ORIGINAL ARTICLES

Potentiation of Coronary Vasoconstriction by Beta-adrenergic Blockade in Patients with Coronary Artery Disease


SUMMARY Although beta-adrenergic blocking agents reduce myocardial oxygen consumption and symptoms of myocardial ischemia in patients with coronary artery disease (CAD), propranolol has been reported to exacerbate coronary artery spasm in some patients with variant angina. To determine whether increased coronary vasomotor tone can be induced by beta-adrenergic blockade, we measured the changes in coronary vascular resistance (CVR) during cold pressor testing (CPT) in 15 patients, nine with severe CAD and six with normal left coronary anatomy, before and after i.v. propranolol (0.1 mg/kg). Coronary blood flow was measured by coronary sinus thermodilution. CVR was calculated as mean arterial pressure divided by coronary sinus blood flow. Heart rate was maintained constant at a paced subungal rate of 95 ± 5 beats/min.

Before propranolol, CPT induced significant increases in coronary vascular resistance in patients with CAD (15.0 ± 2.2%, p < 0.02), but no increase in CVR in the normal patients. After propranolol, the CVR change during CPT was augmented for patients with CAD (29 ± 6%, p < 0.01) and for the normal population (9 ± 5%, NS). The potentiated increase in CVR occurred without significant changes in resting CVR or in the magnitude of the hypertensive response to CPT.

We conclude that beta-adrenergic blockade with propranolol can potentiate coronary artery vasoconstriction in some patients with CAD, possibly mediated by unopposed alpha-adrenergic vasomotor tone. These changes may be important in patients in whom intense adrenergic stimulation may increase coronary artery tone and adversely influence the balance between myocardial oxygen supply and demand.

COMPELLING EVIDENCE suggests that myocardial ischemia may be induced by a reduction in myocardial oxygen supply due to coronary artery spasm. Primary decreases in coronary blood flow associated with abnormal coronary vasomotor reactivity have been found to occur not only in variant angina,\(^1\) but also in classic and unstable angina,\(^2,3\) cold-induced angina,\(^4\) exercise-induced angina\(^5,6\) and myocardial infarction.\(^7,8\)

The mechanism of such variation in coronary artery vasoemotion is unknown, but several studies have implicated a central role for the adrenergic nervous system.\(^9-16\)

Studies in animals have shown that coronary artery vasoconstriction and increases in coronary vascular resistance can be elicited by sympathetic stimulation after beta-adrenergic blockade.\(^12,15,17\) Clinical studies of patients with variant angina have shown exacerbation of coronary spasm after subcutaneous administration of epinephrine in patients receiving propranolol.\(^18\) Beta-adrenergic blockade with propranolol reportedly prolongs myocardial ischemia in patients with documented vasospastic angina pectoris, presumably by inhibiting, through nonselective beta-adrenergic blockade, beta-mediated coronary artery vasodilation and leaving alpha-adrenergically mediated vasoconstriction unopposed.\(^18-21\)

Using the sympathetic stimulus of cutaneous cold and directly measuring coronary blood flow, we studied the effect of beta-adrenergic blockade on the coronary vasomotor response in patients with coronary artery disease (CAD) during cold pressor testing (CPT), challenging the hypothesis that beta-adrenergic blockade in the setting of increased sympathetic stimulation would leave alpha-mediated tone unopposed and potentiate coronary artery vasoconstriction.

Methods

Patients

We studied 15 patients who had classic angina pectoris or atypical chest pain and were undergoing diagnostic cardiac catheterization. The exclusion criteria were unstable angina, coexistent valvular heart disease, severe left ventricular dysfunction, left main coronary artery stenosis, concomitant treatment with calcium-blocking drugs or nonsteroidal antiinflammatory drugs, or contraindications to the use of beta-adrenergic blocking agents. No patient had a clinical history of vascular hyperreactivity.

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Protocol

The investigational protocol and consent form were approved by the Human Subjects Committee of the Brigham and Women’s Hospital. After the patients gave informed consent, treatment with β-adrenergic blocking agents was withheld for at least 12–24 hours before cardiac catheterization, and long-acting nitrate preparations were withheld for at least 6 hours before catheterization. Before coronary arteriography, all patients received 0.4 mg of sublingual nitroglycerin and six also received 0.5 mg of i.v. atropine.

Fifteen minutes after completion of the diagnostic cardiac catheterization and coronary angiography, a #8F coronary sinus thermodilution pacing catheter (Wilton Webster Laboratories) was inserted into an antecubital vein and advanced under fluoroscopic guidance to the coronary sinus. The location of the catheter was confirmed by a 3–5-ml injection of radiographic contrast material. The position of the patient and catheter were held constant throughout each study, and stable coronary sinus catheter position during the study was confirmed by fluoroscopy.

Pulmonary capillary wedge pressure was measured with a #7F balloon-tipped catheter introduced through an antecubital or femoral vein. Mean and phasic arterial pressures were measured with a femoral arterial catheter. Arterial and coronary sinus blood oxygen content was measured using a fuel cell method (Lex-O₂-Con, Lexington Instruments). Arterial and coronary sinus lactate concentration were measured by an enzymatic spectrophotometric method. All pressures, coronary flow signals and the ECG were recorded on an optical strip-chart recording system (Electronics for Medicine).

After placement of the coronary sinus and pulmonary arterial balloon-tipped catheters, phasic and mean arterial pressure, pulmonary capillary wedge pressure, heart rate and coronary sinus blood flow were measured (1) at rest, (2) during pacing with electrodes on the coronary sinus catheter at a constant subangular heart rate (95 ± 5 beats/min) to eliminate the influence of heart rate changes on coronary sinus blood flow determinations, and (3) at the identical paced heart rate during CPT. CPT consisted of immersing the patient’s hand and forearm in ice water for 60 seconds.²⁴

After control recordings were obtained and hemodynamics returned to baseline, i.v. propranolol, 0.1 mg/kg, was administered in three divided doses, each over 2 minutes with a 2-minute observation period between doses. This dosage has been used by other investigators to achieve clinical β-adrenergic blockade.²³ Heart rate, ECG, pulmonary capillary wedge and arterial blood pressure were monitored, and propranolol administration was to be terminated if there was evidence of PR prolongation greater than 0.24 second or second- or third-degree atrioventricular block, more than a 5-mm Hg rise in pulmonary capillary wedge pressure from control, a fall in heart rate to less than 45 beats/min, or a fall in systolic arterial pressure of more than 15 mm Hg from control. However, no patient required termination of propranolol administration.

Ten minutes after the last dose of propranolol, repeat measurements of heart rate, mean arterial pressure, pulmonary artery pressure, coronary sinus blood flow were made at rest, at the identical paced subangular heart rate, and during CPT at the identical heart rate.

In eight patients, arterial and coronary sinus blood samples were simultaneously obtained to determine oxygen content and lactate concentration during control pacing and CPT before and after propranolol administration.

Data Analysis

Coronary sinus blood flow was calculated by the method of Ganz et al.;²⁴

\[
\frac{T_M - T_i}{T_B - T_M} \times K \times Q
\]

where \(T_M\) = temperature of the blood and 5% dextrose/water injectate, \(T_i\) = temperature of the injectate, \(T_B\) = temperature of blood, \(K\) = constant of specific heat and density of blood and injectate (1.08), and \(Q\) = infusion rate of injectate (38–40 ml/min). Coronary vascular resistance was calculated as the quotient of mean arterial pressure and coronary sinus blood flow. The arterial–coronary sinus oxygen content difference was expressed in ml oxygen/dl blood.

The patients were divided into two groups based on the extent of CAD in the left coronary artery system. Three patients with isolated right CAD and no collateral blood flow from the left coronary system were included in the normal population (group 1) because the coronary sinus thermodilution technique primarily measures left coronary artery efflux. Group 2 had significant stenoses of left anterior descending and circumflex coronary arteries. Significant coronary artery stenosis was defined as greater than 70% luminal narrowing assessed by coronary arteriography.

Statistical Analysis

The effects of propranolol before and after CPT were assessed by analysis of variance. Whenever such analysis indicated a significant contribution of a particular variable to total sample variability, subsequent comparisons between groups were performed using the appropriate paired or unpaired two-tailed t test. The results are expressed as mean ± SEM.

Results

Clinical Data

The clinical features and diagnostic catheterization data of the patients are summarized in table 1. Of the 11 patients who had received β-adrenergic blocking agents before the study, eight had received propranolol (mean dose 192 ± 62 mg/day), two metoprolol (100 mg/day) and one nadolol (80 mg/day). Metoprolol and nadolol were withheld for at least 24 hours before the study. Angina occurred during the initial CPT in one patient and after the postprpranolol CPT in one patient. The hemodynamic responses during CPTs be-
fore and after propranolol for both patient groups are summarized in table 2.

Resting Hemodynamic Responses to Propranolol

At rest, the mean heart rate for all patients decreased from 71 ± 3 beats/min to 64 ± 2 beats/min (p < 0.01) after propranolol. There was no significant change in mean arterial blood pressure (from 100 ± 3 to 99 ± 2 mm Hg), pulmonary capillary wedge pressure (from 12 ± 1 to 13 ± 1 mm Hg), coronary sinus blood flow (from 89 ± 9 to 80 ± 12 ml/min) or coronary vascular resistance (from 1.32 ± 0.12 to 1.38 ± 0.15 mm Hg·min·ml⁻¹). There was no significant difference in these variables between patient groups.

Control Pacing and Cold Pressor Responses to Propranolol in Normal Patients

The hemodynamic responses to CPT before and after propranolol for the normal population are shown in figure 1. During CPT before propranolol, mean arterial pressure rose 16%, from 103 ± 4 to 122 ± 2 mm Hg (p < 0.01) and coronary sinus blood flow increased 14%, from 105 ± 14 to 120 ± 13 ml/min, p < 0.05. Thus, in the normal patient group, the calculated coronary vascular resistance remained unchanged (1.09 ± 0.18 vs 1.08 ± 0.17 mm Hg·min·ml⁻¹).

During CPT after propranolol, there was a similar rise in mean arterial pressure (from 105 ± 4 to 122 ± 3 mm Hg, p < 0.01) and coronary sinus blood flow (from 114 ± 18 to 130 ± 30 ml/min, NS) and a nonsignificant increase of 9% in coronary vascular resistance (from 1.06 ± 0.20 to 1.16 ± 0.22 mm Hg·min·ml⁻¹). The product of heart rate times mean arterial pressure was similar with CPT before and after propranolol.

Control Pacing and Cold Pressor Responses to Propranolol in CAD Patients

Patients with severe CAD (group 2) had a substantially different response to CPT than the normal population (fig. 2). During CPT, both before and after propranolol, the mean arterial pressure rose 17% (from 107 ± 4 to 125 ± 4 mm Hg before and from 105 ± 3 to 125 ± 3 mm Hg after propranolol). However, in contrast to the normal response before propranolol, CPT did not increase coronary sinus blood flow (128 ± 26 vs 128 ± 24 ml/min). Thus, coronary vascular resistance increased by 15% (from 1.09 ± 0.20 to 1.25 ± 0.21 mm Hg·min·ml⁻¹, p < 0.02). More
importantly, after propranolol, the CPT elicited a 9% fall in coronary sinus blood flow (from 123 ± 33 to 113 ± 28 ml/min, \( p < 0.05 \)). After propranolol, coronary vascular resistance increased from \( 1.32 \pm 0.30 \) to \( 1.61 \pm 0.32 \) mm Hg·min·ml\(^{-1} \) (\( p < 0.01 \)); this 29% increase is significantly greater than the 15% increase during CPT before propranolol (\( p < 0.01 \)). Myocardial oxygen consumption, as assessed by the product of heart rate and mean arterial pressure during CPT, was the same before and after propranolol.

To evaluate the effects of propranolol on coronary vascular resistance in relation to underlying CAD, we assessed individual patient responses in the two groups by analysis of variance. Propranolol was associated with an increased coronary vascular resistance during CPT in both groups. The magnitude of the increase in coronary vascular resistance after propranolol was not significantly different between the two groups.

Propranolol induced no measured changes in arteriovenous oxygen difference or lactate extraction, nor did it modify the effects of the CPT on these variables. There was no significant correlation between changes in transcoronary oxygen difference in individual patients and the changes in coronary vascular resistance in response to propranolol. The double product during CPT was the same before and after propranolol in both groups.

**Discussion**

The results of the study indicate that \( \beta \)-adrenergic blockade with propranolol leads to an accentuation of coronary vasoconstriction during the adrenergic stimulus of the CPT. Our findings are in agreement with clinical reports of exacerbation of coronary vasospasm by \( \beta \)-adrenergic blockade in some patients with variant angina\(^{19,20} \) and other investigators who have demonstrated coronary vasospasm after propranolol during sympathetic stimulation with exercise or with subcutaneous injection of epinephrine, a mixed \( \alpha \)- and \( \beta \)-adrenergic agonist.\(^5,18,23 \) Our results also indicate that propranolol may potentiate increases in coronary artery vasomotor tone in a broader population of patients who may have augmented coronary vasoreactivity with or without fixed atherosclerotic coronary disease. These findings must be interpreted in the light of previous studies relating to the pathophysiology of the coronary circulation and the design of the current investigation.

Numerous studies have established the presence of both \( \alpha \)- and \( \beta \)-adrenergic receptors in animal and human coronary arteries.\(^9,16,25-28 \) Increases in \( \alpha \)-adrenergic tone have been associated with coronary artery spasm\(^{29} \) and reflex coronary vasoconstriction.\(^3 \) \( \alpha \)-adrenergic blockade has been shown to reduce attacks of variant angina\(^{19} \) and abolish both peripheral and coronary vasoconstriction during CPT.\(^4 \) Extensive study of the interaction of adrenergic coronary receptors and metabolic factors in control of coronary vascular resistance can compete with and overcome opposing metabolic vasodilatory influences. Vatner et al.\(^{15} \) showed that adrenerg-
ergically mediated coronary vasoconstriction in the dog was produced by infusion of norepinephrine after \( \beta \) blockade despite enhanced myocardial metabolic demand and augmented pressure work. Increases in sympathetic discharge, such as direct stellate ganglion stimulation, exercise, or CPT\(^4\) might be expected to induce opposing effects on coronary vascular resistance by increasing myocardial oxygen demand. Thus, under normal circumstances, \( \alpha \)-adrenergically mediated vasoconstriction might be obscured.

In this study, the response to cutaneous cold serves as both a sympathetic and a metabolic stimulus. CPT, a predominantly \( \alpha \)-adrenergic stimulus, is one of several potent stimuli that promote the release of endogenous catecholamines\(^3\) and cause coronary and peripheral vasoconstriction by stimulation of a nonspecific autonomic and peripheral neural reflex. Raizner et al.\(^2\) in addition to finding a global coronary constrictor effect angiographically during CPT, noted focal coronary constriction in two of 14 patients with the diagnosis of CAD, four of six patients with variant angina and one of 15 patients with atypical chest pain. The dose of \( \beta \)-blocking drugs given before CPT was not indicated. In most of these patients, as in most of our patients, the decrease in coronary diameter or increase in coronary vascular resistance during CPT was not accompanied by objective or subjective evidence of myocardial ischemia, such as lactate production or ECG changes.

We believe that a primary metabolic modulation of vasomotor tone is not responsible for the increase in coronary vascular resistance during CPT before or after propranolol in patients with significant CAD. The
precise effect of β-adrenergic blockade on coronary vascular tone in man is difficult to define. A reduction of coronary blood flow after propranolol associated with a widening of the arterial–coronary sinus oxygen difference has suggested a vasoconstrictor effect, while narrowing of transcoronary oxygen difference after β blockade is consistent with reduction of myocardial metabolism. The increase in myocardial oxygen consumption due to the elevated rate-pressure product during CPT was associated with an inappropriate increase in coronary vascular resistance in patients with CAD. The potentiation of coronary vascular resistance during CPT after β-adrenergic blockade occurred with identical CPT-induced changes in the rate-pressure product, suggesting that enhanced α-adrenergic tone, rather than diminished myocardial metabolic demand, was responsible for the further increase in coronary vasoconstrictor tone.

Experimental control of the three major determinants of myocardial oxygen consumption and coronary blood flow in humans is difficult. We attempted to minimize changes in myocardial oxygen consumption induced by the negative chronotropic effect of propranolol by coronary sinus pacing at a constant subbetal rate. However, myocardial oxygen consumption might still be reduced after propranolol due to negative inotropic properties, which are not completely eliminated by pacing at elevated heart rates. Reductions in coronary flow might occur partially as a result of reduction of myocardial inotropic state by propranolol and, although small, represent an appropriate autoregulatory change in coronary vascular resistance. However, previous studies of the effect of propranolol on the coronary circulation by Schang and Pepine, Armstrong et al., and Stephens et al., focusing on drug effects at rest and during atrial pacing, suggest that the metabolic effects of propranolol are related more to the negative chronotropic than to the negative inotropic properties of the drug.

Patients with CAD constitute a heterogeneous population, and it is not surprising that the response of coronary vascular resistance to CPT was variable. This variability was also evident in the normal patients (fig. 3). We postulate that severe CAD and associated chronic myocardial ischemia result in vasodilation of the precapillary arterioles when the vasodilatory capacity of the coronary circulation approaches its maximal state. In this setting, when patients with severe CAD are subjected to sympathetic stimulation, no further vasodilatory capacity remains and neurally mediated coronary vasoconstriction rather than metabolically induced coronary dilation predominates. One explanation for the wide variability in CPT responses may be the amount of remaining coronary vasodilatory reserve. All patients were atrially paced to subbetal heart rates to eliminate the influence of a change in heart rate due to propranolol or CPT and, as importantly, to stress or exhaust the vasodilatory reserve to minimize metabolic autoregulatory mechanisms and, thus, leave the coronary circulation subject to predominant neural regulation.

Coronary artery spasm may involve the precapillary coronary arteriolar resistance. However, the locus of coronary vasoconstriction during CPT has not been precisely defined. Focal spasm of the large epicardial conductance vessels has been demonstrated during CPT. CPT has induced small but statistically significant angiographically visible coronary artery narrowing of large epicardial branches, coronary arteries filled by collaterals and small intramyocardial coronary arteries. The minor degrees of inducible coronary constriction over a substantial length of coronary artery might account in part for the increased coronary vascular resistance during CPT. Small changes in epicardial coronary tone superimposed on severe stenosis may greatly increase coronary vascular resistance in severe CAD patients more than in patients with modest degrees of CAD. For a better understanding of pharmacologic modulation of coronary tone during CPT, further studies are needed to clarify the extent to which metabolic and neurogenic stimuli alter coronary vasodilatory reserve and to define more precisely the locus of action in CPT-induced resistance changes within the coronary bed.

Certain limitations of the study should be mentioned. The coronary vasoconstrictor response may have been influenced by pharmacotherapy used during the study. Six of 15 patients received atropine before CPT. Atropine reportedly prevents coronary vasoconstriction during CPT. Further studies are needed to clarify the extent to which metabolic and neurogenic stimuli alter coronary vasodilatory reserve and to define more precisely the locus of action in CPT-induced resistance changes within the coronary bed.

Adequate resolution of preexisting β blockade after withdrawal of oral β blockers 12–24 hours before study may be difficult to ascertain. Most significant β-blocking effects will have been dissipated after three or more half-lives of the shorter-acting drugs, such as propranolol and metoprolol, have elapsed. However, some investigators have observed β-adrenergic blocking effects lasting a week or longer after cessation of the drug despite the absence of detectable serum levels. The duration of withdrawal of β-adrenergic blockade before the study, although sufficient to greatly reduce plasma propranolol levels, may not have permitted complete elimination of β-blocking drugs from body tissues. Thus, pre-propranolol measurements may not reflect a situation in the absence of β-adrenergic antagonism. However, this probably would not have influenced qualitative aspects of the subsequent response to i.v. propranolol. Residual β blockade would be expected to augment the initial increase in coronary vascular resistance during the CPT and blunt the changes in coronary vascular resistance after propranolol.

The reproducibility of coronary sinus blood flow measurement may be affected by small position shifts of the catheter due to deep inspiration, the Valsalva maneuver, or head and shoulder movements. During flow determinations, slow, regular breathing and, occasionally, quiet, audible counting was encouraged to prevent movement or an unconscious Valsalva maneuver during CPT. Although catheter position may have varied slightly before and after propranolol, the rela-
tive change in flow and resistance have been used to indicate directional changes and not the absolute magnitude of response. Other sources of potential error in coronary sinus flow measurements include right atrial reflux and malposition of coronary sinus thermistor against a side branch of the coronary sinus. Tracings in which atrial reflux, flow signal artifacts or extrasytoles appeared during coronary sinus flow measurement were excluded from analysis.

Maseri and co-workers emphasized that many patients with unstable angina or obstructive CAD have increases in coronary vasomotor tone that can provoke myocardial ischemia. This study demonstrates that adrenergic blockade can potentiate an increase in coronary vasomotor tone during a nonspecific neurogenic stimulus in some patients with CAD. Although the clinical significance of these observations is unknown at this time, the results presented offer further support for the following hypothesis. Because coronary blood flow may be altered by shifting the balance on a physiologic continuum between severe fixed atherosclerotic stenosis and frank coronary spasm, a subset of patients with CAD may have superimposed increased coronary vasoreactivity. In these patients, during periods of increased sympathetic stimulation such as marked cold exposure, emotion, exercise, or unstable angina refractory to conventional therapy, propranolol may accentuate coronary artery vasoconstrictor tone and exacerbate myocardial ischemia.

References


Alpha-adrenergic Blockade for Variant Angina: A Long-term, Double-blind, Randomized Trial

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SUMMARY Recent reports have shown that β-adrenergic blockade may exacerbate variant angina. On theoretical grounds, α-adrenergic blockade may be beneficial in these patients. To test this hypothesis, we assessed the efficacy of prazosin, an α-adrenergic blocking agent, in six men, mean age 49 years, with variant angina. Prazosin, 14.0 ± 2.4 mg/day (mean ± sd) in three equal doses, was compared with placebo in a double-blind, randomized, double-crossover trial lasting 4½ months: 2 weeks of open-label prazosin followed by four 1-month periods of blinded alternating therapy. No other vasoactive medications were administered during the study. Prazosin reduced sitting systolic arterial pressure from 145 ± 18 to 127 ± 16 mm Hg (p = 0.02), but exerted no effect on diastolic arterial pressure or heart rate. Prazosin did not change the weekly number of episodes of chest pain (2.5 ± 2.3 with placebo vs 3.1 ± 3.0 with prazosin, NS), nitroglycerin tablets used (3.9 ± 3.7 with placebo vs 4.6 ± 4.2 with prazosin, NS), or transient ST-segment deviations (by calibrated two-channel Holter monitoring for 24 hours/week throughout the study) (6.5 ± 10.1 with placebo vs 11.8 ± 17.4 with prazosin, NS). During prazosin therapy, three patients had orthostatic dizziness and one patient had headache. Thus, in a long-term, randomized, double-blind trial, prazosin exerted no obvious beneficial effect in patients with variant angina.

ALTHOUGH the cause of coronary arterial spasm is unknown, several studies over the past 10 years have suggested that episodes of spasm may be mediated by stimulation of the α-adrenergic receptors of large coronary arteries. Studies in experimental animals have shown that coronary blood flow can be influenced markedly by stimulation or blockade of these α-adrenergic receptors. Some reports have strongly suggested that in patients with variant angina, α-adrenergic stimulation can induce clinical episodes of spasm, whereas α-adrenergic blockade is effective in alleviating these episodes. However, these studies were relatively brief and were not randomized or double-blind. Therefore, we designed a long-term, placebo-controlled, randomized, double-blind study to assess the efficacy of prazosin, an α-adrenergic blocking agent, in patients with variant angina.

Methods

Patients
Six male patients, mean age 49 years (range 35–57 years), who had variant angina were enrolled in a 4½-month comparison of placebo and prazosin (packaged appropriately for a double-blind study). All six patients had recurrent episodes of angina at rest in conjunction with transient ST-segment elevation (at least 0.2 mV) on a standard 12-lead ECG, and in five, coronary arterial spasm was demonstrated angiographically. None of the six patients complained of exertional chest pain or had evidence of exercise-induced coronary arterial spasm. They had complained of angina at rest for 1.5 ± 1.1 years (range 1 month to 3 years). Selective coronary arteriography revealed obstructive one-vessel coronary artery disease (at least 70% luminal diameter narrowing) in two patients; the four other patients did not have obstructive coronary artery disease. During the study, no patient received other cardioactive medications, including long-acting nitrates preparations.

Study Design
After the diagnosis of variant angina was established and informed consent was obtained, each patient began taking open-label prazosin for 2 weeks, during which the maximal dose of prazosin that did not cause intolerable adverse effects was determined. Subse-
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