Experimental Atherosclerosis at the Carotid Bifurcation of the Cynomolgus Monkey
Localization, Compensatory Enlargement, and the Sparing Effect of Lowered Heart Rate
Polly A. Beere, Seymour Glagov, and Christopher K. Zarins

We have characterized plaque localization, the extent of compensatory artery enlargement, and the effect of heart rate in experimental atherosclerosis at the carotid bifurcation of the cynomolgus monkey. We altered heart rate by sino-atrial node ablation (SNA) and then fed the animals an atherogenic diet for 6 months. Heart rate was measured at four time points by 24-hour telemetry. Of nine animals with SNA, heart rate was reduced significantly in six (from 148±11 to 103±20 beats/min, p<0.001) and was unchanged in three. Sham-operated monkeys had no significant change in heart rate. On the basis of comparison with the preoperative mean for all 17 animals (136±22 beats/min), animals were separated into a low-heart-rate (LHR) group (111±16 beats/min, n=12) and a high-heart-rate (HHR) group (150±16 beats/min, n=5). Blood pressure, serum cholesterol level, and body weight did not differ for the two groups. As in the human, plaques formed predominantly in the proximal portion of the internal carotid artery at the lateral wall opposite the flow divider. Plaque cross-sectional area increased progressively from the relatively uninvolved, adjacent common carotid artery to the mid-sinus region of the internal carotid artery and decreased from the mid-sinus region to the internal carotid artery beyond the sinus. Plaque distribution was the same for the LHR and HHR groups, but lesion area and percent stenosis were greater for the HHR group than for the LHR animals (2.01 ±1.19 compared with 0.76±0.42 mm² for lesion area [p<0.02] and 30.7±4.4% compared with 15.2±7.3% for stenosis [p<0.002]). When the single section with the largest lesion at each bifurcation was considered, all in the HHR group but only half of those in the LHR group had greater than 25% stenosis (p<0.03). Artery size, as indicated by the area encompassed by the internal elastic lamina, increased with plaque area. For the sections with little or no plaque immediately proximal or distal to the bifurcation, the internal elastic lamina area was similar for both groups. We conclude that axial and circumferential plaque distribution about the cynomolgus monkey carotid bifurcation is similar to that observed in humans, that plaque formation induced compensatory artery enlargement, and that plaque progression was retarded by lowered heart rate. The findings suggest that the conditions that determine plaque location and adaptive modeling in human atherogenesis also prevail in the cynomolgus monkey. 

Key Words • experimental atherosclerosis • carotid bifurcation • compensatory enlargement • heart rate • plaque localization

At the human carotid bifurcation, plaques form predominantly in the proximal internal carotid segment, opposite the flow divider, where wall shear stress is low and flow separation and vortex formation occur. In addition, wall shear stress in this region oscillates in both magnitude and direction during the cardiac cycle. At the relatively spared flow-divider side, wall shear stress is high and remains laminar and unidirectional. The oscillations in flow direction in the region of greatest plaque formation occur primarily during the downstroke of systole. Differences in long-term exposure to such variations are therefore dependent on heart rate. We therefore hypothesized that if low and oscillating wall shear stresses favor atherogenesis, then modification of heart rate could affect atherogenesis, particularly in locations of selective involvement such as the proximal segments of the coronary arteries, the carotid bifurcation, and the distal aorta. To test this hypothesis, we designed an experiment in which heart rate was lowered in cynomolgus monkeys by means of sino-atrial node ablation (SNA). The animals were subsequently fed an atherogenic diet. We have reported previously that the development of coronary artery plaques was retarded in the animals with low heart rate.

Other investigators have shown that the coronary arteries of cynomolgus monkeys undergo compensatory enlargement during experimental atherogenesis. We have reported the same effect in human coronary and internal carotid artery disease. In view of the importance of plaque formation at the human carotid bifurcation and of the ongoing therapeutic trials and
prospective studies dealing with atherosclerosis in this region, we have reviewed the carotid artery findings of the heart rate study. In this report, we describe the localization and effects on artery size of atherogenesis at the carotid bifurcation and the relation of lowered heart rate to carotid plaque formation in these animals.

**Methods**

To produce sustained heart rate reduction in cynomolgus monkeys without resort to pharmacological agents, we performed SNA by electrocautery of the crista terminalis. Adult cynomolgus males were randomly allocated to two experimental groups before any determination of heart rate: nine were selected to have SNA and eight to have a “sham” procedure identical in all respects to the ablation operation, except that the sino-atrial node region was not disturbed. The operative procedures have been described in detail elsewhere. After a recovery period of 2 weeks, all 17 animals were fed an atherogenic diet for 6 months. The diet has been in use at this institution for many years, and in addition to an appropriate balance of nutrients, vitamins, and fresh fruits, it contains 2% cholesterol and 25% peanut oil. Serum total and free cholesterol and triglyceride levels as well as body weight were determined monthly. Blood pressure was monitored directly by means of an intra-arterial catheter at surgery and before the animals were killed. Analysis of recordings was performed without knowledge of the type of intervention. The data were collected, and the corresponding areas were calculated by means of a computer on-line with the digitizing tablet.

**Analysis of Data**

Atherosclerosis was evaluated according to several criteria. Plaque cross-sectional area was defined as the difference between the area circumscribed by the IEL and the area of the lumen. Percent stenosis was calculated using the relation lesion area/IEL area x 100. Circumferential localization was evaluated by establishing the circumferential location of the maximum plaque thickness in relation to the flow-divider side. Axial extent and location along the bifurcation region were assessed by comparing involvement at the sequential section levels from the common carotid artery just proximal to the bifurcation to the internal carotid artery just beyond the sinus.

The overall average of lesion area and of percent stenosis for all of the bifurcation sections was calculated for each individual and for each heart rate group. Similarly, the averages for each heart rate group were calculated for the common carotid and distal internal carotid sections. Estimates were also made for left and right sides separately. To characterize severity of involvement, the section from each bifurcation with the greatest lesion area and the section with the maximum percent stenosis were identified and compared with respect to heart rate. For comparison of means from normal distribution values, two-sided *t* tests were used. For values with skewed distributions as in the case of plaque measurements, nonparametric tests were used. The Wilcoxon rank sum test was used for the largest lesions from each animal and the Mann-Whitney *U* test for the average lesion areas.

**Results**

**Heart Rate**

Heart rates before and after surgery are shown in Table 1. The mean heart rate for all of the animals before surgery was 136±22 beats/min. Of the nine animals subjected to SNA, heart rate was reduced in six, from 148±11 to 103±20 beats/min, (*p* < 0.001) and was unchanged in three. The reduced heart rates persisted for each determination throughout the experimental period. The reduction in heart rate of the animals with successful SNA was characterized by a reduction in the mean heart rate for 24 hours and also by a reduction in the degree of heart rate oscillation during the 24-hour recording period. There was no significant change from...
were eccentric and involved principally the outer wall of the internal carotid artery taken distal to the sinus region. Lesions were small or absent in the sections of the common carotid artery. Lesions were there significant differences in serum lipid levels. Total serum cholesterol was 656 ± 144 mg/dl for LHR and 9.5 ± 7.4 mg/dl for the HHR group. Monkeys and 838 ± 324 mg/dl for the HHR animals. LHR animals and 126 ± 29 mm Hg for those in the HHR group.

The average carotid bifurcation angle was 51.1 ± 16.9°. From each bifurcation (right and left) was considered, particularly in the large plaques, but no ulcerations or thrombi were present in any of the sections. When only the single largest lesion and the greatest percent stenosis for each animal were considered (Table 3), averages for all 17 animals were 2.00 ± 1.60 mm² for lesion area and 35.0 ± 17% for stenosis. Corresponding values were 1.75 ± 1.39 mm² and 34.5 ± 10% for those subjected to SNA and 2.31 ± 2.18 mm² and 35.2 ± 22.0% for the sham-operated control monkeys. There were no significant differences for either lesion area or percent stenosis among these groupings. In contrast, comparisons of LHR with HHR animals revealed significant differences. The average age lesion area of 1.22 ± 1.28 mm² and an average stenosis of 18.9 ± 13.1%, whereas the animals subjected to SNA had an average lesion area of 1.05 ± 0.45 mm² and an average stenosis of 20.4 ± 6.1%. When, however, the animals were compared on the basis of heart rate grouping, differences between HHR and LHR groups were highly significant (Table 2 and Figure 3). For the HHR animals, lesion area was 2.01 ± 1.19 mm² and stenosis was 30.7 ± 4.1%. For the LHR group, lesion area was only 0.76 ± 0.42 mm² (p < 0.02 compared with HHR) and stenosis was 15.2 ± 7.3% (p < 0.002 compared with HHR).

Relation to Heart Rate

Plaque areas and percent stenoses according to operative status and segregation into HHR and LHR groups are shown in Table 2. For all 17 animals, average lesion area was 1.11 ± 0.91 mm² and average stenosis 23.3 ± 11.6%. Both operative groups had mean lesion areas and percent stenoses similar to those for all animals. The eight sham-operated animals had an average lesion area of 1.22 ± 1.28 mm² and an average stenosis of 18.9 ± 13.1%, whereas the animals subjected to SNA had an average lesion area of 1.05 ± 0.45 mm² and an average stenosis of 20.4 ± 6.1%. When, however, the animals were compared on the basis of heart rate grouping, differences between HHR and LHR groups were highly significant (Table 2 and Figure 3). For the HHR animals, lesion area was 2.01 ± 1.19 mm² and stenosis was 30.7 ± 4.1%. For the LHR group, lesion area was only 0.76 ± 0.42 mm² (p < 0.02 compared with HHR) and stenosis was 15.2 ± 7.3% (p < 0.002 compared with HHR).

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Distribution, Configuration, and Composition of Plaques

The average carotid bifurcation angle was 51.1 ± 16.9°. Plaques were present primarily in the sinus region of the proximal internal carotid artery. Lesions were small or absent in the sections of the common carotid artery taken just proximal to the bifurcation and in the sections of the internal carotid artery taken distal to the sinus region.

Of a total of 252 sections with plaques, 242 (96%) were eccentric and involved principally the outer wall and the side walls. Eccentric plaques were crescentic on cross section, tapering along the anterior and posterior side walls with concave surface contours facing the lumen (Figure 1). Maximum plaque thickness occurred at the outer wall opposite the flow divider. None of the lesions formed convex bulges into the lumen. Small plaques resulting in less than 20% stenosis consisted mainly of foam cells forming two to four layers in the region of maximum thickness. With increasing lesion size, matrix components increased in abundance, as did extracellular lipid. Penetration of foam cells into the inner media occurred beneath some of the plaques, particularly those that resulted in greater than 25% stenosis. Regions of necrosis, stratification of lesion components, and fibrous cap formation were also evident, particularly in the large plaques, but no ulcerations or thrombi were present in any of the sections.
FIGURE 1. Photomicrographs of typical sections at several carotid bifurcation levels of an animal in the high-heart-rate group. Plaques occurred predominantly on the wall opposite the flow divider (left side of each panel). Plaque cross-sectional area increased from the common carotid artery just proximal to the bifurcation to the mid-sinus region of the internal carotid artery and then diminished from the mid-sinus to the internal carotid level distal to the sinus. The sections shown are from the common carotid level adjacent to the bifurcation (panel A), the proximal internal carotid (panel B), and the mid-sinus (panel C). The area encompassed by the internal elastic layer increases in relation to the plaque area, such that the lumen area remains nearly constant. The lumen remains circular despite the ellipsoidal enlargement of the artery. ×250.

FIGURE 2. Bar graphs of average plaque area at each axial level of the carotid bifurcation for the high-heart-rate (upper panel) and low-heart-rate (lower panel) animals. Values are shown for both the right bifurcation (cross-hatched bars) and the left bifurcation (shaded bars) at successive, equidistant levels (1–8) between the adjacent common carotid ("common") and internal carotid ("internal") sections. Plaque area increased from level 1 to level 3 (mid-sinus) and then decreased from level 5 to level 8. Plaques were smaller in low-heart-rate animals at each level. There were no significant differences between right and left bifurcations at any level.

100% (10 of 10) in the HHR group had greater than 25% stenosis while only 54% (13 of 24) resulted in greater than 25% stenosis in the LHR animals. The relation between average heart rate and maximum lesion area or maximum percent stenosis for each animal, regardless of interventional group, is shown in Figure 4. There is a strong positive correlation between heart rate and maximum lesion area (r=0.59, p<0.01) or maximum percent stenosis (r=0.65, p<0.01).

The axial symmetry of lesion area about the mid-sinus level was particularly striking in HHR animals, where mean plaque area at the mid-sinus section (level 5) reached 3.5 mm² compared with only 0.7 mm² and 1.0 mm² at levels 1 and 8, respectively (Figure 5). For the LHR animals the lesions were smaller at each level.

<table>
<thead>
<tr>
<th>TABLE 2. Carotid Bifurcation Atherosclerosis</th>
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<tr>
<td>Lesion area (mm²)</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>All animals (n=17)</td>
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<tr>
<td>SA node ablation (n=9)</td>
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<tr>
<td>Sham operation (n=8)</td>
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<tr>
<td>Low heart rate (n=12)</td>
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<td>High heart rate (n=5)</td>
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SA, sino-atrial. All values are mean±SD. For the low-heart-rate group, rate <preoperative mean; for the high heart-rate-group, rate >preoperative mean.

*p<0.02, †p<0.002 compared with the high-heart-rate group.
reaching a maximum of only 0.9 mm² at the mid-sinus (level 5). A somewhat different effect was apparent with respect to stenosis (Figure 5). For the HHR animals percent stenosis increased steeply from 13% at level 1 to 45% at the mid-sinus (level 5) but decreased only slightly from mid-sinus to the distal end of the sinus (levels 7 and 8). The effect on percent stenosis was similar for the LHR animals but with smaller degrees of stenosis at each level and a more marked decrease at the most distal levels. The differences in plaque area between HHR and LHR animals were highly significant at levels 3–8 (p<0.01 to p<0.05); for percent stenosis the differences were significant at every level (p<0.05 to p<0.001) but the distal internal carotid. As with lesion area, percent stenosis was least at the common carotid and distal internal carotid levels.

Compensatory Enlargement

In Figure 6, the mean of IEL area is plotted against mean lesion area for each level. IEL area increased with lesion area for both HHR and LHR animals. Nevertheless, IEL area was very nearly the same for HHR and LHR groups in those sections with little or no plaque deposition, i.e., at the common carotid artery proximal to the bifurcation region and at the internal carotid artery distal to the sinus. The absence of a significant difference in these values for HHR and LHR animals at these locations indicate that heart rate per se was not a factor in vessel enlargement and that individual animals did not differ significantly in artery size in the absence of plaque formation. When IEL area is plotted against lesion area for levels 3, 4, 5, and 6, where lesions are largest, and for all animals regardless of interventional group (Figure 7), there is a strong positive correlation, with r=0.74 and p<0.01. As is evident in Figure 1, plaque enlargement was associated with a change in shape of the vessel from circular to ellipsoid while the lumen remained circular. Although plaques were larger for HHR animals, mean lumen area at each level remained similar for the two heart-rate groups (Figure 8), lending further support to the idea of compensatory effect of vessel enlargement.

## Discussion

The circumferential and axial location of plaques at the carotid bifurcation region of the cynomolgus monkey proved to be similar to that found in the human. Plaques were eccentric and thickest at the lateral wall opposite the flow divider. The region of the flow divider was relatively spared. Axial involvement began in the common carotid artery enlargement at the bifurcation and receded at the distal internal carotid artery beyond the sinus. Plaque area increased progressively in successive distal sections, reaching a maximum in the mid-sinus region, and decreased in successive sections beyond this level.

The topographic distribution of plaques, both circumferential and axial, was similar for HHR and LHR animals, but there were marked and significant quantitative differences in relation to average minute heart rate. This effect was consistent whether plaques were evaluated by cross-sectional area, largest plaque area, maximum percent stenosis, or number of largest lesions with greater than 25% stenosis. The finding that heart rate correlated positively with plaque formation in experimental atherosclerosis at the carotid bifurcation lends further support to a role for heart rate as a determinant of the severity of experimental atherogenesis, as was previously demonstrated for the coronary arteries. These observations are in agreement with the experimental findings of others and are in accord with recent epidemiological reports that elevated heart rate is associated with an increased occurrence of clinical cardiovascular events. We have suggested that the combination of flow separation, low wall shear stress, and oscillation in shear stress direction during the cardiac cycle, which occurs at the lateral wall opposite the flow divider about the carotid bifurcation, results in regions of recirculation and increased particle residence time. Affected regions, such as the lateral wall of the internal carotid artery at the carotid bifurcation, are therefore subjected to delayed clearance of putative blood-borne atherogenic factors and are thereby predisposed to atherosclerosis.

Although we included sham-operated animals with spontaneous low heart rate in our LHR group, our data might also have been analyzed by comparing the SNA group with the sham-operated group to minimize effects of possible genetic differences. To detect a heart-rate effect, such an analysis would have required twice the number of sham-operated animals. Since all of our SNA animals had normal heart rates before surgery and reduced heart rates after surgery and both SNA and sham-operated LHR animals had less plaque than the HHR group, we inferred, as in our previous study, that...
heart rates lower than the mean baseline rate had a sparing effect on plaque formation, regardless of the basis for the lower heart rate. Nevertheless, the selection of some animals on the basis of resting heart rate could have introduced nonhemodynamic factors that could influence the findings. It is, for example, conceivable that there is a genetic link between heart rate and atherogenesis, independent of hemodynamics. Although our findings cannot exclude such a genetic link as a contributing factor, similar findings with larger experimental groups could still be associated with genetic differences. We therefore see no reason why such a possibility excludes our interpretation, especially in view of demonstrations of similar effects in other series using a more standard inbred population of the same species.16-17 The analysis represented in Figure 4, where maximum lesion area and percent stenosis are shown to be strongly and linearly correlated with heart rate regardless of intervention, lends further support to the relation between heart rate and lesion area.

SNA resulted not only in reduced average heart rate over 24 hours but also in a marked reduction in the amplitude of minute-to-minute excursions in heart rate under presumably similar environmental conditions. This finding raises questions concerning other features of heart rate that could play a significant role in atherogenesis. These include the time necessary for heart rate to return to baseline after activity-induced elevations, as well as the number and degree of rate excursions in 24 hours of activity. Both of these can be modified by physical conditioning. Recent reviews of published data have suggested that sedentary lifestyles are associated with increased risk of cardiovascular events.21-22 The role of heart rate under both experimental and clinical conditions merits further investigation and should include characterization of features other than single determinations of pulse rate or of mean heart rate for extended periods. Detailed reports based on such determinations in recent further experiments on the cynomolgus monkey will be published elsewhere. Preliminary data reveal that heart rate and blood pressure levels interact to influence atherogenesis more than either variable alone.23

Although plaques were present in the bifurcation region in both heart-rate groups, the increase in plaque size with axial distance from the common carotid level to the mid-sinus was much greater in the HHR group. Furthermore, the process was advanced in the HHR animals after the relatively brief 6-month feeding period.

**Figure 4.** Scatterplots of average heart rate versus maximum lesion area (panel A) and maximum percent stenosis (panel B) regardless of interventional group. There is a strong positive correlation between heart rate and maximum lesion area or percent stenosis (r=0.59 and 0.66, respectively, p<0.01 for each).

**Figure 5.** Bar graphs of average plaque area (upper panel) and average percent stenosis (lower panel) at each carotid bifurcation level (CB1–CB8) for low-heart-rate (LHR) and high-heart-rate (HHR) groups. Values are also shown for the adjacent common carotid ("common") and internal carotid ("internal") sections. The difference in plaque area between HHR and LHR animals was significant at levels CB3-CB8 (• p<0.02, •• p<0.01, ••• p<0.001). Differences for percent stenosis were significant at all levels except for the relatively spared distal internal carotid (• p<0.05, •• p<0.01, ••• p<0.001).
and much less developed in the LHR group. It is therefore reasonable to assume that the larger mid-sinus plaques of the HHR animals accumulated at a more rapid rate than did those of the LHR group during the same 6-month diet period and should therefore show greater complexity. Thus, if lowered heart rate retarded plaque progression, then the plaques in LHR animals would be expected to be less advanced than those of the HHR group. Indeed, we found that the small plaques at relatively less involved levels of HHR animals were similar in structure and composition to those at the more advanced levels in LHR animals. In these lesions, foam cells and matrix fibers were present, but little stratification was evident. In contrast, the large plaques at or near the mid-sinus level of HHR animals had fibrous caps, zones of necrosis, and extension of the lesion into the media. When occasional plaques of LHR animals were large, similar stratified zones were also evident. These findings indicate that histological appearance and organization of plaques in the present study were related mainly to plaque size rather than to heart rate or diet duration. A relation between plaque size and plaque complexity and complication has also been reported for lesions at the human carotid bifurcation. A question has been raised concerning the interpretation of the close association between vessel size and plaque area. Rather than representing an adaptive mechanism to plaque formation, this relation could presumably reflect a tendency for large vessels to have large plaques and small vessels to have small plaques, without any causal relation between plaque formation and artery enlargement. Baseline measurements by angiography of the carotid bifurcation before diet induction, i.e., in the absence of plaques, could have established that the area at the carotid bifurcation also increased with plaque area such that lumen area tended to be maintained independent of plaque area. This compensatory phenomenon has now been noted at the human carotid bifurcation and in previous studies that indicated that human coronary arteries respond in this manner, at least until degrees of stenosis reach 30–40%. A question has been raised concerning the interpretation of the close association between vessel size and plaque area. Rather than representing an adaptive mechanism to plaque formation, this relation could presumably reflect a tendency for large vessels to have large plaques and small vessels to have small plaques, without any causal relation between plaque formation and artery enlargement. Baseline measurements by angiography of the carotid bifurcation before diet induction, i.e., in the absence of plaques, could have established that the
sinuses were not as large to begin with as they were at the end of the experiment. IEL area was, however, closely related to lesion area regardless of subgroup or intervention. Our finding that vessel size in plaque-free sections proximal and distal to the bifurcation was the same for HHR and LHR animals indicates that the differences in artery size at the bifurcation between HHR and LHR groups were not related to heart rate or to underlining differences in individual artery size in vessels constituting the bifurcation before exposure to the atherogenic diet but to the presence of plaque. In 11 animals fed a standard nonatherogenic diet, measurements were made in suitably pressure-fixed material of the common carotid artery immediately proximal to the bifurcation and at the mid-sinus region (Dr. M. Gene Bond, personal communication, Winston Salem, North Carolina). Comparison of the diameters at these levels revealed a close correlation, with an r value of 0.65 and p = 0.03. This finding indicates that there is a close correspondence between diameters at various levels about the bifurcation when plaques are absent. Our data show that this correspondence is lost when plaques are present and reinforce the likelihood that artery cross-section size is closely related to plaque area. Furthermore, as noted in Figure 1 of the present study, enlargement is regularly associated with elliptoidal deformity of vessel shape in relation to outward bulging beneath the eccentric plaque and preservation of a circular lumen.10 These attributes suggest that the enlargement is the result of interaction between plaque and vessel wall. The close positive correlation between plaque area and IEL area in the vulnerable bifurcation region therefore lends support to the compensatory nature of the effect.

The close correspondence in circumferential and axial location between cynomolgus and human plaques at the carotid bifurcation suggests that the putative predisposing hemodynamic factors that have been demonstrated in scale models of the human carotid bifurcation1-3 are probably the same for the cynomolgus monkey. In particular, plaques are most prominent where flow separation occurs and where wall shear stress is low and oscillates in amplitude and direction in the course of the cardiac cycle. A close positive correlation between inter nal thickness and wall shear stress has also been demonstrated at other locations in the human arterial tree6,7 and in experimental aortic coarctations in the cynomolgus monkey, where the stenosis results in a range of wall shear stress values about the stenosis.

The same regions are also predisposed to plaque formation under conditions of hyperlipidemia. Investigation of the cellular changes and molecular events in these vulnerable locations before the intima thickens, before characteristic plaques form, and during plaque evolution should help to identify the hemodynamic and metabolic conditions necessary for the transition from nonatherosclerotic intimal thickening to atherosclerosis. The cynomolgus monkey would therefore appear to be a suitable model for further investigations of these relations and for the role of heart rate in atherogenesis. In addition, the similarities with the human disease with regard to both localization and compensatory changes in artery dimensions indicate that the model is also suitable for evaluating plaque progression and regression in relation to diagnostic imaging and flow studies.

Acknowledgments

The authors wish to thank Ms. Inger Perry and Mr. Agris Slesers for their invaluable technical assistance, Ms. Maureen Okonski for her important contributions to the analysis of the data, and Ms. Willa Henderson and Ms. Debra Pieczynski for their skill and patience in the preparation of the manuscript.

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doi: 10.1161/01.ATV.12.11.1245

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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