Acetylcholine Causes Coronary Vasodilation in Dogs and Baboons

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Intracoronary administration of acetylcholine or efferent vagal stimulation causes coronary vasodilation in dogs. However, in baboons it has been reported that intracoronary acetylcholine results in a fall in coronary blood flow and that stimulation of the vagi is without effect. The dose response of intracoronary acetylcholine and the effect of efferent vagal stimulation on the coronary circulation were reinvestigated in closed-chest, anesthetized dogs and baboons. The left main coronary artery was cannulated and perfused at constant pressure. α-Adrenergic and β-adrenergic receptors were pharmacologically blocked with phenoxybenzamine and propranolol. Heart rate was held constant by right ventricular pacing. In dogs, intracoronary infusion of acetylcholine (1-300 μg/min) elicited a dose-dependent increase in steady-state coronary blood flow and coronary sinus oxygen tension, without a change in myocardial oxygen consumption. Vagal stimulation caused a coronary vasodilation that was attenuated by a metabolically mediated decrease in flow. In baboons, acetylcholine increased steady-state coronary blood flow in the dose range of 1-10 μg/min, caused little change at 30 μg/min, and decreased flow at 100-300 μg/min. Coronary sinus oxygen tension increased in a dose-dependent manner up to 10 μg/min. Myocardial oxygen consumption was unchanged in the dose range of 1-10 μg/min and declined between 30 and 300 μg/min. Efferent stimulation of the vagi resulted in coronary dilation obscured by a metabolic reduction of flow. It is concluded that 1) low doses of acetylcholine elicit a primary coronary vasodilation in both species, but in baboons high doses of acetylcholine cause a reduction of both myocardial oxygen consumption and coronary blood flow below control values and 2) vagal stimulation causes a competition between coronary vasodilation and metabolic reduction of flow in dogs and baboons. (Circulation Research 1989;65:1580-1593)

Although it is well established that canine coronary vessels vasodilate in response to acetylcholine1-3 and efferent vagal stimulation,3-5 there are conflicting reports regarding the response of primate coronary arteries to parasympathetic activation. Isolated epicardial coronary arteries from monkeys have been found to relax6 and to relax or contract7 in response to acetylcholine. Intracoronary administration of acetylcholine in intact Japanese monkeys and baboons has been reported to elicit an intense decrease in coronary blood flow.8-10 Efferent vagal stimulation in baboons has been found to be without effect on coronary blood flow.11

However, coronary vascular resistance is primarily determined by local metabolic factors, not direct neural control. Myocardial oxygen metabolism is affected by heart rate, systolic blood pressure, and myocardial inotropic state.1 Thus, a neural coronary vasodilation may be buffered or even masked by a metabolic vasoconstriction secondary to a decline in any of the above hemodynamic variables.

The purpose of the present study was to ascertain if there is indeed a species difference between dogs and baboons in the effects of intracoronary acetylcholine and vagal stimulation on coronary blood flow and myocardial metabolism. Efferent vagal stimulation and intracoronary infusion of acetylcholine were performed in α- and β-receptor-blocked closed-chest animals in which heart rate was held constant. As expected, dogs responded to acetylcholine with a dose-dependent increase in coronary flow and little change of myocardial oxygen consumption. In baboons, low doses of acetylcholine increased coronary flow, but at high doses myocardial oxygen metabolism fell and the flow response was reversed to a decrease.
Materials and Methods

General Preparation

Thirteen animals of either sex were studied with closed chest: seven dogs (24–36 kg) and six baboons (Papio cynocephalus and Papio anubis, 15–25 kg). Dogs were sedated with morphine sulfate (2.5 mg/kg s.c.) and anesthetized with α-chloralose (100 mg/kg i.v.). Baboons were sedated with ketamine (10 mg/kg i.m.) and morphine sulfate (1 mg/kg i.m.) and anesthetized with α-chloralose (100 mg/kg i.v.). Anesthesia in both species was maintained by a continuous infusion of α-chloralose (10 mg/kg/hr i.v.) plus 500-mg i.v. supplements of α-chloralose as needed.

The animals were intubated and mechanically ventilated with an end-expiratory pressure maintained between 0 and 5 cm H₂O. End-expiratory carbon dioxide was held at 4.5–5%. Inspired air was supplemented with oxygen to maintain an arterial oxygen tension of 90–150 mm Hg. Esophageal temperature was held constant with a heating pad and temperature controller. Metabolic acidosis secondary to chloralose anesthesia was corrected by a continuous intravenous drip of sodium bicarbonate (1.5%, 5 ml/kg/hr) and bolus injections of bicarbonate as needed. To maintain patency of the extracorporeal circuit, the animals were anticoagulated with heparin sodium (750 units/kg + 250 units/kg/hr i.v. in dogs, 1,000 units/kg + 300 units/kg/hr i.v. in baboons). Ibuprofen (12.5 mg/kg i.v. every 4 hours) was administered to inhibit platelet and leukocyte aggregation. Arterial blood pressure was measured with a strain gauge manometer (Statham model P23Dd, Gould, Cleveland, Ohio) via a catheter in the aortic arch. During experimental maneuvers arterial pressure was held constant by means of a blood-filled collapsible reservoir inside a constant-pressure rigid chamber connected to the animal's femoral artery. The experimental preparation is depicted in Figure 1.

Control of Heart Rate

In the dogs, atrioventricular heart block was performed by injection of a small amount (0.1 ml) of formalin into the atrioventricular nodal area. Once the block was attained, the heart was paced from the right ventricular apex by a pacing wire inserted via the right jugular vein (80 beats/min, 0.6-msec duration). In the baboons, control of heart rate was accomplished by overpacing of the intrinsic rate via a pacing wire in the right ventricular apex. The required stimulus frequency varied from 90 to 150 beats/min among baboons.

Coronary Sinus Cannulation and Oxygen Tension Measurement

Under fluoroscopic control, a Sones catheter (model 5423, USCI, Billerica, Massachusetts) was inserted in the coronary sinus. Coronary venous blood was continuously withdrawn with a roller pump (model 4420, Cole-Parmer Instrument, Chicago) and passed over an oxygen electrode before being returned to the femoral vein. Right atrial venous admixture was prevented by insertion of the catheter at least 15 mm into the coronary sinus and limitation of the withdrawal rate to 5–15 ml/min. The oxygen electrode was calibrated frequently with gases of known oxygen content. At the end of each experiment, the tip of the Sones catheter was verified to be well into the coronary sinus (33–58 mm in dogs, 19–26 mm in baboons), and the tubing transit time was determined. Transit times ranged from 11 to 22 seconds in the dogs and 10 to 21 seconds in the baboons. The oxygen tension values shown in the original records have been shifted along the time axis to correct for the transit delay. 

FIGURE 1. Schematic diagram of closed-chest experimental preparation. Left main coronary artery was perfused with blood withdrawn from a femoral artery via a stainless steel cannula advanced from right carotid artery and seated in left coronary ostium. Pressure at cannula tip was held constant at 90 mm Hg with a servo-controlled pump. Coronary flow was measured with an electromagnetic flowmeter in perfusion circuit. Coronary sinus blood was withdrawn continuously for determination of myocardial venous oxygen tension. Left ventricular pressure was measured with a catheter-tip manometer inserted in left ventricle via a femoral artery. Aortic pressure was stabilized with a pressurized blood reservoir. Heart rate was held constant by pacing of right ventricular apex with catheter-tip electrodes. Acetylcholine was infused into perfusion line just proximal to hub of coronary cannula. ACh, acetylcholine; EM, electromagnetic.
**Left Ventricular Pressure and **\( \frac{dp}{dt} \)**

A catheter-tip pressure transducer (Millar Instruments, Houston, Texas) was placed in the left ventricle via the right femoral artery. Left ventricular rate of change of pressure (\( dp/dt \)) was obtained with an electronic differentiator (linear up to 20 m Hg/sec) of the left ventricular pressure signal.

**Left Coronary Perfusion and Blood Flow Measurement**

The left main coronary artery was cannulated with a balloon-tipped stainless steel cannula via the right carotid artery of the closed-chest animal, and perfused with blood from the left femoral artery. Coronary artery pressure at the tip of the cannula was measured by means of a small internal tube and a strain gauge manometer (Statham model P23ID, Gould). Coronary pressure was held constant at 90 mm Hg with a servo-controlled roller pump. The seal of the balloon-tip cannula in the coronary ostium was considered satisfactory if, upon interruption of inflow, coronary pressure fell below 25 mm Hg and 2) if injection of crystal violet at the end of the experiment, while coronary pressure was maintained 50 mm Hg above aortic pressure, stained perfused myocardium and vessels but not the ascending aorta. If these two criteria were not met, the animal was excluded from the study. Coronary flow was measured with an extracorporeal electromagnetic flowmeter (model SWF-5, Zepeda Instruments, Seattle, Washington). Flow per gram was calculated from the flowmeter measurement and the weight of the stained myocardium excised post mortem. Occlusive flow zeros were obtained repeatedly during the experiment. The flowmeter was calibrated at the end of each experiment by timed collection of blood at several flow rates.

**Determination of Myocardial Oxygen Consumption**

A subset of arterial and coronary sinus samples was analyzed for oxygen content by the fuel cell method (Lex-O2-Con), and hemoglobin was determined by the cyanmethemoglobin method. In all samples, oxygen tension, carbon dioxide tension, and pH were measured (IL 1302, Instrumentation Laboratory, Lexington, Massachusetts). From the blood gas tension and pH values, oxygen contents were calculated with a computer subroutine. The Lex-O2-Con values were used to construct a calibration curve for the blood gas subroutine. Myocardial oxygen consumption was calculated as the product of coronary flow and the difference in arteriovenous oxygen content and expressed as microliters of oxygen per minute per gram of myocardium.

**Solutions**

Drugs were mixed fresh for each experiment. Ibuprofen (1 4883, Sigma Chemical, St. Louis) was dissolved in 0.2 M sodium carbonate at a concentration of 25 mg/ml, and pH was adjusted between 7 and 8 with 1 M HCl. Phenoxybenzamine (Smith Kline & French, Philadelphia), propranolol (P0884, Sigma Chemical), and acetylcholine chloride (A 6625, Sigma Chemical) were diluted in normal saline.

**Experimental Protocol**

Propranolol (0.5-1.0 mg/kg i.v. bolus+0.2 mg/kg/hr i.v. infusion in dogs, 0.3-1.0 mg/kg i.v. bolus+0.2 mg/kg/hr i.v. infusion in baboons) was given to blunt β-receptor-mediated changes in myocardial oxygen consumption. Some animals could not tolerate the 1 mg/kg loading dose of propranolol (pronounced arterial hypotension developed during drug administration); these animals received the smaller bolus injections of propranolol. Phenoxybenzamine (0.25 mg/kg intracoronary) was administered to all dogs and four baboons to avoid cholinergic-adrenergic interactions. Results from the baboons that did not receive α-adrenergic blockade did not differ from those of the drug-treated animals.

The acetylcholine dose response was constructed in half-log increments from 0.1 to 300 µg/min (6.8x10^{-7} to 2.05x10^{-6} mol/min). The concentration of each dose was adjusted so that a constant volume of 0.1 ml/min was always infused into the coronary cannula with a syringe pump (model 945, Harvard Apparatus, South Natick, Massachusetts). Coronary arterial and sinus blood samples were drawn just before and then during acetylcholine infusion, when flow and venous oxygen tension had become steady. Coronary blood flow, coronary sinus oxygen tension, and left ventricular \( dp/dt \) were allowed to return to baseline between doses of acetylcholine. Both cervical vagi were double tied and/or cut and the distal ends stimulated with pulses of 0.5-msec duration, 30 Hz, and 15 V (model 509 stimulator, Grass Instrument, Quincy, Massachusetts), as monitored on an oscilloscope. Before stimulation, baseline coronary arterial and coronary sinus blood samples were obtained. The stimulation was long enough (usually 50 seconds) to obtain steady coronary blood flow and coronary sinus oxygen tensions and to permit withdrawal of coronary arterial and venous blood samples. After completion of the acetylcholine dose response and vagal stimulation, atropine (0.5 mg/kg i.v.) was given to both species. One dose of acetylcholine, determined to be on the steep portion of the dose response, and vagal stimulation were then repeated.

**Determination of Myocardial Lactate Metabolism**

Three additional baboons were studied to determine if the decrease in coronary blood flow observed with high doses of acetylcholine was accompanied by net myocardial lactate production. The animals (two P. anubis, one Papio hamadryas; 21-24-kg males) were prepared identically to those described above except that the left ventricular pressure trans-
FIGURE 2. Effect of 10 (left panel) and 300 (right panel) μg/min intracoronary acetylcholine (ACh) in one dog, with heart rate and coronary pressure held constant. Coronary arterial and venous blood samples were taken just before infusion of drug and during plateau phase of flow and venous oxygen tension response. Coronary sinus oxygen tension (PO₂) trace has been shifted to adjust for transit delay. dP/dt, rate of change of pressure.
Acetylcholine Dose Response

which plots coronary flow (expressed as oxygen tension in the dose range of 1–10 µg/min. At 30 µg/min acetylcholine, the increase in flow was less than that observed with 10 µg/min, and at 100–300 µg/min, coronary flow fell below control values (Figure 3). The increase in coronary sinus oxygen tension in response to acetylcholine gradually diminished over the dose range of 30–300 µg/min, although response values always exceeded control oxygen tensions. Myocardial oxygen consumption did not change in response to acetylcholine doses of 0.1–3 µg/min; above 10 µg/min, however, myocardial metabolism declined (Figure 4). Figure 5 shows that at acetylcholine doses of 1–10 µg/min a pure coronary vasodilation occurred (upward vertical arrows); above this dose the arrows rotate, indicating that there was a progressive decrease in myocardial metabolism along with the primary vasodilation.

Vagal Stimulation

In dogs, efferent stimulation of the vagi elicited a transient increase in coronary blood flow (Figure 7). Coronary flow at the steady portion of the response was similar to baseline blood flow (0.56±0.08 ml/min/g vs. 0.58±0.07 ml/min/g). Coronary sinus oxygen tension peaked transiently, then declined to a plateau value 6±2 mm Hg above control (25±2 mm Hg at plateau vs. 19±1 mm Hg at control, p<0.05). Myocardial oxygen consumption was decreased by 17±3 µl/min/g, from 70±6 to 53±3 µl/min/g (p<0.05). Left ventricular dP/dt was not statistically different from control. When these data were plotted as coronary flow (expressed as oxygen delivery) versus myocardial oxygen consumption (Figure 8), it can be seen that while there was a considerable decrease in oxygen consumption, there was only a modest decline in coronary blood flow. This indicates that there was a primary coronary vasodilation opposing a secondary, metabolically mediated decrease in flow.

In one baboon, stimulation of the efferent vagi resulted in a transient increase followed by a slight decrease in coronary blood flow. The characteristic pattern was a transient decrease in coronary blood flow at the onset of stimulation followed by a partial recovery of flow to control values (1.10±0.28 ml/min/g vs. 1.01±0.28 ml/min/g). The response of coronary sinus oxygen tension to vagal stimulation was variable; although the mean response was a 2.2±1.6 mm Hg increase in oxygen tension, this difference did not achieve statistical significance. As with dogs, vagal stimulation in baboons evoked a sustained decrease in myocardial oxygen consumption (73±14 µl/min/g). Left ventricular dP/dt declined during vagal stimulation in baboons (1.6±0.09 mm Hg/sec).
FIGURE 3. Comparison of acetylcholine dose response in dogs and baboons for coronary blood flow (left panel) and coronary sinus oxygen tension (PO2) (right panel). Not all animals were able to tolerate high doses of acetylcholine due to systemic effects. Some coronary sinus oxygen tension (PO2) data points were lost during sample handling; this is reflected in the variable n in these graphs.
FIGURE 4. Comparison of acetylcholine dose response in dogs and baboons for myocardial oxygen consumption (left panel) and left ventricular rate of change of pressure (dP/dt) (right panel). Control values for both variables at each dose of acetylcholine are displayed on graphs as "Initial Value."
Figure 5. Graphical representation of myocardial oxygen consumption, coronary flow, and oxygen extraction data for four doses of acetylcholine in dog (top panel) and baboon (bottom panel). Myocardial oxygen consumption is plotted on abscissa. Ordinate represents coronary flow and is expressed as oxygen delivery (coronary blood flow times arterial oxygen content). Thus, the line of unity reflects 100% extraction of delivered oxygen, and the radial lines as they progress counterclockwise represent successively lower fractions of oxygen extraction. Tail of each arrow represents control values for oxygen consumption and delivery before acetylcholine infusion; arrowhead reflects changes that ensue during infusion of one dose of acetylcholine. An arrow pointing vertically upward would indicate pure vasodilation without change in myocardial oxygen consumption; an arrow pointing vertically downward would indicate pure vasoconstriction. Arrows that point above and left of a radial line of constant extraction indicate a mixed vasodilation and decrease in myocardial oxygen consumption. Note that there can be no points below 100% extraction line, as this would indicate that more oxygen is consumed than is delivered.

$p<0.05$). Figure 8 shows coronary flow versus oxygen consumption data.

Effect of Atropine

The effect of atropine on the response to infused acetylcholine was tested by infusion of a dose of acetylcholine that had previously evoked a robust response; this dose varied between 10 and 100 μg/min. In both dogs and baboons, administration of atropine virtually eliminated any response to the infused acetylcholine. After the injection of atropine, vagal stimulation in both dogs and baboons elicited only insignificant changes in measured variables. None of the responses to acetylcholine infusion or vagal stimulation achieved statistical significance.

Lactate

Myocardial lactate extraction was measured in three additional baboons (Figure 9). Control arterial and venous lactate concentrations before each dose of acetylcholine were not significantly different. Data are plotted as the arteriovenous lactate differ-
FIGURE 6. Effects of two doses of intracoronary acetylcholine in one baboon. During infusion of 10 μg/min acetylcholine (at steady portion of response, left panel), coronary blood flow was increased by 50% over control values. Coronary sinus oxygen tension (PO₂) was also increased for the period of infusion. With 300 μg/min acetylcholine (right panel), coronary blood flow increased transiently; this effect was followed by a 43% decrease in flow that was sustained for the duration of the infusion. Coronary sinus PO₂ increased at start of infusion, then returned toward baseline. dP/dt, rate of change of pressure.
ence before, during, and after the infusion of acetylcholine. There was no consistent change in arteriovenous lactate difference with infusion of acetylcholine in the dose range of 0.1–30 µg/min. However, there was a trend for lactate extraction to approach zero during the infusion of acetylcholine in the dose range of 100–1,000 µg/min, and net lactate production occurred during the off-response of doses 100 and 1,000 µg/min.

Discussion

These data indicate that the difference in coronary vascular response to cholinergic activation in dogs and baboons is quantitative rather than qualitative, since infusion of acetylcholine elicited vasodilation in both species. However, the negative inotropic effect of acetylcholine was much more pronounced in baboons than in dogs, so that the net effect of high doses of acetylcholine was a decrease in flow. The interpretation of these results differs from the studies in which it was concluded that acetylcholine is a coronary vasoconstrictor in primates.

The present results in dogs, in which intracoronary acetylcholine elicited a dose-dependent increase in coronary blood flow and coronary sinus oxygen tension, confirm previous studies. At the doses evaluated, myocardial oxygen consumption did not change. However, in baboons only low doses of acetylcholine produced a dose-dependent increase in coronary blood flow and coronary venous oxygen tension without a change in myocardial metabolism.

At high doses of acetylcholine in the baboons, a hyperemic off-response always occurred. Hyperemia and hyperfunction after cessation of acetylcholine administration have been reported previously, but were abolished after adrenergic blockade and, thus, were most likely due to release from cholinergic inhibition of norepinephrine release. The combined α- and β-adrenergic blockade used in the present study should prevent this effect, so the etiology of the off-response observed in baboons remains unclear. Since ischemic myocardium shifts from net lactate extraction to net myocardial lactate production, the observation of a trend toward lactate production at high doses of acetylcholine is consistent with the possibility of vasoconstriction at high doses (Figure 9). However, coronary sinus oxygen tension was elevated during high doses of acetylcholine. Therefore, it is unlikely that the off-response represents a release from globally ischemic conditions, but regional ischemia remains a possibility at very high doses of acetylcholine.

The differences between dogs and baboons is unlikely to be the result of a widely disparate concentration of acetylcholine in the coronary vascular bed. Control coronary flow before the 10-µg/min acetylcholine infusion was 95 ml/min (0.70 ml/min/g) in dogs and 55 ml/min (0.97 ml/min/g) in baboons. Thus, the difference in control conditions is less than the half-log dose intervals illustrated in Figures 3 and 4.

It has been shown that parasympathetic-sympathetic interactions occur and that in some preparations a component of cholinergic vasodilation may be due to prejunctional inhibition of norepinephrine release and a resultant inhibition of α-adrenergic vasoconstriction. However, the present study employed combined α- and β-adrenergic blockade.

In both species, efferent vagal stimulation resulted in a decrease in myocardial oxygen consumption. In dogs, an initial increase in coronary blood flow and a large, sustained rise in coronary sinus oxygen tension indicated a coronary vasodilation. In baboons, coronary blood flow showed little change and coronary venous oxygen tension rose slightly. It is possible that a difference in pattern and density of parasympathetic cholinergic innervation between dogs and baboons is the cause of the difference in degree of the observed response to vagal stimulation. Acetylcholinesterase–positive fibers have been reported to invade the adventitia-media border of dog coronary arteries. However, an examination of baboon coronary arteries found only sparse-to-absent cholinergic innervation. If in primates a preponderance of cholinergic fibers terminated on myocytes rather than vascular smooth muscle, it might be expected that vagal stimulation would elicit the response observed in the baboon.

The decrease in coronary blood flow during large intracoronary doses of acetylcholine in nonhuman primates in the present study confirms the observations from other laboratories. However, the interpretation of the previous data was that acetylcholine induces a primary coronary vascular constriction. The initial studies used bolus intracoronary injections of acetylcholine, which complicates the interpretation of the results since steady responses were not achieved. Furthermore, in those studies in which it was concluded that the decrease in coronary flow was due to primary vascular constriction, factors that affect myocardial metabolism (e.g., heart rate, aortic pressure) were not controlled and myocardial oxygen consumption in the perfused region was not measured. In the study of Taira and coworkers, changes in myocardial metabolism were estimated by use of left ventricular dP/dt, which is a global measurement of cardiac contractility, but the infusion of acetylcholine went only to myocardium supplied by the distal left anterior descending artery. Thus, a global index of cardiac contractility showed little change during a regional infusion of acetylcholine. A similar problem may explain the conclusions of Young et al: although coronary sinus blood was withdrawn for calculation of myocardial oxygen consumption in baboons, acetylcholine was infused into the right coronary artery. Since the coronary sinus blood is predominantly venous drainage from the left ventricle, a change in right ventricular venous oxygen tension may have been obscured.

With a continuous infusion of 20 µg/kg acetylcholine, Taira and coworkers observed a sustained
FIGURE 7. Effect of efferent vagal stimulation in one dog (left panel) and one baboon (right panel). In dog, vagal stimulation elicited a transient increase in coronary blood flow and coronary sinus oxygen tension (PO2), which decayed to a plateau that was sustained for the duration of stimulus. In baboon, vagal stimulation elicited a transient biphasic flow response that was followed by a sustained modest decrease in flow. Coronary sinus PO2 was increased for the duration of stimulus. Left ventricular rate of change of pressure (dP/dt) showed a pronounced reduction during vagal stimulation in baboon.
The observation that isolated human vessels contract in response to acetylcholine has been observed in several laboratories. However, endothelium-dependent cholinergic relaxation of isolated human coronary arteries has been reported by other laboratories; the relaxation was attenuated or abolished by the presence of atherosclerosis. Recent clinical studies have shown that intracoronary bolus doses of acetylcholine increase estimated coronary flow and vascular conductance. In conclusion, the present data obtained during combined α- and β-receptor blockade indicate that the primary effect of low-dose acetylcholine on coronary vessels in dogs and baboons is vasodilation independent of cholinergic-adrenergic interactions.

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CORONARY BLOOD FLOW

BABOON

CORONARY SINUS PO2

CORONARY BLOOD FLOW

MYOCARDIAL OXYGEN CONSUMPTION

LACTATE

FIGURE 9. Acetylcholine dose-response data for three baboons in which myocardial lactate metabolism was measured. Lactate data (lower right panel) are graphed as arterial minus venous lactate concentration; thus, a positive value indicates net lactate extraction by heart and a negative value indicates net myocardial lactate production. Coronary arteriovenous lactate differences are plotted before and during acetylcholine infusions. *After data were obtained during hyperemic offresponse observed after cessation of high doses of acetylcholine (compare Figure 6). PO2, oxygen tension.
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