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Tortuosity and Atherosclerosis in the Femoral Artery: What is Cause and What is Effect?

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Abstract—Earlier studies have demonstrated a correlation between tortuosity and atherosclerosis in the femoral artery. One conceivable explanation is that atherosclerosis causes an elongation of the artery, resulting in vessel tortuosity; another is that blood flow phenomena (such as flow separation) due to the vessel geometry may affect the progression of atherosclerosis. To determine which of these hypotheses is most likely, a group of 232 hyperlipidemic patients was followed with angiography for 3 years during lipid-lowering treatment. After digitization of the films, a tortuosity value and an atherosclerosis measure (edge roughness) were computed. In the group with lower tortuosity values, there was a significant ($p < 0.0001$) decrease in edge roughness, but not in the group with a higher tortuosity values. On the other hand, neither the group with higher edge roughness values nor that with lower edge roughness values displayed a significant change in tortuosity. When tortuosity, roughness, and treatment were studied simultaneously, only the effect of tortuosity on roughness change was significant. These findings are more consistent with tortuosity influencing the development of atherosclerosis than with its being a consequence of atherosclerosis.

Keywords—Vascular geometry, Blood flow, Fluid mechanics, Shear rate, Separated flow, Angiography

INTRODUCTION

It is a common clinical observation that atherosclerotic arteries tend to be more tortuous than other arteries (19,21). This observation has led to speculations in two directions. One possible explanation is that the atherosclerotic process leads to elongation of the artery, giving it a more tortuous course (5). On the other hand, the disturbed blood flow dynamics in a tortuous vessel may affect the development of atherosclerosis in its wall, which would make atherosclerosis a consequence rather than a cause of the tortuosity (12). Several studies using various methods have indicated that either low shear stress or flow separation may increase the risk of atherosclerotic progression (3,10,11,14). Both of these flow phenomena are prone to arise at the inner curvature of curved arteries, which is where most atherosclerotic lesions are found (7,14, 17,21).

Friedman et al. have found, in model experiments, that certain geometric features of the aortic bifurcation give rise to flow phenomena that have been suspected to stimulate the development of atherosclerotic lesions (9). On the basis of these findings, they have proposed the concept of geometric risk factors for atherosclerosis. Since curved vessels give rise to similar flow disturbances, tortuosity is a candidate for a geometric risk factor in the femoral artery.

In an earlier paper, our group studied arterial tortuosity in the femorals by means of digitized angiography and found a correlation between tortuosity and atherosclerosis (16). However, from this finding it was not possible to infer whether tortuosity might cause atherosclerosis—or vice versa. It was concluded that such questions cannot be answered without a longitudinal approach, evaluating both tortuosity and atherosclerosis on at least two occasions.

The measure applied in that study to assess atherosclerosis was edge roughness, which has been used in several other studies (6,13). It has been found to correlate both to clinical symptoms of arterial disease and to the cholesterol content of the vessel (1,6).

The methodological part of our previous article discussed a number of measures of tortuosity, concluding in a recommendation to use either the distance factor (DF), obtained by dividing the length of the vessel segment by the distance between its end points, or the total curvature, computed as a line integral of local curvature values. A subsequent work from another group, which generalized the analysis to three dimensions, used the distance factor subtracted by one and called this value "tortuosity" (2). The effect of the subtraction is that a straight line is assigned a tortuosity value of zero. This definition appears to be useful for future work.

The purpose of our present study was to shed some light on the question of whether tortuosity is an effect or a contributing cause of atherosclerosis, by studying changes

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in tortuosity and edge roughness with digitized angiography over a 3-year period.

METHODS

Two hundred thirty-two hypercholesterolemic patients, of either sex and 27–70 years of age at the beginning of the study, underwent angiography on two occasions separated by a 3-year interval, as part the Probucol Quantitative Regression Swedish Trial (PQRST) (20). All had slight or moderate femoral atherosclerosis, confirmed by angiography. At the time of the first examination, they had been put on a diet and lipid-lowering drug treatment with cholestyramine and probucol, limited to two 8-week test periods. In the interval between the two examinations, the lipid-lowering treatment consisted of diet and cholestyramine with ("active") or without ("placebo") the addition of probucol.

The angiography and digitization procedures have been described in detail earlier (13). In brief, a standard angiographic technique was used with the same equipment on both occasions. During the angiography, the patient's foot was fixed in a device that ensured consistent positioning between investigations. The films were then digitized and analyzed on an image-processing workstation (Imtec Epsilon; Imtec AB, Uppsala, Sweden). On each occasion, two femoral angiography series were obtained, 10 min apart. Four consecutive segments, 5 cm long, were digitized, so that the superficial femoral artery was available for study within a 20-cm portion of the thigh. Branching points were considered as reliable landmarks, which were used to identify the same portion of the vessel on both occasions.

The edges and midline of the vessel were detected, and the midline was filtered as described earlier (13,16). From the midline coordinates x_j and y_j of the filtered midline, the tortuosity was computed as

$$DF - 1 = \frac{L}{d} - 1 =$$

$$\frac{\sum_{j=1}^{n} \sqrt{(x_j - x_{j-1})^2 + (y_j - y_{j-1})^2}}{\sqrt{(x_n - x_0)^2 + (y_n - y_0)^2}} - 1, \qquad (1)$$

where L is an approximation of the length of the curve and d is the distance between its end points.

The amount of atherosclerosis was assessed as edge roughness (6,13). To compute this measure, two versions of the edge are compared, one slightly filtered (11-pixel average) and one strongly filtered (113-pixel average) (cf. Fig. 1). The roughness is defined as the root mean square distance between these filtered edges. To be more specific: if the coordinates of the two filtered curves are denoted by f_j and g_j, then the edge roughness is expressed by the formula

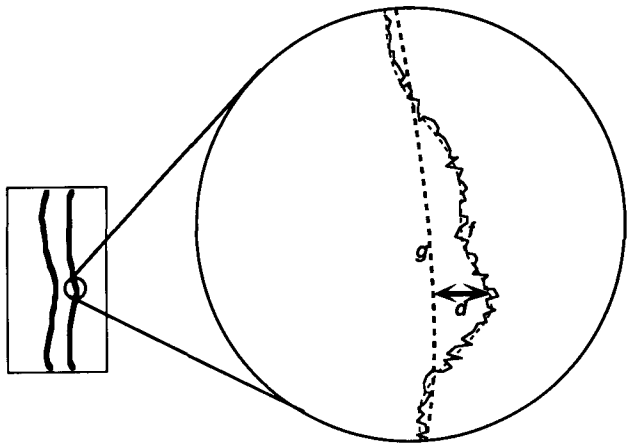

FIGURE 1. Calculation of edge roughness. From the original edge (solid curve), two filtered versions (dashed) are obtained by forming the average over 11 (curve *f*) or 113 (curve *g*) consecutive pixels. The two filtered curves are compared by studying the distance *d* between them over the entire 20-cm segment.

$$Ro = \sqrt{\frac{1}{n}\sum_{j=1}^{n} (f_j - g_j)^2}, \qquad (2)$$

where n is the number of pixels.

The mean roughness was calculated as the mean of the roughness values for year 1 and year 4, and the roughness change was calculated as the difference between the roughness values for year 4 and year 1. Mean tortuosity and tortuosity change were defined analogously. Thanks to the two angiographic series performed on each occasion, duplicate values could be obtained for all four of these variables.

The reproducibility of each variable was computed as Pearson correlation coefficients (r). All remaining calculations used the average of the duplicate measurements. The significance of the changes in tortuosity and edge roughness was tested with a one-sample t-test. Descriptive correlations between variables were calculated as r with 95% confidence intervals, whereas hypothesis testing was performed with simple linear regression. Because of the marked skewness of the distributions of the mean tortuosity and mean roughness, some analyses were repeated after a logarithmic transformation of these variables. To account for the effect of age, multiple linear regression was used. The interaction between mean tortuosity, mean roughness, and treatment group was studied with analysis of variance (a three-way factorial model).

RESULTS

Average, standard deviation, and reproducibility values for each variable are given in Table 1. It is evident that the edge roughness decreased somewhat over the 3-year period, whereas the tortuosity increased. The changes were quite small, however, compared with the variation within the population studied. Reproducibility was very high for mean tortuosity and mean roughness and somewhat lower for the changes over the study period.

A strong positive correlation was found between mean tortuosity and mean roughness ($r = 0.899$; 95% confidence limits, 0.871 and 0.921). Moreover, there was a positive but weaker correlation between tortuosity change and roughness change ($r = 0.457$; 95% confidence limits, 0.349 and 0.553).

The significance of the change in edge roughness was tested both for the whole population and separately for the two subgroups, with mean tortuosity values below and above the median value (Table 2). The decrease was significant when the whole material was studied. However, as seen in the table, no significant change was present in the group with higher mean tortuosity values, whereas it was strongly significant in the low-tortuosity group.

Conversely, the change in tortuosity was studied separately for two subgroups with high and low mean roughness values (Table 3). In this case, there was a moderately significant increase for the whole material, but no significant changes when the subgroups were analyzed separately.

The simultaneous effect of mean tortuosity, mean roughness, and treatment group on changes in roughness and tortuosity is illustrated in Figs. 2 and 3. As above, the groups with high and low tortuosity and high and low roughness were defined by values above and below the median value. Figure 2 shows that the roughness change had lower values in patients with high tortuosity than in those with low tortuosity. In the analysis of variance including tortuosity group, edge roughness group, and treatment group as independents, the difference between low- and high-tortuosity groups was statistically significant ($p < 0.01$), whereas there was no significant effect of roughness or treatment. In other words, the difference between the low-tortuosity and high-tortuosity groups was not explained by differences in mean roughness or treatment. For the change in tortuosity (Fig. 3), there was no significant effect of any of the three factors.

When change in edge roughness was plotted against mean tortuosity (Fig. 4), the regression line displayed a significant slope, with the roughness increasing for high tortuosity values and decreasing for small tortuosity values. This coefficient was higher (58.2 mm; $p < 0.01$) when the regression was carried out in the subgroup treated with probucol and lower in the placebo group (20.2 mm; not significant). When, on the other hand, tortuosity change was related to mean edge roughness, no significant association was found (Fig. 5). As evident from the figures the distributions of mean tortuosity and mean roughness are markedly skewed. A logarithmic transformation of these two variables resulted in approximately normal distributions. However, even after this transformation, a significant relationship ($p < 0.01$) remained between roughness change and mean tortuosity, whereas no association was present between tortuosity change and mean roughness.

The relationships shown in Figs. 4 and 5 were also studied with adjustment for the effect of age (not shown). In this case also, a significant relationship ($p < 0.05$) was found between roughness change and mean tortuosity, but not between tortuosity change and mean roughness ($p > 0.10$).

When the analyses were restricted to two compara-

TABLE 1. Average, standard deviation, and reproducibility (r) of mean levels and changes in tortuosity and edge roughness ($n = 232$)

Variable	Average	SD	Reproducibility
Mean roughness (mm)	0.884	0.347	0.98
Roughness change (mm)	−0.027	0.151	0.76
Mean tortuosity	$5.8 \cdot 10^{-4}$	$6.0 \cdot 10^{-4}$	0.96
Tortuosity change	$+0.6 \cdot 10^{-4}$	$3.8 \cdot 10^{-4}$	0.68

TABLE 2. Average roughness change in groups with high and low mean tortuosity.

Group	n	Roughness change (mm) (mean ± SD)	p
Low tortuosity ($<3.75 \cdot 10^{-4}$)	116	−0.060 ± 0.151	<0.0001
High tortuosity ($\geq 3.75 \cdot 10^{-4}$)	116	+0.005 ± 0.179	NS
Total	232	−0.027 ± 0.151	<0.01

Significance levels for change compared to 0 (one-group t-test). NS, not significant.

TABLE 3. Average tortuosity change in groups with high and low mean roughness.

Group	n	Tortuosity change (mean ± SD)	p
Low roughness (<0.781)	116	$+2.3 \cdot 10^{-5} \pm 15.9 \cdot 10^{-5}$	NS
High roughness (≥0.781)	116	$+9.2 \cdot 10^{-5} \pm 51.3 \cdot 10^{-5}$	NS
Total	232	$+5.7 \cdot 10^{-5} \pm 38.0 \cdot 10^{-5}$	<0.05

Significance levels for change compared to 0 (one-group t-test). NS, not significant.

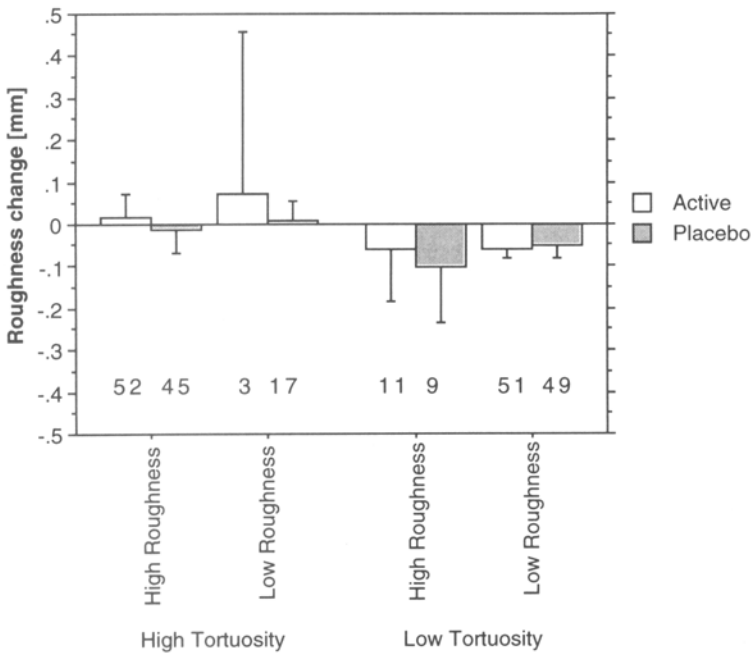

FIGURE 2. Roughness change in groups defined by mean tortuosity, mean roughness, and treatment. Error bars denote 95% confidence limits. The figure below each bar denotes number of observations. Statistical testing with analysis of variance.

ANOVA

Source	df	Sum of Squares	Mean Square	F-Value	p-Value
Treatment	1	0.01473	0.01473	0.67475	0.4123
Tortuosity group	1	0.20904	0.20904	9.57689	0.0022
Roughness group	1	0.01658	0.01658	0.75948	0.3844

tively healthy subpopulations—those with mean roughness below 0.8 mm (n = 132) and with mean tortuosity less than 0.0005 (n = 155)—the regression coefficient in Fig. 4 increased in value and became more strongly significant, whereas the slope in Fig. 5 never reached significance. On the other hand, when the analyses were repeated for the more severe cases—with mean roughness values exceeding 1.0 mm (n = 52) and mean tortuosity exceeding 0.001 (n = 36)—the two slopes never even approached significance.

DISCUSSION

It is a fundamental scientific rule that statistical association is not a proof of a causal relationship. Only a combination of studies differing in methodology can answer the question concerning the relationship between tortuosity and atherosclerosis. Nevertheless, the correlations found between the levels and changes in these entities can make a causal relationship in one direction more plausible than one in the opposite direction.

The significant decrease in edge roughness found in the whole population indicates a regression of atherosclerosis over the 3-year treatment period. This finding is consistent with the overall findings in the PQRST (20). However, from Table 2 it is evident that the entire decrease can be attributed to the low-tortuosity group, a plausible explanation being that the potentially beneficial effects of lipid-lowering treatment (which all our patients received in the form of diet and cholestyramine) may be counteracted by a tortuous course of the femoral artery. As no difference in tortuosity change was detected between the low-roughness group and the high-roughness group, we have no corresponding evidence for effects of edge roughness on tortuosity. The interaction illustrated in Fig. 2 suggests that tortuosity has a greater effect on atherosclerosis progression than both the type of treatment and the mean level of atherosclerosis involvement. As reported elsewhere, there were marked differences in blood lipid levels between the active drug and placebo groups (20).

Furthermore, the connection between high tortuosity values and an increasing edge roughness in our popula-

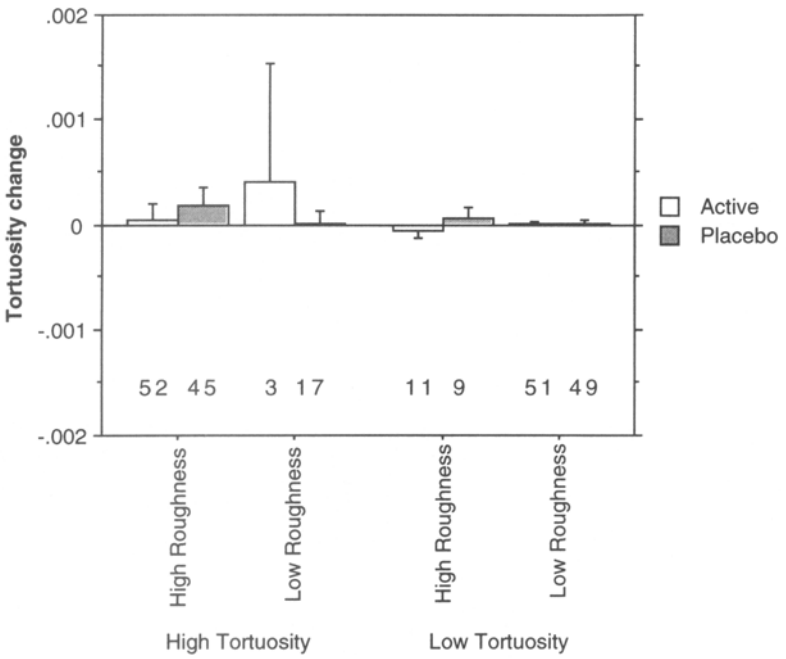

FIGURE 3. Tortuosity change in groups defined by mean tortuosity, mean roughness, and treatment. Error bars denote 95% confidence limits. The figure below each bar denotes the number of observations. Statistical testing with analysis of variance.

ANOVA

Source	df	Sum of Squares	Mean Square	F-Value	p-Value
Treatment	1	1.51510E-7	1.51510E-7	1.05403	.3057
Tortuosity Group	1	1.63923E-7	1.63923E-7	1.14039	.2867
Roughness Group	1	2.32551E-8	2.32551E-8	.16178	.6879

tion, illustrated in Fig. 4, is compatible with the concept of tortuosity being a contributory cause of atherosclerosis. The absence of significant relationships in the converse direction (Fig. 5) makes the opposite causal relationship less likely. As these findings persisted even after a logarithmic transformation that made the distributions close to normal, they are not likely to be due to the skewness of the data. The different results of the regression analysis in the active and the placebo group suggest that the effect of tortuosity on edge roughness change may be modulated by

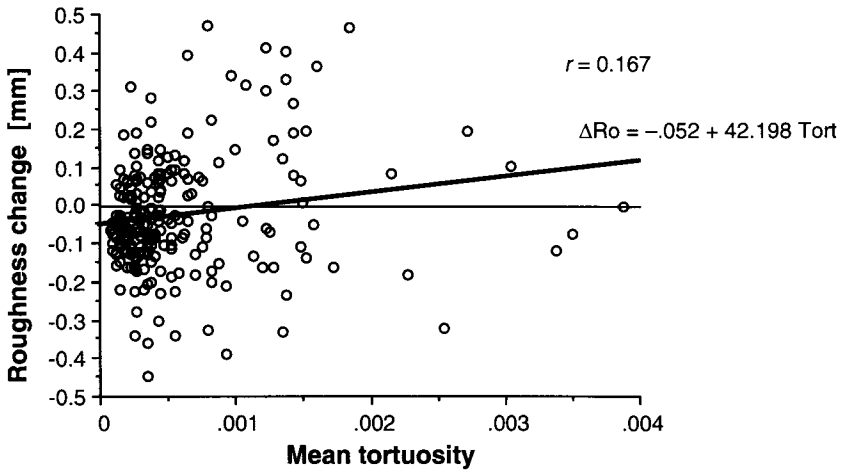

FIGURE 4. Change in edge roughness as a function mean tortuosity (n = 232). The slope of the regression line is significant (p = 0.0108).

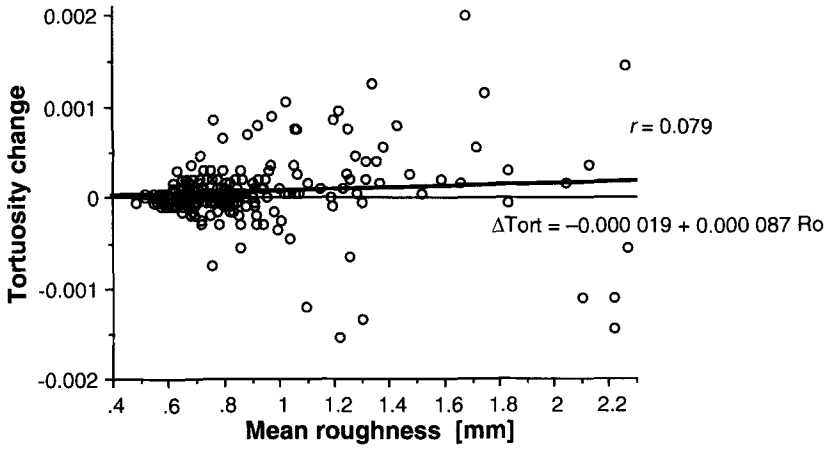

FIGURE 5. Change in tortuosity as a function of mean edge roughness (n = 232). The slope of the regression line is not significant (p = 0.2241).

the type of treatment given. However, since no real placebo group was included in the trial (this was considered ethically unacceptable) we cannot draw any definite conclusions concerning the effect of lipid lowering.

The most satisfactory explanation for our findings is probably the assumption that either low shear stress or separated flow, arising in the curved vessels, promotes atherogenesis, as has been suggested by several other authors (2,3,7,9–12,14). In the PQRST material, our group has demonstrated significantly higher edge roughness values in inner curves than in outer curves and straight segments (17). Since both low shear stress and flow separation tend to occur in the same locations, *i.e.*, mainly in the inner curves, it is not possible with our approach to implicate either of these phenomena more than the other. The same dilemma, however, is likely to arise in flow studies using more direct methods, in view of the close correlations demonstrated between several flow-related variables (8).

As discussed in our previous report (16), the physiological parameters present in the femoral artery makes it reasonable to assume that flow separation does take place in the inner curves of the femoral artery. Using digitized cineangiography, we have found that flow disturbances, most likely corresponding to separation regions, are common in the femoral artery and tend to occur in inner curvatures rather than in outer curvatures (15). We have also found that the presence of these flow disturbances is associated with less favorable development of atherosclerosis than in other segments (18).

It should be noted that, in comparison with most clinical materials, a majority of the PQRST patients have rather mild forms of arterial disease (17). Since our findings were accentuated when the two healthier subpopulations were studied (results given in text above), but did not hold good in the more diseased ones, the potential relationship between tortuosity and atherosclerosis would seem to concern the inception of atherosclerotic lesions rather than their further progression. In more advanced stages of atherosclerosis, our conclusion may not apply. The clinical observation of arterial elongation seems to have been made in a later stage, when the patients had developed severe symptoms of their disease (5). It must also be realized that once a raised plaque has formed, areas of low and high shear can both emerge as a result of even a minimal geometric disturbance (4,22). Assuming that a relationship exists between the fluid mechanical environment and atherogenesis, this may lead to a quite complex interaction between the vessel wall and the blood flow. The rather crude concept of tortuosity is not likely to account for such a situation.

The most striking limitation of our way of measuring tortuosity is the use of a two-dimensional projection of the artery. However, this method can easily be generalized to three-dimensional circumstances. With access to two projections of the vessel, three-dimensional tortuosity computations corresponding to those made here can be carried out, as done in the study by Brinkman *et al.* (2).

In conclusion, our longitudinal analysis indicated that progression of atherosclerosis was associated with high mean values of tortuosity, whereas no corresponding relation was found between progression of tortuosity and the mean degree of atherosclerosis, and that tortuosity was more important for atherosclerosis progression than both the type of treatment and the level of atherosclerosis involvement. The most plausible explanation is that tortuosity contributes to the development of atherosclerosis by affecting blood flow patterns.

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