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THE QUANTITATION OF ATHEROSCLEROSIS
I. RELATIONSHIP TO ARTERY SIZE

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The Quantitation of Atherosclerosis: Relationship to Artery Size

In the past three decades the evaluation of atherosclerosis has been in a gradual transition from purely qualitative and intuitional approaches to highly quantitative direct measurements. Early attempts at quantitation of atherosclerosis in the cerebral arteries were made by Volkoff in 1933 (1). More recent studies directed toward quantitation are exemplified by the broad evaluation of coronary atherosclerosis by White, Edwards, and Dry (2). In all these studies the severity of atherosclerosis was graded roughly from 0 to 4. The roughness of grading in previous studies provides data inadequate to understand the intricate interrelationship between atherosclerosis and other parameters which are highly quantitatively measured. Thus, in the past, many probable relationships have been completely obscured.

It is generally agreed that atherosclerosis is more prevalent in the large and medium sized arteries than in the arterioles. However, the degree of atherosclerosis specifically as a function of the size of an artery has never been studied quantitatively. Without measuring arterial size, White and his associates (2) demonstrated that atherosclerosis was much higher in the proximal part of a particular coronary artery than in the distal part. This observation suggests the possibility of some relationship between the distribution of atherosclerosis and the size of the coronary artery, since the proximal part of an artery is usually wider than its distal part. Subsequently, Blumenthal (3) after combining his observations on atherosclerosis with the data on dogs of Green (4) and the calculations of Burton (5) also proposed that the incidence of plaque formation was higher in arteries with large lumens than those with small lumens. However, his grading measurements indicated a somewhat lower degree of atherosclerosis in the internal carotid artery than in the middle cerebral and basilar arteries. Winter and his associates (6) also noted this apparent discrepancy in the distribution of cerebral atherosclerosis by their methods of grading. These discrepancies could certainly arise

from inconsistencies in the techniques used for grading. With a truly quantitative measure of atherosclerosis this problem may be clarified.

Analysis of the degree of atherosclerosis along any branch of an artery can also serve to differentiate the contribution of local factors from that of general metabolic ones (7,8,9) in the atherosclerotic process. For such analyses it is essential to have some definite quantitative measure of atherosclerosis as well as of the size of the artery. This report presents a technique for the quantitation of the extent of atherosclerosis in any artery and the results obtained from application of this technique to human tissue samples.

In the past several years we have applied this technique principally to the coronary and cerebral arteries along their major branches (10). This report is primarily concerned with the interrelationship between the size of an artery and the degree of its atherosclerosis. The relationship of calcification to distance is also considered.

Material and Method

This study is based upon 4331 sections of coronary and cerebral arteries removed at autopsy (in the Napa State Hospital) from 143 consecutive hearts and brains. Sixteen standard sections were taken from the heart and twenty-four sections were taken from the brain (fig. 1a,b). Histologic sections were prepared by standard techniques and stained with hematoxylin and eosin. Sections were occasionally stained according to the method of hematoxylin Van Gieson counter-stained with that of Weigert to differentiate the amount of collagen and elastic tissue in different layers.

The quantitation of the atherosclerotic process in any arterial section was based on the direct measurement of the physical changes in the arterial tissue. The most obvious physical change concomitant with the atherosclerotic process is the increase in the intimal material. Since the amount of intimal tissue is negligible in the uninvolved artery, for a cross-section of artery the total area of intimal tissue (all tissue between the endothelial surface and the internal elastic lamella) was considered as evidence of accumulation of

atherosclerosis. In order to correct for variation in the size of artery from section to section and from case to case, the area of intimal atherosclerotic material was referred to the total arterial cross-sectional area of each section and the results expressed as a percentage of the total cross-section. Atherosclerosis will thus be defined in this study by the following:

$$\text{Atherosclerosis} = \frac{\text{I(Area of intimal material)}}{(\text{Total arterial cross-section area})}$$

All area measurements were made by planimetry on a precisely enlarged tracing of the histological arterial section. The degree of calcification was derived from the calcified area in the histological slide by similar area measurement. No attempt was made to grade the very early phase of calcification. However, it could be done by counting the calcified granules under higher magnification.

Figure 2 shows the tracing arrangement, which is essentially a projecting microscope. A photographic plate can also be used instead of an enlarged tracing. Three typical tracings are illustrated in figure 3. At the bottom of each tracing are indicated the degree of atherosclerosis and of calcification, respectively.

Results

All sections of coronary and cerebral arteries were grouped into nine categories (0-0.50, 0.51-0.75, 0.76-1.00, 1.01-1.25, 1.26-1.50, 1.51-1.75, 1.76-2.00, 2.01-2.50, 2.51-3.00 mm. in radius) according to their size, disregarding the arterial branch they represent. The distribution of coronary and cerebral arterial sections are listed in table 1 and 3 separately.

(1) Atherosclerosis and the radius of coronary arteries.

The relationship of atherosclerosis to the radius of the coronary artery is shown in table 1. The degree of atherosclerosis is significantly related to the radius of the artery.

These data show that the bigger the artery, the higher the degree of atherosclerosis. However, for radii above 2 mm. there appears a plateau since further increases in the radius of the artery are not associated with proportional increases in atherosclerosis values.

An analysis of the relationship between atherosclerosis and the radii of the different arterial branches is shown in table 2 a,b,c,d. All individual branches of the coronary arteries show a similar trend; that is, the degree of atherosclerosis decreases toward the peripheral end of the artery. The anterior descending branch shows the highest sclerosis ($I/E = 59.8$) in the proximal part, yet it decreases sharply at its distal end ($I/E = 33.0$). The left circumflex and the right coronary artery yield I/E values of 55 and 56 for the proximal part and 43 and 46 for the distal part. This discrepancy in degree of atherosclerosis in the distal parts of these different branches can be easily explained by the fact that the actual sizes are different in these branches. (Table 2 a,c,d).

(2) Atherosclerosis and the radius of cerebral arteries.

A similar distribution of the degree of atherosclerosis was found in all branches of the cerebral arteries so far studied. (Table 3). The middle cerebral arteries exhibited the severest sclerosis. The posterior cerebral arteries exhibited less sclerosis than the middle cerebral while the anterior cerebral arteries exhibited the least sclerosis of the three (Table 4a,b,c).

There is practically no difference between the atherosclerosis of the cerebral arteries of the left and right sides. This is probably due to the almost symmetrical anatomical distribution of the cerebral arteries.

The degree of atherosclerosis of the internal carotid artery was found to be higher ($I/E=39$) than that of the middle cerebral artery ($I/E=37,32,26$) but is definitely lower than the highest value in the basilar artery ($I/E=42,38,31$).

(3) Interrelationship between atherosclerosis and the size of arteries.

The data for the overall relationship between atherosclerosis and the radius of the artery, including all coronary and cerebral vessels studied, are shown in fig. 4. There is almost a linear relationship between the degree of atherosclerosis and the radius of the artery. The Pearson coefficient of correlation (r) is 0.77 when calculated from the data derived from 4531 artery sections. The p value is much smaller than 0.001 and the relationship between atherosclerosis and radius is therefore highly significant. The atherosclerotic gradient was found to be in the neighborhood of 2.14 (I/E) units per 100 micra change in the radius of the artery.

(4) Atherosclerosis and the distance from the origin of the arterial branch.

Another approach to a study of the relationship between the size of the artery and its sclerosis (but independent of measuring the radius of the artery) is to measure the degree of atherosclerosis as a function of the distance from the origin of the arterial branch. White and his associates (2) showed that the degree of atherosclerosis decreased progressively from the proximal to the distal part of the coronary artery in any decade from 30 to 90 years. It would be of interest to measure the actual distance and the exact amount of intimal mass according to the technique described above.

Figure 5 shows that relationship between the distance from the origin of the artery and severity of the sclerosis based on 1670 sections of coronary arteries. All the branches measured show a similar trend of sclerosis, that is, the degree of the atherosclerosis decreases toward the peripheral ends. In the anterior descending branch, however there is a higher degree of sclerosis at 2 cm. from its origin than at the origin itself. The slightly higher value at 6 cm. from the origin for the right coronary artery (in comparison with the anterior descending branch) can be explained if one takes into account its actual radius. The radius of the right coronary at 6 cm. is comparable with the

radius at 4 cm. for the anterior descending branch in most cases.

(5) Calcification of arteries and the distance from the origin of the arterial branch.

Figure 5 also shows, for the anterior descending branch, the relationship between the frequency of calcification* and the distance of the arterial section from its origin. The highest incidence of calcification is at 2 cm. from the origin. The calcification approaches zero at 6 or 7 cm. from the origin. The cerebral arteries are nearly free from calcification.

Discussion

The quantitative studies reported here establish a significant relationship between atherosclerosis and a) size of artery and b) distance from the origin of artery. From these data an atherosclerosis gradient can be evaluated, which can be shown to have definite physical interpretation in terms of area measurements.

Factors responsible for such a gradient may be listed as being the following: a) general metabolic factors - lipoproteins, hormones, heparin etc., and b) local factors such as pressure, turbulence, etc. Atherosclerosis and lipoproteins have been studied extensively (7,8,9). Furthermore, it has been found that certain species of lipoproteins are especially associated with the occurrence of atherogenesis (11). Since the above measurements were carried out in the same branch of the arterial system, the influence of a general metabolic factor such as lipoproteins may be considered to be effectively the same throughout an individual branch. Thus, attention is directed to local factors such as pressure and turbulence in determining the nature of this atherosclerosis gradient.

*Frequency of calcification Number of arterial sections showing, calcified
= area of $5\mu^2$ or more
 Number of arterial sections studied

If the pressure gradient is calculated* along any arterial branch and the resulting gradient compared with the distribution of quantitative atherosclerosis there is some similarity in distribution of degree of atherosclerosis and pressure (4). Such comparison will be reported elsewhere in detail (12). Notwithstanding the difficulties in explaining the exact cause of the observed atherosclerosis gradient, it is now clear that such a gradient exists and can be related to such important factors as intravascular pressure.

The measurement of atherosclerosis at different distances from the origin of an arterial branch not only confirms but also extends the observations made by White, Edward and Ackerman (2). The frequency and severity of calcification also appears to be related similarly to the distance (fig. 5). It is worthwhile to note that the calcification in cerebral arteries is much less frequent and less severe than that of coronary arteries.

$$\text{* Pressure Drop} = f \cdot \frac{l}{d} \cdot \frac{V^2}{2g} \cdot \frac{P_1}{P_2}$$

Where f= friction factor

l= length of the artery

d= diameter of the artery

V= velocity of blood flow

g= gravity acceleration

P_1 = specific gravity of blood

P_2 = specific gravity of Hg.

Examination upon dissection of the arteries very frequently shows plaques to be scattered all the way along an arterial branch. An artery of considerable length uniformly and concentrically coated with lipid material without localized regions of atherosclerosis is quite rare. On the contrary, plaques are in majority of cases deposited eccentrically. Unfortunately our measurements in this study did not differentiate between concentric or eccentric deposits. Nonetheless, attention can be directed to certain strategic spots as in section 2 (fig. 1a) of the anterior descending branch of the left coronary artery which is particularly prone to deposition. This section shows the highest deposition among all the branches measured in spite of an average smaller radius than section 1. The eccentric deposition and the geometrical distribution of the plaque cannot be explained readily by the pressure gradient alone. It seems more likely that other hemodynamic factors play a major role in such arterial plaque formation. The influence of turbulent flow and shear stress on the arterial wall with respect to plaque formation will be discussed elsewhere (12).

Summary

1. A quantitative method for grading atherosclerosis in arteries was described.
2. The radius of the artery and its atherosclerosis of 4331 sections of coronary and cerebral arterial sections were quantitatively measured by this method.
3. The degree of atherosclerosis was found to be highly correlated with the radius of the artery. The arteries with larger radii showed significantly greater sclerosis.
4. The severity of sclerosis was also correlated with the distance of sections from the origin of any branch of the artery.
5. The distribution and properties of an atherosclerosis gradient and an intravascular pressure gradient were discussed.

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Table 1

The Relationship Between Coronary Atherosclerosis and the Radius of the Coronary Arteries

No Sections	Range of Radius (mm)	Mean r in mm.	(I/E)c
48	2.6-3.0	2.672	58.2
152	2.1-2.5	2.206	58.5
212	1.6-2.0	1.737	55.0
228	1.0-1.5	1.253	43.8
118	0.5-1.0	0.798	28.1

(I/E)c = Coronary Atherosclerosis

I = intima material area

E = total arterial cross-section area

c = coronary

Table 2

The Arterial Size and Atherosclerosis

A. Anterior descending branch of left coronary artery

Number of Sections	Radius in mm.	Degree of Atherosclerosis
135	$2.097 \pm 0.350^*$	$59.8 \pm 11.8^*$
139	1.650 ± 0.370	54.8 ± 13.7
139	1.376 ± 0.344	48.5 ± 15.4
125	1.200 ± 0.307	42.7 ± 16.4
105	1.036 ± 0.318	32.9 ± 14.3

B. Left anterior branch

135	1.131 ± 0.392	38.9 ± 18.3
123	0.981 ± 0.319	34.7 ± 15.1
99	0.839 ± 0.279	28.0 ± 13.8

C. Left Circumflex Branch

139	1.864 ± 0.439	55.1 ± 13.4
134	1.636 ± 0.416	50.2 ± 13.5
123	1.380 ± 0.399	43.4 ± 16.1

D. Right Coronary Artery

143	2.066 ± 0.411	56.6 ± 10.5
144	1.883 ± 0.387	53.5 ± 11.6
128	1.763 ± 0.458	50.1 ± 13.8
101	1.607 ± 0.458	46.7 ± 14.5

*Standard deviation of distribution

Table 3

The Relationship Between Cerebral Atherosclerosis and Radius of Cerebral Arteries

No. Sections	Range of Radius (mm)	Mean Radius in mm.	$(I/E)_b$
37	2.1-2.5	2.246	58.5
151	1.6-2.0	1.700	49.0
518	1.1-1.5	1.214	32.0
354	0.6-1.0	0.867	19.8
2	0.2-0.5	0.47	18.0

$(I/E)_b$ = Brain Atherosclerosis

I = intimal material area

E = total arterial cross-section area

b = brain

Table 4

The Cerebral Arterial Size and Atherosclerosis

A. Posterior Cerebral Arteries

No.	Left Radius	Atherosclerosis	No.	Right Radius	Atherosclerosis
143	1.213 $\pm$ 0.273	33.4 $\pm$ 19.4*	139	1.22 $\pm$.303	34.5 $\pm$ 20.5*
135	1.053 $\pm$ 0.243	29.5 $\pm$ 19.5	135	1.046 $\pm$.285	31.0 $\pm$ 20.1
114	0.888 $\pm$ 0.260	26.5 $\pm$ 16.8	105	0.893 $\pm$.279	27.0 $\pm$ 16.7

B. Middle Cerebral Arteries

Internal carotid	138	1.767 $\pm$.403	39.2 $\pm$ 19.5	124	1.800 $\pm$.423	39.4 $\pm$ 18.3
	140	1.466 $\pm$.307	37.3 $\pm$ 20.6	140	1.451 $\pm$.294	37.1 $\pm$ 20.5
	137	1.178 $\pm$.260	31.8 $\pm$ 20.4	134	1.209 $\pm$.291	33.0 $\pm$ 19.8
	121	0.965 $\pm$.239	25.7 $\pm$ 16.5	119	1.000 $\pm$.248	26.9 $\pm$ 17.8

C. Anterior Cerebral Arteries

138	1.144 $\pm$.254	25.7 $\pm$ 15.4	140	1.170 $\pm$.261	27.3 $\pm$ 16.6
133	0.988 $\pm$.230	23.5 $\pm$ 15.0	137	1.090 $\pm$.238	24.0 $\pm$ 15.1
110	0.867 $\pm$.192	22.8 $\pm$ 13.6	108	0.867 $\pm$.204	23.3 $\pm$ 13.8

*Standard Deviation of Distribution

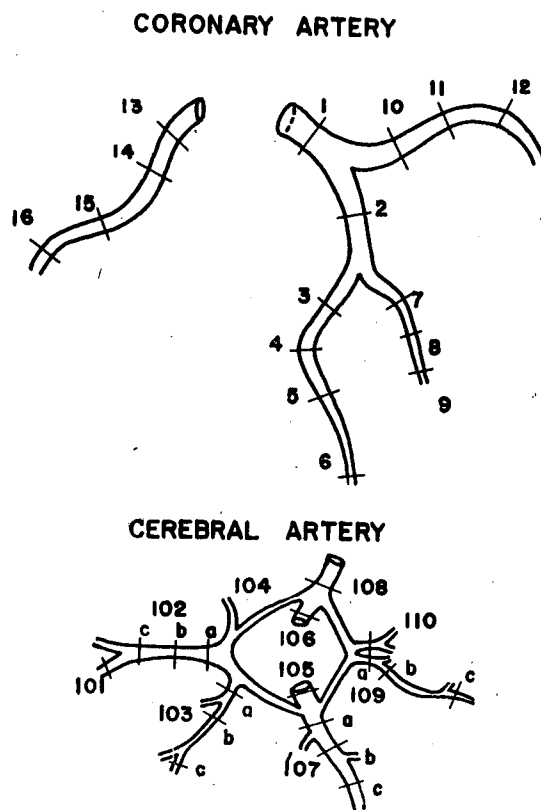


Fig. 1. Segments of the arteries analyzed for atherosclerosis.
a. Upper, sixteen segments of coronary arteries.
b. Lower, twenty-four segments of brain arteries.

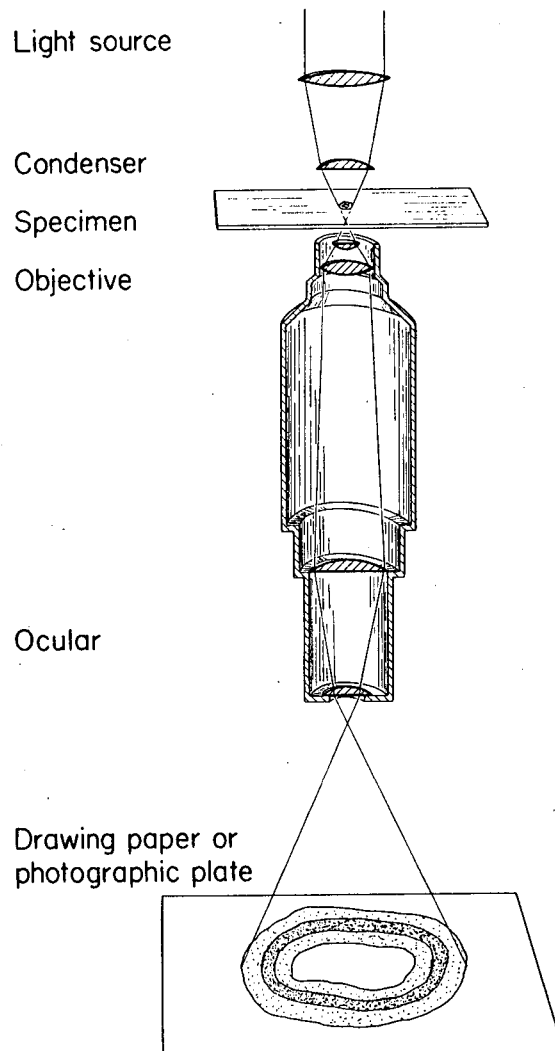


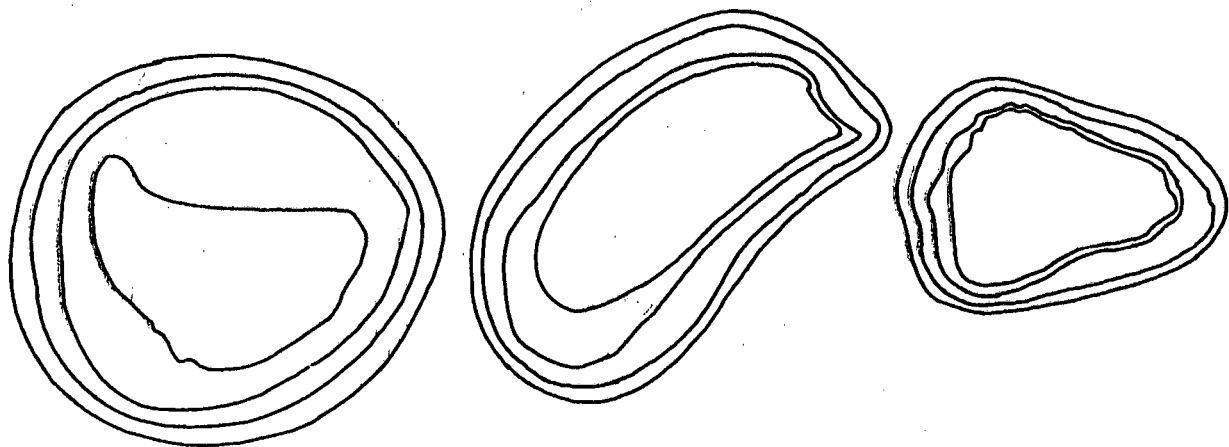
Fig. 2. Schematic representation of assembly for enlargement of histological arterial section.

Pathological No. 7356

Section No. 10

34

52



Atherosclerosis: 52.8

29.7

18.6

Calcification: 6.8

0

0

Fig. 3. Typical tracings and planimetric measurements.

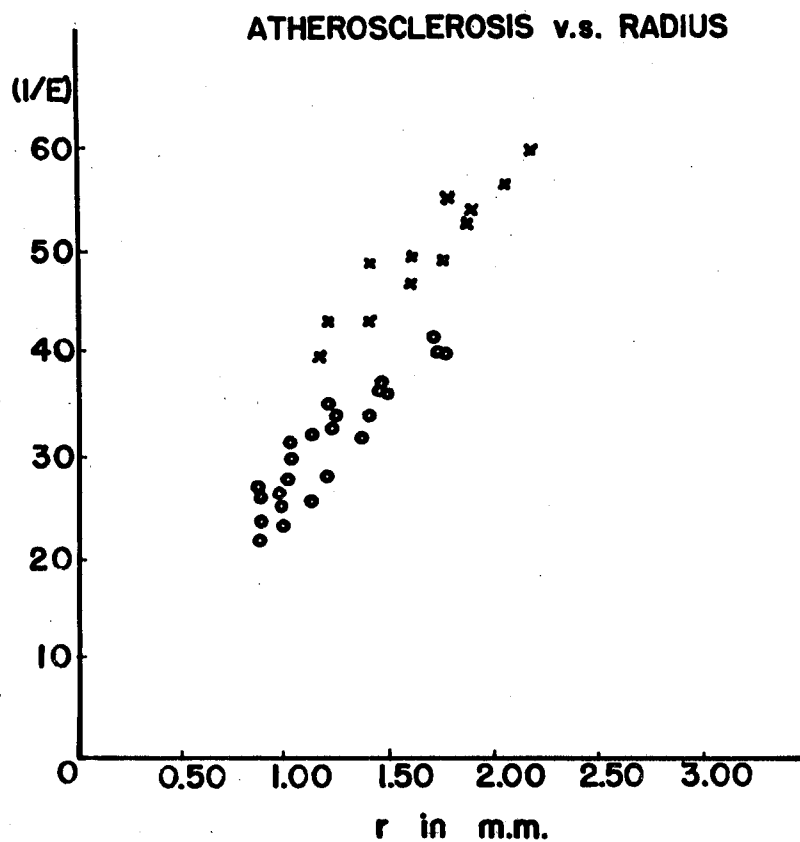


Fig. 4. Relationship between atherosclerosis and radius of the artery. x, coronary arteries. o, cerebral arteries. Each point represents an average of 100 sections.

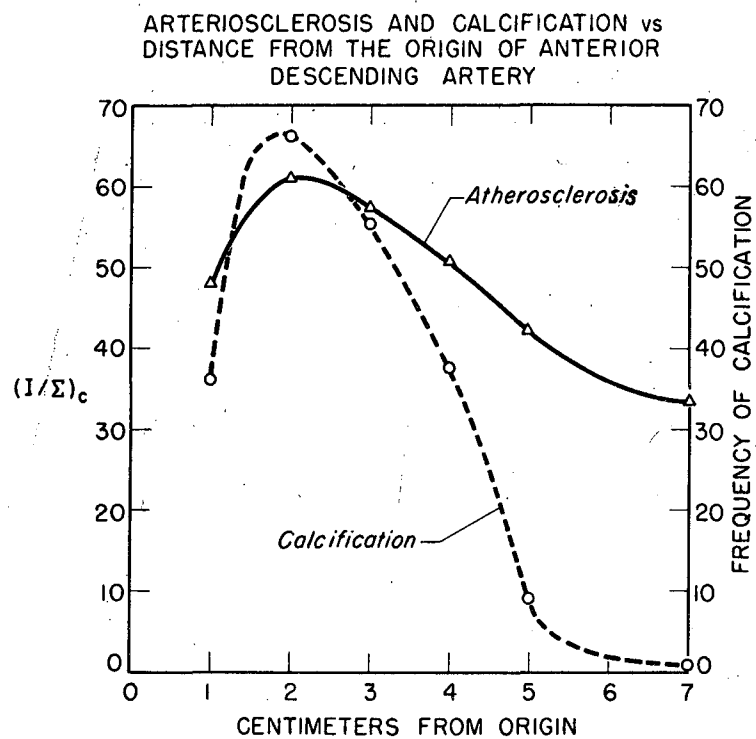


Fig. 5. Atherosclerosis and calcification v.s. distance from the origin of anterior descending branching of left coronary artery.

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