Is Coronary Flow Reserve in Response to Papaverine Really Normal in Syndrome X?

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Background An impaired coronary flow reserve in syndrome X has been demonstrated by many studies. Recently, however, a normal coronary flow reserve in response to papaverine was reported, but the number of patients in these studies was small. The aim of this study was to investigate whether coronary flow reserve in response to intracoronary papaverine is really impaired in syndrome X.

Methods and Results We investigated 53 syndrome X patients (typical angina, a positive exercise test, and completely normal coronary arteries on angiography) and 26 heart transplant patients with normal coronary arteries (control group). All antianginal medications were stopped 48 hours before the study. A 3.6F intracoronary Doppler catheter was positioned in the proximal left anterior descending coronary artery and was connected to a Millar velocimeter. The coronary blood flow velocity at rest and in response to a hyperemic dose of papaverine was measured. Coronary flow reserve was defined as the ratio of hyperemic coronary blood flow velocity in response to papaverine and resting coronary blood flow velocity. The coronary flow reserve (mean±SD) in the syndrome X group was 2.72±1.39. The coronary flow reserve in the control group was significantly higher at 5.22±1.26 (P<.01). In both groups there was no significant difference in the heart rate or the mean arterial pressure during the study.

Conclusions Our study shows that coronary flow reserve in response to intracoronary papaverine is impaired in syndrome X patients. (Circulation. 1994;89:1998-2004.)

Key Words • syndrome X • coronary flow reserve • papaverine

Syndrome X Group
Fifty-three syndrome X patients were studied, 22 men and 31 women. All patients gave a history of chest pain typical of angina pectoris. There was no evidence of cardiovascular disease on physical examination. The exercise ECG was positive in every patient. The Bruce protocol was used for the exercise test, and the test was said to be positive if there was at least 1 mm of horizontal or downward-sloping ST segment depression at 80 milliseconds after the J-point. The left ventricle and the coronary arteries were completely normal on angiography, as confirmed by two independent observers; if there was no consensus between the two observers, patients were excluded. All patients had to have completely smooth coronary arteries on angiography; patients with even minor irregularities were excluded from the study. 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 catheterization and were taking antianginal medications.

Transplant Group
Twenty-six heart transplant patients were studied, 22 men and 4 women. All patients were more than 1 year after their heart transplant operation. None of these patients had chest pain. There were no ischemic changes on exercise testing in these patients. Coronary flow reserve studies were performed at the time of their routine follow-up cardiac catheterization. Currently, we follow our transplant patients annually with repeat coronary angiography for the detection of coronary occlusive disease. In all patients, the coronary angiograms were reviewed before the study by two independent observers, and only patients with completely normal coronary arteries were included in the study.

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

Blood Analysis
Patients’ blood was analyzed for full blood count, serum urea and electrolytes, and fasting lipids on the morning of their cardiac catheterization study.

Ethical Approval
The study was approved by the Huntingdon Health Authority Ethical Committee as part of a coronary flow reserve study. Full informed consent was obtained from all patients before the study.

Catheterization Protocol
All the patients were fasted overnight for their cardiac catheterization. All cardiac medications had been stopped for at least 48 hours. Patients were premedicated with diazepam 10 mg before their cardiac catheterization. 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 radiopaque contrast medium (Niopam). Cine film recordings were performed in multiple projections. The proximal left anterior descending coronary artery was centered for optimal viewing after the initial angiograms had been obtained. To eliminate vasoactive effects of the contrast medium, at least 10 minutes was allowed to elapse before the coronary blood flow study.

Heparin sodium 10 000 units IV was then given. An 8F angioplasty guiding catheter was positioned at the left coronary ostium. Through this, a 0.014-in guide wire was advanced into the distal part of the left anterior descending coronary artery. By a monorail technique, a 3.6F 20-MHz Doppler-tipped catheter (Schneider) was then advanced over the guide wire and positioned in the proximal segment of the left anterior descending coronary artery. The Doppler catheter was connected to a Millar velocimeter (model MDV-20, Millar Instruments). The velocimeter was rate gated and calibrated so that 1 kHz equaled 3.75 cm/s. The Doppler catheter and the range gate of the velocimeter were adjusted to obtain high-quality phasic and mean coronary blood flow velocity signals. These signals were recorded on a Mingograf recorder (Siemens-Elema). The range gate of the Doppler velocimeter was kept constant throughout the study.

Baseline mean resting and phasic coronary blood flow velocities were then recorded. After an initial 2-mg intracoronary test dose of papaverine hydrochloride through the guide catheter, further injections of up to 14 mg papaverine (2 mg/mL in 0.9% saline) were given in 2-mg increments until maximum flow was achieved. The hyperemic response was recorded in the form of maximum mean and phasic blood flow velocity.

Coronary Angiography
Left ventricular ejection fraction was calculated from a monoplane angiogram in a 30° right anterior oblique projection by the area-length method. To assess the effect of intracoronary papaverine on the left anterior descending coronary artery diameter, angiography was performed in a preselected view before and 20 seconds after the hyperemic dose of intracoronary papaverine. Quantitative measurements of the coronary artery diameters were made with digital electronic calipers (Sandhill Scientific Inc) by an independent observer. This method has been used previously to assess the arterial diameter of coronary vessels and is reproducible with minimal interobserver and intraobserver variation; it has been described in detail. Briefly, the selected view of the left anterior descending coronary artery was projected by a Tagarno system, and the arterial diameter was measured from the tracings of the projected images in diastole 2 mm from the tip of the Doppler catheter.

Coronary Flow Reserve
Coronary flow reserve was defined as the ratio of mean flow velocity achieved at peak hyperemia to the mean resting flow velocity. Doppler velocity recordings were also 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 is the 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 millimeters per minute), the resting cross-sectional area of the coronary artery (in square centimeters) was multiplied by the mean coronary blood flow velocity (in centimeters per second) and by 60 seconds.

Statistical Analysis
Values are given as mean±SD. Unpaired t tests were used for comparison of group means. Paired t tests were used to compare the arterial diameter measurements before and after the hyperemic dose of papaverine. Differences were considered to be statistically significant at the P<.05 level.

Results
The patient variables are shown in Table 1. The mean age of the syndrome X group was 56 years (range, 36 to 69 years); that of the transplant group, 44 years (range,
TABLE 2. Echocardiographic Measurements

<table>
<thead>
<tr>
<th></th>
<th>Syndrome X Group (n=53)</th>
<th>Transplant Group (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVPWT, mm</td>
<td>9.3±0.6</td>
<td>9.7±0.5</td>
</tr>
<tr>
<td>ST, mm</td>
<td>8.8±0.9</td>
<td>9.1±0.6</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>29.6±3.3</td>
<td>28.5±2.0</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>48.6±2.8</td>
<td>46.9±2.9</td>
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LVPWT indicates left ventricular posterior wall thickness; ST, septal thickness; LVEDD, left ventricular end-diastolic dimension; and LVESD, left ventricular end-systolic dimension. Values are expressed as mean±SD.

23 to 56 years). The mean duration after the heart transplant was 42±19 months. There was no significant difference in the left ventricular ejection fractions between the two groups.

Echocardiographic Measurements

The echocardiographic measurements are presented in Table 2. There were no significant differences between the two groups.

Exercise Test Data

The exercise test data are presented in Table 3. The transplant group had a significantly higher resting heart rate and systolic pressure than the syndrome X group. All the syndrome X patients developed their typical anginal chest pain during the exercise test, and the exercise test was positive in all patients as defined earlier. The maximum ST-segment depression in the syndrome X group was 1.84±0.63 mm. The exercise test was discontinued in all transplant patients because of fatigue, and none of the patients developed chest pain. There were no significant ECG changes on exercise in any of the transplant group. The peak heart rate response and the rate-pressure product were significantly higher in the syndrome X group. The maximal exercise duration was significantly shorter in the transplant group.

Papaverine Dose-Response Data

In the syndrome X group, an 8-mg dose of papaverine produced maximal hyperemia in only 34 (64%) of the 53 patients and a 10-mg dose in 46 (87%), but maximal hyperemic response was obtained in all patients after 12 mg of papaverine. Similarly, in the transplant group, an 8-mg dose of papaverine produced maximum vasodilation in only 18 (69%), a 10-mg dose in 22 (85%), and a 12-mg dose in all.

Coronary Flow Reserve Measurements

The mean values for the measurements of coronary flow velocity and coronary flow reserve are shown in Table 4. There was no significant change in the heart rate or mean arterial pressure on injection of the hyperemic dose of intracoronary papaverine. The coronary flow velocity at rest was not significantly different between the two groups. The coronary flow reserve was significantly lower in the syndrome X group (2.72±1.39) compared with the transplant group (5.22±1.26; P<.01; Figure).

Quantitative Measurements

There was no significant difference in the resting diameter of the left anterior descending coronary artery in the region of the Doppler catheter between the syndrome X group (3.87±0.21 mm) and the transplant group (3.92±0.11, P=NS). There was no significant difference in estimated coronary blood flow at rest (coronary blood flow velocity corrected for changes in coronary cross-sectional area) between the syndrome X and transplant groups (63±33 versus 54±28 ml/min, P=NS). The left anterior descending coronary artery diameter also did not change significantly at peak hyperemia after papaverine in both the syndrome X (3.91±0.20 mm, P=NS) and the transplant (3.98±0.15 mm, P=NS) groups. The mean percentage change at peak hyperemia in the luminal diameter of the left anterior descending coronary artery was 4.0±6.0% in the syndrome X group and 1.6±2.4% in the transplant group. The coronary flow reserve calculated as the ratio of volumetric flow at rest (mean Doppler velocity readings corrected for the changes in arterial cross-sectional area) and volumetric flow after peak hyperemic dose of papaverine was again significantly lower in the syndrome X group (2.78±1.41) compared with the transplant group (5.39±1.38, P<.01).

Discussion

An impaired coronary flow reserve in syndrome X was first reported by Opherk et al.9 This was subsequently confirmed by several investigators using different techniques and has been reviewed recently by Cannon et al.1 A reduced coronary reserve in conjunction with the presence of angina and ECG changes closes the loop of the classical ischemic cascade, and this has been used to support the presence of myocardial ischemia in syndrome X. However, the recent demonstration of a normal coronary flow reserve in
response to papaverine in syndrome X has raised doubts.2,3

Simonetti et al2 measured the vasodilatory responses to a maximal vasodilatory dose of intracoronary papaverine in 20 consecutive patients with normal coronary arteries and chest pain using an intracoronary Doppler catheter. Eleven of these patients had a positive exercise test, and their responses were compared with the remaining 9 with a negative exercise test. In patients with a positive exercise test, the coronary flow reserve was 4.13±0.33 (mean±SEM) compared with 4.13±0.18 in patients with a negative exercise test. A depressed coronary flow reserve (defined as being <3.5) was found in only 2 of the patients with a positive exercise test, and both of these had a history of hypertension without left ventricular hypertrophy. According to the definition of an impaired coronary flow reserve as being <3.5, 40 (76%) of the 53 syndrome X patients and only 1 (4%) of the 26 heart transplant patients had an impaired coronary flow reserve in our study.

Holdright et al3 using an identical technique, compared the coronary flow reserve in 7 syndrome X patients (those with chest pain, a positive exercise test, and normal coronary angiogram) with 8 control patients (chest pain, negative exercise test, and normal coronary angiogram). Coronary flow reserve was 3.98±0.74 (mean±SEM) in the syndrome X group and 3.70±0.49 in the control group. Both groups of investigators concluded that coronary flow reserve in response to papaverine is normal in syndrome X. However, the results of our study clearly indicate that the coronary flow reserve in response to intracoronary papaverine is impaired in syndrome X. This is in keeping with the other numerous reports of an impaired coronary flow reserve in syndrome X.1

It is clear from our results that there is a scatter in the coronary flow reserve values, with some syndrome X patients having a high flow reserve. This raises the possibility that there may be no statistical difference between syndrome X and true normal subjects with flow reserves of 3.5 to 4.0. However, a normal heart with normal coronary arteries is capable of increasing coronary flow by approximately fourfold to fivefold.10 Previous animal studies have demonstrated that intracoronary papaverine is capable of inducing maximal hyperemia, resulting in a fourfold to sixfold increase in coronary blood flow after intracoronary administration.11-13 Several studies in humans have shown that the coronary flow reserve values obtained in response to papaverine, by the same technique as used in our study, averaged 4.7,14-17 with a wide range of flow reserve values (3.7 to 8.3). It is notable that a great many syndrome X patients in our study had a flow reserve <3.0 (34 patients, 64%) or <3.5 (40 patients, 76%). In comparison, only 1 patient (4%) in the transplant group had a flow reserve <3.5. It would not be unreasonable to conclude that the findings of our study demonstrate an impaired coronary flow reserve in response to papaverine in syndrome X, since the flow reserve is reduced well below the 95% confidence intervals previously defined for normal values as well as compared with the control measurements in the heart transplant group.

In the studies reported by Simonetti et al2 and Holdright et al,3 the number of patients is small and a proper control group is lacking. The control groups in both studies consisted of patients with chest pain, normal coronary angiograms, and a negative exercise test. In many previous studies of patients with chest pain and normal coronary arteries, such patients have been classified as "syndrome X." The ideal control group would have been healthy volunteers, but such a study is not possible because of ethical considerations.

In our study, a much larger number of syndrome X patients were studied, and patients were included only after strict selection criteria had been satisfied. The
response of heart transplant patients to intracoronary papaverine was reported previously. The coronary flow results in the transplant group in our study are in keeping with normal coronary flow reserve values reported previously. The heart transplant group in our study provides a "normal" control group. All the transplant patients had completely normal coronary arteries, and the normal response to papaverine seen in this study reflects this. The presence of even minor coronary occlusive disease causes an impairment in coronary flow reserve in orthotopic heart transplants. In the absence of an ideal control group of normal healthy volunteers, the transplant group in this study probably provides the best alternative comparison.

It may be argued that hearts with normal innervation show basal α-mediated vasoconstrictor tone that limits coronary flow reserve and that, therefore, the heart transplant subjects are simply not true normal control subjects. However, the subject of resting adrenergic tone in humans is controversial. The presence or absence of resting adrenergic tone in the coronary vasculature has been the subject of much investigation. Conflicting results have been found by previous studies in untr至少conscious animals and humans. Whereas some studies demonstrated significant decreases in vascular resistance after α-blockade, others were unable to demonstrate any change. Significant α-adrenergic coronary constrictor tone at rest has been suggested by studies in anesthetized dogs and conscious dogs. In contrast, Chilian et al., in well-controlled experiments, were unable to demonstrate any α-adrenergic coronary constrictor tone in conscious dogs. Some evidence for resting α-adrenergic coronary constrictor tone in humans was provided by the observation that normally innervated patients are characterized by a higher resting coronary resistance and a higher coronary arteriovenous oxygen difference than cardiac transplant patients, the difference being abolished by nonselective α-blockade with phentolamine. However, the conclusions of this study are based largely on the use of coronary sinus thermodilution, which is not suitable to detect small changes in coronary blood flow.

The influence of the autonomic nervous system on coronary flow reserve has been investigated predominantly in the animal model. In contrast to these animal studies, Hodgson et al. recently demonstrated that significant neurally mediated α-vasoconstrictor tone is not present in resting, unstressed humans and that maximal vasodilator responses are not limited by the adrenergically mediated vasomotor tone. They studied 56 patients with denervated hearts after cardiac transplantation (an average of 17±2 months [mean±SD] from transplant to study) and 19 normally innervated patients with angiographically normal coronary arteries. Coronary blood flow velocity was measured with a subselective intracoronary Doppler catheter, and coronary flow reserve was assessed by intracoronary papaverine. Regional α-blockade was produced by intracoronary injection of the nonselective α-blocker phentolamine. The mean coronary flow velocity decreased significantly in both groups of patients, but this was associated with a significant reduction in mean arterial pressure. However, there was no change in the calculated coronary vascular resistance, which takes the changes in arterial pressures into account.

Coronary flow reserve also did not change in either patient group after α-blockade, suggesting that α-receptor-mediated vascular tone is negligible in both denervated transplant patients and normally innervated subjects. Indolfi et al. also recently showed that regional infusion of an α2-adrenergic receptor blocking agent (yohimbine) does not change resting coronary blood flow in normal coronary arteries, suggesting that resting α2-adrenergic vasoconstriction does not exist in humans. To avoid the effects of β-adrenergic-stimulation on regional coronary blood flow, their study was performed in the presence of β-blockade.

The mean Doppler coronary flow velocity at rest in our study was not significantly different in the syndrome X and transplant groups. This is in contrast to studies using positron emission tomography that have indicated that resting coronary flow is increased in patients with syndrome X, suggesting that the reduction in flow reserve in syndrome X is related to an increase in resting myocardial perfusion as opposed to the maximal perfusion available during stress. In the study by Galassi et al., the baseline myocardial blood flow was greater in the syndrome X group than in healthy subjects and was more heterogeneous (as assessed by the coefficient of variation among myocardial regions ≤2.3 cm²). Myocardial blood flow after dipyridamole, however, was similar to that in the healthy subjects, although it was still more heterogeneous than in the healthy subjects. Geltman et al. also demonstrated greater baseline myocardial blood flow in patients with angina and normal coronary arteries than in healthy subjects, but in contrast to the study by Galassi et al., the mean blood flow after dipyridamole and the myocardial perfusion reserve were significantly lower in patients with chest pain and normal coronary arteries than in the healthy subjects. Geltman et al., using larger tissue regions of interest, also reported that myocardial perfusion was homogeneous in normal subjects and patients at rest and after dipyridamole. It is notable that the resting myocardial blood flow of the control subjects in the study by Geltman et al. was higher than that in the study by Galassi et al. (1.25±0.28 versus 1.00±0.22 mL/g per minute) and was very similar to the syndrome X patient group of Galassi et al. (1.22±0.29 mL/g per minute). In agreement with the data of Geltman et al., regional myocardial perfusion in syndrome X patients was found to be homogeneous both at rest and after the administration of dipyridamole by Camici et al. Previous studies in patients with angina and normal coronary arteries in which myocardial blood flow was measured using argon washout or thermodilution have also not shown alterations of baseline myocardial blood flow. The results of our study have also not shown alterations of baseline coronary flow in syndrome X. Quantitative measurements have demonstrated that the coronary diameter in the regions of the Doppler catheter were of similar dimensions in the syndrome X and the transplant groups. Although the coronary flow velocity and the calculated coronary flow at rest was higher in the syndrome X group, this difference was not statistically significant. It may be that the different findings in these studies are due to the different techniques used for coronary flow measurements. Doppler measurements in our study represent flow responses in large regions of the myocardium, as opposed to the
technique used by Galassi et al to detect flow in small myocardial regions. Therefore, small regional flow abnormalities, as seen in the study by Galassi et al, may be missed.

A number of definitions of syndrome X with differing criteria have been used in the past. The definition we used (typical chest pain, a positive exercise test, and completely normal coronary angiogram) is now widely used. Others, however, require the presence of objectively documented myocardial ischemia. Cannon and Epstein\(^{38}\) coined the term "microvascular angina" to indicate the presence of an abnormal vasodilator capacity of the coronary microcirculation. This finding is the sine qua non of the syndrome of microvascular angina, whereas exercise-induced ST depression is of no relevance to the diagnosis. By this definition, in one study only 10% of 115 patients with documented microvascular angina had ischemic ST changes with exercise testing.\(^{37}\) It was suggested that this low sensitivity of the ECG for detecting myocardial ischemia is probably caused by the ischemia being mild in such patients and possibly by the existence of a diffuse pattern of ischemia obviating the development of a net electric vector. In a separate study, however, Camici et al\(^{52}\) found that the exercise ECG was abnormal in 86% of 14 patients with an impaired flow reserve, but it was also positive in 16 (55%) of the 29 patients with a normal flow reserve. Therefore, in the study by Camici et al, in contrast to that by Epstein et al, the exercise ECG had a good sensitivity (86%) in identifying patients with an impaired coronary flow reserve but had a rather low specificity (45%). This illustrates the difficulties in conducting investigations in syndrome X. Patients who do not have a positive exercise test may indeed have an abnormal flow reserve, as shown by Epstein et al.\(^{37}\) This may particularly distort the results when small numbers are used in the measurement of coronary flow reserve, and this possibility cannot be discounted in the studies reported by Simonetti et al\(^{12}\) and Holdright et al.\(^{3}\)

Holdright et al estimated coronary blood flow before and after intracoronary bolus injections of 8 mg of papaverine. It was shown previously that many patients do not achieve maximal coronary vasodilation in the left coronary artery until at least 12 mg is administered.\(^{16}\) The observations in the present study also confirm this. Therefore, there is also the possibility that in the study by Holdright et al, some patients did not achieve maximal vasodilation.

The mechanism of action of papaverine is not dependent on the endothelium or adenosine production. The reduced flow response to papaverine in the syndrome X group seems to exclude the possibility that impaired flow responses could be related to an abnormal endothelium-dependent function or adenosine responsiveness. The results of our study suggest that the abnormalities in flow reserve in syndrome X are related to either a structural abnormality in the microcirculation or a functional abnormality in smooth muscle relaxation that affects both adenosine- and papaverine-mediated vasodilation. However, the presence of an impaired endothelium-dependent vasodilation in syndrome X patients has also been reported previously.\(^{58}\) It is clear from our study that a number of syndrome X patients have a normal flow response to papaverine, and the possibility that some of these patients may have an impaired endothelium-dependent vasodilation cannot be ruled out.

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. 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 impaired flow reserve. This suggests that other factors must also be important. An abnormal pain perception,\(^{39}\) a significant reduction in coronary blood flow on esophageal acid stimulation,\(^{40}\) a significant reduction in coronary blood flow on hyperventilation with and without epicardial coronary constriction,\(^{8,41}\) a heightened sympathetic tone,\(^{42}\) insulin resistance,\(^{43,44}\) and an abnormal microvascular endothelial dysfunction\(^{58}\) have all been reported in syndrome X; these findings highlight the heterogeneous nature of this syndrome.

Limitations of the Study

We recognize that the use of heart transplant patients as "normal" control subjects is far from ideal. However, they probably provide the best alternative given the ethical considerations involved in studying completely normal individuals.

There is now evidence that spontaneous reinnervation of the transplanted heart does occur.\(^{45}\) However, we did not study the transplant patients for the presence of sensory innervation. It is theoretically possible that sympathetic denervation may affect the responses of the coronary arteries to pharmacological stimuli.

Conclusions

The findings of this study have shown that the coronary flow reserve in response to papaverine is impaired in syndrome X patients, and they support the concept of microvascular dysfunction in a significant number of these patients. The results suggest that the abnormalities of flow reserve in syndrome X are related to either a structural abnormality in the microcirculation or a functional abnormality in smooth muscle relaxation.

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References


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