Effects of Short-term, Diet-Induced Hypercholesterolemia on Systemic Hemodynamics, Myocardial Blood Flow, and Infarct Size in Awake Dogs With Acute Myocardial Infarction

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**Background.** Short-term cholesterol feeding has been shown to affect vasomotor tone and increase infarct size in anesthetized rabbits. The purpose of the study was to determine whether acute hypercholesterolemia reduced collateral flow to ischemic myocardium and increased infarct size in the awake dog.

**Methods and Results.** Acute myocardial infarction was produced in awake dogs by a 4-hour left anterior descending coronary artery occlusion followed by 6-hour reperfusion after either a cholesterol-supplemented diet (n=14) or a control diet of dog chow (n=15) for 10 days. Infarct size was determined using nitroblue tetrazolium staining. In two subgroups, a 15-minute transient occlusion of the left anterior descending coronary artery was produced before the diet treatments and was compared with occlusion after diet treatments, so that the effects of hypercholesterolemia on collateral flow could be determined by paired comparisons. Cholesterol feeding increased plasma cholesterol to 288±52 mg/dl, which was twofold to threefold that in the control group (127±35 mg/dl), but had no effects on baseline systemic hemodynamics and myocardial blood flow. Coronary artery occlusion produced similar increases in heart rate, mean aortic pressure, left atrial pressure, and plasma norepinephrine in both groups of animals. However, cholesterol feeding reduced collateral flow to ischemic myocardium and increased infarct size, compared with the control group. The infarct size correlated with ischemic myocardial blood flow in both groups, but the slopes of regression lines relating the two variables did not differ between the two groups.

**Conclusions.** Short-term, diet-induced hypercholesterolemia increased infarct size in awake dogs. This change results, at least in part, from a decrease in collateral blood flow to ischemic myocardium during coronary artery occlusion. *(Circulation* 1991;84:378–386)

Hypercholesterolemia is a well-recognized risk factor for coronary artery disease.\textsuperscript{1,2} It causes atherosclerosis and coronary artery obstruction. In addition, high cholesterol content is reported to influence coronary vasomotor tone and to affect the outcome of acute myocardial infarction independently of atherosclerotic coronary lesions. Studies have shown that elevated cholesterol potentiates the contractile response of systemic and coronary arterial smooth muscles to norepinephrine, serotonin, ergonovine, and calcium ions\textsuperscript{3–6} and impairs endothelium-dependent relaxation of vascular smooth muscle.\textsuperscript{7,8} High plasma cholesterol also impairs the functional integrity of the coronary vasculature and increases ischemia–reperfusion injury to the heart.\textsuperscript{9} Furthermore, as it increases platelet turnover and sensitizes platelets to aggregating agents,\textsuperscript{10–12} hypercholesterolemia may alter coronary flow by platelet aggregation and vasoconstrictor actions of thromboxane A\textsubscript{2}, serotonin, and histamine released from platelets.
Recently, short-term hypercholesterolemia has been shown to impair the return of myocardial blood flow after coronary reperfusion\textsuperscript{13} and increase the severity of myocardial damage\textsuperscript{14} and infarct size\textsuperscript{13} in anesthetized rabbits. The effects have been attributed to either exaggerated platelet aggregation\textsuperscript{15} or impaired endothelium-dependent coronary relaxation induced by hypercholesterolemia.\textsuperscript{14} However, it is not known whether these findings in anesthetized rabbits can be extrapolated to conscious animals or humans with hypercholesterolemia because the use of anesthetics and heightened sympathetic tone in rabbits may have exerted significant effects on platelet function.\textsuperscript{16–18} Thus, we proposed to study the effect of short-term, diet-induced hypercholesterolemia on systemic and coronary hemodynamics and infarct size in awake dogs during acute myocardial infarction produced by a 4-hour coronary artery occlusion and 6 hours of reperfusion.

**Methods**

**Surgical Preparation**

Adult healthy beagles weighing 9.0–15.6 kg were used. Dogs were anesthetized with 25 mg/kg i.v. sodium pentobarbital and ventilated with a Harvard respirator (Harvard Apparatus, South Natick, Mass.). A sterile left thoracotomy through the fifth intercostal space was performed to expose the heart. The left anterior descending coronary artery was dissected free below the tip of the left atrial appendage, and a silicone rubber Jones balloon occluder (R.E. Jones, Silver Spring, Md.) (3.5 mm i.d.) was placed around the vessel. The balloon was transiently filled with saline to determine the amount of solution required to occlude the vessel. Tygon catheters (Norton, Inc., Plastics and Synthetics Division, Akron, Ohio) (1.02 mm i.d.) were inserted into the descending thoracic aorta and left atrium. Catheters were tunneled subcutaneously and exteriorized at the nape of the neck. The chest was closed, and the dog was returned to the vivarium for recovery. The protocol was approved by the University of Rochester Committee on Animal Resources and conform to the guiding principles approved by the Federation Board of the Federation of American Societies for Experimental Biology in the use and care of animals and the National Institutes of Health guide for the care and use of laboratory animals.

**Experimental Procedure and Protocol**

Animals were randomized into a control group and a cholesterol group after surgery, according to their diet treatments. The cholesterol group received a 10-day feeding of cholesterol (4 g/kg/day) (Sigma Chemical Co., St. Louis, Mo.) mixed with c/d prescription canned food (Hill’s Pet Products, Topeka, Kan.) in addition to a commercial dog chow. The control group received the same diet with no cholesterol supplement.

The study comprised two related projects. In project 1, diet treatment was started 3–5 days after surgery, and a 4-hour coronary artery occlusion was carried out 10 days later to determine the effects of hypercholesterolemia on the hemodynamic responses to acute myocardial infarction, ischemic blood flow, and infarct size. In project 2, a 15-minute transient occlusion of the left anterior descending artery was carried out 7 days after surgery, then diet treatment was begun. Ten days later, the coronary artery was reoccluded for 4 hours, in a manner identical to that in project 1. In project 2, each animal could serve as its own control, and effects of coronary occlusion could be determined both before and after cholesterol feeding.

For the experiment, dogs were sedated with 0.5 mg/kg i.m. morphine sulfate and placed in a lateral decubitus position. The previously implanted catheters were connected to Statham P23Db pressure transducers (Statham Instruments, Inc., Oxnard, Calif.) and a Brush 480 multichannel recorder (Gould, Inc., Cleveland, Ohio) for measuring pressures. Heart rate was calculated from the electrocardiogram. In project 1, a micromanometer-tip catheter (Millar Instruments, Inc., Houston, Tex.) was advanced into left ventricular (LV) cavity through a common carotid artery, under local anesthesia with lidocaine (Astra Pharmaceutical Products, Inc., Westborough, Mass.), and connected to the Brush recorder for measuring LV pressure. The rate of pressure rise of LV pressure (dP/dt) was measured using an electronic differentiator. The ratio of LV dP/dt at a developed pressure of 50 mm Hg during isovolumetric contraction to the developed pressure (dP/dt/P) was obtained as an index of LV contractility.

Experiments involving acute myocardial infarction were begun at least 90 minutes after morphine injection. During a 20-minute baseline period, systemic hemodynamics were measured at 5-minute intervals; these measurements were averaged to yield baseline values. Blood samples were obtained during the baseline period for measuring choles- terol\textsuperscript{19} using the American Monitor Enzymatic Cholesterol ST reagent system (American Monitor Corp., Indianapoli s, Ind.). Baseline myocardial blood flows were also measured (see below). After the baseline measurements had been completed, the balloon occluder previously implanted around the left anterior descending coronary artery was inflated with the predetermined amount of normal saline for 4 hours. Acute myocardial infarction was evidenced by ST segment elevations and increases in heart rate and left atrial pressure.

Systemic hemodynamic measurements were repeated in duplicate at 15 and 30 minutes and 1, 2, 3, and 4 hours of coronary artery occlusion and at 15, 30, and 60 minutes after reperfusion. Regional myocardial blood flows were measured again at either 30 minutes (project 1) or 15 minutes (project 2) and 4 hours of coronary artery occlusion and 6 hours after coronary reperfusion. In addition, to determine whether hypercholesterolemia enhances the sympathetic nervous system response to acute myocardial...
infarction, we measured plasma norepinephrine at baseline, 1 and 4 hours of coronary artery occlusion, and 6 hours after reperfusion in project 1, using the Cat-A-Kit radioenzymatic assay system (Amerham Corp., Arlington Heights, Ill.).

Regional myocardial blood flow was measured by the radioactive microsphere method. NEN-TRAC microspheres (New England Nuclear, Boston, Mass.) at a specific activity of 10 mCi/g, 15̊±3 μm in diameter and labeled with 141Ce, 113Sn, 103Ru, 95Nb, or 48Sc, were used. Microspheres were injected into the left atrium followed by a 10-ml normal saline flush over a 30-second period. Approximately 1 million microspheres were injected before coronary artery occlusion and after reperfusion, and 2–3 million microspheres were injected during coronary artery occlusion. Blood flow was calculated using the arterial reference blood method. The reference blood was collected beginning 10 seconds before microsphere injection and continuing for 90 seconds thereafter at a rate of 7.75 ml/min. The number of microspheres injected was sufficient to yield in the total ischemic tissue for each flow measurement at least 475 microspheres, at which blood flow can be measured with 10% accuracy at the 95% confidence level and with duplicate variability of 14%. After the final measurements had been obtained, the animal was killed with a lethal dose of sodium pentobarbital and the heart was removed. The left anterior descending coronary artery was cannulated with two catheters, one at the site of the occlusion and the other at the origin through the left coronary ostium. The left circumflex and right coronary arteries were also cannulated through their respective ostia. The heart was then perfused with two different dye solutions via the selective coronary cannulae under a constant pressure of 100 mm Hg for 15 minutes. The area supplied by the left anterior descending coronary artery or “region at risk” was stained by 1% Acramin Pink dye (Mobay Chemical Co., Rock Hill, S.C.), whereas the normal myocardium outside the left anterior descending coronary artery distribution was stained by 1% Monastral Blue dye (Sigma Chemical Co.).

The left ventricle, including the interventricular septum, was then separated from the right ventricle and sectioned into six or seven transverse slices, each approximately 6–7 mm thick. The slices were weighed and photographed from apical and basal views. They were then immersed in a nitroblue tetrazolium solution for 15 minutes at 37°C and photographed again. The normal myocardium was stained blue, and the infarct area was unstained. The total area, region at risk, and infarct zone were planimetrated on photographs coded to conceal the identity of the experiment to the observer. The percent risk or infarct size relative to the entire slice was determined by averaging the percent values for both the apical and basal sections of the slice. The weight for the risk or infarct area of the slice was obtained by multiplying the percent value and the weight of the slice. Total risk region and infarct size were determined by adding individual values of all slices.

Finally, each tissue slice was cut radially into four to nine wedge-shaped pieces that were subdivided into endocardial and epicardial halves. The tissue samples, along with reference arterial blood samples, were weighed and counted for radioactivity to measure regional myocardial blood flow. LV segments were grouped into regions according to their endocardial blood flows determined 15 or 30 minutes after coronary artery occlusion. Transmural segments within the region at risk, having endocardial blood flow of less than 0.25 ml/g/min, were pooled and designated as ischemic myocardium, whereas areas with endocardial blood flow greater than 0.75 ml/g/min were considered nonischemic myocardium. The “border zone” with endocardial blood flow between 0.25 and 0.75 ml/g/min was excluded. This method permits maximal sampling of markedly ischemic myocardium within the region at risk and provides an estimate of the size of ischemic myocardium.

Statistical Analysis

Data were analyzed using the RS/1 (BBN Software Products Corp., Cambridge, Mass.) and BMDP PC-90 (BMDP Statistical Software, Inc., Los Angeles, Calif.) microcomputer programs. The sample size computation was based on a power calculation using a twosided t test at α=0.05 and β=0.05. To detect a 30% difference between the means of infarct size or collateral blood flow for the control and cholesterol groups, given a pooled variance of 20% of the means at better than 95% power, required a total of at least 19 dogs in the two groups. Results are mean±SD. The statistical significance of differences between the two groups was determined by two-way analysis of variance for independent groups with repeated measures. Dunnett’s test was used to determine the statistical significance of difference between the baseline values and the serial repeated measurements. The statistical significance of a difference between two groups was determined by Student’s t test or Fisher’s exact test. Correlation and regression analyses were used to determine the relation between infarct size and ischemic myocardial blood flow. The equality of regression lines across groups was determined using a BMDP multiple linear regression program (Program 1R). Differences were considered statistically significant if the probability value is less than 0.05.

Results

Acute myocardial infarction was successfully produced in project 1 in 10 dogs on the control diet and 10 dogs on the high cholesterol diet. Three dogs (one in the control group and two in the cholesterol group) died shortly after coronary artery occlusion. In project 2, 19 dogs were studied with two coronary artery occlusions separated by 10 days. However, because of unexpected rupture of coronary artery balloons, seven dogs (four in the control and three in...
the cholesterol group) showed early coronary reperfusion, as evidenced by abrupt disappearance of the ST segment elevation and return of ischemic myocardial blood flow to preocclusion values between 30 minutes and 4 hours of coronary artery occlusion. Thus, successful 4-hour coronary artery occlusion and reperfusion was produced only in six control and six hypercholesterolemic dogs in project 2. Because the changes produced by acute myocardial infarction and cholesterol treatment were similar in the two projects, animals were grouped together according to diet treatments for final statistical analyses. Fisher's exact test showed that the mortality rate in the two groups did not differ significantly ($p=1.0$). The cholesterol group exhibited a significantly higher plasma cholesterol (288±52 mg/dl) than the control group (127±35 mg/dl, $t=9.767$, $p<0.0001$). The following results are based on the 14 hypercholesterolemic dogs and 15 control dogs, unless specified otherwise.

**Systemic Hemodynamics**

Figure 1 shows the systemic hemodynamics and LV function. Baseline heart rate, mean aortic pressure, left atrial pressure, and LV dP/dt did not differ in the control and cholesterol groups; nor did LV dP/dt/P differ between the control (45±5 sec$^{-1}$, $n=9$) and the cholesterol groups (46±5 sec$^{-1}$, $n=8$). Coronary artery occlusion increased heart rate, mean aortic pressure, and left atrial pressure in both groups of animals but had no effects on LV dP/dt and dP/dt/P. These changes did not differ between the two groups. Release of coronary artery occluders had no effects on mean aortic pressure, left atrial pressure, or LV dP/dt, but it consistently caused ventricular tachycardia and increased heart rate.

**Regional Myocardial Blood Flow**

Figures 2 and 3 show the effects of coronary artery occlusion and reperfusion on blood flow to ischemic and normal myocardium. Blood flow did not differ in the two regions before coronary artery occlusion in either group. As expected, coronary artery occlusion caused a marked reduction of blood flow to the ischemic myocardium within the distribution of the left anterior descending artery (Figure 2) but had no effects on blood flow to normal myocardium (Figure 3). Deflation of the occluder balloon restored coronary blood flow and increased blood flow to the ischemic myocardium to levels comparable to the preocclusion controls (Figure 2). Blood flow to the nonischemic myocardium increased after coronary

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*Figure 1. Plots showing heart rate, mean aortic pressure, left ventricular (LV) dP/dt, and mean left atrial pressure before (baseline) and after coronary artery occlusion and reperfusion in the control (○) and cholesterol (●) groups. Bars indicate SD. The number of experiments was 15 for the control group and 14 for the cholesterol group, except for LV dP/dt, where the numbers of experiments were 9 and 8, respectively. *Values that differ from the baseline values at $p<0.05$, as determined by Dunnett's test.

*Figure 2. Bar graphs showing epicardial (open columns) and endocardial (hatched columns) blood flows in the ischemic myocardium before (baseline) and after coronary occlusion (early, 15-30 minutes; late, 4 hours) and reperfusion in the control (n=15) and cholesterol (n=14) groups. Bars indicate SD. *Values that differ from the baseline at $p<0.05$. †Value that differs from the early occlusion value of the control group at $p<0.05$. 
FIGURE 3. Bar graphs showing epicardial (open columns) and endocardial (hatched columns) blood flows in the non-ischemic myocardium before (baseline) and after coronary occlusion (early, 15–30 minutes; late, 4 hours) and reperfusion in the control (n=15) and cholesterol (n=14) groups. Bars indicate SD. *Values that differ from the baseline at p<0.05.

Myocardial blood flow remained reduced in ischemic myocardium throughout coronary artery occlusion; there was no significant difference between the values measured at 15 and 30 minutes and 4 hours of coronary artery occlusion in either group of animals (Figure 2). However, endocardial and epicardial blood flow values obtained at 15 and 30 minutes of coronary artery occlusion were significantly smaller in the cholesterol group compared with the control group. We also averaged the endocardial and epicardial blood flow measurements obtained during coronary artery occlusion in both groups. The averaged transmural blood flow in the cholesterol group was statistically smaller than that in the control group (Figure 4). Furthermore, compared with the control group, the cholesterol group showed a larger area of myocardium with endocardial blood flow of less than 0.25 ml/g/min after coronary artery occlusion, expressed either as absolute weight (Figure 4) or as percent of total left ventricle (23.4±4.8% versus 16.5±6.4% of LV weight for the cholesterol and control groups, respectively; t=3.237, p=0.003).

The effects of hypercholesterolemia on collateral blood flow to ischemic myocardium was further examined in project 2 by measuring myocardial blood flows during two separate coronary artery occlusions performed 10 days apart before and after the cholesterol or control feeding. The first coronary artery occlusion was necessarily brief, limited to 15 minutes to avoid causing permanent myocardial damage. Of the ischemic myocardium, baseline myocardial blood flows prior to the first and second occlusions did not differ significantly (Figure 5). Figure 5 also shows the ischemic epicardial and endocardial blood flows obtained at 15 minutes of the two coronary artery occlusions. In the control group, the second coronary artery occlusion did not reduce epicardial blood flows as much as that after the first occlusion. In contrast, in the cholesterol group, ischemic epicardial blood flow was significantly lower after the second coronary artery occlusion than after the first occlusion (Figure 6). The changes in ischemic endocardial blood flows in both groups were qualitatively similar to those in epicardial blood flows, but the differences between the first and second occlusions were not statistically significant. On the other hand, when the second occlusion results were expressed as percent changes from the first occlusion values, both epicardial and endocardial blood flows showed significant reductions after the second occlusion in the cholesterol group compared with the control group (Figure 7).

Myocardial Infarct Size

Table 1 summarizes the region at risk and infarct size in both control and cholesterol groups. The two groups did not differ in body weight, LV weight, or normalized risk regions. Infarct size, however, was significantly greater in the cholesterol group than in the control group.
Because infarct size correlates with collateral blood flow, we studied the relation between infarct size and ischemic myocardial blood flow in both control and cholesterol groups. Infarct size correlated significantly with ischemic transmural blood flow (Figure 8). Furthermore, because the regression lines were indistinguishable between control and cholesterol groups, we pooled the data from the two groups, giving a highly significant correlation coefficient of 0.730 ($p<0.0001$).

**Arterial Plasma Norepinephrine Concentrations**

Plasma norepinephrine values increased after coronary artery occlusion (Table 2). They remained elevated during 4 hours of coronary artery occlusion and after reperfusion; these changes did not differ significantly between the control and cholesterol groups.

**Discussion**

Our present study shows that short-term administration of a cholesterol-enriched diet produced a 126% increase in plasma cholesterol in dogs and that the short-term, diet-induced hypercholesterolemia

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**FIGURE 5.** Bar graphs showing basal epicardial and endocardial blood flows and their responses to 15-minute coronary artery occlusion in the cholesterol (n=9) or control (n=10) groups. Open columns denote values obtained at the first coronary artery occlusion prior to diet treatment; hatched columns denote values obtained at the second occlusion performed after a 10-day cholesterol or control feeding. Bars indicate SD. *Values that differ from the first coronary artery occlusion at $p<0.05$.

**FIGURE 6.** Plots showing changes in ischemic epicardial and endocardial blood flows before and after cholesterol feeding in nine dogs.

**FIGURE 7.** Bar graphs showing effects of Control (n=10) and Cholesterol (n=9) feeding on ischemic epicardial and endocardial blood flows, expressed as percent changes from the values obtained at initial coronary artery occlusion before diet treatment. Bars indicate SD. *Values that differ from the control group at $p<0.05$. 

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**FIGURE 8.** Bar graphs showing basal epicardial and endocardial blood flows and their responses to 15-minute coronary artery occlusion in the cholesterol (n=9) or control (n=10) groups. Open columns denote values obtained at the first coronary artery occlusion prior to diet treatment; hatched columns denote values obtained at the second occlusion performed after a 10-day cholesterol or control feeding. Bars indicate SD. *Values that differ from the first coronary artery occlusion at $p<0.05$.
TABLE 1. Infarct Size in Control and Cholesterol Groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n=15)</th>
<th>Cholesterol (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>11.5±1.4</td>
<td>11.7±1.9</td>
</tr>
<tr>
<td>LV/body weight (g/kg)</td>
<td>5.5±0.7</td>
<td>5.4±0.6</td>
</tr>
<tr>
<td>Risk size (% LV weight)</td>
<td>33±4</td>
<td>35±4</td>
</tr>
<tr>
<td>Infarct size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV weight (%)</td>
<td>17±5</td>
<td>23±5*</td>
</tr>
<tr>
<td>Risk size (%)</td>
<td>52±12</td>
<td>67±12*</td>
</tr>
</tbody>
</table>

LV, left ventricle. Values are mean±SD. *p<0.01, as determined by Student’s t test.

caused a greater reduction of blood flow to a larger area of myocardium during acute coronary artery occlusion, resulting in an increase in infarct size. Because short-term hypercholesterolemia does not cause atherosclerosis in dogs,3,31 the effects of hypercholesterolemia on systemic and coronary circulations during acute myocardial infarction probably could not be explained by fixed vascular lesions. Similarly, Osborne et al4 have shown that the damaging effects on the ischemic myocardium of 2-week high-cholesterol feeding in rabbits are not associated with atherosclerosis. The effects of hypercholesterolemia as shown by our present study could have been caused by either an increased release of vasoactive substances or potentiation of the vascular effects of these substances by high cholesterol content.

Myocardial blood flow was reduced in the ischemic myocardium of hypercholesterolemic dogs to a level significantly lower than that in the control group or that obtained during the first occlusion before cholesterol feeding. The total area of the reduced blood flow was also larger in the hypercholesterolemic dogs, suggesting that a larger area of the myocardium was in jeopardy in this group. The larger area of reduced blood flow also suggests that the greater reduction of myocardial blood flow in the cholesterol group was not due to selective sampling of more ischemic myocardium compared with the control group. Results of our present study, however, do not allow us to conclude the mechanism(s) by which hypercholesterolemia reduced collateral blood flow to ischemic myocardium. The present study showed that cholesterol feeding did not enhance the increase in plasma norepinephrine that occurred after coronary artery occlusion, but an exaggerated vasoconstrictor response to norepinephrine could have occurred during acute myocardial infarction and played a role in reducing ischemic myocardial flow in the cholesterol group. Earlier studies have shown that hypercholesterolemia or acute exposure to cholesterol is capable of making coronary vessels hyperreactive to the constrictor effects of norepinephrine, serotonin, ergonovine, and calcium.3-6

The decrease in coronary collateral flow also could have been caused by reduced endothelium-derived relaxing factor release in response to vasoactive agents and reduced production of the vasodilator prostacyclin after the 2-week cholesterol feeding.14 The interaction between endothelial cells and platelets has received considerable investigation.32 Endothelial cells have been shown to produce an antiplatelet substance,33 but their ability to inhibit platelet aggregation is significantly impaired by an alteration in lipid composition of the extracellular fluid.34 Because acute myocardial infarction causes platelet aggregation and release of vasoactive substances into the coronary circulation,35-37 the reduction of ischemic myocardial flow in the cholesterol group also could have been caused by the potentiating effect of hypercholesterolemia on platelet aggregation and the vasoconstrictor action of thromboxane, serotonin, and histamine.10-12 Enhanced platelet aggregation probably is responsible for the reduced myocardial blood flow and increased infarct size that occurs in anesthetized rabbits after 2-3 days of

TABLE 2. Plasma Norepinephrine During Coronary Artery Occlusion and Reperfusion

<table>
<thead>
<tr>
<th></th>
<th>Plasma norepinephrine (ng/ml)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control (n=9)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.17±0.06</td>
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<tr>
<td>Coronary occlusion</td>
<td></td>
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<tr>
<td>1 hour</td>
<td>0.27±0.09*</td>
</tr>
<tr>
<td>4 hours</td>
<td>0.28±0.09*</td>
</tr>
<tr>
<td>Coronary reperfusion</td>
<td>0.43±0.12*</td>
</tr>
</tbody>
</table>

Values are mean±SD. *p<0.05. Values did not differ significantly between the two groups at each time interval.
cholesterol feeding because these effects of hypercholesterolemia are prevented by platelet depl.

Likewise, as thromboxane synthetase inhibitors and thromboxane receptor antagonists have been shown to reduce the severity of myocardial ischemia and infarct size in experimental myocardial infarction, thromboxane release may be detri-

mental to the ischemic myocardium.

Recently, Kaplan et al advanced a novel hypothesis that the vasoconstriction produced by short-term cholesterol feeding is caused by a toxic effect of oxidized light-density lipoprotein. They found that the increased renal vascular tone produced by 3 weeks of cholesterol-supplemented diet in rats was prevented by adding the antioxidant drug probucol to the diet. In addition, they found that cholesterol feeding increased prostaglandin E2 and thromboxane B2 in proximal tubular fluid and urine and that infusion of a thromboxane A2 antagonist into the aorta above the renal arteries of cholesterol-fed rats caused a prompt return to normal of all renal hemo-
dynamic abnormalities. These findings suggest that the vasoconstriction by cholesterol feeding is mediated by increased production of thromboxane A2 caused by oxidized light-density lipoprotein.

In their study of anesthetized rabbits with hypercholesterolemia, Golino et al showed that the increase in infarct size after 2–3 days of a 2\% cholesterol diet was associated with poor return of myocardial blood flow after coronary reperfusion (no-reflow phenomenon). Furthermore, because the effect of hypercholesterolemia was abolished by platelet depl., they speculated that the no-reflow phenomenon was caused by platelet accumulation. However, in our present study, ischemic myocardial blood flow increased significantly after coronary reperfusion. Furthermore, because there was no significant difference in the blood flow to the previously ischemic myocardium between the control and cholesterol groups after coronary reperfusion, it is unlikely that the increase in infarct size produced by hypercholesterolemia in our study can be explained by an exaggerated no-reflow phenomenon alone. The discrepancies in results between our study and that of Golino et al cannot be readily explained. Possible reasons include the difference in animal species, methods of measurements, duration of coronary artery occlusion or cholesterol feeding, and presence or absence of coronary reperfusion or anesthesia.

The increase in infarct size in our present study probably was related to the greater reduction of ischemic myocardial blood flow to a larger area of the left ventricle in the cholesterol group. Infarct size correlated significantly with ischemic myocardial blood flow in the two groups. Myocardial oxygen consumption probably did not differ significantly between the two groups because there were no differences in the systemic hemodynamic and LV dP/dt and dP/dt/P responses to acute coronary artery occlusion and reperfusion between the groups. Sim-

ilarly, Osborne et al have shown that the increase in ischemia-induced cardiac damage produced by short-

KEY WORDS: hypercholesterolemia • occlusions • reperfusion • collateral blood flow
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