td>&lt;0.001</td>
</tr>
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</table>

EDV indicates endothelium-dependent vasodilatation; ACh, acetylcholine; and NTG, nitroglycerin. Values are mean±SEM on number of individuals.

FFB Studies

The investigations were performed with the subjects in the supine position in a quiet laboratory with controlled temperature. The subjects were allowed a light breakfast without caffeine-containing drinks or alcohol and were instructed not to smoke on the day of the study. With the subjects under local anesthesia, a percutaneous catheter was inserted in the proximal direction into the brachial artery of the nondominant arm for infusions, blood sampling, and measurement of blood pressure. Another catheter was inserted into a deep cubital vein of the same arm for blood sampling. Intra-arterial pressure was measured by a capacitative transducer (Siemens-Elema). FBF was measured simultaneously in both arms by venous occlusion plethysmography with an air-filled cuff applied to the widest part of the forearm. Venous occlusion pressure was 50 mm Hg, and during the recording of inflow curves, the circulation of the hands was occluded by infusing a wrist cuff to 20 mm Hg above systolic blood pressure. After 30 minutes of supine rest, 0.9% NaCl was infused into the brachial artery for 5 minutes at a rate of 0.5 mL/min. Basal FBF was calculated as the mean blood flow during the last 2 minutes of the saline infusion.

In protocol 1 (Figure 1), the selective ET$_A$ receptor antagonist BQ788$^{14}$ (10 nmol/min) was infused into the brachial artery for 110 minutes at a rate of 0.5 mL/min. After 40 minutes, an infusion of the selective ET$_A$ receptor antagonist BQ123$^{15}$ (10 nmol/min) at a rate of 0.5 mL/min was administered along with BQ788 for the remainder of the protocol. The doses of BQ788 and BQ123 were based on a

Protocol 1

<table>
<thead>
<tr>
<th>NaCl BQ788</th>
<th>big ET-1</th>
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<tr>
<td>-5 0</td>
<td>40 80 110 min</td>
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</table>

Protocol 2

<table>
<thead>
<tr>
<th>NaCl BQ123</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5 0</td>
</tr>
<tr>
<td>40 80 min</td>
</tr>
</tbody>
</table>

Figure 1. Study protocols 1 and 2.
previous report. To further evaluate the receptor blockade, the ET-1 precursor, big ET-1 (15 pmol/min), was infused at a rate of 1 mL/min during the last 30 minutes of the BQ788 plus BQ123 administration. On a separate occasion, big ET-1 (15 pmol/min) was administered in the absence of ET receptor blockade on a subgroup of patients (n=4) and control subjects (n=7).

In protocol 2, BQ123 (10 nmol/min) was infused into the brachial artery at a rate of 0.5 mL/min for 80 minutes (Figure 1). Inflow curves were recorded for 2 minutes every 10 minutes during the infusions. At the end of the protocol, sodium nitroprusside (3 μg/min) was infused during 2 minutes to test the forearm vasodilator capacity of the subjects. Sodium nitroprusside increased FBF by a similar degree in patients and control subjects (241±52% and 225±49%, respectively).

Intra-arterial pressure was recorded before and immediately after each infusion. Heart rate was followed continuously from the ECG. Venous plasma samples for measurement of ET-like immunoreactivity were obtained before and at 20, 40, and 80 minutes of each infusion of the ET receptor antagonists. Arterial samples were collected before and immediately after each infusion. Venous blood samples for determination of cholesterol and fibrinogen were collected before drug infusion at the first visit of each subject.

The ET<sub>B</sub> receptor blockade by BQ788 was evaluated in a separate study on 5 healthy control subjects as follows: the selective ET<sub>B</sub> receptor antagonist sarafotoxin 6c (10 pmol/min) was infused before and during coinfusion of BQ788 (10 nmol/min). Sarafotoxin 6c reduced FBF by 29±8% in the absence compared with 3±7% in the presence of BQ788 (P<0.05).

**Endothelial Function Measurements**

As a basal characterization, microvascular and brachial artery endothelium-dependent vasodilatation was determined in a subgroup of the patients (n=8) and the control subjects (n=8) on a separate occasion. Microvascular endothelium-dependent vasodilatation was determined by the infusion of acetylcholine (10 μg/min) at a rate of 2.5 mL/min together with saline (0.5 mL/min) into the brachial artery during measurement of FBF. Flow-dependent dilatation of the brachial artery was performed before and during reactive hyperemia according to a previously described method by using an Accuson 128 XP/10 apparatus with a 6-MHz ART linear array transducer. Endothelium-independent dilatation of the brachial artery was determined by sublingual nitroglycerin (0.4 mg).

**Plasma Analyses**

Blood was sampled into test tubes containing EDTA (10 mmol/L final concentration) on ice. After centrifugation (15 minutes, 4°C), plasma (1 mL) was stored at −80°C until analysis. After ethanol extraction, ET-like immunoreactivity was analyzed by radioimmunoassay with the use of commercially available antiserum (rabbit anti-ET-1 6901, Peninsula Laboratories) as described previously. Plasma fibrinogen was measured by using the Behring Nephelometer Analyzer II with particle-enhanced immunonephelometric assay.

**Drugs**

BQ123 and BQ788 (Clinalfa AG) were dissolved in sterile 0.9% NaCl and stored frozen at −80°C. Big ET-1 (Peninsula Laboratories) was dissolved in sterile water containing 0.5% albumin and, thereafter, injected through a Millipore sterile filter. The peptide was then stored at −80°C until use. On the day of the experiments, all substances were diluted to the proper concentrations in sterile 0.9% NaCl.

**Calculations**

FBF was calculated as the mean of 8 inflow recordings during 2 minutes. The ratio of flows in the infused and noninfused arms at each time point is expressed as percent change from baseline. All data are given as mean values and SEM. Statistical differences were calculated by using the Student unpaired t test for between-group comparisons or ANOVA for repeated measures. A value of P<0.05 was regarded as significant.

**Results**

**Study Subject Characteristics**

The basal characteristics of the patients and the control subjects are summarized in Table 1. There was no difference in LDL cholesterol, but HDL cholesterol was lower in the patients. Fibrinogen levels were significantly higher in the patients than in the control subjects (Table 1). Flow-dependent dilatation tended to be reduced in the patients, but this difference was not statistically significant. There were no significant differences in baseline hemodynamics between patients and control subjects (Table 2). Furthermore, there were no significant changes in blood flow in the noninfused forearm or in arterial blood pressure during the course of the 2 protocols.

**Hemodynamic Effects of ET Receptor Antagonists**

**Protocol 1**

Infusion of the selective ET<sub>B</sub> receptor antagonist BQ788 evoked a slight but significant decrease in FBF in the control subjects (Figure 2A). The maximum reduction was 20±9% at 30 minutes. In contrast, BQ788 increased FBF by 31±13% at 10 minutes in the patients. FBF was significantly greater in the patients than in the control subjects during the entire infusion of BQ788 alone (Figure 2A).

Addition of BQ123 to the infusion of BQ788 evoked no significant change in FBF in the control subjects (Figure 2A). In contrast, the addition of BQ123 evoked pronounced vasodilatation in the patients. The maximal increase in FBF in response to combined ET<sub>A</sub> and ET<sub>B</sub> receptor antagonism in
the patients was 102±25% at 80 minutes. The corresponding change in FBF in the control subjects was -3±9% (P<0.001 versus patients).

Administration of big ET-1 for 30 minutes in the presence of combined ET<sub>A</sub> and ET<sub>B</sub> receptor antagonism did not significantly affect FBF in the control subjects (14±13%) or in the patients (-14±11%). In the absence of ET receptor blockade, big ET-1 reduced FBF by 47±5% (n=4) and 32±4% (n=7) in patients and control subjects, respectively.

**Protocol 2**

Selective ET<sub>A</sub> receptor antagonism with BQ123 caused a slowly developing increase in FBF from baseline that was significant in the patients and in the control subjects (P<0.05, Figure 2B). There were no significant differences between the groups during the course of the infusion. The increase in FBF in the patients during selective ET<sub>A</sub> antagonism (39±11%) was significantly smaller than that seen during combined ET<sub>A</sub> and ET<sub>B</sub> receptor antagonism in protocol 1 (102±25%, P<0.05). On the other hand, BQ123 alone evoked significantly greater vasodilatation than the combination of BQ123 and BQ788 in the control subjects (41±11% versus -3±9% at 80 minutes, P<0.01).

**ET Levels**

Deep venous plasma levels of ET were significantly elevated at 40 minutes of infusion of BQ788 and at 40 minutes of coinfusion of BQ788 and BQ123 (Figure 3A). Venous ET levels did not change during the infusion of BQ123 alone (Figure 3B). Arterial ET levels were not changed by either antagonist.

**Discussion**

The main finding of the present study is that combined ET<sub>A</sub> and ET<sub>B</sub> receptor blockade evokes a significantly more pronounced vasodilator response in the forearms of patients with atherosclerosis as compared with selective ET<sub>A</sub> receptor blockade and compared with healthy controls. Selective ET<sub>B</sub> receptor blockade resulted in a slight but significant increase in FBF in patients compared with a slight decrease in FBF in control subjects. Finally, there was no difference in vasodilator response to selective ET<sub>A</sub> receptor blockade between the 2 groups. These findings suggest an enhanced endogenous ET<sub>B</sub>-mediated vasoconstrictor tone in patients with atherosclerosis and may explain the more prominent vasodilator response to combined ET<sub>A</sub> and ET<sub>B</sub> receptor antagonism in this patient group.

When the ET<sub>A</sub> receptor antagonist BQ123 and the ET<sub>B</sub> receptor antagonist BQ788 were coinfused, a marked (2-fold) increase in FBF was observed in the patients, whereas no significant change was seen in the control subjects. Furthermore, the vasodilator response to combined ET<sub>A</sub> and ET<sub>B</sub> receptor blockade was significantly greater than that to selective ET<sub>A</sub> receptor blockade in the patient group. In the control subjects, on the other hand, the vasodilator response to combined ET<sub>A</sub> and ET<sub>B</sub> receptor blockade was blunted compared with selective ET<sub>A</sub> receptor blockade, which is in agreement with previous observations. The present findings clearly demonstrate that the vasoconstrictor tone mediated by endogenous ET-1 is more pronounced in patients with atherosclerosis than in healthy control subjects. Because the vasodilator response to selective ET<sub>A</sub> receptor blockade was similar in the 2 groups, the present results indicate that the ET<sub>B</sub> receptor plays a more important role in the vasoconstrictor tone mediated by endogenous ET-1 in atherosclerosis. Greater vasodilatation in response to nonselective ET<sub>A</sub> and ET<sub>B</sub> blockade than to selective ET<sub>A</sub> blockade has also been reported in patients with hypertension. Important differences from the present study and the study of Cardillo et al.
are that the present study evaluates the effect of ET receptor blockade in patients with normal blood pressure and severe atherosclerosis, whereas the study of Cardillo et al describes the situation in younger hypertensive patients without clinical symptoms of atherosclerosis. The results in the present study differ from those found in hypercholesterolemic subjects in which combined ET receptor blockade evoked less vasodilation than did selective ET<sub>A</sub> receptor blockade. In the present study, LDL cholesterol did not differ between the 2 study groups. In a recent study, it has been demonstrated that the administration of BQ123 evokes a more pronounced increase in the diameters of epicardial arteries in patients with coronary artery disease than in angiographically normal arteries. However, one limitation of that study was that the effect of BQ123 on blood flow and microvascular resistance could not be determined. The observations in the present study, together with our earlier finding of increased vasoconstriction to ET<sub>B</sub> receptor stimulation in patients with atherosclerosis and the in vitro findings of ET<sub>B</sub> receptor upregulation in the atherosclerotic human coronary artery and aorta, suggest that a shift toward more ET<sub>B</sub> -mediated vasoconstriction occurs in atherosclerosis. Taken together, the present findings suggest that a mixed ET<sub>A</sub> and ET<sub>B</sub> receptor antagonist is more effective than a selective ET<sub>A</sub> receptor antagonist in increasing blood flow and may, therefore, be of greater therapeutic value in patients with atherosclerosis.

The increase in FBF induced by combined ET<sub>A</sub> and ET<sub>B</sub> blockade in the patients was larger than what could be expected from the increase in blood flow induced by the ET<sub>A</sub> and ET<sub>B</sub> receptor antagonists separately. Thus, the combined effect was more than additive. The reason for this is unclear. One possibility is that ET<sub>B</sub> receptor blockade displaces ET-1 from ET<sub>B</sub> clearance receptors, as demonstrated by the increase in venous plasma levels of ET during the administration of BQ788, which results in increased stimulation of ET<sub>B</sub> receptors. This increased activation of vasoconstrictor ET<sub>A</sub> receptors may then be inhibited when ET<sub>A</sub> and ET<sub>B</sub> receptors are both blocked. However, if this was an important mechanism, the selective ET<sub>B</sub> antagonist would most likely reduce blood flow, which was not the case in the patients. Another possibility is that cross talk exists between the 2 receptors, such that if only 1 receptor is blocked, the other receptor can compensate for the loss of activity. Blockade of 1 of the receptors may attenuate an inhibitory action on the other receptor. Such a mechanism may explain the potentiated effect of combined ET<sub>A</sub> and ET<sub>B</sub> receptor blockade in the atherosclerotic patients in the present study. The finding that sodium nitroprusside resulted in similar degrees of vasodilatation in the 2 groups indicates that the ability of the VSMCs to relax did not differ between patients and control subjects.

Because ET<sub>B</sub> receptors are present on endothelial cells (where they cause dilatation) and on VSMCs (where they cause vasoconstriction), the overall effect mediated by ET-1 on the ET<sub>B</sub> receptor depends on a balance between these 2 actions. In healthy blood vessels, it seems as if the balance of effects of ET-1 favors vasodilatation via the endothelial ET<sub>B</sub> receptor. Our results demonstrating vasoconstriction in response to selective ET<sub>B</sub> receptor blockade with BQ788 in the somewhat older healthy control subjects supports this view. However, the vasodilator response evoked with BQ788 in the atherosclerotic patients suggests that this balance is shifted toward vasoconstriction via the VSMC ET<sub>B</sub> receptors in these patients. The vasodilator response to selective ET<sub>B</sub> blockade in the atherosclerotic patients may either be due to an upregulation of ET<sub>B</sub> receptors on VSMCs or to an impairment of ET<sub>A</sub>-mediated vasodilatation in the patients. In line with findings in hypertensive patients, we found that the vasodilator response to BQ788 faded over time in the patients. This could be related to an increase in the amount of ET-1 available to produce ET<sub>A</sub>-mediated vasoconstriction when the peptide is displaced from the ET<sub>A</sub> clearance receptors. Accordingly, an increase in circulating ET levels was found after 40 and 80 minutes of infusion of BQ788.

The degree of ET receptor inhibition was tested by the infusion of big ET-1, which reflects the vasoconstrictor effect of endogenously formed ET-1. Administration of big ET-1 for 30 minutes during combined ET<sub>A</sub> and ET<sub>B</sub> receptor antagonism did not significantly affect blood flow in either control subjects or patients, whereas a clear-cut reduction of FBF was induced in the absence of ET receptor blockade. In addition, BQ788 completely blocked the vasoconstrictor response to the ET<sub>B</sub> receptor agonist sarafotoxin 6c. These observations suggest that the doses of the antagonists were sufficient to inhibit the ET receptors.

There were no differences between patients and control subjects in basal FBF, and there were no changes in blood flow in the control arm or in systemic blood pressure in either protocol. Therefore, it seems unlikely that differences in autonomic vasomotor tone interfered with the observed changes in blood flow. Flow-dependent dilatation tended to be reduced in the patients, but there was no difference in acetylcholine-mediated dilatation between patients and control subjects. These findings are in agreement with previous observations suggesting that endothelial function is reduced at an older age and may reflect subclinical disease of the control subjects in the present study. One difference between the study groups was ongoing medication. Because most patients were treated with acetylsalicylic acid, all subjects were given this compound to avoid differences due to the possible stimulation of prostacyclin release by ET<sub>B</sub> receptor stimulation. This may be one of the reasons why the present results in the control subjects appear to be a little different from the results reported by some of the previous investigators. All other drugs were withheld for at least 4 half-lives to avoid possible interference with vascular reactivity. Because both NO and angiotensin II modulate ET-1 production, it cannot be excluded that nitrates, ACE inhibitors, and angiotensin II receptor antagonists taken by some of the patients affected their ET-1 production, which may influence the results. Another limitation of the present study is that the vascular effects were investigated in the forearm. It may be argued that the forearm circulation does not properly reflect changes in other vascular beds. However, atheromatous lesions in the arteries of the forearm are correlated with atherosclerotic lesions in the arteries of other vascular beds, such as coronary arteries and carotid arteries.

In conclusion, the present study is the first to demonstrate that the vasodilator response to combined ET<sub>A</sub> and ET<sub>B</sub>
receptor blockade in patients with atherosclerosis is greater than that to selective ET\textsubscript{A} receptor blockade and compared with the response in healthy control subjects, indicating an enhanced ET\textsubscript{B}-mediated vascular tone in vivo in these patients. These findings may have important therapeutic implications, inasmuch as combined ET\textsubscript{A} and ET\textsubscript{B} receptor antagonism seems to be more efficient than selective ET\textsubscript{A} receptor antagonism in reducing vascular tone in patients with atherosclerosis.

Acknowledgments

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References

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