

Degrees of Cross-Sectional-Area Luminal Narrowing of the Four Major Epicardial Coronary Arteries in Patients With Otherwise Functionally and Anatomically Normal Hearts



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Described herein are necropsy findings in the 4 major (left main, left anterior descending, left circumflex, and right) epicardial coronary arteries in 86 patients aged 10-70 years who never had symptoms of myocardial ischemia, and at autopsy had otherwise anatomically normal hearts. All 86 died of a non-cardiovascular condition. In each of these patients all 4 major epicardial coronary arteries were excised intact from the heart, divided into 5-mm segments, and each segment prepared for histologic examination. The degrees of *cross-sectional area (CSA) narrowing* were determined from histologic examination of each 5-mm segment. The degree of narrowing in each 5 mm segment was divided into 4 categories: 0% to 25%, 26% to 50%, 51% to 75%, and 76% to 100%. Twelve patients (14%) had ≥ 1 artery narrowed $>75\%$ in CSA, a single artery in 9 patients, and 2 arteries in each of 3 patients. In contrast to the relative infrequency of narrowing $>75\%$, narrowing 51-75% was common, and was present in 36 (42%) of the 86 patients. Of the 258 major coronary arteries (excludes the left main) studied in the 86 patients, 15 (6%) were narrowed $>75\%$, and 70 (24%) were narrowed 51% to 75% in CSA. Even mild narrowing (26% to 50%) of the left main coronary artery (66 patients) was generally accompanied by 51% to 75% or greater narrowing of at least one of the other major coronary arteries. In conclusion, even hearts which have functioned normally and are otherwise anatomically normal, usually have some degree of atherosclerotic plaque in the major epicardial coronary arteries. © 2021 Elsevier Inc. All rights reserved. (Am J Cardiol 2021;147:39–43)

Although there is considerable information on the status of the epicardial coronary arteries in patients with fatal myocardial ischemia, there is much less morphologic information about the status of the major epicardial coronary arteries in persons without symptoms of myocardial ischemia. Earlier studies of the prevalence of coronary disease in the general population have not focused exclusively on asymptomatic persons with otherwise morphologically and functionally normal hearts. Such is the purpose of this report.

Method

The 86 asymptomatic (from a cardiac standpoint) patients, aged 10 to 70 years, 43 male and 45 female, were studied in the Pathology Branch of the National Heart, Lung, and Blood Institute of the National Institutes of Health in the years 1975 and 1976. Of the 86 patients, 77 (90%) had died from neoplastic diseases (carcinoma 37, lymphoma 19, leukemia 15, sarcoma 6) and 9, from non-neoplastic diseases (systemic lupus erythematosus 2, and

one each from 7 different conditions). Among the 86 patients, 10 (12%) had had systemic hypertension; 6 (7%), diabetes mellitus; 25 (29%) had received corticosteroids for >1 month, and 15 (17%) had received therapeutic irradiation to the mediastinum, possibly also to the heart (Table 1). None had ever reported symptoms or had signs compatible with heart disease. In each the electrocardiogram was either normal, or if abnormal only because of nonspecific ST-T abnormalities. The serum total cholesterol values (71 patients) ranged from 66 to 400 mg/dl (mean 169): in 17 patients (24%) the level was >200 mg/dl, and in 26 (37%) the level was ≤ 150 mg/dl. In each patient, the heart weighed ≤ 400 g, the left and right ventricular wall thicknesses and cavity sizes were normal, and each was free of foci of myocardial fibrous and necrosis (Table 2). The mean heart weights in the patients >20 years of age were as follows: 240g in the group aged 10 to 30 (13 patients were >20 years of age); 272 g in those aged 31 to 50, and 303 g for the group aged 51 to 70 years. In the patients >20 years of age, the body weight ranged from 26 to 123 Kg (mean 61) (57 to 218 lbs [mean 134]).

The major epicardial coronary arteries were dissected intact from the heart, and each was placed in a separate container and fixed in 10% buffered formalin. After fixation, each artery was decalcified (if needed) and cut transversely at 5-mm intervals. The 5-mm segments were placed in individual plastic containers. The tissues were then dehydrated (alcohols), cleared (xylene), imbedded in paraffin, and cut

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Table 1
Clinical features (n = 86)

Variable	Age group (Years)			Totals (n = 86)
	10 – 30 (n = 22)	31 – 50 (n = 27)	51 – 70 (n = 37)	
Males	15 (71%)	11 (41%)	16 (42%)	42 (49%)
Females	7 (29%)	16 (59%)	21 (58%)	44 (51%)
Systemic Hypertension	1 (4%)	2 (7%)	7 (18%)	10 (12%)
Diabetes Mellitus	0	1 (4%)	5 (14%)	6 (7%)
Corticosteroids Rx >1 month	9 (40%)	9 (33%)	12 (32%)	25 (29%)
Mediastinal Irradiation	3 (13%)	8 (30%)	4 (11%)	15 (17%)
Total cholesterol (mg/dL)	84-226 (m 136)	106 – 248 (m 168)	66 – 400 (m 179)	66 – 400 (m 169)
Body weight (Kg)	29 – 83 (m 52)	44 – 99 (m 64)	26 – 96 (m 64)	26 – 99 (m 61)

into 6-um thick sections. Two histologic sections, one stained with hematoxylin and eosin, and the other by the Movat method, were prepared from each 5-mm section. In each of the 86 patients, the left anterior descending, right, and left circumflex coronary arteries were so prepared. In addition, in 66 of the 86 patients the left main coronary was of sufficient length to prepare a good right angle section, and it also was so prepared. Each histologic section was examined microscopically and the degree of cross-sectional area (CSA) luminal narrowing scored as 0 to 25%, 26% to 50%, 51% to 75%, and 76% to 100%. The most narrowed 5-mm section in each of the major coronary arteries was the one reported in this study. In addition to determining the degree of CSA luminal narrowing, the various components of the luminal plaques were determined, and the presence or absence of intramural hemorrhage and luminal thrombus was recorded. A total of 3501 histologic sections representing 1,750 cm of coronary artery were examined.

Results

The maximal degree of CSA luminal narrowing of any of the 3 major epicardial coronary arteries (left anterior descending, left circumflex, and right) is shown in Table 3. Of the 22 patients aged 10 to 30 years, 2 (9%) (single artery in both) had a coronary artery narrowed >75%; of the 27 patients aged 31 to 50 years, 3 (11%) had a coronary artery narrowed >75%, and among the 37 patients aged 51 to 70 years, 7 (19%) had at least one artery narrowed >75%. A total of 258 coronary arteries (3 per patient) were examined in the 86 patients, and 12 (14%) had a major coronary artery narrowed >75%: a single artery in 9 patients, and 2 arteries in each of 3 patients (Table 4). Of the latter 3

Table 2
Heart weight (n = 86)

Heart Weight (g)	Age group (Years)		
	10 - 30 (n=22)*	31 – 50 (n=27)	51 – 70 (n -37)
Males	180 – 400 (263)	210 – 380 (287)	280 – 400 (340)
Females	180 – 260 (217)	150 – 350 (263)	130 – 370 (275)
Totals	180 – 400 (247)*	150 – 380 (272)	130 – 400 (303)

* Of the 22 patients, 13 were >20 years (10 male and 3 female). Their heart weights ranged from 210 – 400g, (average 296 g).

patients, 2 were men aged 65 and 66 years, respectively, and the third was a woman aged 68 years. In contrast to the relative infrequency of CSA narrowing >75%, 51% to 75% CSA narrowing was common, and was present in 36 ([42%] of the 86 patients), and was often present in >1 coronary artery. Of the 258 major coronary arteries 70 (24%) were 51% to 75% narrowed. The left anterior descending coronary artery was the one most often narrowed >75% (9 patients), and the right was the next most commonly narrowed to this degree (6 patients). In none of the patients was the left circumflex coronary artery narrowed >75% (Table 5).

In 66 of the 86 patients the left main coronary artery was of sufficient length to prepare a perfect right angle cross section. Of the patients 10 to 30 years of age, 2 (11%) had 26% to 50% narrowing of the left main coronary. Among the patients aged 31 - 50, seven (37%) had at least 26% to 50% narrowing, and among those aged 51 to 70 years, 14 (38%) had at least 26% to 50% narrowing of the left main, 3 (10%) of whom had 51% to 75%, and one (3%) of whom

Table 3
Maximal degree of Cross-Sectional Area (CSA) luminal narrowing (Excludes the left main)

Maximal CSA narrowing	Age group (Years)			Totals
	10 – 30	31 – 50	51 – 70	
0 – 25%	11 (50%)	8 (30%)	4 (11%)	23 (27%)
26 – 50%	5 (23%)	5 (19%)	5 (14%)	14 (16%)
51 – 75%	4 (18%)*	11(41%) [†]	21(57%) [‡]	37 (43%)
76 – 100%	2 (9%) [§]	3 (11%) [¶]	7 (19%) ^{**}	12 (14%)
TOTALS	22 (100%)	27 (100%)	37 (100%)	86 (100%)

* One coronary artery in 3 patients and 2 coronary arteries in 1 patient

[†] One coronary artery in 6 patients, 2 coronary arteries in 3 patients, all 3 coronary arteries in 2 patients

[‡] One coronary artery in 5 patients, 2 coronary arteries in 6 patients, all 3 coronary arteries in 10 patients

[§] One coronary artery in 2 patients

[¶] One other coronary artery 51 - 75% in 2 patients, 2 other coronary arteries 51 - 75% in 1 patient

^{**} Three patients with 2 coronary arteries > 75%, 1 of whom had 51 - 75% of the third coronary artery, and 2 patients who had < 50% of the third coronary artery

Four patients with 1 coronary artery >75%, 1 of whom had 51 - 75% of the other 2 coronary arteries, 2 patients with 51 - 75% of 1 coronary artery and < 50% narrowing of the third coronary artery, 1 patient with <50% narrowing of the other 2 coronary arteries

Table 4

Ages and maximal degree of cross-sectional area coronary narrowing (n=86)

Number of coronary arteries maximally narrowed	Age group (Years)			Totals
	10 – 30 (n=22)	31 – 50 (n=27)	51 – 70 (n=37)	
Categories of Narrowing	Patients			
26 – 50%				
0	11 (50%)	8 (30%)	4 (11%)	23 (27%)
1	4 (18%)	4 (15%)	3 (8%)	11 (13%)
2	1 (5%)	0	1 (3%)	2 (2%)
3	0	1 (4%)	1 (3%)	2 (2%)
			333	
51 – 75%				
1	3 (14%)	6 (22%)	5 (14%)	14 (16%)
2	1 (5%)	3 (11%)	6 (16%)	10 (12%)
3	0	2 (7%)	10 (27%)	12 (14%)
≥75%				
1	2 (9%)	3 (11%)	4 (11%)	9 (10%)
2	0	0	3 (8%)	3 (3%)
3	0	0	0	0

had >75% narrowing of the left main coronary artery. Thus, of the 19 patients 31 to 50 years old more than a third had >25% left main narrowing, and almost half of the 29 patients aged 51 to 70 years also had at least >25% luminal narrowing of the left main (Table 6). The degrees of narrowing of the other 3 major coronary arteries in the 23 patients who had >25% narrowing of the left main are shown in Table 7. Among patients with the left main narrowed (26% to 50%), 3 quarters had 51% to 75% or >75% narrowing of the left anterior descending, and over 80% had 51% to 75% or >75% narrowing of the right coronary artery. More than half of them also had >50% narrowing of the left circumflex.

Both eccentric and concentric coronary artery atherosclerotic plaques were frequent in all 3 age groups (Table 8).

Fibrous tissue was frequently present in the coronary plaques, including those aged 10 to 30 years old, and universally present in the 2 older age groups. Foam cells, cholesterol clefts, pultaceous debris, and calcium deposits were common even in the youngest age group, usually present in the 31 to 50 years age group, and virtually always present in the 51 to 70 year old patients (Table 9).

Table 5

Age group and maximal degree of Cross-Sectional Area (CSA) luminal narrowing of the 3 major epicardial coronary arteries (n=86 patients)

Coronary artery	Maximal degree of cross-sectional luminal narrowing	Age (Years)			
		10-30 (n=22)	31-50 (n=27)	51-70 (n=37)	Total (n=86)
Left anterior descending	51 - 75%	3 (14%)	7 (26%)	19 (51%)	29(34%)
	76 - 100%	2 (9%)	2 (7%)	5 (14%)	9 (10%)
Right	51 - 75%	2 (9%)	8 (30%)	18 (49%)	28 (33%)
	76 - 100%	0	1 (4%)	5 (14%)	6 (7%)
Left circumflex	51 – 75%	0	3 (11%)	10 (27%)	13 (15%)
	76 - 100%	0	0	0	0

Of 258 major epicardial coronary arteries, 15 (5%) were narrowed >75% in cross-sectional area and an additional 70 (27%) were narrowed 51% to 75%.

Table 6

Frequency and severity of left main coronary artery narrowing

Degrees of narrowing	10 – 30 (n=18)	31 – 50 (n=19)	51 – 70 (n=29)	Total
26 – 50%	2 (11%)	5 (26%)	10 (34%)	17 (26%)
51 – 75%	0	2 (11%)	3 (10%)	5 (8%)
>75%	0	0	1* (3%)	1 (2%)

* A 65-year-old woman with diabetes mellitus and systematic hypertension. The LAD, right, and left circumflex were all 51 – 75% narrowed.

Table 7

Degree of narrowing of the major epicardial coronary arteries in patients with left main narrowing >25% (23 pts)

Coronary artery	Degree of left main narrowing		
	26 – 50% (n=17)	51 – 75% (n=5)	>75% (n=1)
Left Anterior Descending	< 25%	1 (6%)	0
	26 – 50%	3 (18%)	1 (20%)
	51 – 75%	10 (59%)	2 (40%)
Right	> 75%	3 (18%)	2 (40%)
	< 25%	1 (6%)	3 (60%)
	26 – 50%	2 (12%)	1 (20%)
Left Circumflex	51 – 75%	11 (65%)	1 (20%)
	> 75%	3 (18%)	0
	< 25%	3 (18%)	2 (40%)
	26 – 50%	5 (29%)	1 (20%)
	51 – 75%	9 (53%)	2 (40%)
	> 75%	0	0

Table 8

Coronary artery plaque morphology

Age (Years)	Eccentric	Concentric	Both
10 – 30	11	9	5
31 – 50	26	19	17
51 – 70	38	31	28

Discussion

This study is unique in several ways. First, the clinical histories of all the patients were available and were reviewed in detail. All 86 patients studied had died of non-cardiovascular causes, mainly cancer. Their hearts were of normal size, neither ventricle was dilated, and the wall

Table 9
Components of coronary arterial plaques

Variable	Age (years)		
	10 – 30 (n=22)	31 – 50 (n=27)	51 – 70 (n=37)
Fibrous tissue	14 (64%)	27 (100%)	37 (100%)
Foam cells	7 (32%)	23 (85%)	36 (97%)
Cholesterol clefts	4 (18%)	15 (56%)	30 (81%)
Calcium	4 (18%)	11 (41%)	28 (76%)
Pultaceous debris	4 (18%)	14 (52%)	30 (81%)
Acid mucopolysaccharide	14 (64%)	26 (96%)	37 (100%)
Intraplaque hemorrhage	0	2 (7%)	8 (23%)
Luminal Thrombus	0	1	1 (3%)

thicknesses of both ventricles were normal. There were no areas of myocardial necrosis or fibrosis. The epicardial coronary arteries in each patient were removed intact, and all histologic sections were stained with both Movat and hematoxylin and eosin.

A major finding in this study was the relative infrequency (14%) of severe (>75% CSA) coronary narrowing. Of the 86 patients, 12 (14%) had at least one major coronary artery narrowed >75%. Of the 258 major coronary arteries in the 86 patients (3 per patient), excludes the left main, 15 (6%) were narrowed to this degree. (A 50% diameter narrowing - the unit of angiography - is considered roughly equivalent to a 75% CSA narrowing, the unit used in this study, and in intracoronary echocardiography.) In contrast to the relative infrequency of >75% CSA narrowing, 51% to 75% narrowing was frequent, an occurrence in 36 (42%) of the 86 subjects and in 70 (24%) of the 258 coronary arteries.

Another finding in this study was the relatively high frequency of >25% CSA narrowing of the left main coronary artery. In contrast to previous studies, a 90-degree section was made of the artery after the artery was removed from the heart, something rarely possible if the coronary arteries are cut before they are removed from the heart. Even mild left main narrowing was frequently accompanied by more severe narrowing of the other 3 major epicardial coronary arteries.

Similar to findings in other histologic studies of coronary artery plaque, lipid was virtually universally present in the plaques causing coronary narrowing >50%, and in patients >30 years of age. In older patients with more extensive atherosclerotic disease, plaque hemorrhage was present in about 20%; intraluminal coronary thrombus, non-obstructing, was present in 2 patients (2%).

All 86 patients had hearts weighing ≤400g. The mean weights increased with each age group.

The mean weights were approximately 20% heavier in the men than the women. (The heart weights today are heavier than those of 45 years ago because of the obesity epidemic which has led to an increase in cardiac adipose tissue.¹)

The serum total cholesterol levels – all before the statin drugs were introduced – averaged 169 mg/dL. These levels increased with each advancing age group.

Although 39 patients in this study had received corticosteroid therapy and/or irradiation (for cancer), only 7 (18%) of them had a major coronary artery narrowed >75% in CSA, numbers similar to that in the group who had not received these therapies (Table 10).

Table 10
Frequency of coronary arterial narrowing in patients treated with steroids, mediastinal irradiation or both

Age (Years)	No steroids/No RAD's			Steroids/No RADs			RADs/No steroids			Steroids/RAD's		
	No. Pts	No. CAs	>76 – 100%	No. Pts	No. CAs	>76 – 100%	No. Pts	No. CAs	>76 – 100%	No. Pts	No. CAs	>76 – 100%
10 - 30	11	33	4 (8%)	8	24	1 (8%)	2	6	1 (17%)	1	3	0
31 - 50	13	39	7 (18%)	4	12	6 (33%)	5	15	3 (20%)	5	15	5 (56%)
51 - 70	23	69	32 (46%)	9	27	16 (59%)	2	6	1 (17%)	3	9	3 (33%)
TOTALS	47	141	43 (27%)	21	63	23 (40%)	9	27	5 (19%)	9	27	7 (39%)

Abbreviations: CAs = coronary arteries; Pts = Patients; RADs = radiation

The present study is not, of course, the first to describe the degrees of coronary atherosclerosis in patients without clinical evidence of coronary disease. Differing methods of examining the arteries, and the inclusion of patients with clinical evidence of coronary disease makes the comparison with earlier studies difficult. Some, for example, simply tried to learn how often coronary atherosclerotic plaque was seen at autopsy in consecutive series of cases.²⁻⁴ The coronary arteries in these earlier studies were likely opened longitudinally, with no attempt made to determine the degrees of luminal narrowing. Two studies from the Mayo Clinic^{5,6} appear to be the first to examine the epicardial coronary arteries grossly by cross-sectional cuts with the coronary arteries still attached to the heart. Each study included 600 autopsy cases. The lead author provided the data in each study as part of his thesis. In addition, each of these studies included patients with and without known clinical evidence of coronary disease. No histologic sections of the coronary arteries were described.

Joseph and associates⁷ described the status of the major epicardial coronary arteries in 111 patients aged 14 to 35 (mean 26) years coming to autopsy at a single hospital in Louisville. The arteries while still attached to the heart were cross-sectioned at 3-mm intervals, and “representative [sections] of the most involved area” were submitted for histologic slide preparation. The prepared slides were stained by both hematoxylin and eosin, and elastic Van Gieson stain. The authors graded the degree of narrowing of the sections as 0% to 25%, 25% to 50%, 50% to 75% and 75% to 100%. Of the 111 patients, 24 (23%) had no coronary atherosclerosis; 64 patients (58%) had narrowing up to 50%, and 23 (21%) had CSA narrowing >50%.

Often quoted necropsy studies are those of soldiers killed in wars. French and Dock⁸ described autopsy findings in 80 male soldiers aged 20 to 36 years killed in World War II. All had either clinical or necropsy evidence of coronary heart disease. Cases without clear evidence of coronary heart disease were not included. Enos and colleagues⁹ described necropsy finding in 200 male soldiers aged 18 to 48 years killed in the Korean War. In 155 cases (77%) some gross evidence of coronary atherosclerosis was found, including 22 cases in whom there was luminal narrowing between 70% and 100%. It is likely that these epicardial coronary arteries were opened longitudinally by a number of different prosectors. In 1987, thirty-four years later, Virmani et al¹⁰ examined previously uncut coronary arteries from the hearts of 94 American male combat casualties (mean age 20 years) from the Korean War. They prepared cross-sections of the first 1.5 cm of the left anterior descending and “all areas of grossly discernible luminal narrowing and/or segments of [other] coronary arteries

suspicious of atherosclerotic plaque formation ...” Six (6%) of the soldiers had 75% to 90% CSA luminal narrowing. (Thus, this study has similarities to the present study.) McNamara and associates¹¹ studied the hearts of 105 U.S. male soldiers killed in Vietnam: 47 (45%) had some evidence of atherosclerosis, 5 (5%) had gross evidence of severe coronary disease. Webber and colleagues¹² examined *autopsy reports* in 3832 service members who died of combat or unintentional injuries in Iraq from 2001-2011. They ranged in age from 18 to 59 years (mean 26), and 98% were men. The prevalence of any coronary atherosclerosis was 8.5%, severe in 2.3%, moderate in 4.7% and minimal in 1.5%. The degree of luminal narrowing was classified as minimal (fatty streaking only), moderate (10% to 49% luminal narrowing), and severe ($\geq 50\%$ narrowing). Multiple different prosectors performed the necropsies.

No Author Credit statement

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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