Intracoronary $\alpha_2$-Adrenergic Receptor Blockade Attenuates Ischemia in Conscious Dogs During Exercise

Rainald Seitelberger, Brian D. Guth, Gerd Heusch, Jong-Dae Lee, Kazuhiro Katayama, and John Ross Jr.

Studies on the role of $\alpha$-adrenergic constrictor tone in the coronary vascular bed during ischemia were performed in dogs running on a treadmill. The animals were instrumented with a left ventricular pressure transducer, and regional systolic wall thickening (%WTh) was assessed by sonomicrometry in the anterior and posterior walls of the left ventricle. An intracoronary catheter was implanted chronically in the circumflex coronary artery, and a hydraulic cuff was placed proximally around the artery. After $\beta$-adrenergic blockade with propranolol (0.8 mg/kg i.v.), acute stenosis of the coronary artery was performed during running in five dogs to induce severe regional myocardial dysfunction in the posterior wall. Intracoronary infusion of the selective $\alpha_2$-adrenergic blocking agent idazoxan (80 $\mu$g/kg) improved %WTh in the ischemic region from 5.1 ± 1.6 to 10.8 ± 2.8% ($p < 0.05$), without any significant effect on the anterior wall. Blood flow to the subendocardium of the posterior wall (radioactive microspheres) increased from 0.17 ± 0.05 to 0.45 ± 0.30 (ml/min)/g ($p < 0.05$). It is concluded that in exercising dogs subjected to $\beta$-adrenergic blockade, significant postjunctional $\alpha_2$-adrenergic receptor-mediated coronary vasoconstriction exists, even during severe ischemia. Regional $\alpha_2$-adrenergic receptor blockade can reduce regional ischemia and improve contractile function by attenuating exercise-induced sympathetic vasoconstriction in this conscious animal model.

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Humoral and neuronal release of norepinephrine activates not only myocardial $\beta$-adrenergic receptors, but also coronary $\alpha_1$- and $\alpha_2$-adrenergic receptors. In the absence of ischemia, pharmacological stimulation of both $\alpha$-receptor subtypes and direct sympathetic nerve stimulation are known to produce coronary vasoconstriction,1,2 and $\alpha_2$-adrenergic tone competes with coronary vasodilation caused by local metabolic mechanisms.3 In contradiction to the classic view that a maximally dilated coronary vascular bed during ischemia were performed in dogs running on a treadmill. The animals were instrumented with a left ventricular pressure transducer, and regional systolic wall thickening (%WTh) was assessed by sonomicrometry in the anterior and posterior walls of the left ventricle. An intracoronary catheter was implanted chronically in the circumflex coronary artery, and a hydraulic cuff was placed proximally around the artery. After $\beta$-adrenergic blockade with propranolol (0.8 mg/kg i.v.), acute stenosis of the coronary artery was performed during running in five dogs to induce severe regional myocardial dysfunction in the posterior wall. Intracoronary infusion of the selective $\alpha_2$-adrenergic blocking agent idazoxan (80 $\mu$g/kg) improved %WTh in the ischemic region from 5.1 ± 1.6 to 10.8 ± 2.8% ($p < 0.05$), without any significant effect on the anterior wall. Blood flow to the subendocardium of the posterior wall (radioactive microspheres) increased from 0.17 ± 0.05 to 0.45 ± 0.30 (ml/min)/g ($p < 0.05$). It is concluded that in exercising dogs subjected to $\beta$-adrenergic blockade, significant postjunctional $\alpha_2$-adrenergic receptor-mediated coronary vasoconstriction exists, even during severe ischemia. Regional $\alpha_2$-adrenergic receptor blockade can reduce regional ischemia and improve contractile function by attenuating exercise-induced sympathetic vasoconstriction in this conscious animal model.

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of left ventricular pressure through the fluid-filled catheter (Statham P23Db), zero pressure reference being taken at the estimated level of the right atrium. A silicone rubber catheter (1.57 mm i.d.) was inserted into the descending aorta for blood withdrawal and determination of arterial pressure. An additional catheter was placed into the left atrium through the atrial appendage.

The proximal left circumflex coronary artery was dissected free and a heparin-filled Tygon catheter (0.5 mm i.d.) was inserted near its origin. The catheter was maintained in position by sewing a Dacron patch attached to the catheter to the surrounding tissue. Special care was taken to place the tip of the intracoronary catheter proximal to the origin of the first main branch of the circumflex artery. A hydraulic cuff was then placed proximal to the coronary catheter.

For the measurement of regional wall thickening dynamics, two pairs of miniature ultrasonic crystals were implanted in the left ventricular wall using standard techniques.9 One pair was implanted in the posterior wall supplied by the circumflex coronary artery, and the other was positioned in the anterior wall within the distribution area of the left anterior descending artery.

The pericardium was left open and all wires and tubes were passed subcutaneously to the back of the dog and brought through the skin between the scapulae. The pneumothorax was evacuated through a chest tube in the 6th intercostal space. Ampicillin (6.6 mg/kg i.m.) was administered for 3 days postoperatively.

**Measurement of Regional Myocardial Blood Flow**

Regional myocardial blood flow was determined using radionuclide-labeled microspheres by the reference withdrawal method, as previously described.9 Two of the following radionuclide labels were used randomly in each dog: 42Ce, 110Sn, 103Ru, 95Nb, or 65Sc (15 u.m diameter, New England Nuclear, Boston, Massachusetts). For each measurement, 1–2 ml containing 6–10 million microspheres (suspended in 10% dextran with Tween-80) were injected within approximately 5 seconds into the left atrial catheter and then flushed with warm saline. The arterial reference sample was withdrawn from the aortic catheter (8 ml/min over a period of 90 seconds), starting at least 5 seconds before the microsphere injection. In no experiment reported in this study were regional or systemic hemodynamic changes observed during microsphere injections or during withdrawal of the arterial blood sample. At the end of the study, the animals were killed with an overdose of barbiturate, and the heart was removed and placed in 10% formalin for 3–5 days. The atria, right ventricle, and blood vessels were then removed, and the left ventricular surface was cleaned of epicardial fat. The ventricle was sliced perpendicular to the long axis and then sectioned as described previously.9 Data are reported only from transmural tissue samples containing the ischemic and control crystal pairs. However, blood flow was examined in the entire circumference of the left ventricle at the level of the ischemic crystal pair to assure that the crystals lay within the central zone of ischemia.

Each transmural plug (weighing 3–4.5 g) was subdivided into endocardial, midwall, and epicardial pieces, weighed, and placed in glass counting vials. The radioactivity of tissue and arterial blood samples was counted in a Packard Autogamma spectrometer (model 5912) with a multichannel analyzer and energy windows set to correspond to the primary emission peak of each radionuclide.8 The number of counts per energy window were determined and corrected for background activity and overlapping counts from accompanying isotopes by solving simultaneous equations using a matrix inversion technique.8 Myocardial blood flow is reported as milliliters per minute per gram of myocardium [(ml/min)/g]. To help ensure that each contained no fewer than 400 microspheres, no sample weighed less than 0.5 g. The number of spheres in each tissue sample was calculated using the number of counts per minute per sphere that had been previously measured for each microsphere label employed. Tissue samples from the ischemic zone later underwent histological examination to assess whether small emboli from the intracoronary catheter induced myocardial necrosis. No dog in this study showed tissue damage between the sonomicrometers, and in each study reported, the sonomicrometers were appropriately positioned across the wall.

**Data Analysis**

Data were recorded on a Brush forced-ink recorder and 1/2 inch magnetic tape. Data recorded on the magnetic tape were used for subsequent digitization, beat averaging, and analysis by computer (PDP/11/03).9 Fifteen consecutive beats were averaged for each observation. Parameters measured and analyzed included peak left ventricular (LV) pressure and end-diastolic pressure (LVEDP), maximum positive left ventricular dP/dt (max (+) dP/dt), heart rate, mean arterial pressure, and anterior and posterior wall thickness (WTh) at end-diastole (defined as the time coincident with the onset of a positive dP/dt) and end-systole [defined as the point of maximal systolic thickening within 20 msec before maximum (—) LV dP/dt].10 Systolic wall thickening is presented as the percentage change from the end-diastolic thickness (%WTh).

**Preliminary Studies**

In preliminary studies carried out in conscious instrumented dogs at rest after β-adrenergic blockade, we assessed the effectiveness of the selective α2-antagonist idazoxan in blocking the coronary vasoconstrictor effect of intracoronary norepinephrine given in doses sufficient to elicit a sizeable degree of coronary vasoconstriction, without appreciable systemic effects.11 Prior to α2-blockade, norepinephrine (0.5 μg/kg) caused an average increase in end-diastolic coronary resistance of 34% (n = 9). The α2-antagonists rauwolscine (70 μg/kg in saline, n = 3) or idazoxan (50 μg/kg in saline, n = 3) were then given...
by the intracoronary route; a mild increase in mean arterial pressure occurred (average 12 mm Hg), without significant changes in left ventricular max (+) LV dP/dt, heart rate, or coronary vascular resistance. Administration of norepinephrine (0.5 μg/kg) after α2-blockade with either drug no longer produced significant increases of end-diastolic coronary resistance, a response consistent with previous reports that the norepinephrine constrictor response in dogs is mainly α2-receptor mediated. To ensure adequate α1-blockade in the present studies during the marked sympathetic stimulation of exercise, a somewhat higher average dose of idazoxan (40–100 μg/kg, average 80 μg/kg) was used.

**Study Protocol**

Experiments were conducted at least 10 days after surgery, when the animals had completely recovered and were capable of performing the same treadmill workload as before the operation. For each dog, the treadmill speed (at 5% elevation) was adjusted during running to increase the heart rate by 1.6- to 1.8-fold from the value while standing at rest. It was technically difficult to achieve fully instrumented dogs for these experiments, primarily because of a relatively high incidence of thrombosis of the coronary artery when both an intracoronary catheter and hydraulic cuff were placed. Complete instrumentation and successful running experiments with ischemia were accomplished in five dogs (success rate 33%).

Ten minutes before the start of exercise, the animals were given propranolol (0.8 mg/kg i.v.). This was done in order to obviate positive inotropic effects of α1-adrenergic blockade on the myocardium during exercise, as well as to prevent indirect effects of β-adrenergic stimulation of the coronary vascular bed by enhanced norepinephrine release produced by α2-adrenergic blockade. Throughout the entire exercise period, 0.9% NaCl (2 ml/min) was continuously infused through the intracoronary catheter, except when the intracoronary α-blocking drug was infused over a period of 1 minute at exactly the same infusion rate.

One minute after the start of treadmill exercise, an acute stenosis of the circumflex coronary artery was set by partially inflating and then adjusting the hydraulic cuff to achieve an average decrease of 75% in systolic thickening of the posterior wall. When all recorded hemodynamic measurements, and both the anterior and posterior %WTh, had reached a steady state for at least 1 minute, no further adjustments of the cuff were made and withdrawal of the arterial reference blood sample was started. Microspheres were then injected to assess regional myocardial blood flow during acute coronary stenosis. Immediately after the withdrawal period of 90 seconds, the selective α1-blocking agent idazoxan was infused by the intracoronary route over 1 minute. When %WTh of the posterior wall had reached a new steady state lasting at least 30 seconds (at most 4 minutes after the end of the intracoronary drug infusion), withdrawal of the second reference blood sample was commenced and microspheres were injected, with a steady-state maintained for the next 90 seconds. After the end of the withdrawal period (90 seconds), the hydraulic cuff was deflated and the run terminated.

Control experiments with ischemia but without administration of the α-blocking drug were performed in three dogs. In these experiments, the animals continued running on the treadmill for at least 8 minutes after the acute coronary stenosis was set, a period equivalent to the total running time when microsphere injections and drug administration were performed during ischemia.

**Statistical Analysis**

All data are reported as mean ± SD. Serial changes in hemodynamic variables and regional wall thickness values were analyzed by a repeated measures analysis of variance, and when a significant overall effect was observed, single mean values were compared with Tukey's test. Since blood flow measurements were made in the steady state at only two time points (the control microsphere injection during running and the microsphere injection after selective α1-blockade) a paired nonparametric test was utilized (Mann-Whitney test).

**Results**

Figure 1 shows an original tracing of a complete experiment. Because of the prior β-blockade with propranolol, the increase in regional and global myocardial function and heart rate were relatively small immediately after the onset of exercise (Table 1). The production of acute coronary stenosis reduced peak left ventricular pressure and maximum (+) LV dP/dt, but the small increase in heart rate was not significant.

After the production of coronary stenosis, %WTh of the posterior wall fell by an average of 75.7% (Table 1). Intracoronary infusion of the selective α1-blocking agent idazoxan increased %WTh of the posterior wall in every dog, the average increasing from 5.1 to 10.8%, but it had no effect on %WTh of the anterior wall (Figure 2, Table 1). Hemodynamic variables were not significantly changed after the drug infusion.

Changes in regional myocardial blood flow are shown in Table 2 and Figure 3. After acute circumflex stenosis, blood flow to the anterior wall was not affected and showed normal blood flow distribution. However, there was maldistribution of transmural blood flow in the posterior wall, with the lowest flow in the subendocardium.

Intracoronary infusion of idazoxan markedly improved blood flow to the endocardium and midmyocardium of the posterior wall in all five dogs (Table 2, Figure 3). Average blood flow to the subendocardium increased from 0.17 to 0.45 (ml/min)/g. Drug infusion had no effect on subepicardial blood flow, and the endocardial/epicardial blood flow ratio increased in the posterior wall (Table 2, Figure 3).

In control experiments with running after β-blockade but without intracoronary infusion of α-blocking drugs, inflation and setting of the hydraulic cuff caused a decrease in posterior %WTh by 84.8% under steady-
state conditions (2 minutes after the stenosis was set), and the run was then continued for more than 8 minutes without further adjustment of the cuff. During this period, %WTh of the posterior wall did not improve over time in any of the three animals, but rather showed a tendency toward further decreases averaging $-3.5 \pm 1.6\%$, $-1.6 \pm 3.1\%$, $-2.8 \pm 2.4\%$, and $-1.9 \pm 3.4\%$ at 2, 4, 6, and 8 minutes, respectively. Hemodynamic variables remained unchanged throughout this exercise period.

Discussion

These studies, in which regional ischemia was induced during treadmill exercise following β-adrenergic blockade, demonstrate that acute regional α₂-blockade can diminish regional myocardial dysfunction due to ischemia and improve blood flow to the ischemic zone. This finding provides evidence for sympathetic vasoconstriction (neurally and/or hormonally mediated) in acutely ischemic myocardium during a physiological form of stress in the conscious dog.

The role of sympathetically mediated coronary vasoconstriction during ischemia has been investigated in the past in other experimental settings. Buffington and Feigl demonstrated α-adrenergic receptor-mediated sympathetic coronary vasoconstriction in the presence of coronary stenosis in anesthetized dogs, and Mudge et al. reported an adrenergically induced reflex increase in coronary vascular resistance in patients with ischemic heart disease. Heusch and Deussen showed an unmasking of sympathetic vasoconstriction with increasing severity of coronary stenosis and identified postsynaptic α₂-receptors as the main mediators of sympathetic coronary vasoconstriction produced by

| TABLE 1. Influence of Intracoronary Infusion of the Selective α₂-Blocker Idazoxan (80 μg/kg) on Hemodynamics and Regional Myocardial Function During Treadmill Exercise With Acute Coronary Stenosis |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Before propranolol | After propranolol | Before stenosis | During run |
| HR              | 104.4 ± 22.3     | 105.6 ± 17.4     | 160.2 ± 14.1††  | 165.2 ± 20.4    | 167.2 ± 21.7    |
| LVPmax          | 137.6 ± 9.2      | 149.1 ± 8.7*     | 149.9 ± 28.3    | 127.3 ± 27.3‡‰  | 127.2 ± 22.0‡‡  |
| LV dP/dt        | 3610 ± 338       | 2697 ± 72**      | 3068 ± 570†     | 2593 ± 528‡     | 2704 ± 628‡‡    |
| LVEDP           | 13.7 ± 5.9       | 17.5 ± 7.4       | 28.0 ± 2.9†     | 28.5 ± 6.1      | 26.6 ± 4.1      |
| AP-mean         | 113.8 ± 10.9     | 122.2 ± 13.6*    | 136.4 ± 14.5†   | 120.6 ± 14.4‡   | 119.7 ± 14.3‡   |
| PW-ED           | 10.8 ± 2.3       | 11.0 ± 1.7       | 10.5 ± 2.1      | 10.5 ± 2.2      | 10.6 ± 2.2      |
| PW-%WTh         | 22.5 ± 4.0       | 17.6 ± 2.9**     | 21.0 ± 1.8†     | 5.1 ± 1.6‡     | 10.6 ± 2.2‡‡    |
| AW-ED           | 12.4 ± 3.2       | 12.3 ± 3.1       | 12.1 ± 3.3      | 12.2 ± 3.2      | 12.3 ± 3.2      |
| AW-%WTh         | 20.4 ± 8.4       | 14.3 ± 6.1**     | 15.6 ± 5.2†     | 15.6 ± 5.8      | 15.4 ± 5.6      |

HR, heart rate; LVPmax, maximum systolic left ventricular pressure, (+)LV dP/dt, maximum first derivative of LVEDP; LVEDP, left ventricular end-diastolic pressure; AP, aortic pressure; PW-ED, posterior wall thickness at end-diastolic; %WTh, percent systolic wall thickening; AW, anterior wall thickening.

*p<0.05, **p<0.01 rest after vs. before propranolol.
†p<0.05, ††p<0.01 run before stenosis vs. rest after propranolol.
‡p<0.05, ‡‡p<0.01 run after stenosis vs. before stenosis.
§p<0.05, §§p<0.01 run before idazoxan (control) vs. after idazoxan.
blockade by permitting doses that had little or no effect conceivable that ischemia and continued exercise could same run. * p<0.05, n=5.

The results of the present study suggest that in the coronary vasoconstriction during exercise can aggravate presence of (3-adrenergic blockade, sympathetic cor-

peripherally and centrally. To unmask and define the extent of a-receptor-mediated coronary vasoconstriction during exercise, a setting that should cause significant activation of local metabolic coronary vasodilation as well as activation of the sympathetic nervous system. The results of the present study suggest that in the presence of (3-adrenergic blockade, sympathetic coronary vasoconstriction during exercise can aggravate regional myocardial ischemic dysfunction by limiting myocardial blood flow to the ischemic area.

The experimental design of this study allowed the assessment of regional myocardial effects of (3-blockade by permitting doses that had little or no effect vasoconstriction mediated by (3-adrenoceptors also affects ischemic myocardium during the physiological stress of exercise, a setting that should cause significant activation of local metabolic coronary vasodilation as well as activation of the sympathetic nervous system. The results of the present study suggest that in the presence of (3-adrenergic blockade, sympathetic coronary vasoconstriction during exercise can aggravate regional myocardial ischemic dysfunction by limiting myocardial blood flow to the ischemic area.

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The increases in myocardial blood flow after idazoxan occurred exclusively in the subendocardial and midmyocardial regions, with no significant changes in the subepicardium. One potential explanation for this response is that (3-receptors appear to mainly regulate vasoconstriction of small resistance vessels, rather than larger superficial coronary arteries. Another possible explanation could relate to the previous observation that the influence of sympathetic vasoconstriction appears to increase with severity of ischemia. Since the maximal reduction in blood flow prior to drug infusion was located in the subendocardial and mid-

myocardial regions, confinement of the flow increase to these areas after (3-blockade might be expected.

In contrast to the deleterious role of (3-adrenergic coronary vasoconstriction during myocardial ischemia previously reported by Heusch and Deussen during direct cardiac sympathetic nerve stimulation, and also shown by the findings of the present experiments during exercise, Nathan and Feigl reported a possible benef-
cial effect of (3-adrenergic vasoconstriction during four degrees of coronary hypoperfusion in anesthetized dogs. These authors reported that during intracoronary norepinephrine infusion the ratio of subendocardial to subepicardial blood flow was lower in a region treated with the (3-blocking drug phenoxybenzamine than in an untreated region. They concluded that (3-receptor activation by norepinephrine serves to favorably affect coronary blood flow distribution during hypoperfusion by causing subepicardial vasoconstriction, so that (3-blockade under these conditions produces an unfavor-

able effect on transmural blood flow distribution. There are several possible explanations for the differences between these findings and those of the present study, including the differing experimental models and the application of different blocking drugs. The constant coronary inflow preparation used by Nathan and

Table 2. Myocardial Blood Flow in (ml/min)/g During Exercise With Acute Coronary Stenosis Before and After Intracoronary Idazoxan

<table>
<thead>
<tr>
<th>Ischemic area</th>
<th>Control</th>
<th>Idazoxan</th>
<th>Control</th>
<th>Idazoxan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endo</td>
<td>0.170±0.05</td>
<td>0.452±0.30*</td>
<td>0.975±0.24</td>
<td>1.160±0.21</td>
</tr>
<tr>
<td>Mid</td>
<td>0.421±0.08</td>
<td>0.882±0.21*</td>
<td>0.985±0.09</td>
<td>1.157±0.28</td>
</tr>
<tr>
<td>EPI</td>
<td>0.831±0.21</td>
<td>0.783±0.15</td>
<td>0.839±0.48</td>
<td>0.900±0.34</td>
</tr>
<tr>
<td>Transmural</td>
<td>0.474±0.08</td>
<td>0.685±0.41*</td>
<td>0.933±0.10</td>
<td>1.073±0.26</td>
</tr>
<tr>
<td>Endo/epi</td>
<td>0.219±0.09</td>
<td>0.595±0.41*</td>
<td>1.177±0.37</td>
<td>1.219±0.47</td>
</tr>
</tbody>
</table>

* p<0.05.
Feigl might have prevented the most significant beneficial effect of $\alpha_2$-blockade observed in the present experiments and in the study of Heusch and Deussen (i.e., an increase in absolute myocardial blood flow). Also, it is possible that in Nathan and Feigl's study the ischemia was not severe since only normalized blood flow ratios (not absolute subendocardial blood flows) were presented for the phenoxymethylamine-treated region, and regional contractile, metabolic, or electrocardiographic measures to provide evidence for aggravation of ischemia by a transmural coronary steal in the subendothelial and subepicardial blood flows is presented with the transmural blood flow (endo/epi). *p < 0.05, n = 5.

It should also be pointed out that under nonischemic conditions in the dog, $\alpha_2$-adrenergic receptors contribute approximately 25% and $\alpha_1$-receptors 75% to the increase in coronary resistance during cardiac sympathetic nerve stimulation or intracoronary norepinephrine infusion. Under ischemic conditions, responses to the $\alpha_1$-agonist methoxamine appear to progressively diminish as the severity of coronary hypoperfusion is increased, whereas the responses to the $\alpha_2$-agonist BHT 920 persist even in the presence of severe coronary stenosis. Therefore, during severe ischemia produced during the marked sympathetic activation of exercise in the present study (in which sympathetic coronary vasodilator influences were prevented by $\beta$-blockade), it is possible that an $\alpha_2$-adrenergic constrictor influence was markedly dominant.

Recent experiments from our laboratory show that chronic instrumentation of the left circumflex coronary artery does not cause a functionally important loss of myocardial responsiveness to reflex sympathetic activation. In addition, studies by Chilian et al indicate that $\alpha$-adrenergic coronary vasoconstriction during exercise in the normal dog (without ischemia) is primarily due to circulating catecholamines, rather than to norepinephrine released from coronary sympathetic nerves. Although Young et al have reported only minor cardiac responses to high levels of circulating catecholamines, the studies by Chilian et al suggest that sympathetic nerves could have a relatively unimportant role in $\alpha$-adrenocorticotrope–mediated coronary vasoconstriction during exercise. However, it remains to be elucidated whether or not these findings also apply to the regulation of the coronary vasculature during exercise-induced ischemia, when local feedback mechanisms may potentiate cardiac sympathetic nerve activity or stimulate the local release of norepinephrine and thereby enhance the contribution of sympathetic stimulation to the regulation of coronary vascular resistance.

The treadmill exercise performed in these experiments constitutes a physiological form of stress and
therefore may have relevance to the clinical setting. This supposition is supported by recent findings in patients with chronic stable angina pectoris, in whom the exercise-induced ischemic response without prior beta-adrenergic blockade was less severe following non-selective alpha-blockade by the intracoronary route.28 The role of alpha-adrenergic receptors in the coronary circulation of man remains to be elucidated.

References


Key Words • idazoxan • coronary stenosis • myocardial blood flow • myocardial contraction
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