

Assessment of Atherosclerosis from Angiographic Images¹ (38000)

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Conventional clinical diagnosis of atherosclerosis now is determined principally by recognition of ischemia in target organs. Diagnostic techniques that are more direct are desired to evaluate the disease in earlier stages. Previously we reported a densitometer-computer technique for precise measurement of vessel shadow edge irregularity in peripheral vascular and coronary angiograms for assessment of atherosclerosis (1). We performed postmortem angiograms under conditions producing films of clinical quality and reported that a densitometer-computer-derived measure of edge irregularity correlated significantly with raised lesion prevalence determined by visual inspection.

We now use edge-irregularity measurement as a clinical tool; we have measured femoral edges in 40 hyperlipoproteinemic patients and have scheduled them for re-examination after 1 yr of treatment (2). The clinical status of these individuals currently does not indicate need for coronary angiography.

Clinical studies in man preclude direct comparison of any new atheroma assessment with visual estimates of vessel lesion prevalence. Animal studies allow comprehensive comparison, but do not adequately represent human anatomy and lesion characteristics. We have, therefore, performed additional human postmortem studies and

are reporting that densitometer-computer measurements of edge irregularity are significantly correlated with visual estimates of raised lesion prevalence in another major blood vessel. We also report a densitometer-computer index which correlates highly with local vessel wall and plaque cholesterol concentration.

Materials and Methods. Twenty-eight distal aortas with common iliac arteries attached were removed at autopsy and were injected with a radiopaque thorium in silicone rubber suspension which polymerized *in situ*. Injected segments were cut longitudinally to remove the radiopaque cast, fixed in 10% formalin, stained with Sudan IV, and graded by modification of the International Atherosclerosis Project method (3). Four examiners graded each specimen independently at four separate sessions and grades were averaged. Specimens ranged from 40% to 90% involvement in the area studied. An analysis of the variances associated with visual grading showed variances among graders and among aortas, both significant at the 0.001 level (Table I). The major component of variance was inconsistency among grading sessions within graders (residual).

Radiopaque casts were radiographed in positions corresponding to the anteroposterior and lateral planes, using a Faxitron 805 X-ray Unit.² Exposures were all made at 42 kV; the other exposure factors depended on the thickness of the specimens. Films were made on Kodak type-M indus-

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² Field Emission Corp., McMinnville, OR.

TABLE I. Analysis of Variance of Visual Grading of Raised Aortic Atheromas.

Source of variance	Sum of squares	Degrees of freedom	Mean squares	F value	Component of variance
Graders	16,235	3	5,412	13.63 ^a	40
Aortas	22,511	28	804	2.02 ^a	25
Interaction	12,663	84	151	0.38	61
Subtotal	51,409	115			
Residual	138,199	348	397		397
Total	189,608	463			

^a $P < 0.001$.

trial film and processed in an X-omat³ at 75°C for 7 min.

The 5-cm segment of aortic shadow proximal to its bifurcation was scanned with an image dissector densitometer⁴ at 25- μ m intervals. The density profile of each scan line was examined for maximum rate of change to locate vessel edges. Irregularity of each vessel edge was estimated individually by determining the difference between 10 and 400 point smoothing of each edge. In coronary artery the coefficient of variation of this measurement is 1.1% (1). Serial estimates of integrated density along the vessel were determined by calculating a line by line average of densities observed within the boundaries and removing background density. All of these methods, except estimation of integrated density, have been described in detail previously (1).

The cholesterol concentration in milligrams per gram was determined for each segment after bringing it to constant weight over Drierite. Specimens were immersed in 6% ethanolic KOH at 37°C until dissolved, then equilibrated twice against an equal volume of redistilled petroleum ether. Petroleum ether was reduced to a 10-ml volume and then 0.5- or 1.0-ml aliquots were dried and reacted with Liebermann Burchard reagent by the method of Abell and co-workers (4).

Results. The correlation matrix for pairs of variables in this experiment is shown in Table II. Grade 1 lesions are fatty streaks;

Grade 2 lesions are raised atheromas not complicated by ulceration, calcification, or hemorrhage; Grade 3 lesions are lesions complicated by ulceration, calcification, or hemorrhage.

Grade 2 lesions are significantly correlated with densitometer-computer-derived edge irregularity measurements ($P < 0.01$) and aortic wall cholesterol concentration ($P < 0.001$). In our previous experiment, Grade 2 lesions were found significantly correlated with angiographic edge irregularity ($P < 0.005$) in the proximal right coronary artery. We now propose that visual estimates of raised lesions and angiographic edge irregularity measurement are, in fact, alternate methods of examining the same phenomenon.

Discussion. The importance of estimating Grade 2 lesion prevalence is clearly indicated by the International Atherosclerosis Project (5). Coronary heart disease (recent myocardial infarction, healed myocardial infarction, or sudden death with coronary occlusion) or its absence was determined in 6108 autopsied men at age 35-64 from six population groups. Variables considered in discrimination of coronary heart disease from noncoronary heart disease were: (1) age, (2) height, (3) trunk length, (4) body weight, (5) heart weight, (6) abdominal wall thickness, (7) percentages of coronary surface covered by any atheroma, (8) by raised lesions, (9) by complicated lesions, (10) by calcified lesions, and (11) number of points of lumen narrowing greater than 50%. Percentage of coronary surface covered by raised lesions was the most important

³ Eastman Kodak.

⁴ Dicomed D-57 Image Dissector Densitometer.

TABLE II. The Same Segment of Each Aorta Was Graded Visually, Evaluated for Densitometer-Computer, and Assayed for Cholesterol Concentration. Visual Grades are Expressed as Percentage of Aortic Surface Covered by Lesions of the Designated Type.

	Visual grading of atherosclerosis (%)				Cholesterol concentration (mg/g)	Edge irregularity	Variation in cross-sectional density
	1	2	3	2 + 3			
Visual grading of atherosclerosis (%)							
1	1.00						
2	-0.03	1.00					
3	-0.54 ^a	-0.01	1.00				
2 + 3	-0.49 ^a	0.50 ^a	0.87 ^b	1.00			
Cholesterol (mg/g)	-0.01	0.64 ^b	0.08	0.39 ^c	1.00		
Edge irregularity	-0.25	0.53 ^a	-0.07	0.21	0.69 ^b	1.00	
Variation in cross-sectional density	-0.03	0.46	0.10	0.31	0.69 ^b	0.44 ^c	1.00

^a $P < 0.01$.

^b $P < 0.001$.

^c $P < 0.05$.

single variable separating coronary heart disease patients from noncoronary heart disease patients in five of the six groups.

Cholesterol concentration is significantly correlated with raised lesion prevalence (Table II). Reduction of cholesterol content is a logical intermediate goal for atherosclerosis therapy designed to cause lesion regression. Cholesterol concentration of aortic wall was found significantly correlated with two densitometer-computer derived measurements; edge irregularity and variation in cross-sectional density (Table II). It was important to find to what extent the angiographic information from an aortic segment could be combined into a more reliable estimate of cholesterol concentration. By regression techniques, an angiographic index (AI) was constructed by a linear combination of the edge irregularity measures of right and left edges (RED and LED) and the cross-sectional density variability (CSD): $AI = 7.72 + 0.58 \text{ RED} + 0.123 \text{ LED} + 5.45 \text{ CSD}$. The correlation coefficient of this index with cholesterol concentration was 0.83 ($P < 0.0001$).

Summary. Raised aortic atheromas can be quantitated by densitometer-computer analysis of edge irregularity on angiographic shadows. Combined measurement of edge irregularity and variation in cross-sectional density provides an angiographic index indicative of local cholesterol concentration in aorta walls and atheromas.

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