Comparison of Metabolic and Vasoconstrictor Stimuli on Coronary Vascular Resistance in Man

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SUMMARY Coronary blood flow (CBF) is considered proportional to metabolic demand (MVO₂). However, recent studies have reported inappropriate vasoconstrictor response to α-adrenergic stimulation in patients with coronary artery disease (CAD). To assess the interaction of vasodilatory reserve and adrenergic vasoconstriction, we compared changes in coronary vascular resistance (CVR) during the metabolic stress of rapid atrial pacing and during the α-adrenergic stimulus of cutaneous cold (cold pressor test, CPT) in 13 control patients and 14 patients with CAD. Similar heart rates were achieved with pacing in both control and CAD patients, and both groups had a similar hypertensive response to CPT; thus, both pacing and CPT increased major determinants of MVO₂. In association with this increased MVO₂, CVR decreased with rapid pacing in control and CAD patients (−24% and −27%, respectively), but increased in CAD patients (+24%) during CPT. Seven of 13 CAD patients actually had a reduction in CBF, whereas CBF increased in all control patients in response to CPT. Compression of intramural coronary vessels by elevated ventricular diastolic pressure was excluded as a pathogenic mechanism for increase in CVR in two CAD patients who showed marked reduction in CBF during CPT.

These data are further evidence that patients with CAD may have limited coronary vasodilatory mechanisms. Superimposed α-adrenergically mediated coronary vasoconstriction may contribute significantly to myocardial ischemia in patients with CAD.

ALTHOUGH CORONARY BLOOD FLOW (CBF) has been regarded as regulated primarily by the metabolic demands of the myocardium, extensive evidence indicates that such coronary autoregulation can be overridden at least partially by adrenergic vasoconstriction both clinically and experimentally. Enhanced myocardial oxygen demand would lead to myocardial ischemia unless increased perfusion pressure or a compensatory decrease in coronary vascular resistance (CVR) served to provide the required increase in CBF, and thus oxygen supply. In patients with coronary artery disease (CAD), angina pectoris is provoked when increased myocardial oxygen demand exceeds a limited supply. Coronary artery vasoconstriction has been documented in Prinzmetal's variant angina and suggested as a possible pathogenic mechanism in patients with normal coronary anatomy who have sustained myocardial infarctions. Normal coronary vascular tone can respond to sympathetic and parasympathetic stimuli. Orlick and co-workers recently compared normal subjects with cardiac-denervated transplant patients and concluded that α-adrenergic tone accounts for about 12% of resting CVR in man. Withdrawal of this neural component was considered to be responsible for the initial vasodilatory response to a metabolic stimulus. Recent studies in patients with CAD have reported defective vasodilatory mechanisms. Patients with CAD demonstrated inappropriate coronary vasoconstrictor response to cutaneous cold, an α-adrenergic stimulus. Berndt et al. recently reported that spontaneous angina is associated with a significantly lower double product (heart rate × systolic blood pressure) and triple product (heart rate × systolic blood pressure × ejection time) than pacing-induced ischemia. They suggest that changes in CBF, rather than myocardial oxygen consumption, may cause spontaneous pain at rest in patients with the clinical syndrome of unstable angina. If such adrenergic mechanisms do play a role in ischemic heart disease, α-adrenergic blockade should be considered in the treatment of myocardial ischemia.

The present investigation compares the primary metabolic stimulus of pacing-induced tachycardia and the α-adrenergic stimulus of cutaneous cold on CBF and CVR both in subjects with normal coronary arteries and in subjects with obstructive CAD. Thus, we hope to clarify further the pathophysiologic mechanisms underlying transient myocardial ischemia.

Methods

The study population comprised 13 patients with normal coronary arteriograms and 14 patients with significant CAD involving one or both major divisions of the left coronary artery. Patients with normal coronary anatomy (control group) were studied to define the etiology of chest pain syndromes. No patients in the control group had electrocardiographic evidence of myocardial infarction or exercise tests positive for ischemic heart disease. The patients with significant CAD had 70% or greater obstruction in at least one of the major branches of the left coronary arteries.
of the 13 patients with normal coronary anatomy and nine of the 14 patients with obstructive CAD were on propranolol therapy before cardiac catheterization; propranolol, however, was discontinued 8 hours before the study. Patients with isolated obstruction of the right coronary artery were excluded from the study. The protocol and consent forms were approved by the Human Studies Committee of the Peter Bent Brigham Hospital. Resting left ventricular end-diastolic pressure was measured and left ventriculography and coronary arteriography performed at either a previous catheterization or before this study. If the research study was coincident with diagnostic cardiac catheterization, sufficient time was allowed after angiography for hemodynamics to return to baseline values. An arterial catheter was introduced percutaneously into either the femoral or brachial artery and a thermocoupled coronary sinus catheter with a pacing tip was positioned in the coronary sinus via a brachial vein cutdown. The position of the catheter was confirmed angiographically and rechecked frequently. Coronary sinus blood flow was measured by the continuous thermocoupled method of Ganz et al., as previously used in our laboratory. Electrocardiogram, arterial blood pressure, and coronary sinus blood flows were simultaneously recorded at rest, during rapid atrial pacing, and during the cold pressor test.

After recordings at rest, heart rate was controlled by pacing at a sublingual rate of approximately 95 beats/min. With a steady state reestablished, the patient's hand was immersed in a mixture of water and ice for 1 minute, and coronary sinus flow and arterial pressure, mean and phasic, were continuously recorded. Measurements were taken at peak mean arterial pressure, which indicated maximum response to the cutaneous cold stimulus. The cold stimulus was removed, and basal conditions were reestablished. Heart rate was then increased by 20 beats/min every 2 minutes until angina, atrioventricular block, or a rate of 150 beats/min was reached. Flow and pressure recordings were taken at least 2 minutes after maximal heart rate was reached, and the pacing stimulus was then stopped.

CVR was calculated as the quotient of mean arterial pressure and coronary sinus flow, \(^1,2,11,13,15,17\) and the "double product" (a measure of myocardial metabolic requirements) was calculated as the product of mean arterial pressure and heart rate. Comparison of heart rate, mean arterial pressure, coronary sinus blood flow, and CVR was made between the resting basal state and rapid atrial pacing, and the cutaneous cold stimulation.

To determine if an increase in left ventricular end-diastolic pressure might account for an increase in CVR by decreasing left ventricular perfusion through transmural compression of coronary vessels, left ventricular diastolic pressure was recorded with a micromanometer-tipped catheter during both cutaneous cold stimulation and rapid atrial pacing in two patients with CAD who had a particularly marked fall in CBF during the cold pressor test. In these two patients, CVR was also calculated as the ratio of [mean aortic diastolic pressure-mean left ventricular diastolic pressure]/CBF.

Data were analyzed using the \(t\) test for paired and unpaired variables, and differences were considered significant when \(p < 0.05\).

**Results**

**Clinical Data**

Clinical data are summarized in table 1. There were more women in the control group, but there was no significant difference in age between the two groups. In the control group, resting hemodynamics were normal and no patient had ventricular dysfunction; left ventricular end-diastolic pressure was 10 ± 1 mm Hg (mean ± SEM) and left ventricular ejection fraction 0.65 ± 0.03.

Patients with CAD had slightly higher left ventricular end-diastolic pressures at rest (12 ± 1 mm Hg) than patients in the control group. Six of the 14 patients with CAD had expected abnormalities in left ventricular wall motion, and left ventricular ejection fraction was lower than in the control group (0.57 ± 0.03).

**Pacing Results**

With pacing-induced tachycardia, heart rate in the control group was increased from 79 ± 4 beats/min to 145 ± 6 beats/min (fig. 1). Mean arterial pressure rose significantly during pacing (99 ± 4 mm Hg to 105 ± 4 mm Hg, \(p < 0.05\)), and the double product (heart rate \(\times\) mean arterial pressure) increased from 7818 ± 465 mm Hg/min to 15,428 ± 912 mm Hg/min (\(p < 0.001\)), indicating a major increase in myocardial oxygen demand. The increase in heart rate, mean arterial pressure, and double product was accompanied by an increase in coronary sinus blood flow (125 ± 11 ml/min to 187 ± 18 ml/min, 13/8)

<table>
<thead>
<tr>
<th>Table 1. Clinical Data</th>
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<tbody>
<tr>
<td>Group (n)</td>
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<tr>
<td>-------------</td>
</tr>
<tr>
<td>Control (13)</td>
</tr>
<tr>
<td>CAD (14)</td>
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Abbreviations: LVEDP = left ventricular end-diastolic pressure; EF = ejection fraction by angiography; LVWM = left ventricular wall motion.
p < 0.005), and a decrease in CVR (0.87 ± 0.07 to 0.64 ± 0.06 mm Hg/ml/min, p < 0.05), indicating vasodilation (fig. 2).

The effects of pacing-induced tachycardia in the CAD group are shown in figure 1. Patients with CAD had a slightly lower heart rate at rest (73 ± 4 beats/min) and with maximum pacing (135 ± 4 beats/min) than patients in the control group, but these differences were not significant. Mean arterial pressure rose significantly (97 ± 4 to 111 ± 5 mm Hg) and the double product increased (7212 ± 676 mm Hg/ml/min to 15,013 ± 947 mm Hg/minute, p < 0.001) as in the control group. As shown in figure 2, coronary sinus blood flow increased (127 ± 11 ml/min to 215 ± 21 ml/min, p < 0.01) and CVR fell (0.79 ± 0.06 to 0.57 ± 0.06 mm Hg/ml/min (p < 0.005), responses similar to those of the control group. Thus, patients with obstructive CAD and patients with normal coronary arteries both responded to the increased metabolic demand resulting from pacing-induced tachycardia with increased CBF and decreased CVR, suggesting coronary vasodilatation.

Cold Pressor Test

In patients with normal coronary anatomy, heart rate was maintained constant at 101 ± 2 beats/min (fig. 3). The cold pressor test elicited an increase in mean arterial pressure of 18 mm Hg (105 ± 3 mm Hg to 123 ± 4 mm Hg, p < 0.01), thus increasing the double product significantly (10,715 ± 426 mm Hg/ml/min to 12,544 ± 492 mm Hg/ml/min p < 0.005). As shown in figure 4, coronary sinus blood flow increased proportionally, from 149 ± 13 to 187 ± 19 ml/min, and CVR was unchanged (0.73 ± 0.07 to 0.70 ± 0.07 mm Hg/ml/min).

The patients with obstructive CAD had a significantly different response. In this group, heart rate was controlled at 96 ± 2 beats/min. The cold pressor test elicited an increase in mean arterial pressure of 20 mm Hg (102 ± 4 mm Hg to 122 ± 5 mm Hg, p < 0.01), and the double product increased significantly (9872 ± 514 mm Hg/ml/min to 11,781 ± 631 mm Hg/ml/min, p < 0.05) (fig. 3). In contrast to the control group (fig. 4), coronary sinus flow did not in-
creases proportionally with pressure in the CAD group (151 ± 9 ml/min to 147 ± 11 ml/min), and in eight of the CAD patients, coronary sinus flow decreased. Calculated CVR increased 24% in the CAD group, (0.69 ± 0.04 to 0.86 ± 0.05 mm Hg/ml/min, p < 0.05). Thus, despite similar increases in an index of myocardial oxygen demand (the double product), patients in the control group and patients in the CAD group exhibited disparate responses in CBF to the cold pressor test.

Role of Left Ventricular Diastolic Pressure

The CAD patients exhibited altered left ventricular function on angiogram, and had a slightly higher resting left ventricular diastolic pressure than the control patients. To assess whether the increase in CVR in CAD patients in response to cutaneous cold might be caused by an increase in left ventricular diastolic pressure and concomitant transmural compression of the distal resistance vessels, left ventricular diastolic pressure was measured in two CAD patients whose response to the cold pressor test was a marked reduction in coronary sinus flow (table 2). CVR (quotient of mean arterial pressure and coronary sinus flow) increased from 0.80 to 1.01 mm Hg/ml/min in patient A, and from 0.81 to 1.10 mm Hg/ml/min in patient B. When CVR was calculated as the ratio of [mean arterial diastolic pressure-mean left ventricular diastolic pressure]/CBF, a significant rise in CVR was still noted. Thus, the reduction in coronary sinus flow and increase in CVR in response to cutaneous cold cannot be explained by extrinsic compression of intramural coronary vessels in these patients.

Angina with Pacing and Cold Pressor Test

Three patients with CAD developed angina during both pacing and the cold pressor test. As shown in table 3, the double product was lower with angina induced by the cold pressor test than with angina induced by pacing, and CVR was higher during angina with the former stimulus than the latter. This suggests that ischemic pain in these patients occurred at a
Table 2. Response to CPT in Two Patients

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Control CPT</td>
<td>Control CPT</td>
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<tr>
<td>CBF (ml/min)</td>
<td>156</td>
<td>143</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>125</td>
<td>145</td>
</tr>
<tr>
<td>LVDP (mm Hg)</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Coronary vascular resistance</td>
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<td></td>
</tr>
<tr>
<td>MAP/CBF (mm Hg/ml/min)</td>
<td>0.80</td>
<td>0.81</td>
</tr>
<tr>
<td>ADP-LVDP/CBF (mm Hg/ml/min)</td>
<td>0.72</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Abbreviations: CBF = coronary blood flow measured by thermodilution technique; MAP = mean arterial pressure; LVDP = mean left ventricular diastolic pressure; ADP = mean aortic diastolic pressure; CPT = cold pressor test.

Discussion

Transient myocardial ischemia in man has traditionally been considered to represent an imbalance between a fixed, restricted myocardial oxygen supply and enhanced metabolic demand. In the experimental animal, the normal coronary vascular bed can respond to neural and pharmacologic stimuli. Central sympathetic stimulation results in direct coronary vasoconstriction mediated by activation of \( \alpha \)-adrenergic receptors. In the conscious dog, release of \( \alpha \)-adrenergic tone by carotid-sinus stimulation will produce profound reductions in CVR, while administration of norepinephrine results in sustained coronary vasoconstriction despite increased myocardial oxygen requirements. Physiological investigations of CVR in man have been limited by the inability to measure rapid changes in coronary flow. Nitrous oxide washout and coincidence counting techniques will not permit second-to-second detection of changes in CBF. The coronary sinus thermodilution technique permits determination of coronary sinus flow, which closely approximated left ventricular myocardial blood flow. The technique is comparable to flow as determined by an electromagnetic flowmeter in the open-chest dog (\( r = 0.90 \)). Duplicate measurements of coronary sinus blood flow in a stable physiological setting vary by less than 5%.

Recent comparisons between the denervated transplanted heart and normal hearts have provided physiological evidence for important tonic \( \alpha \)-adrenergic coronary vasoconstrictor activity in man. Measuring CVR by coronary sinus thermodilution technique, Orlick and colleagues showed that the two patient populations had significantly different hemodynamic responses to intravenous administration of phentolamine. Normal subjects had a 20% decrease in CVR after \( \alpha \)-adrenergic blockade, while cardiac transplant patients had a 9% diminution in CVR. There was no significant difference in metabolic demand, reflected as the product of systolic arterial pressure and heart rate, between the two groups. These results were interpreted to suggest that \( \alpha \)-adrenergic tone accounts for approximately 12% of resting CVR in man. These investigators also compared the response of the same groups to the metabolic stimulus of rapid atrial pacing. Normal subjects exhibited a rapid rise in CBF to metabolic demand that was not seen in transplanted hearts or in those normal subjects pretreated with the \( \alpha \)-adrenergic blocking agent, phentolamine. After 20 seconds of atrial pacing, coronary vasodilation and CVR were comparable in the two groups. This suggested to the authors that initial coronary vasodilation to metabolic stimulation may be mediated by withdrawal of \( \alpha \)-adrenergic constrictor tone.

Such competition between \( \alpha \)-adrenergic vasoconstricting influences and metabolically induced vasodilation has been more recently demonstrated by Mohrman and Feigl, who reported definite competition between sympathetic vasoconstriction and metabolic vasodilatation in the canine coronary circulation. Using a closed-chest dog anesthetized with chloralose, they showed that \( \alpha \)-adrenergic vasoconstrictor tone restricted metabolically induced coronary vasodilation by 30%. In a previous study we found a 27% rise in CVR during the application of cutaneous cold in patients with CAD. In three patients, CBF actually fell, despite a rise in arterial blood pressure, and angina pectoris developed. \( \alpha \)-adrenergic blockade with phentolamine prevented increases in arterial blood pressure or CVR in response to the cutaneous cold stimulus. In the present investigation, we have compared changes in the coronary vascular tone of control and CAD patients to two different stimuli, rapid atrial pacing and application of cutaneous cold. Each stimulus increased the major determinants of metabolic demand for both groups. The results show that the \( \alpha \)-adrenergically

Table 3. CVR and Double Product During Angina

<table>
<thead>
<tr>
<th>Patient</th>
<th>CPT</th>
<th>Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CVR (mm Hg/ml/min)</td>
<td>HR×MAP (mm Hg/min)</td>
</tr>
<tr>
<td>D</td>
<td>0.64</td>
<td>9770</td>
</tr>
<tr>
<td>E</td>
<td>1.01</td>
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</tr>
<tr>
<td>F</td>
<td>0.66</td>
<td>15390</td>
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</table>

Abbreviations: CVR = coronary vascular resistance; CPT = cold pressor test; HR = heart rate; MAP = mean arterial pressure.
mediated reflex stimulus of cutaneous cold caused a significant increase in CVR in patients with CAD. This response differed qualitatively from that seen with rapid atrial pacing, where coronary vasodilation accompanied the enhanced metabolic demand.

The double product is proportional to myocardial oxygen consumption,\textsuperscript{22-26} and increased significantly with both pacing and adrenergic stimuli. Other determinants of myocardial oxygen consumption which affect wall stress — systolic ejection time, contractility, and left ventricular size — were not readily measured in this study but might be significant.\textsuperscript{26, 27} CBF in patients in both groups increased with rapid atrial pacing, as reported by other investigators using similar methods,\textsuperscript{28, 29} and indicated a competent response of vasodilatory mechanisms in normal and diseased coronary arteries to a purely metabolic stimulus. However, with $\alpha$-adrenergic stimulation and subsequent enhanced metabolic demand, control patients failed to show vasodilatation, while patients with significant CAD showed paradoxic vasoconstriction.

Three of the patients with CAD had angina during both pacing and cutaneous cold. In each instance, the double product was lower at the time of angina during cutaneous cold than at the time of angina during rapid atrial pacing. Corresponding CVR was higher in each case of cold-induced angina. This observation suggests that actual vasoconstriction may have precipitated transient ischemia, and is in agreement with the recent observations of Berndt et al.,\textsuperscript{19} who report seven patients with CAD whose double product (heart rate $\times$ systolic pressure) and triple product (heart rate $\times$ systolic pressure $\times$ ejection time) were significantly lower at the onset of spontaneous angina than during pacing-induced angina. Hattenhauer and Neill\textsuperscript{20} reported four patients who developed angina in response to cold air inhalation at a lower double product than in response to pacing-induced angina. Both studies concluded that changes in CBF rather than myocardial oxygen consumption might be responsible for angina in certain patients with CAD. Such a hypothesis has recently been supported by Raizner and co-workers,\textsuperscript{5} who reported angiographic evidence for vasospasm during the cold pressor test in patients with CAD not suspected of having Prinzmetal's variant angina.

It seems unlikely that the increases in CVR in CAD patients we report are mediated by extrinsic compression of the distal coronary vasculature by increased left ventricular diastolic pressure, with a resulting decrease in coronary perfusion pressure. In two patients, there was still a significant increase in CVR when left ventricular diastolic pressure was incorporated into the numerator. Active coronary vasoconstriction is a probable pathogenic mechanism in these two patients.

Certain limitations of this study should be emphasized. First, while the accuracy of the thermodilution technique for coronary sinus blood flow measurement is suggested by animal studies reported by Ganz et al.\textsuperscript{20} and VanDevantner et al.,\textsuperscript{31} the method measures combined flow in all areas of myocardium which drain to the coronary sinus. Thus, no changes in flow might be detected if equal and opposite flow changes occurred in regional beds within the drainage area. For example, the opening (or closing) of large, collateral channels between normally perfused and ischemic regions could result in substantial redistribution of flow with no change in net flow. Thus, CVR might have decreased in certain regional beds during the cold pressor test despite a calculated increase in resistance for the entire coronary sinus drainage area.

Second, small shifts in the coronary sinus catheter tip position can potentially result in changes in measured flow by including or excluding venous drainage branches. In addition, atrial pacing could potentially alter geometric relations of the right atrium and coronary sinus, and has been implicated as causing reflux of right atrial blood into the coronary sinus.\textsuperscript{32} While such considerations may have introduced into our results an error of unknown magnitude, it seems unlikely that such an error would systematically influence the results in the CAD group differently from the results in the control group. In the report by Mathey and co-workers,\textsuperscript{29} a reflux of blood from the right atrium to the coronary sinus occurred in dogs during interventions which raised right atrial pressure. This reflux caused falsely high estimations of CBF by the thermodilution technique, compared with electromagnetic measurement of CBF, which served as a control. If a similar artifact were introduced into this study during pacing-induced tachycardia, true flows might have been lower, and the fall in resistance might have been less than that observed. With the cold pressor studies, if true flow were lower, the increases in CVR would be even greater than reported. Substantial increases in coronary flow with rapid atrial pacing in this study are similar to the findings of others, who used different methods to measure CBF.\textsuperscript{1, 32}

Third, the increased calculated coronary resistance found in this study may in part have been due to factors other than adrenergically mediated coronary vasoconstriction. Ellis and Klocke\textsuperscript{34} reported that increased preload produced by elevation of mean left atrial pressure from 5 mm Hg to 20 mm Hg led to increased resistance to myocardial blood flow, particularly in the subendocardium, presumably due to the transmural compressive force of the increased left ventricular diastolic pressure. We have tried to analyze for this effect in two patients with CAD in whom total coronary sinus flow fell during the cold pressor test and in whom left ventricular diastolic pressures were simultaneously recorded. In these two patients, calculated CVR rose, even when corrected for preload. Nevertheless, this factor might have played some part in causing the observed changes in resistance. We could not distinguish subendocardial from subepicardial flow and resistance in our patients, and cannot estimate the potential magnitude of this important effect.

We present the following hypothesis to explain the data of this study. With a primary metabolic stimulus, both control patients and patients with CAD are able
to respond to depressed local oxygen tension, increased adenosine concentration, and parasympathetic and \( \beta \)-adrenergic mechanisms with coronary vasodilatation. Hence, CVR falls. When heart rate is increased to 100 beats/min, and an \( \alpha \)-adrenergic stimulus is superimposed, the control patients can offset the vasoconstrictror stimulation because of substantial vasodialatory reserve, so that no change occurs in calculated CVR. However, when patients with CAD are paced to a similar subbingual rate, lesions in the proximal conductance vessels have resulted in near-maximal metabolic vasodilation in the more distal resistance vessels. In this instance, when a competitive \( \alpha \)-adrenergic vasoconstrictor influence is superimposed, vasoconstriction predominates. CBF fails to rise, or even falls, despite elevated coronary perfusion pressure, and hence calculated CVR rises.

Myocardial ischemia may therefore result from an imbalance between myocardial oxygen supply and demand, caused by primary changes in either variable. Various stresses in patients with CAD, such as cold exposure or emotional excitement, may exert a pathophysiologic effect through both mechanisms. Chronic \( \alpha \)-adrenergic blocking drugs, particularly those which are cardioselective, may have a role in the management of certain patients with chronic angina pectoris and ischemic heart disease.

References


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