Do Atherosclerotic Coronary Arteries Undergo Compensatory Enlargement in Humans?

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UPDATE: Coronary arteries of monkeys with diet-induced atherosclerosis have been proven to enlarge, which allows lumen diameter to be maintained despite continued plaque growth. To ascertain whether such adaptive enlargement occurs in human coronary arteries, we did postmortem studies on cross sections of the left main coronary artery in 136 adult hearts. There was a strong correlation between plaque area and the area encompassed by the internal elastic lamina area (the potential lumen area if there were no plaque) but only a slight correlation between plaque area and age or heart weight. Lumen area did not change significantly in arteries with up to 40% stenosis, indicating that artery enlargement was sufficient to maintain an adequate lumen diameter, even in the presence of advanced disease. Knowledge of how clinical risk factors or local hemodynamic conditions may enhance or inhibit this compensatory process could have prognostic significance.

Coronary and femoral arteries of cynomolgus monkeys have been proven to increase in size in response to diet-induced plaque formation.\(^1\)\(^,\)\(^2\) As a result of these ob-
FIGURE 1 Diagram representing areas measured from samples of 136 atherosclerotic left main coronary arteries obtained from human hearts at autopsy. The area encompassed by the internal elastic lamina (left) represents the potential lumen area (middle) if there were no plaque. Lesion area (right) is the cross-sectional area of the plaque. Measurements of percentage of stenosis were determined by lesion area over internal elastic lamina area multiplied by 100.

Observations, questions have been raised concerning the significance of such a change. These questions include the following: does this also occur in human arteries? If so, does arterial enlargement keep pace with the increase in lesion size enabling lumen diameter to be maintained despite continued plaque growth, at least up to a certain point? And, if the phenomenon of compensatory arterial enlargement in response to atherosclerosis does occur in man, what is the mechanism for this change and what is it that limits the process so that, in many cases, vessels eventually become critically narrowed.

To ascertain whether such adaptive enlargement occurs in human coronary arteries, we analyzed cross sections of the left main coronary artery of 136 adult human hearts obtained postmortem. This particular artery was selected because it is often diseased and, under normal conditions, is similar in size in most adult hearts. The arteries were pressure-fixed in order to approximate vessel dimensions in the living person. We measured lumen area, the opening through which blood flows; lesion area, which is the area occupied by plaque; and the area encompassed by internal elastic lamina, the structure which usually defines the inner boundary of the normal artery wall. This latter area is the same as the lumen area when there is no plaque. When plaque is present, however, the internal elastic lamina area represents what the lumen area would be if there were no plaque. Therefore the percentage of stenosis, or the extent to which plaque fills the lumen...
and obstructs flow, is determined by lesion area over internal elastic lamina area multiplied by 100 (Figure 1). The determinations were made by computer-assisted measuring techniques.

As expected, lesion area grew with patients' increasing age, and lumen area decreased correspondingly as lesion area increased. This association was significant and the correlation coefficients, although opposite in sign, had nearly the same magnitudes ($r = +0.32$ and $r = -0.31$, respectively; $p < 0.01$).

As might be expected, lesion area correlated strongly with both percentage of stenosis and internal elastic lamina area (Figure 2). Internal elastic lamina area, the measure of arterial size and of the potential lumen area, increased with lesion area ($r = 0.44$, $p < 0.001$). For all 136 artery samples, internal elastic lamina area increased by 0.60 mm$^2$ for each square-millimeter increase in lesion area.
area. The standard error of the internal elastic lamina area in relation to the lesion area along the regression line was 4.8 mm². Thus, even though an increase in lesion area generally resulted in the eventual narrowing of the lumen, vessels enlarged as the lesions developed. Internal elastic lamina area also expanded as age and heart weight increased, but the correlation coefficients were low ($r = 0.22$ and $r = 0.25$, respectively; $p < 0.01$). Multiple regression analysis was used to assess the relative contributions of lesion area, age, and heart weight to internal elastic lamina area. The following equation was generated for this purpose: internal elastic lamina area $= 9.26 + 0.88$ (plaque area) $+ 0.026$ (age) $+ 0.005$ (heart weight). A significance of $p < 0.001$ was found for the coefficient for lesion area. No significance was found for coefficients for age and heart weight.

When lumen area was charted against percentage of stenosis, the data points could be divided into two regions (Figure 3). There was no significant association between lumen area and percentage of stenosis in arteries with up to 40% stenosis. Beyond 40% stenosis, however, lumen area decreased markedly as the internal elastic lamina area filled with plaque. In Figure 3, lines of best fit are drawn to correspond to transition points at 30% and 40% stenosis. Values were not statistically significant for the points up to 30% and 40% ($r = 0.098$ and $r = -0.001$, respectively). However, differences were significant for the points above 30% and 40% stenosis ($r = -0.75$ and $r = -0.73$; $p < 0.001$). Thus, the data indicated that the enlarged internal elastic lamina area was not overtaken by the lesion until the lesion area reached about 40% of the internal elastic lamina area, or 40% stenosis (Figure 4). Compared with the entire study sample, arteries with less than 20% stenosis showed that during the early stages of plaque development, the cross-sectional lumen area enlarged beyond the normal area (overcompensation), indicated by a higher rate of increase in internal elastic lamina area in relation to the lesion area.

Thus, the answer to the question asked earlier—does the phenomenon that occurs in cynomolgus monkeys also occur in human coronary arteries—is yes. The results further suggest that vessel enlargement is an adaptive process and tends to maintain lumen diameter in the event of advanced plaque formation. Variation among individuals is, however, considerable.

With respect to understanding the mechanism of this phenomenon, we can only surmise that there are two possibilities. One is that the plaque, which is usually eccentric, weakens the underlying wall and allows it to extend. The other possibility is that plaque encroachment on the lumen reduces vessel diameter; the resulting increase in flow velocity causes the relatively spared sector of the artery opposite the plaque to extend and restore the lumen to its original diameter. There is evidence for both hypotheses. First, the artery wall under the plaque does show atrophic changes and, second, arteries subjected to elevated flow rates do increase in diameter.

Experiments indicate that arteries will enlarge until the original level of wall-shear stress related to flow is restored. When the plaque entirely encircles the vessel lumen, compensatory enlargement may no longer be possible. This may occur when plaque area consumes about 40% of internal elastic lamina area.

On coronary angiograms, the lumen is viewed in the longitudinal projection. Extent of stenosis is quantified by comparing lumen
FIGURE 3 Lumen area of 136 atherosclerotic left main coronary arteries charted against percentage of stenosis on cross section. Lines of best fit are drawn with inflection points at 30% (top) and 40% (bottom). For stenoses less than 30% or 40%, there is no association between lumen area and percentage of stenosis. For stenoses greater than 40%, lumen area decreases steadily with percentage of stenosis.

diameter at an evident narrowing with the diameter of a nearby segment that presumably is not occluded. Our study suggests that lesion size or extent of atherosclerotic involvement may be greatly underestimated if only the arterial lumen is examined. Lack of obvious lumen narrowing on angiograms does not always indicate that little or no
disease is present. Thus, blood flow interference is not necessarily determined by plaque size if the artery enlarges to preserve a near-normal or adequate lumen. Of most importance is the absolute diameter or cross-sectional area of the lumen rather than the size of the plaque.

Although there was considerable variation in the association between plaque area and internal elastic lamina area among the vessels studied, our findings indicate that many persons have an adequate, if not normal, lumen cross-sectional area in the presence of advanced atherosclerosis, and that such a possibility should be taken into account when evaluating the extent of disease with angiography.

Knowledge of how clinical risk factors and local hemodynamic conditions affect plaque enlargement, and of compensatory enlargement of arteries in response to plaque formation and/or alterations in flow velocity, could prove valuable for understanding individual differences in the progression and consequences of atherosclerosis.

REFERENCES


