Myocardial Lactate Metabolism:
Evidence of Lactate Release During Net Chemical Extraction in Man

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SUMMARY Myocardial blood flow has been recognized to be heterogeneous in patients with coronary artery disease. Traditional arterial-coronary sinus sampling methods cannot demonstrate comparable heterogeneity of myocardial metabolism. In this study we used a tracer technique to investigate possible heterogeneity of myocardial lactate metabolism. Twenty-one patients with symptoms of ischemic heart disease were studied. We injected 14C-lactate intravenously as a constant infusion after a priming dose. Coronary sinus and arterial samples were obtained for chemical and radioisotopic analyses. At rest, myocardial lactate extraction by chemical analysis was 24.6 ± 8.5% (mean ± SD). By radioisotopic analysis, the lactate extraction was 41.0 ± 10.2% (p < 0.001). Thus, certain areas of the myocardium were releasing lactate despite global net extraction of lactate. In the 12 patients with significant left main or both left anterior descending (LAD) and left circumflex (LCX) lesions, the calculated amount of lactate released at rest was 0.136 ± 0.045 μmol/ml of blood (mean ± SD). In contrast, the amount released in the six patients with a significant lesion in only the LAD or LCX was 0.076 ± 0.019 μmol/ml, and in the three patients without left coronary arterial lesions it was 0.039 ± 0.004 μmol/ml.

Using a tracer method, myocardial lactate metabolism was demonstrated to be heterogeneous at rest in patients with ischemic heart disease. A significant amount of lactate can be released by the myocardium at a time when chemical arterial-coronary sinus analysis indicates global myocardial extraction. The amount of lactate released appears to be related to the severity of the coronary artery disease.

IT HAS LONG BEEN SUSPECTED that patients with functionally significant coronary artery disease have marked heterogeneity of myocardial blood flow. Significant differences in regional myocardial blood flow in patients with coronary artery disease have been demonstrated at rest. More recently, transient defects have been found in resting thallium-201 myocardial scintigrams in patients with severe coronary lesions. These findings indicate that coronary perfusion is not uniform in these patients at rest. As myocardial oxygen extraction is close to maximal during normal perfusion at rest, a decrease in perfusion may produce regional disturbances or heterogeneity of myocardial metabolism.

Even in animals with normal coronary arteries, several investigators have found heterogeneity in myocardial blood flow. In addition, a transmural myocardial gradient of certain glycolytic enzymes and substrate stores has been shown in experimental animals. Both nonuniformity of blood flow and differences from epicardium to endocardium in substrate concentrations are consistent with the hypothesis that myocardial metabolism is heterogeneous.

Traditional chemical analysis of arterial and coronary sinus blood samples cannot detect such a heterogeneous state of metabolism. The purpose of this study was to determine if heterogeneity of myocardial lactate metabolism is present at rest in patients with ischemic heart disease. We used 14C-lactate as a tracer to detect the release of lactate by the myocardium. In addition, by determining the 14CO2 in the arterial and coronary sinus blood, the actual amount of lactate undergoing oxidative decarboxylation by the myocardium was calculated.

Methods

The study population was composed of 21 male patients, ages 38-71 years, with symptomatic but stable ischemic heart disease who were about to undergo clinically indicated selective coronary angiography. The protocol was approved by the Committee on Human Research of the University of California at San Francisco and the Human Research Committee at the San Francisco Veterans Administration Medical Center. Written consent was obtained from each subject.

All patients were treated with nitroglycerin and long-acting nitrates. For 8 hours before the study, all nitrates were discontinued; no patient had chest pain during this period. Otherwise, there was no other alteration in drug therapy. Ten patients were receiving propranolol. As their metabolic data did not differ from the data obtained from the 11 patients not receiving propranolol, all data are combined.
Protocol

The patients were fasting for 12 hours before the study. An anteromedial vein was exposed with lidocaine anesthesia; a coronary sinus catheter was inserted into the vein and positioned under fluoroscopy in the mid region of the coronary sinus. To verify that the catheter was in the coronary sinus, pressure and oxygen content were measured; no contrast agent was injected. The stability of the catheter position was verified by comparison of video disc images recorded at the beginning and the end of the procedure. Patients were included in this study only if the coronary sinus catheter was sampling the venous drainage of both the left anterior descending and left circumflex arteries (LAD and LCX). This was determined retrospectively from cineangiograms by observing the distribution of the venous filling phase after intraarterial injection of the left coronary. The sampling orifice was at least 30 mm from the ostium of the coronary sinus in all cases. The decision to include the study was made after coronary angiography, but before the results of the metabolic study were available. No patient included in this study had a mean right atrial pressure greater than 4 mm Hg.10

For arterial blood samples, a short polyethylene sheath was inserted into the femoral artery by the Seldinger method. All patients received heparin (10,000 units) as an i.v. bolus before the femoral arterial puncture. To ensure that heparin did not influence our findings, three additional patients underwent similar procedure with blood samples obtained before and after the heparin bolus.

The L-(-)14C-1-lactate was obtained from New England Nuclear (specific activity 8.95 mCi/mmole). It was sterilized by ultrafiltration (0.22 μm) and diluted in 0.9% NaCl to a concentration of 10 μCi/ml for the bolus injection, and 0.3 μCi/ml for the subsequent constant infusion. After a priming bolus of 10 μCi,14C-1-lactate was infused intravenously at a constant rate of 12 μCi/hour.

We obtained simultaneous arterial and coronary sinus blood samples for chemical and radiisotopic analyses of lactate, glucose, pyruvate, and 14CO2 and the chemical determination of free fatty acids. No sample was obtained less than 20 minutes after the priming dose of 14C-lactate. To ensure equilibration of the tracer, three paired arterial and coronary sinus blood samples were obtained at 5–7-minute intervals in all patients. No patient had evidence of ischemia by symptoms or ECG changes during the sampling period.

In all patients the metabolic study preceded left ventriculography and selective coronary angiography. The coronary angiograms were reviewed by two independent observers who had no knowledge of the metabolic results. Significant coronary lesions were defined as stenosis ≥ 75% of the cross-sectional luminal area, reported by both reviewers.

Chemical Analysis

Blood samples for lactate, pyruvate and glucose were mixed immediately with a measured volume of cold 7% perchloric acid and centrifuged; the supernatant fluid was taken for future analysis.

Lactate concentration was determined on the protein-free fluid by an enzymatic spectrophotometric method.11 For this method the coefficient of variation of 50 analyses of one blood sample in our laboratory was 1.6%. Pyruvate was measured on the protein-free fluid after neutralization with a Tris buffer (pH 7.2) by a modification of the method of Lowry.12

Glucose was measured on the protein-free fluid by a hexokinase/glucose-6-phosphate dehydrogenase-coupled enzymatic method,13 with a coefficient of variation of 1.5%.

Glucose, lactate and pyruvate were separated by ion exchange chromatography by the method of Searle and co-workers.14 The protein-free fluid was neutralized and passed successively through Dowex 50 and Dowex 1 to remove labeled ionized compounds. Portions of the eluates containing glucose in H2O, lactate in 0.25 M sodium acetate and pyruvate in 0.25 M sodium acetate, respectively were assayed by the described enzymatic methods. Other portions were mixed with Aquasol and 14C was measured in a scintillation counter. Results of scintillation counting are expressed as disintegrations per minute (dpm). The specific activity of the substrate is calculated as dpm/μmol. In our laboratory the coefficient of variation for the specific activity of lactate was 2.5% (six analyses of one sample).

The 14CO2 was collected directly from blood by a diffusion method.15 Blood samples were placed in the outer well of a double-chambered Erlenmeyer flask. With the system airtight, lactic acid was added to the blood and the flask was agitated on a shaker table for 3 hours at room temperature. The center well of the flask contained NaOH, which traps the released 14CO2 as NaH14CO3. A portion of the NaH14CO3 solution was mixed with Aquasol and counted. The recovery of 14CO2 from NaH14CO3 added to whole blood was 99.5%; the coefficient of variation for this method in our laboratory was 2.9% (eight analyses of one sample).

Blood for free fatty acids was placed in iced heparinized glass tubes within 30 seconds of sampling, centrifuged at 4°C and then separated. Free fatty acids levels were determined immediately on the plasma by the Trout modification16 of the Dole procedure.17 The coefficient of variation for this determination was 3.5%.

Calculations

The chemical extraction ratio was calculated from the arterial and coronary sinus substrate concentration as

\[
\frac{A-CS}{A} \times 100,
\]

where A = arterial concentration of the substrate and CS = coronary sinus concentration.
The isotope extraction ratio was calculated from the disintegrations per minute per milliliter of blood in the arterial and coronary sinus as

$$ \frac{A \text{ dpm/ml} - CS \text{ dpm/ml}}{A \text{ dpm/ml}} \times 100. $$

Disintegrations per minute per milliliter of blood were calculated from the specific activity (dpm/μmol) and the chemical concentration (μmol/ml).

Myocardial lactate uptake was determined from the isotope technique by multiplying the arterial concentration of lactate by the isotope extraction ratio/100 and was expressed as μmol/ml. The difference between the myocardial lactate uptake determined from the isotope technique and the arterial–coronary sinus chemical concentration was the amount of lactate released or produced by the myocardium.

In this study lactate was labeled in the C-1 position. This carbon is released as 14CO2 when pyruvate is decarboxylated to acetyl-CoA. By measuring the coronary sinus–arterial 14CO2 difference, the amount of lactate per milliliter of blood undergoing oxidative decarboxylation was determined as

$$ \frac{(CS-A)14\text{CO}_2 \text{ dpm/ml}}{\text{arterial specific activity of lactate}}. $$

**Results**

Figure 1A shows the arterial and coronary sinus specific activity of lactate in an individual patient. The infusion of 14C-lactate was begun immediately after the priming dose (time 0). The arterial and coronary sinus specific activity reach a plateau after 20 minutes of infusion (fig. 1A). To ensure equilibration of the labeled lactate, only the results of samples obtained 20 minutes or longer after beginning the infusion of tracer are included in this report. The specific activity of lactate in the coronary sinus (342 dpm/μmol) was lower than the arterial value (425 dpm/μmol). For this patient (fig. 1), the difference between arterial and coronary sinus specific activity was 19.7%. In all 21 patients at rest, the specific activity of lactate was lower in the coronary sinus than in the artery; for the group the mean percent difference between the arterial specific activity and that in the coronary sinus was 22.5% (range 6.6–41.4%).

Having obtained the disintegrations per minute for lactate per milliliter of blood in the coronary sinus and artery, an isotope extraction ratio can be calculated. Figure 2 is a comparison of the traditional chemical extraction of lactate with the isotope extraction ratio for the patients at rest. If the chemical extraction were equal to the isotope extraction ratio, the points would fall on the line of identity (fig. 2). In all patients, the extraction ratio by isotopic analysis was greater than the ratio obtained by chemical analysis. The mean chemical extraction ratio was 24.6 ± 8.5% (mean ± sd) for the patients at rest and the isotope extraction ratio was 41.0 ± 10.2% (p < 0.001).

The arterial level of free fatty acids in the 21 patients at the time of the metabolic samples was 1.23 ± 0.22 mmol/l (mean ± sd). All patients had
received heparin before we took the samples. Three additional patients with severe three-vessel disease had blood samples before and after heparin. The mean arterial level of free fatty acids before the heparin was 0.68 mmol/l (range 0.62–0.75 mmol/l) and rose to 1.15 mmol/l (range 1.09–1.21 mmol/l) at 10 minutes after the 10,000-unit heparin bolus. Before the heparin, the mean percent difference between the arterial specific activity of lactate and that in the coronary sinus for these three patients was 31.5% (range 23.7–40.3%); after heparin, the difference was 32.3% (range 25.5–41.0%). The chemical extraction ratio was 34.5% (range 28.4–45.8%) and the isotope extraction ratio was 56.0% (range 45.5–62.0%) before heparin; after heparin bolus the ratios were 28.4 (17.2–43.2%) and 51.8% (41.9–59.3%), respectively.

Severity of Coronary Disease

Three of the 21 patients had no lesions in the LAD and LCX arteries on angiography. Six patients had a significant lesion (≥ 75% of cross-sectional luminal area) in the LAD or LCX and 12 patients had significant lesions involving both these vessels. As the venous sampling site was the mid-coronary sinus, the venous drainage of the right coronary artery is not included. This was verified during angiography.

For the three patients without lesions, the isotope extraction ratio was 36.8 ± 2.7% (mean ± sd) and the chemical extraction ratio was 30.3 ± 2.1% at rest. For the six patients with a significant stenosis in one of the vessels, these values were 31.1 ± 4.4% and 19.0 ± 7.1% respectively. In contrast, the isotope extraction ratio for the 12 patients with significant lesions in both vessels was 47.0 ± 9.1% and the chemical ratio was 26.0 ± 8.9%.

The myocardial lactate uptake as determined by the tracer can be calculated by multiplying the arterial concentration of lactate by the isotope extraction ratio and is expressed as micromoles per milliliter of blood. This represents the "true" or actual myocardial uptake of blood lactate. The difference between this value (isotope uptake) and the traditional arterial–coronary sinus chemical value is the amount of lactate released by the myocardium.

In the three patients without lesions the calculated amount of lactate released or produced at rest was 0.039 ± 0.004 μmol/ml of blood (mean ± sd) (fig. 3). For the patients with significant coronary disease, the amount of lactate released by the myocardium was 0.076 ± 0.019 μmol/ml for the six patients with one-vessel disease and 0.136 ± 0.045 μmol/ml for the 12 patients with significant lesions in both vessels. The difference between the amount of lactate released in the patients with one-vessel disease and those with two-vessel disease was significant (p < 0.001).

14CO2 Data

In this study, lactate was labeled specifically in the C-1 position. As pyruvate undergoes oxidative decarboxylation, i.e., pyruvate is converted to acetyl-CoA, the carbon in the first position is released as CO2. By measuring the coronary sinus and arterial 14CO2 difference and the arterial specific activity of lactate, the amount of lactate undergoing oxidative decarboxylation can be calculated. Figure 1B shows the CS-A 14CO2 difference during the infusion of labeled lactate. Our infusion technique requires at least 15 minutes for 14CO2 to equilibrate with the myocardial CO2 pool.

When 14CO2 is used to assess lactate oxidation, the contribution of 14C from other metabolic substrates must be measured. Secondary labeling of glucose and pyruvate occurs when 14C-lactate is infused. After 40 minutes of 14C-lactate infusion, the specific activities of arterial glucose and pyruvate are 40 dpm/μmol and 285 dpm/μmol, respectively, compared with an arterial specific activity of 819 dpm/μmol for lactate for an individual patient. Having determined the specific activity of glucose and pyruvate and the extraction ratios for these substrates, we calculated the total amount of 14CO2 that could be derived from glucose and pyruvate oxidation. After 40 minutes of infusion the maximal amount of 14CO2 derived from glucose and pyruvate is 18 dpm/ml, compared with 305 dpm/ml from lactate. This assumes that the metabolic fate of all the glucose extracted by the myocardium is oxidation, and that no glucose is stored as glycogen or enters the hoxose monophosphate pathway. In this report we corrected the coronary sinus–arterial 14CO2 difference for the possible complete oxidation of all secondary labeled substrates before calculating the amount of lactate undergoing oxidative decarboxylation.

The calculated value for oxidative decarboxylation of lactate was 0.268 ± 0.114 μmol/ml (mean ± sd) for the entire group. For each patient the amount of lactate undergoing oxidative decarboxylation was compared with the uptake of lactate measured by the
arterial–coronary sinus chemical difference and the uptake determined by the tracer method (fig. 4). In 18 patients, the amount of lactate undergoing oxidation is greater than the myocardial uptake as assessed by the arterial–coronary sinus chemical difference (range 112–311%). In figure 4, the lactate undergoing oxidative decarboxylation is divided by the myocardial lactate uptake calculated by the isotope technique. For the group, 85% of the lactate extracted by the myocardium undergoes oxidative decarboxylation (range 59–110%). Thus, the $^{14}$CO$_2$ data indicate that the arterial–coronary sinus chemical difference underestimates the actual myocardial uptake and oxidation of lactate, and most (mean of 85%) of the lactate extracted as determined by the isotope method undergoes oxidation.

Discussion

Differences from epicardium to endocardium in the concentration of substrates and glycolytic enzymes have been demonstrated in the canine heart. Jedeikin' documented increased levels of lactogen in the subendocardium. Lundsgaard-Hansen et al. demonstrated transmural gradients of glycolytic enzyme activities. Leunissen and Piatnek-Leunissen showed an increase in the glyogen and lactate content of the subendocardium compared with the epicardium during acute ischemia. In addition, differences in oxygen tension in the various layers of the left ventricle were reported by Kirk and Honig in open-chest canine preparations.

More recently, heterogeneity of myocardial blood flow has been demonstrated using radioactive microspheres in animal preparations. In patients with significant coronary artery disease Klocke and associates have reported a decrease in myocardial blood flow per unit of left ventricular mass in the resting state. Using a $^{13}$Xe washout technique, Cannon and associates demonstrated decreased myocardial blood flow in patients with significant coronary artery lesions. This decrease in blood flow was seen at rest and was in the distribution of significantly obstructed arteries. Similarly, Gewirtz and co-workers have reported transient defects in resting thallium-201 myocardial scintigrams. Twenty of their 23 transient defects were found in the distribution of a severely stenotic (> 90% stenosis) but not totally occluded vessel. With a regional decrease in myocardial blood flow, one might expect regions of the myocardium to be relatively ischemic and producing lactate while other areas are extracting this substrate.

If the myocardium were releasing or producing unlabeled lactate, the specific activity or concentration of $^{14}$C-lactate would be lower in the coronary sinus than in the artery. Likewise, if unlabeled lactate is released by the myocardium, its concentration would increase in the coronary sinus and the arterial–coronary sinus chemical difference would be falsely low. The isotope extraction ratio, which measures the true extraction, would be higher than the chemical ratio. After the equilibration of $^{14}$C-lactate, all 21 patients had evidence of myocardial release of lactate despite net extraction of this substrate. By using a tracer method, we have demonstrated heterogeneity of lactate metabolism.

Although the patients had a history suggestive of ischemic heart disease, they had no clinical evidence of ischemia, such as chest pain or dyspnea or ECG changes, during this study. Therefore, in such patients at rest without clinical evidence of ischemia, lactate is being released or produced by the myocardium when net chemical arterial–coronary sinus difference shows extraction. Our findings are similar to those of Forbath and colleagues. Using $^{14}$C lactate, they showed lactate production at rest in four patients with documented severe coronary artery disease when enzymatically measured lactate concentration showed lactate extraction.

The amount of lactate released appears to be related to the severity of the coronary disease (fig. 3). There was a significant difference in the amount of lactate released between the patients with a significant lesion in the LAD or the LCX artery and those with significant lesions in both these vessels ($p < 0.001$). Lactate was released even in the three patients without lesions in the left coronary artery (fig. 3), suggesting that release of lactate from the myocardium may occur normally. Two of the three patients had significant lesions in the right coronary artery. However, in these patients the venous drainage of the right coronary artery was near the ostium of the coronary sinus, which was distal to the sampling site of the catheter. Leunissen and Piatnek-Leunissen have reported myocardial release of lactate in anesthetized dogs. The possibility of myocardial release or production of lactate in the normal myocardium needs to be further investigated.
Many of our patients were receiving propranolol and nitrates. However, 11 patients were not receiving propranolol and all nitrates were withheld at least 8 hours before the study. The results in the patients who took propranolol and nitrates did not differ from those obtained in patients who received only nitrates. Therefore, we do not believe that propranolol or its metabolites affected the chemical or isotopic results.

All the patients in this study received heparin. Heparin raises free fatty acids by activating lipoprotein lipase. To evaluate the effects of heparin or high free fatty acids on our findings, three patients underwent the protocol with blood samples obtained before and after heparin. The difference between the isotope and chemical extraction ratios was present before the heparin and appeared unaltered after the heparin bolus. Although few patients were studied, making statistical comparison difficult, the lactate extraction ratios decreased as the arterial level of free fatty acids increased. This is in agreement with our previous report, which demonstrated that lactate extraction decreases with elevation of arterial free fatty acids.

In addition to demonstrating that lactate metabolism is heterogeneous in patients at rest, the $^{14}$CO$_2$ data show that the amount of lactate undergoing oxidative decarboxylation is greater than that measured by the traditional chemical arterial-coronary sinus difference (fig. 4). This implies that the contribution of lactate to myocardial oxidative metabolism may be underestimated by the chemical arterial-coronary sinus differences. Using a tracer technique in experiments of acute ischemia in dogs, Griggs and colleagues reported that lactate continues to undergo oxidative decarboxylation at a time when the net arterial-coronary sinus differences shows myocardial lactate production.

The amount of lactate undergoing oxidative decarboxylation is approximately 85% of the uptake determined by isotopic analysis (fig. 4). These data substantiate the premise that the lactate uptake measured by the isotope extraction ratio is the actual or "true" myocardial uptake. The deficit of 15% may be a result of the manner in which $^{14}$CO$_2$ is collected. Analysis in our laboratory has shown a 99.5% recovery of the NaH$^{14}$CO$_3$ added to blood. However, small amounts of $^{14}$CO$_2$ may be lost during the collection of the blood sample and its placement in the air tight flask. In addition, the arterial-coronary sinus $^{14}$CO$_2$ difference was corrected for extraction of other labeled substrates. These substrates may not have undergone oxidative metabolism (i.e., the glucose may have been stored as glycogen). Rovetto and associates have shown an increase in the intracellular lactate pool in isolated rat hearts during acute ischemia. If such a pool is present in patients with coronary disease, the isotopic lactate determinations might reflect lactate that is being exchanged within this pool.

The source of the unlabeled lactate may be glycogen, glucose, pyruvate or amino acids. Dual isotope experiments would help to assess the contribution of exogenous glucose or pyruvate as the source of the lactate released or produced by the myocardium.

Our study demonstrates heterogeneity of myocardial lactate metabolism at rest in patients with ischemic heart disease. Lactate is released or produced by the myocardium when there is no clinical evidence of ischemia and the chemical arterial-coronary sinus lactate difference shows net global lactate extraction. The degree of heterogeneity appears to be related to the severity of the coronary artery disease.

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References

Myocardial Metabolic and Hemodynamic Effects of Dobutamine in Heart Failure Complicating Coronary Artery Disease

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SUMMARY Eighteen patients with congestive heart failure (CHF) complicating coronary artery disease (CAD) and seven patients with CHF due to primary cardiomyopathy (CM) were studied during infusions of dobutamine in doses of 2.5–15.0 μg/kg/min. There were statistically significant (p < 0.05) improvements in cardiac index, stroke volume index, left ventricular stroke work index and nuclear ejection fraction in both groups. Significant decreases (p < 0.05) in pulmonary capillary wedge pressure, right atrial pressure, and systemic and pulmonary vascular resistances were also observed in both groups. However, five patients increased an already elevated pulmonary capillary wedge pressure during dobutamine infusion, which was associated with either the development of angina pectoris or with a significant elevation of the mean arterial pressure. In the CHF patients, gated cardiac scans analyzed for segmental wall motion showed improvement in 77% of the abnormally contracting segments during dobutamine infusion. Finally, the effects of dobutamine on myocardial metabolism were assessed with arterial and coronary sinus lactate analysis. Fourteen of the 18 CAD patients (78%) showed no metabolic abnormality during dobutamine infusion; four CAD patients (22%), three of whom developed typical angina pectoris, displayed abnormal lactate metabolism. None of the CM patients developed angina pectoris or displayed abnormal lactate metabolism. Of the seven patients with an adverse hemodynamic or metabolic response, four had recently been withdrawn from propranolol therapy. In conclusion, dobutamine produced favorable effects on hemodynamics, left ventricular ejection fraction, and segmental wall motion abnormalities in most patients with CHF without a deleterious effect on myocardial metabolism.

Dobutamine is a new inotropic agent, structurally related to other catecholamines, that is used to treat patients with congestive heart failure (CHF) of diverse etiologies. Although studies have shown significant hemodynamic improvements in groups of patients with CHF treated with dobutamine, there has been little effort to discriminate the characteristics of patients who have an adverse hemodynamic response.1-13 Moreover, few studies have systematically examined whether these hemodynamic changes are at the expense of altering the balance of myocardial oxygen supply and demand. This study was designed to relate the hemodynamic effects of dobutamine to its myocardial metabolic effects in patients with CHF complicating coronary artery disease (CAD), using a group of patients with primary cardiomyopathy (CM) for comparison. In addition, gated cardiac nuclear scans were performed to assess changes in left ventricular ejection fraction (LVEF) and regional wall motion in response to dobutamine.
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