Protection from atherosclerotic lesion formation by reduction of artery wall motion


We have studied mechanical factors that could determine how stenosis protects against distal atherosclerosis in cynomolgus monkeys fed an atherogenic diet. Critical aortic stenosis was produced by coarctation of the thoracic aorta. After 3 months, coarcted monkeys had a mean aortic pressure gradient of 25 ± 1 mm Hg and a 76% ± 2% lumen stenosis. Aortic wall motion was measured by means of in vivo ultrasonic sonomicrometry. Dynamic tracings of aortic pressure and diameter were recorded simultaneously at standard locations proximal and distal to the stenosis and at comparable sites in noncoarcted control animals. In the proximal aorta, mean blood pressure and pulse pressure were increased (p < 0.05), but wall motion and intimal lesion area were not different from those determined in control monkeys. In the aorta distal to the coarct, mean blood pressure was no different from that in control animals but pulse pressure was diminished; in addition, there was marked reduction of arterial wall motion (p < 0.001). This was accompanied by a significant reduction of intimal plaque area (p < 0.05) and acid lipase activity (p < 0.001). Thus, inhibition of plaque formation in the distal aorta coincided with reduction of pulse pressure and aortic wall motion rather than with blood pressure or hypercholesterolemia. Inhibition of arterial wall motion may account for the sparing effect often encountered in human arteries distal to stenosing atherosclerotic plaques. (J Vasc Surg 1987;5:59-67.)

Arterial segments distal to long-standing atherosclerotic obstructions usually have atrophic walls and are relatively uninvolved by plaques.1,4 Such sparing has usually been attributed to the reduced blood pressure that commonly occurs distal to high-grade obstruction. A direct relationship between blood pressure and severity of atherosclerotic disease in human beings is suggested by the observation that in general patients with hypertension are at higher risk for having atherosclerosis and its complications than normotensive subjects.2,6 However, the precise mechanism by which blood pressure affects lesion initiation and/or evolution is not clear. Under experimental conditions, monkeys with a severe thoracic aortic coarctation had much less atherosclerosis distal to the stenosis than did animals without a coarctation, despite normal or elevated arterial pressure below the stenosis.7-10 Pulse pressure rather than mean blood pressure level has been associated with lesion formation under similar circumstances by others.11 These observations suggest that hypertension per se may not be the offending stimulus for the development or enhancement of atherosclerotic lesions but that other mechanical factors that may be associated with hypertension could determine the development and localization of plaques. In the present study we investigated the relationships among blood pressure, degree of cyclic change in artery diameter (arterial wall motion), and the extent of atherosclerosis proximal and distal to a critical thoracic aortic stenosis in nonhuman primates fed an atherogenic diet. We report that reduction of distal wall motion resulting from the placement of the stenosis was associated with protection from lesion formation despite the presence of normal or elevated blood pressure and hypercholesterolemia.

MATERIAL AND METHODS

Fifteen male cynomolgus monkeys (Macaca fascicularis), weighing 5 to 6 kg, underwent thoracic aortic coarctation. Animals were sedated with intramuscular ketamine hydrochloride (10 mg/kg), anesthetized with intravenous pentobarbital (25 mg/kg) supplemented as necessary, intubated, and ventilated by means of a volume ventilator. Before the surgical procedure, each animal received parenteral antibiotics (intravenous cefazolin sodium, 250 mg).

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Table I. Hemodynamic measurements

<table>
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<th></th>
<th>No stenosis (mm Hg)</th>
<th>Stenosis (mm Hg)</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Mean proximal pressure</td>
<td>102 ± 4</td>
<td>122 ± 6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean distal pressure</td>
<td>101 ± 4</td>
<td>98 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean aortic gradient</td>
<td>1 ± 1</td>
<td>25 ± 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proximal pulse pressure</td>
<td>43 ± 4</td>
<td>63 ± 5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Distal pulse pressure</td>
<td>44 ± 2</td>
<td>26 ± 3</td>
<td>&lt;0.001</td>
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NOTE. Values listed as mean ± standard error of the mean.

The brachial and femoral arteries were catheterized and blood pressure was monitored with pressure transducers and recorded on a strip chart recorder during the surgical procedure. The descending thoracic aorta was exposed through a left lateral thoracotomy and encircled by a constricting band midway between the left subclavian artery and celiac axis. A localized high-grade stenosis was produced by tightening the band until a stable mean brachial-femoral pressure gradient of 45 mm Hg or greater was achieved. Animals tolerated the operation well, ate and drank normally beginning on the first postoperative day, and demonstrated no cardiac, visceral, or lower extremity dysfunction. After a 2-week convalescent period, animals were given an atherogenic diet consisting of 2% cholesterol and 25% peanut oil, which was maintained for a period of 3 months. Thirteen nonoperated cynomolgus monkeys served as control animals and received the same atherogenic diet for 3 months.

All animals were handled and cared for according to National Institutes of Health guidelines for humane treatment of laboratory animals. Animals were housed in individual cages and were given free access to food and water. Body weight, hemoglobin, and hematocrit values as well as serum lipid and bilirubin levels and liver function studies were determined at the onset of the study and at the time the animals were killed. All operative procedures, excluding sacrifice, were conducted by means of sterile technique.

After 3 months on the atherogenic diet and one week before being killed, all coarcted animals underwent transfemoral aortography; intramuscular ketamine hydrochloride was given for sedation and local 1% lidocaine for anesthesia. The degree of aortic stenosis was assessed from bilateral magnification aortography by the comparison of the lumen diameter in the coarct channel to the lumen diameter in the descending thoracic aorta 2 cm proximal to the constriction.

At the time the animals were killed, all were sedated with ketamine hydrochloride, anesthetized with intravenous pentobarbital, intubated, and ventilated with a volume ventilator. Brachial and femoral arteries were catheterized for direct measurement of arterial pressure. Through a left thoracotomy the descending thoracic aorta was exposed. In coarcted animals, the aorta 2 cm proximal and 2 to 4 cm distal to the coarct was mobilized; in noncoarcted animals, corresponding sites in the descending thoracic aorta were selected for study. Arterial wall motion was determined simultaneously 2 cm proximal to the coarct and 2 cm distal to the coarct by means of sonomicrometry. A third measurement of wall motion was subsequently made in the aorta distal to the coarct and past the area of maximum poststenotic dilatation. Two piezoelectric disks, 2.5 mm in diameter (Triton Technology, Inc., San Diego, Calif.) were positioned at each location on the adventitial surface of the aorta at 180 degrees from each other. Ultrasound transit times between the two disks were measured and provided a precise on-line determination of vessel diameter throughout the cardiac cycle. The degree of arterial wall motion was defined as the difference between peak systolic vessel diam-
Table II. Aortic diameter changes

<table>
<thead>
<tr>
<th></th>
<th>No stenosis</th>
<th>Stenosis</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Diastolic aortic diameter (mm)</td>
<td>7.15 ± 0.25</td>
<td>7.96 ± 0.35</td>
<td>NS</td>
</tr>
<tr>
<td>Proximal</td>
<td>6.51 ± 0.22</td>
<td>7.79 ± 0.43</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Distal</td>
<td>0.44 ± 0.03</td>
<td>0.53 ± 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Aortic wall motion (mm)</td>
<td>0.42 ± 0.02</td>
<td>0.23 ± 0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(systolic-diastolic diameter)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>6.3 ± 0.5</td>
<td>6.8 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Distal</td>
<td>6.4 ± 0.5</td>
<td>3.1 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cyclic change in aortic diameter (%)</td>
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NOTE: Values listed as mean ± standard error of the mean.

eter and mid-diastolic diameter. The percentage change in vessel diameter was expressed as the difference between systolic and diastolic vessel diameter divided by the diastolic vessel diameter times 100. Recordings of arterial blood pressures proximal and distal to each stenosis were performed simultaneously with arterial wall motion recordings.

Animals were killed with an overdose of pentobarbital and the aorta and major arterial branches excised, opened, and pinned flat on a scaled grid. The intimal surface was photographed and projected as a magnified image onto a digitizing plate and the percentage of intimal surface area covered by atherosclerotic lesions was determined by means of computer-assisted planimetry. The proximal thoracic aorta from the aortic root to the region of the mid-thoracic stenosis was compared with the distal thoracic aorta, from the coarctation to the level of the diaphragm. The perimeters of each of these aortic segments and the areas occupied by atherosclerotic lesions were traced to determine the total intimal surface area and the area covered by intimal plaque proximal and distal to sites of stenosis. Samples for histologic study were taken from standard locations 2 cm proximal and 2 cm distal to the coarctation. Semithin plastic embedded sections were stained with methylene blue basic fuchsin. Segments of aorta were taken from the same standard locations and from comparable sites in control monkeys for chemical analysis.

Acid lipase activity was determined as an estimate of lesion macrophage content and activity proximal and distal to the coarctation. Acid lipase substrate micelles were prepared with 1.0 mmol/L α-naphthyl palmitate and 10 mmol/L Triton X-100 in 0.1 mol/L sodium acetate buffer, pH 4.2, containing 0.1% fatty-acid-poor bovine serum albumin. Two hundred microliters of homogenized tissue supernatant was assayed in 1 ml of substrate at 25°C with continuous agitation for 2 to 4 hours. The reaction was stopped by placement of the samples in boiling water for 2 minutes. One milliliter of 1.0 mmol/L sodium acetate buffer, pH 4.2, containing 10% Tween 20 (wt/vol) and 0.5 mg fast garnet GBC salt was added to each sample. Diazocoupling of liberated α-naphthol was performed at 25°C for 16 hours. Absorbance of samples, heat-inactivated blanks, and α-naphthol standards were then measured at 535 nm. Enzymatic activity was expressed as micromolar/hour/square centimeter of aorta.

Results were expressed as mean value ± standard error of the mean. Differences between groups were analyzed by means of the unpaired two-tailed Student t test. Significance was assumed for p values less than 0.05.

RESULTS

All animals remained well during the experimental period. Baseline total serum cholesterol was 96 ± 6 mg/dl and high-density lipoprotein (HDL) cholesterol was 45 ± 3 mg/dl with no differences between the two groups. After 3 months of the atherogenic diet, total serum cholesterol increased markedly in both groups compared with the baseline value (p < 0.001) and was 836 ± 165 mg/dl for the coarcted animals and 776 ± 65 mg/dl for the unoperated control animals. HDL cholesterol levels decreased over the same period from a baseline value of 45 ± 3 mg/dl to 29 ± 7 mg/dl for coarcted animals and 26 ± 2 mg/dl for control animals (p < 0.001). The change in total serum cholesterol and HDL cholesterol levels between the beginning and the end of the experiment was the same in the two groups. The ratios of total serum cholesterol to HDL cholesterol were also similar for the two groups. There were no significant changes in body weight or serum hemoglobin, hematocrit, bilirubin, or liver enzymes during the course of the study.

Three months after coarctation, operated animals had a 76% ± 2% reduction in aortic lumen diameter as determined by angiography (Fig. 1) and a mean aortic pressure gradient across the stenosis of 25 ± 1
mm Hg (Table I). Mean arterial blood pressure proximal to the stenoses was increased to 122 ± 6 mm Hg compared with a mean arterial pressure of 102 ± 4 mm Hg in control animals (p < 0.05). Mean arterial pressure distal to the coarctation was 98 ± 6 mm Hg, which was not significantly different from mean distal pressure in control animals. Pulse pressure in the aorta proximal to coarctation (63 ± 5 mm Hg) was increased compared with that of control animals (43 ± 4 mm Hg; p < 0.01), whereas pulse pressure in the aorta distal to the coarct was decreased (26 ± 3 mm Hg) compared with that of control animals (44 ± 2 mm Hg; p < 0.001).

Changes in aortic diameter are shown in Table II. Diastolic aortic diameter proximal to coarctation was 7.97 ± 1.06 mm compared with 7.15 ± 0.65 mm in control animals. This difference was not statistically significant (p = 0.096). Diastolic aortic diameter 2 cm distal to the coarctation was increased (7.79 ± 1.30 mm) compared with the control value (6.51 ± 0.58 mm; p < 0.05) and corresponded to the area of poststenotic dilatation. Diastolic diameter distal to the poststenotic dilatation was no different from that found in control animals. Aortic wall motion or excursion (systolic-diastolic diameter) proximal to the stenoses was 0.53 ± 0.03 mm in coarcted animals compared with 0.44 ± 0.03 mm in control animals, but this difference was not statistically significant (p = 0.074). However, distal to the coarctation arterial wall motion was markedly diminished (0.23 ± 0.03 mm) compared with that of control animals (0.42 ± 0.02 mm) (p = 0.0002). In control animals the percentage change in diameter between systole and diastole in the distal aorta was 6.4% ± 0.5% compared with a 3.1% ± 0.5% change in coarcted animals. This represented more than a 50% reduction in the cyclic change in aortic diameter distal to the stenosis. Arterial wall motion in the aorta distal to the poststenotic dilatation was similarly diminished (0.19 ± 0.06 mm; p < 0.05) compared with the control value. There was no difference in percentage change in aortic diameter proximally and distally in control animals.

Intimal lesions in both groups appeared grossly as slightly raised, white or pale yellow streaks and plaques. The lesions were predominantly cellular and consisted mainly of foam cells and in the largest lesions also contained smooth muscle cells. Typical hi-
tologic appearances of proximal and distal lesions in diet-control animals and in animals with coarctation are shown in Figs. 2 and 3. In control animals the intima was thickened by the accumulation of several layers of lipid-vacuolated foam cells. The extent of thickening was nearly the same for both proximal and distal regions (Fig. 2). In the animals with coarctations, intimal lesions were thick and complex proximal to the stenosis and contained foam cells, smooth muscle cells, and matrix fibers. Distal to the coarctation, the intima was focally slightly thickened by occasional foam cells. No foam cells were seen on most of the standard sections (Fig. 3, B).

Proximal to the coarctation, atherosclerotic lesions covered 41% ± 14% of the intimal surface area. This was not significantly different from the control group, which at this early 3-month period had 36% ± 6% of the proximal aorta involved by intimal plaque (Table III). However, in coarcted animals the aorta distal to the stenoses had significantly less atherosclerotic disease than control animals. Only 7% ± 3% of the intimal surface was involved by atherosclerotic lesions in the coarcted group compared with 39% ± 12% surface involvement in the control animals (p < 0.05). There was no difference in intimal lesion area between the proximal and distal aorta in control animals but a marked reduction was observed in the distal aorta of coarcted animals compared with the proximal aorta (p < 0.05).

There was no significant difference in acid lipase activity in the proximal aorta between coarcted and noncoarcted animals (Table IV). However, distal to the coarctation, acid lipase activity was markedly reduced compared with that of control animals (p < 0.05) as well as with activity in the proximal aorta in coarcted animals (p < 0.05). This represented an 85% reduction in acid lipase activity compared with the proximal aorta and corresponded to the relative absence of foam cells seen on histologic sections.

DISCUSSION

Arterial stenosis results in changes in blood flow and pressure that alter the distribution and absolute
Table III. Percentage of surface area atherosclerosis

<table>
<thead>
<tr>
<th></th>
<th>No stenosis</th>
<th>Stenosis</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal aorta</td>
<td>36 ± 6</td>
<td>41 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Distal aorta</td>
<td>39 ± 12</td>
<td>7 ± 3</td>
<td>&lt;0.05</td>
</tr>
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</table>

NOTE: Values listed as mean ± standard error of the mean.

Table IV. Aortic acid lipase activity

<table>
<thead>
<tr>
<th></th>
<th>No stenosis (μmol/L/hr/cm²)</th>
<th>Stenosis (μmol/L/hr/cm²)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal aorta</td>
<td>13.4 ± 1.2</td>
<td>9.6 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Distal aorta</td>
<td>8.0 ± 1.6</td>
<td>1.4 ± 0.2</td>
<td>&lt;0.05</td>
</tr>
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</table>

NOTE: Values listed as mean ± standard error of the mean.

level of the associated mechanical stresses in the arterial wall and induce changes of vessel wall composition. Proximal to a stenosis the wall tends to thicken, and both cell and matrix fiber content are modified. Distally the wall may undergo thinning and atrophy of its component elements. These differences, as well as differences in the distribution of atherosclerosis, have been attributed to differences in mean blood pressure levels in the two segments. In the experiment that forms the basis of this report, blood pressure was not significantly reduced distal to the coarctation. Nevertheless, the distal region was spared of plaque formation compared with that in control animals. Coarctation did raise the blood pressure above the stenosis. Although this region was somewhat more atherosclerotic than found in control animals as reflected by the extent of intimal area covered by lesions, the difference was not significant at the 3-month interval of observation.

In addition, we found that acid lipase activity was increased in those regions of the aorta that contained lesions and was markedly decreased in the spared region distal to the coarctation. Other studies have also demonstrated increases in acid lipase activity in atherosclerotic arteries when compared with normal vessels. In both experimental and human plaques this change may be attributed in large part to the presence of macrophages; the lesions that occurred after 3 months of dietary induction in monkeys consisted primarily of macrophage-derived foam cells. Although the relative absence of acid lipase activity in the distal aorta of the coarcted monkeys corresponded to the absence of foam cell lesions, it may also correspond to some extent to atrophy of the artery wall in this location. Bomberger et al. studied cynomolgus monkeys that had thoracic aortic coartations for 6 months and found that the distal aortic wall was atrophic, including a decrease in both cell and connective tissue matrix content. Conversely, earlier experiments from our laboratories revealed that cyclic stretching of arterial smooth muscle cells in culture increases the rate of collagen, hyaluronate, and chondroitin-6-sulfate synthesis. Thus, the decrease in arterial wall motion distal to a stenosis is likely to be associated with a reduction in arterial wall metabolism and in the biosynthesis of matrix components as well as in an increase in degradation of wall components. The manner in which these effects may influence the ingress or egress of atherogenic agents or foam cell precursors remains to be determined.

In addition to modifications of arterial wall metabolism and matrix fiber composition, reduced cyclic excursions of the artery wall could influence atherosclerotic lesion formation by altering vessel wall permeability and/or reducing the elaboration or release of endothelial or smooth muscle cell–derived growth factors. Changes in arterial wall permeability to large macromolecules in vessels subjected to cyclic stretching have been examined in vitro by Chien et al., who found that a 4% cyclic change in length resulted in a 40% increase in albumin uptake. Most of the increased uptake could be accounted for by increases in vessel wall surface area. Additional time-sequence studies dealing with the effects of cyclic stretching or its inhibition on arterial permeability, cell-derived growth factors, arterial wall metabolism, and arterial wall composition could help to illuminate the mechanisms by which cyclic tensile stress affects plaque formation and thereby provide new insights into the nature of atherogenesis.

Although considerable interest has developed in the role of shear forces in the localization of atherosclerotic lesions, our findings indicate that the amplitude of the stretching movements of the arterial wall associated with the excursion in blood pressure over the cardiac cycle may also be implicated in the pathogenesis of atherosclerosis. Since we examined the relationship between diet-induced lesion localization and the degree of cyclic arterial wall stretching directly, our data imply a direct cause-and-effect relationship between reduced cyclic arterial stretching and sparing from atherosclerosis. Further evidence for such an interpretation has been obtained in experiments in which cyclic stretching of short segments of aorta was restricted by encirclement, without narrowing, by a surrounding rigid tube. The intimal surface in the immobilized segment remained free of atherosclerotic lesions. Pulse pressure and in-
traluminal flow were presumably unchanged. Similar findings have been reported by others in less than critical constrictions by rigid collars.  

Sparing distal to stenosis is seen clinically in patients with long-standing chronic occlusions of the abdominal aorta. Whether restoration of arterial wall motion to normal by removal of a proximal obstruction would accelerate the distal atherosclerotic process and/or enhance intimal hyperplasia at an anastomotic site is unknown. Preliminary experimental data from our own laboratory suggest that restoration of aortic wall motion to normal after 3 months of stenosis returns the rate of distal lesion formation to control levels but does not accelerate it. Further investigations of the relationships among wall composition, wall compliance, pulse pressure, and plaque localization in both human vessels and experimental models could provide information of practical value with regard to the likely effects on distal segments of the relief of proximal stenosis.

REFERENCES


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riosclerosis, with special reference to relation between hemody-
namic change and developments of cellulosibrous intimal
16:185-243.

DISCUSSION

Dr. William M. Abbott (Boston, Mass.). Although this is a study of arterial wall, the important implication of this work for vascular surgeons involves arterial graft occlusion resulting from disease progression. The key question is: Does restoration of normal hemodynamics influence the distal vessel to re-activate or accelerate occlusive disease and, if so, what is the specific cause?
The authors have shown that decreased disease and diminished wall motion are correlated. But they would have us believe that these have a cause-and-effect relationship. But the possible causes are considerably more numerous and complicated than simply diminished wall motion.
These causes are in general divisible into hemodynamic vs. local mechanical categories and whether it is one or the other of these has very different implications. In the presence of a critical stenosis there are changes in total flow, flow velocity, pulse wave velocity, and shear forces, and any or all of these could cause changes within the distal wall. On the other hand, the causal effects may be local, such as the wall motion itself or in the artery's viscoelastic properties or compliance, which may be functionally higher distal to a stenosis since pressure is lower or may be lower if dilatation and/or wall thinning have occurred. Knowing the differences between these possibilities is not purely academic. The authors believe their results are best explained by a mechanical cause; although the authors haven't proved it yet, they are probably right.
There are three sources of information that support their view. Two old studies, one from Japan and one from Ohio State, show that decreased wall motion in arteries and vein grafts, respectively, was associated with decreased intimal thickening or atherosclerosis.

Data from our laboratory show that proximal and distal to an arterial suture line, or a graft for that matter, there is a paradoxical increase in compliance, which we have termed the para-anastomotic hypercompliant zone. It is in this location of increased stresses from increased wall motion that we see maximal subintimal hyperplasia.

If the genesis of lessened atherosclerosis is in fact mechanical, we have some options to consider to truly inhibit wall motion such as in experiments from our laboratory in which we inhibit wall motion by external meshing.

Dr. Zarins, do you have any evidence in the primate atherosclerosis model whether there is decreased atheroma in the presence of normal hemodynamics but truly inhibited wall motion?

In addition, do you have histologic evidence of changes in wall structure so that we would know whether the observed diminished wall motion is pressure related or due to an actual change in viscoelastic properties?

Dr. Alexander W. Clowes (Seattle, Wash.). This study adds further evidence to the hypothesis that hemodynamic factors are important in the localization of atherosclerosis. This study examines the influence of coarctation on lesions formed in cholesterol-fed monkeys; in a sense there are two opposing processes at work here.

On the one hand, the coarctation causes the wall to atrophy and that is associated with decreased pulse pressure. On the other hand, cholesterol feeding causes the formation of a lesion and wall thickening. It is apparent that below the coarctation these two opposing forces permit the wall to remain in a normal state; that is to say, there is very little in the way of a lesion. This is a most interesting observation because it suggests that this wall somehow is less susceptible to the atherosclerotic stimulus.

Dr. Zarins, have you compared control diet with normal diet in animals receiving coarctation and then investigated whether the same amount of atrophy occurs distal to the coarctation? One would expect that it might. Second, can we conclude that the major difference between coarctation and no coarctation in the animals fed cholesterol, as in this study, is the lack of the accumulation of macrophages and lipid? The authors suggest that this might be true from their lipase studies.

Their observations suggest that lipid transport and therefore subsequent macrophage influx are critically affected by pulse pressure; this points to the question of atherogenic susceptibility. From a different point of view, this observation may be very important when we consider what occurs in the atherosclerotic vein graft. This is a system in which a vein is transposed from a low pulse pressure system, the venous system, to a high pulse pressure system, the arterial system. These veins, particularly aortocoronary grafts, are highly susceptible to atherosclerosis and might provide an example of increased pulse pressure associated with increased atherosclerotic susceptibility.

Dr. Jon R. Cohen (New Hyde Park, N.Y.). Dr. Zarins, how do you account for the finding that the control data for acid lipase in the distal group are 40% lower than control data in the proximal aorta? Last year you reported interesting data about increased collagenase and elastase activation distal to an obstructed lesion. Would this finding not lend support to the theory that there is actually increased metabolic activity distal to an obstructed lesion; and in this light did you study elastase and collagenase in this primate model?

Dr. Francis Robiesek (Charlotte, N.C.). I join Dr.
Abbott in expressing a serious doubt that decreased wall motion is in fact a protective factor. When an experimental coarctation is created, other changes are also created in a variety of factors—velocity, shear stress, turbulence, sympathetic tone, and renin production.

In the whole work I did not see any proof that decreased arterial wall motion protects against atherosclerosis. I would also like to call your attention to the observation that the intramyocardial coronary arteries probably have the greatest wall motion of any arteries in the human body, and those arteries are uniformly protected from atherosclerosis. Do you have any explanation for that?

Dr. Zarins (closing). Dr. Abbott, thank you for your comments. You asked about what happens when normal hemodynamics are restored after a stenosis has been relieved. This is an intriguing question and one that we face clinically. We have addressed this question experimentally with the same coarctation model presented in this study. It is interesting that the coarctation inhibits distal plaque formation, but after the stenosis is relieved, the rate of atherosclerosis in the distal aorta returns to normal; that is, the rate of plaque development is the same as in non-coarcted animals. It is not accelerated.

Dr. Abbott correctly pointed out that there are many potential explanations for the observations we found. Certainly, mechanical causes are important but they are translated into metabolic causes. Arterial wall metabolism studies on the distal aorta show that there is an inhibition of glycolysis and lactic acid production. Thus not only is there a decrease in arterial wall motion, but there is a decrease in metabolic activity of the medial smooth muscle cells. Therefore, the state of the media may be a more important factor in determining whether plaques form than the state of the endothelium, which in these experiments was normal.

Yes, we have performed studies in which arterial wall motion was inhibited directly. We wrapped arteries to limit wall motion without producing a stenosis and found that plaque formation was inhibited.

We have also examined the structure of the arterial wall. There is a decrease in deoxyribonucleic acid content and there is an atrophic appearance of the arterial wall. This fits with our concepts of decreased metabolic activity in the media.

Dr. Clowes, I appreciate your comments. You asked whether arterial wall changes were found distally in non-diet-fed coarcted animals. Yes, they had the same atrophic changes and decreased metabolic response in the arterial wall but they did not get atherosclerotic lesions anywhere in the aorta because they were not receiving the atherogenic diet.

In reference to your question regarding macrophages, the acid lipase test we performed is a specific test for macrophage activity. About 90% of the cells in the foam cell lesions that developed in these animals consisted of macrophages. This comprises about 50% of the total lesion volume. Thus the acid lipase was a specific macrophage marker and evidence of macrophage activity.

The pulse pressure is an important factor, and I think it ties in directly with the arterial wall motion measurements. Proximally where pulse pressure is increased, there is an increase in atherosclerosis. Distally where pulse pressure and wall motion are decreased, we have a decrease in atherosclerosis.

Dr. Cohen, the acid lipase was a more variable test and, as you saw, the amount of lesion was quite variable. Statistically, the variances were much higher in the acid lipase and the acid lipase was diminished in that distal aorta.

Regarding collagenase and elastase, there are different kinds of metabolic activities. Increased collagenase reflects lytic activity and a breakdown of matrix components of the arterial wall. At 6 months there is a decrease in total collagen content of the wall as well as a decrease in DNA. It is probably a matter of what the cells are doing. If in fact the cell is adjusting itself to a decreased pulse pressure, perhaps it is appropriately reducing the amount of collagen that it needs to support the wall. This type of metabolic activity does not appear to support lesion formation. Thus, there may be different types of metabolic functions and it is perhaps simplistic to merely say decreased metabolism. You are correct in noting that we need to be more specific in noting the metabolic functions under discussion.

Dr. Robicek, it is true that there are many hemodynamic factors that are altered when coarctation is produced. Although we did not address those factors specifically in this study, we have addressed those in several different studies with this model. Shear stress is obviously increased within the coarctation channel and plaque is inhibited in that area. There is a negative correlation between shear stress and plaque formation. However, in the distal aorta shear stress returns to normal but plaque is still inhibited. Turbulence is increased distal to the coarctation and is maximum in the area of the poststenotic dilatation. There is also an inverse relationship between turbulence and plaque formation. Turbulence levels return to normal past the poststenotic dilatation but plaque is still inhibited. Most of the hemodynamic disturbances that you mentioned occur at or near the coarctation. At the level of the diaphragm and certainly in the abdominal aorta and below, hemodynamic conditions have virtually returned to normal with the exception of pulse pressure. However, wall motion continues to be inhibited in the abdominal aorta and plaque is inhibited, thereby producing a close association.

As far as the coronary arteries are concerned, you are quite correct that plaque does not form in the intramyocardial portion of coronary arteries, and I would submit to you that this supports our argument. The intramyocardial coronary artery is protected and encased by cardiac muscle. When the ventricle contracts, it splits the artery at the time the peak systolic pulse tends to expand the artery, thereby perhaps limiting its motion, which in turn may inhibit plaque formation. On the other hand, the epicardial portions of the coronary arteries do not have that external support and do have plaques.