JACC Vol. 8, No. 3
September 1986:545–57

MORPHOLOGIC STUDIES

Intramural ("Small Vessel") Coronary Artery Disease in Hypertrophic Cardiomyopathy

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Many patients with hypertrophic cardiomyopathy have signs and symptoms of myocardial ischemia and dysfunction. Although hypertrophy and increased left ventricular pressure can account for such abnormalities, altered small intramural coronary arteries have also been described in such patients. To determine the prevalence and extent as well as the clinical relevance of abnormal intramural coronary arteries, a histologic analysis of left ventricular myocardium obtained at necropsy was performed in 48 patients with hypertrophic cardiomyopathy (but without atherosclerosis of the extramural coronary arteries) and in 68 control patients with either a normal heart or acquired heart disease.

In hypertrophic cardiomyopathy, abnormal intramural coronary arteries were characterized by thickening of the vessel wall and a decrease in luminal size. The wall thickening was due to proliferation of medial or intimal components, or both, particularly smooth muscle cells and collagen. Of the 48 patients with hypertrophic cardiomyopathy, 40 (83%) had abnormalities of intramural coronary arteries located in the ventricular septum (33 patients), anterior left ventricular free wall (20 patients) or posterior free wall (9 patients); an average of 3.0 ± 0.7 abnormal arteries were identified per tissue section. Altered intramural coronary arteries were also significantly more common in tissue sections having considerable myocardial fibrosis (31 [74%] of 42) than in those with no or mild fibrosis (31 [30%] of 102; $p < 0.001$). Abnormal intramural coronary arteries were also identified in three of eight infants who died of hypertrophic cardiomyopathy before 1 year of age.

In contrast, only rare altered intramural coronary arteries were identified in 6 (9%) of the 68 control patients (0.1 ± 0.05 abnormal arteries per section; $p < 0.001$) and those arteries showed only mild thickening of the wall and minimal luminal narrowing. Moreover, of those patients with abnormal intramural coronary arteries, such vessels were about 20 times more frequent in patients with hypertrophic cardiomyopathy (0.9 ± 0.2/cm^2 myocardium) than in control patients (0.04 ± 0.02/cm^2 myocardium).

Hence, abnormal intramural coronary arteries with markedly thickened walls and narrowed lumens are present in increased numbers in most patients with hypertrophic cardiomyopathy studied at necropsy and may represent a congenital component of the underlying cardiomyopathic process. Although the clinical significance of "small vessel coronary artery disease" in hypertrophic cardiomyopathy is unclear, the occurrence of structurally altered intramural coronary arteries in areas of substantial myocardial fibrosis suggests a causal role for these arteries in producing ischemia.

(J Am Coll Cardiol 1986;8:545–57)

Hypertrophic cardiomyopathy is a cardiac disease with a variety of clinical and morphologic features (1–11). Many patients with hypertrophic cardiomyopathy manifest evidence of myocardial ischemia or damage, including angina pectoris or atypical chest pain (4,6,12), certain electrocardiographic abnormalities (13–16), myocardial fibrosis (10,17) and abnormalities in coronary blood flow and lactate production during stress (18,19). In this investigation, we considered the possibility that structural alterations in the intramural coronary arteries (20–22) could contribute to myocardial ischemia in patients with hypertrophic cardiomyopathy. We examined histologic sections of ventricular myocardium from 48 patients with hypertrophic cardiomyopathy and from 68 patients with acquired cardiac disease or a normal heart to determine the prevalence and severity of abnormal intramural coronary arteries and their relation to areas of fibrosis.

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Manuscript received November 22, 1985; revised manuscript received February 24, 1986, accepted April 24, 1986.

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0735-1097/86/$3.50

JACC Vol. 8, No. 3
September 1986:545–57

Methods

Selection of patients. The cardiovascular registry of the Pathology Branch of the National Heart, Lung, and Blood Institute was reviewed and 154 hearts of children and adults with hypertrophic cardiomyopathy were identified and considered for inclusion in the study. Of this number, 106 were excluded for one or more of the following reasons: 1) there was associated cardiac disease such as systemic hypertension, aortic valve stenosis, mitral valve prolapse or coronary heart disease (>50% narrowing of the cross-sectional lumen of one or more extramural [epicardial] coronary arteries) (37 patients) or systemic disease including insulin-dependent diabetes mellitus (7 patients); 2) the patient had had a previous operation (ventricular septal myotomy-myectomy) and had survived more than 1 month postoperatively (19 patients); 3) the specimen was in poor condition and tissue suitable for histologic analysis could not be obtained from the standard three sites in the septum and left ventricular free wall described below (18 patients); or 4) the heart was considered to be a particularly good example of hypertrophic cardiomyopathy that we wished to preserve intact (25 patients). The remaining 48 patients constitute the study group. Each patient met our definition of hypertrophic cardiomyopathy by virtue of having a hypertrophied, nondilated left ventricle in the absence of another cardiac or systemic disease that could produce left ventricular hypertrophy (23). In addition to these 48 patients, 8 infants who died of hypertrophic cardiomyopathy (24,25) (7 live-born and 1 stillborn) were examined separately as part of this investigation.

Control patients. In addition, 68 patients without hypertrophic cardiomyopathy were selected as controls, including 14 without evidence of cardiac disease and 54 with a variety of relatively common acquired cardiac diseases characterized by an increase in left ventricular mass (Table 1). Because our control group was defined in this fashion, it did not include several congenital cardiac or systemic diseases in which intramural coronary artery abnormalities had already been described (21,26,27). Each of the 54 patients with cardiac disease had clinically or hemodynamically significant lesions and died suddenly, or of complications of surgery or cardiac catheterization, or of congestive heart failure. Certain demographic, clinical and morphologic data in patients with hypertrophic cardiomyopathy and control patients are summarized in Tables 2 and 3.

Table 1. Cardiac Disease in 68 Control Patients

	No. of Patients	No. With Abnormal IMCAs
Disease		
Coronary heart disease*	18	1
Aortic valvular disease	15†	2‡
Systemic hypertension	13	1
Dilated cardiomyopathy	8	0
Normal	14	2
Total	68	6

*Heart weight > 400 g. †Includes 11 patients with predominant or pure aortic stenosis as well as 2 with combined aortic stenosis and regurgitation, 1 with associated coronary heart disease and 1 with an associated atrial septal defect. ‡Includes one patient with combined aortic stenosis and atrial septal defect and one patient with aortic stenosis and associated coronary heart disease. IMCAs = intramural coronary arteries.

Preparation of tissue. Each of the 124 hearts utilized in this study (from 48 children or adults with hypertrophic cardiomyopathy, 8 infants with hypertrophic cardiomyopathy and 68 control subjects) was fixed in formalin. Tissue blocks were taken from the full thickness of the ventricular wall in a plane perpendicular to the long axis of the left ventricle (that is, a transverse plane), about half the distance between the aortic valve and left ventricular apex. Tissue sections were obtained from three locations: ventricular septum, anterior left ventricular free wall (about 2 cm lateral to the left anterior descending coronary artery) and posterior left ventricular free wall (between the papillary muscles) (Fig. 1) (28). Each tissue block was embedded in paraffin, sectioned at 6 μ and stained with Movat's pentachrome stain (29).

Analysis of intramural coronary arteries. Assessment of intramural coronary artery anatomy was confined to those arteries (<1,500 μ in diameter) that were viewed in cross section (transverse cut) without obvious obliquity and that did not appear to be branches of another intramural vessel, or portions of a "tunneled" epicardial vessel. Small coronary arteries in trabeculae or papillary muscles were excluded from analysis.

The extent to which abnormal intramural coronary arteries occurred in each tissue section was graded semiquantitatively based on the number of abnormal arteries and on an estimation of the degree of wall thickening and luminal narrowing. The grading system used to express the magnitude of these abnormalities was as follows. First, the *frequency* of altered arteries in a tissue section was assessed and numeric values of 0.5 to 9.5 were assigned to reflect the number of abnormal intramural coronary arteries identified. Sections with only a single altered intramural coronary artery were not considered abnormal. Second, for each intramural coronary artery judged to be abnormal the *severity* of wall thickening and apparent luminal narrowing was graded qualitatively as mild (1+), moderate (2+) or severe (3+). Grades for frequency and severity were then averaged to yield an overall assessment of abnormal intramural coronary artery morphology for each section. These values were then summed for all three tissue sections taken from each patient, giving an overall "abnormal intramural coronary artery tissue section grade."

Prior knowledge of whether or not tissue sections studied were from patients with hypertrophic cardiomyopathy or control patients was usually unavoidable because particularly large tissue section size or the presence of marked

cardiac muscle cell disorganization suggested the presence of hypertrophic cardiomyopathy.

Analysis of myocardial fibrosis. The extent of fibrous tissue formation was assessed qualitatively in each tissue section: 0 (none), 1+ (mild), 2+ (moderate) and 3+ (severe). Mild fibrosis was judged to be present when an isolated small scar or interstitial fibrous tissue formation, or both, was identified; severe fibrosis was characterized by extensive replacement scarring occupying substantial portions of the section. Moderate fibrosis consisted of degrees of replacement scarring intermediate in extent between that observed with the mild and severe grades. Transmural infarction was defined as involving at least the inner two-thirds of the ventricular wall.

Measurement of tissue section area. The area of each of the 348 tissue sections analyzed in this study was calculated using a previously described method (30). The boundaries of each section (exclusive of trabeculae and papillary muscles) were traced on ordinary tablet paper with a fine point marking pen and the area was then measured (in square centimeters) utilizing a video planimeter.

Clinical features. Of the 48 patients with hypertrophic cardiomyopathy, 26 died suddenly and unexpectedly; 9 died from progressive congestive heart failure, 10 died at operation and 1 each died from cerebrovascular accident, complications of cardiac catheterization and suicide. Sixteen patients (34%) had been asymptomatic or minimally symptomatic; the remaining 32 (66%) had experienced substantial functional limitation, including 10 with moderate symptoms (New York Heart Association functional class II) and 22 with marked symptoms (class III or IV). Nineteen (40%) of the 48 patients had chest pain.

Of 33 patients having cardiac catheterization, 18 had a subaortic gradient of 30 mm Hg or more under basal conditions (40 to 160 mm Hg; average 88), and the remaining 15 patients had zero basal gradient or a small gradient of 15 mm Hg or less. Of the latter 15 patients, 10 had provocative maneuvers performed in the cardiac catheterization laboratory (Valsalva maneuver, isoproterenol infusion or amyl nitrite inhalation), which induced a gradient of 20 mm Hg or less in 8 patients and 50 mm Hg or more in the other 2. Five other patients with no or a small gradient at rest did not have provocative maneuvers performed.

The eight infants with hypertrophic cardiomyopathy ranged in age at the time of death from stillborn to 11 months (mean 4 months); six were male and two were female. Of the seven live-born infants, four died of progressive congestive heart failure, one died suddenly and two died postoperatively.

Interobserver variation. To assess interobserver variability in the identification of abnormal intramural coronary arteries, 36 tissue sections (12 each of ventricular septum, anterior and posterior free wall) from 12 study patients (10 with hypertrophic cardiomyopathy and 2 with other cardiac diseases) were analyzed independently by two observers. Each investigator determined whether or not individual tissue sections showed two or more abnormal arteries.

Statistical methods. Data were expressed as the mean ± SEM. Differences between means were assessed with the Student's *t* test. Differences between proportions were evaluated with the chi-square test.

Results

Histologic features of abnormal intramural coronary arteries. Compared with normal intramural coronary arteries (Fig. 2), abnormal arteries were characterized by increased size and thickened walls (Fig. 3 to 6); usually the lumen was narrowed, although some of these arteries had a normal-sized or apparently dilated lumen. Thickening of the arterial wall was due to proliferation of medial or intimal components, particularly smooth muscle cells and collagen. Also, increased numbers of elastic fibers were often present in the intima, and mucoid deposits (acid mucopolysaccharide) were occasionally identified in the intima or media. In some arteries isolated intimal proliferation was localized to only a portion of the luminal circumference. The internal elastic membrane was frequently distorted or obscured, making it difficult or impossible to discern the relative contribution of the intima or media to thickening of the arterial wall.

Control patients. Of the 68 control patients with a normal heart or cardiac disease other than hypertrophic cardiomyopathy, 6 (9%) had abnormal intramural coronary arteries present in at least one tissue section, including ventricular septum (5 patients) or posterior free wall (1 patient) (Fig. 7 and 8). Therefore, abnormal arteries were present in only 6 (3%) of the 204 individual tissue sections analyzed, and were most common in the ventricular septum. The remaining 62 (91%) patients did not show altered intramural arteries in any of the tissue sections examined.

A total of 15 abnormal intramural coronary arteries were identified in the 204 sections, an average of 0.1 ± 0.05/section and 0.04 ± 0.02/cm^2 of myocardium analyzed (Table 4). The maximal number of abnormal arteries present in any single section was three.

Altered intramural coronary arteries ranged in external diameter from 90 to 390 μ (mean 215). Most abnormal arteries (13 [87%] of 15) were midly or moderately narrowed with localized or modest intimal or medial thickening; only 2 (13%) of 15 were considered to be markedly thickened and appeared narrowed. The overall abnormal intramural coronary artery tissue section grade, reflecting the frequency and severity of arterial abnormalities for combined ventricular septum and free wall, was 0.08 ± 0.03 (Fig. 9; Table 4).

Patients with hypertrophic cardiomyopathy. Of the 48 patients with hypertrophic cardiomyopathy, 40 (83%) had abnormal intramural coronary arteries in at least one

Table 2. Clinical and Morphologic Data in 48 Patients With Hypertrophic Cardiomyopathy

Case	Age (yr) & Sex	Mode of Death	CP	FC	LVOT PSG (mm Hg) Rest	LVOT PSG (mm Hg) Prov.	HW (g)	VS (mm)	PW (mm)	VS/PW
1	11F	SD	0	1	—	—	400	17	9	1.9
2	12M	SD	0	1	—	—	270	18	10	1.8
3	13M	CHF	0	3	15	50	520	23	17	1.3
4	13M	SD	0	1	—	—	450	21	14	1.5
5	14M	SD	0	1	15	—	360	18	12	1.5
6	15F	SD	0	1	55	115	400	38	16	2.6
7	15F	SD	0	1	—	—	320	22	11	2.0
8	15M	SD	0	1	—	—	650	35	18	1.9
9	17M	SD	0	1	—	—	370	27	13	2.1
10	17M	SD	0	1	—	—	530	21	12	1.8
11	19F	SD	+	2	40	—	320	24	15	1.6
12	19F	Op	+	3	160	—	730	28	25	1.1
13	20F	CHF	+	2	40	55	1,250	42	10	4.2
14	20M	SD	0	1	—	—	630	33	20	1.7
15	21F	Op	+	3	80	100	390	29	15	1.9
16	21F	SD	0	1	—	—	400	24	9	2.7
17	22M	SD	0	1	—	—	500	21	13	1.6
18	23M	SD	0	1	0	—	500	20	15	1.3
19	23M	SD	0	1	—	—	750	30	15	2.0
20	24F	SD	0	2	—	—	720	44	26	1.7
21	24F	CVA	0	2	0	—	385	24	11	2.2
22	25F	Op	+	3	0	0	400	25	15	1.7
23	26F	SD	+	2	65	—	500	23	14	1.6
24	26F	CHF	0	3	10	—	390	22	16	1.4
25	27F	SD	+	3	100	—	640	33	20	1.6
26	27M	Op	+	3	70	—	950	34	27	1.3
27	27F	Cath	+	2	130	—	490	30	19	1.6
28	28F	Op	+	3	80	—	580	28	17	1.6
29	29M	SD	0	4#	0	0	450	25	12	2.1
30	30F	SD	0	1	—	—	445	17	15	1.1
31	30F	CHF	+	2	0	20	525	17	21	0.8
32	33M	SD	+	2	0	15	1,020	34	25	1.4
33	33F	CHF	+	4	0	10	430	27	13	2.1
34	33M	CHF	+	3	0	0	580	15	15	1.0
35	33F	SD	0	2	120	—	550	35	19	1.8
36	35F	SD	+	3	100	—	620	36	25	1.4
37	37M	Op	+	3	65	160	680	27	18	1.5
38	38M	SD	+	3	0	0	560	25	15	1.7
39	38M	SD	0	2	85	130	600	26	21	1.2
40	41F	Op	0	4	0	—	530	25	16	1.6
41	41M	Op	0	3	15	100	700	27	17	1.6
42	43F	SD	0	1	—	—	300	18	11	1.6
43	43F	CHF	0	4	55	75	310	18	16	1.1
44	50F	Su	+	3	130	—	450	20	19	1.1
45	50F	CHF	0	3	0	5	550	15	10	1.5
46	53M	Op	0	3	110	140	800	32	18	1.8
47	59F	Op	+	3	100	—	610	23	23	1.0
48	60M	CHF	0	4	—	—	530	16	12	1.3

*Denotes number of abnormal intramural coronary arteries per tissue section. †Qualitative assessment (1+ to 3+) of the degree of wall thickening and luminal narrowing in all abnormal intramural coronary arteries in the tissue section (with 1+ the most mild and 3+ the most severe). ‡Mean external diameter of all abnormal intramural coronary arteries in the tissue section. §Qualitative assessment (1+ to 3+) of the degree and extent of fibrosis observed in the tissue section; mild (1+) fibrosis was judged to be present when an isolated small scar or interstitial fibrous tissue formation, or both, was identified; severe (3+) fibrosis was characterized by extensive replacement scarring occupying substantial portions of the section; moderate (2+) fibrosis consisted of degrees of replacement scarring intermediate in extent between that observed with the mild or severe grades. ‖"Tissue section grade" (TSG) is a numeric expression of the frequency and severity of abnormal intramural coronary arteries in combined ventricular septal and free wall tissue

Table 2. (*continued*)

Abnormal Intramural Coronary Arteries												
Ventricular Septum				Anterior LVFW				Posterior LVFW				Overall
No.*	S†(0 to 3+)	D‡(μ)	Fi§	No.*	S†(0 to 3+)	D‡(μ)	F§	No.*	S†(0 to 3+)	D‡(μ)	Fi§	TSG‖
2	2+	315	1+	2	2+	355	1+	0	0	0	0	2.35
12	2+	370	2+	4	1+	215	1+	0	0	0	1+	3.35
4	2+	335	3+	0	0	0	1+	0	0	0	0	1.40
2	2+	700	1+	0	0	0	0	0	0	0	0	1.30
4	2+	410	2+	0	0	0	1+	0	0	0	0	1.30
0	0	240	1+	3	3+	355	1+	0	0	0	1+	1.60
0	0	0	1+	0	0	0	0	0	0	0	0	0
7	1+	300	3+	4	3+	580	2+	0	0	0	1+	3.35
5	2+	350	2+	2	1+	150	1+	0	0	0	1+	2.25
0	0	0	1+	0	0	0	1+	0	0	0	0	0
2	1+	305	1+	0	0	0	0	2	1+	185	1+	1.60
2	3+	370	1+	2	1+	270	1+	0	0	0	2+	2.15
5	1+	155	3+**	3	1+	175	3+	6	1+	225	3+	3.75
15	2+	455	1+	0	0	0	0	0	0	0	1+	2.75
0	0	0	1+	0	0	0	1+	0	0	0	0	0
10	2+	395	2+	2	2+	400	1+	2	1+	140	1+	4.10
0	0	0	1+	0	0	0	1+	2	2+	240	0	1.30
0	0	0	0	0	0	0	0	2	1+	295	0	0.80
0	0	0	1+	0	0	0	1+	0	0	0	2+	0
0	0	0	1+	2	2+	205	1+	0	0	0	1+	1.05
18	2+	250	3+	3	2+	205	2+	4	2+	360	2+	5.90
6	2+	360	2+	5	2+	205	2+	3	1+	225	1+	4.25
4	1+	290	1+	0	0	0	0	0	0	0	0	1.05
2	1+	305	2+	0	0	0	0	0	0	0	1+	0.80
50	3+	290	3+**	0	0	0	2+	0	0	0	1+	6.50
3	2+	295	0	4	2+	195	3+	0	0	0	2+	2.70
0	0	0	1+	0	0	0	2+	0	0	0	1+	0
0	0	0	2+	0	0	0	1+	0	0	0	0	0
3	1+	205	1+	0	0	0	0	0	0	0	0	0.95
0	0	0	0	5	1+	200	1+	0	0	0	0	1.40
4	2+	230	3+**	2	2+	230	3+	0	0	0	1+	1.75
3	2+	355	2+	2	2+	475	3+	0	0	0	1+	2.50
16	2+	360	3+	0	0	0	3+	0	0	0	1+	2.00
76	3+	345	3+**	0	0	0	2+	0	0	0	1+	9.25
0	0	0	2+	0	0	0	1+	0	0	0	1+	0
4	2+	295	1+	0	0	0	1+	0	0	0	1+	1.30
0	0	0	0	8	1+	100	0	0	0	0	1+	1.50
4	2+	145	1+	7	2+	160	3+**	0	0	0	1+	3.10
7	1+	255	1+	0	0	0	1+	0	0	0	1+	1.55
7	2+	215	3+**	0	0	0	2+	0	0	0	1+	1.76
0	0	0	0	3	2+	360	0	0	0	0	1+	1.30
8	2+	325	1+	0	0	0	1+	0	0	0	0	1.95
3	1+	315	2+	3	1+	270	2+	0	0	0	1+	2.05
3	2+	190	1+	0	0	0	0	0	0	0	1+	1.30
22	2+	370	3+**	0	0	0	2+	5	2+	355	2+	4.90
4	1+	360	1+	7	1+	180	0	2	1+	180	0	3.55
0	0	0	0	0	0	0	0	0	0	0	1+	0
15	2+	245	3+**	0	0	0	1+	0	0	0	1+	2.80

sections for each patient (see text for details). #Assigned to functional class IV by virtue of experiencing and surviving an episode of cardiovascular collapse (associated with documented ventricular fibrillation) 8 months before his sudden death. **Replacement fibrosis is transmural. Cath = cardiac catheterization; CHF = congestive heart failure; CP = chest pain; CVA = cerebrovascular accident; D = (external) diameter; F = female; FC = functional class; Fi = fibrosis; HW = heart weight; IMCA = intramural coronary artery; LVFW = left ventricular free wall; LVOT = left ventricular outflow tract; M = male; Op = operation; Prov. = provokable; PSG = peak systolic gradient; PW = posterior left ventricular free wall thickness; S = severity; SD = sudden death; Su = suicide; TSG = tissue section grade; VS = ventricular septal thickness; + = present; 0 = absent.

Table 3. Demographic, Clinical and Morphologic Data in 48 Patients with Hypertrophic Cardiomyopathy and 68 Control Patients*

	No. Patients	Age at Death (yr)	Sex (% male)	VS† (mm)	PW† (mm)	VS/PW	No. (%) With Abnormal IMCAs	Heart weight (g)
Hypertrophic cardiomyopathy	48‡	29 (11 to 60)	44	26 (15 to 44)	16 (9 to 26)	1.7 (0.8 to 4.2)	40/48 (83%)	542 (270 to 1,250)
Controls	68	48 (13 to 80)	69	16 (10 to 34)	15 (9 to 23)	1.1 (0.8 to 2.0)	6/68 (9%)	526 (250 to 900)
p Value		<0.001		<0.001	NS	<0.001	<0.001	NS

*Data presented as mean and range, where applicable. †Ventricular septal measurements were made at the point of maximal thickness, usually about half the distance between the aortic valve and left ventricular apex. Left ventricular posterior wall measurements were taken behind the midpoint of the posterior mitral leaflet, at a level corresponding to the tips of the mitral leaflets; trabeculae, papillary muscles and crista supraventricularis muscle were, by convention, excluded from these measurements. ‡Does not include eight infants with hypertrophic cardiomyopathy who were analyzed separately; ventricular septal thicknesses were 8 to 30 mm (mean 16), posterior free wall thicknesses were 3 to 15 mm (mean 9) and septal-free wall ratios were 1.4 to 2.7 (mean 1.9). IMCAs = intramural coronary arteries; NS = nonsignificant; PW = posterior left ventricular free wall; VS = ventricular septum; VS/PW = ventricular septal to free wall thickness ratio.

tissue section; hence, the prevalence of abnormal sections was significantly greater in the patients with hypertrophic cardiomyopathy than in control patients (83 versus 9%; $p < 0.001$) (Fig. 7). In patients with hypertrophic cardiomyopathy, altered intramural coronary arteries were identified in the ventricular septum (33 patients), anterior free wall (20 patients) or posterior free wall (9 patients) (Table 2; Fig. 8). Therefore, abnormal arteries were present in 62 (43%) of the 144 individual tissue sections analyzed and most commonly appeared in ventricular septum. Of the 40 patients with abnormal intramural coronary arteries, such vessels were identified in one of the three tissue sections in 23 patients, in two sections in 12 patients and in all three sections in only 5 patients.

A total of 433 abnormal intramural coronary arteries were identified in the 144 tissue sections, an average of 3.0 ± 0.7/section and 0.9 ± 0.2/cm^2 of myocardium analyzed; their frequency was significantly greater in patients with hypertrophic cardiomyopathy than in control patients, ($p < 0.001$) (Table 4). The maximal number of altered arteries present in any single section was 76.

Occasionally, numerous abnormal intramural coronary arteries appeared in clusters, but the distribution of abnormal arteries throughout the tissue section showed no particular predilection for the subendocardial or subepicardial regions. There was no significant relation between the frequency of abnormal arteries and thickness of either ventricular septum ($r = 0.18$) or posterior free wall ($r = 0.43$).

Abnormal intramural coronary arteries in patients with hypertrophic cardiomyopathy were also larger (range 50 to 1,330 μ in external diameter; mean 300) (Table 2) than those in controls (90 to 390 μ; mean 215). Most altered arteries (288 [64%] of 452) were markedly thickened and usually narrowed, whereas the remainder (164 or 36%) were judged only mildly or moderately narrowed with mild or localized intimal or medial thickening.

The overall "abnormal intramural coronary artery tissue section grade" (for septum and free wall combined) was substantially greater in patients with hypertrophic cardio-

Figure 1. Section of left ventricle (LV) in the anteroposterior (transverse) plane about half the distance between base and apex, showing the location of the three tissue sections that were analyzed quantitatively in each study patient. LVFW = left ventricular free wall; RV = right ventricle.

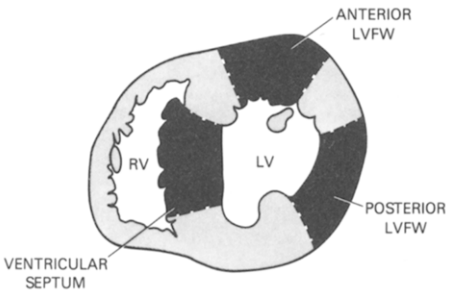
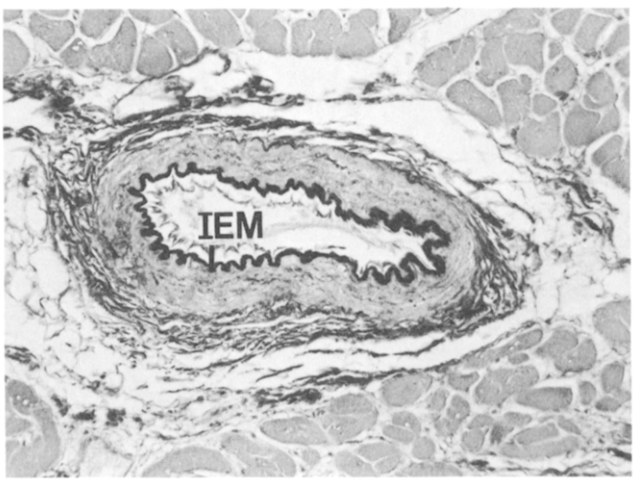


Figure 2. Normal intramural coronary artery in the ventricular septum. The internal elastic membrane (IEM) is well visualized adjacent to the sizeable lumen. Original magnification ×220, reduced by 26%.



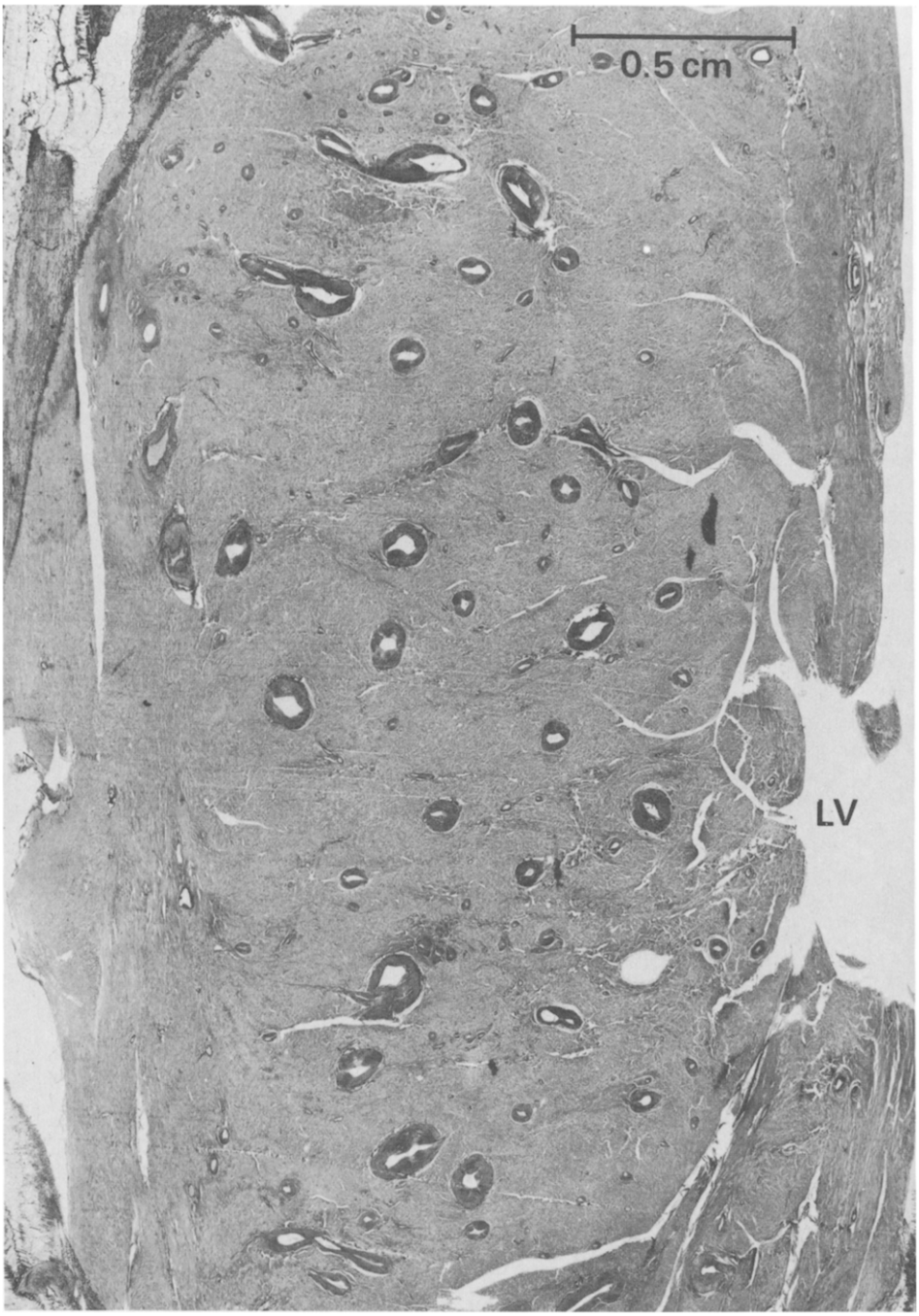


Figure 3. Portion of ventricular septum from a patient with hypertrophic cardiomyopathy. Numerous abnormal intramural coronary arteries are present; most are larger than normal and have a thicker wall than normal and a small lumen. This patient is not included in the present study group because she died more than 1 month after the septal myotomy-myectomy operation. Original magnification ×5, reduced by 26%. LV = left ventricular cavity.

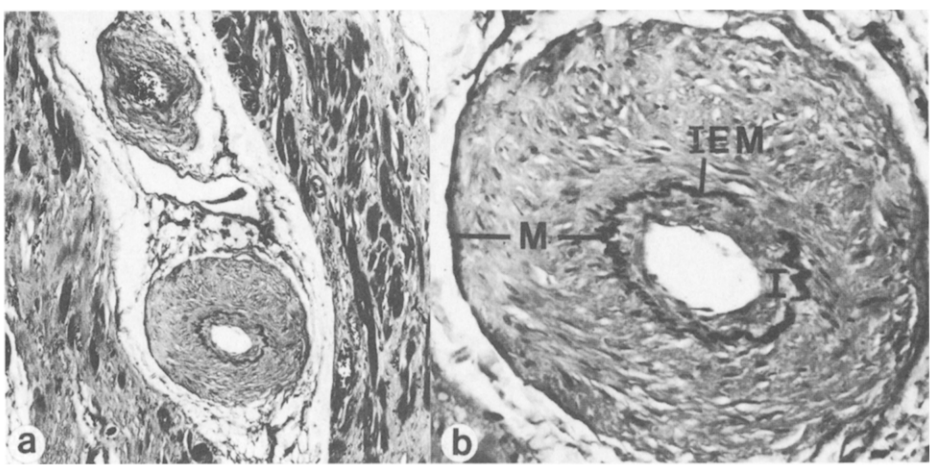


Figure 4. a, A single large abnormal intramural coronary artery is seen in an interstitial space of the left ventricular free wall. Original magnification ×100. **b**, The same vessel at higher magnification (×350). The wall thickening is due primarily to proliferation of medial (M) components, although the intima (I) is also mildly thickened. The internal elastic membrane (IEM) is well defined. Both panels reduced by 26%.

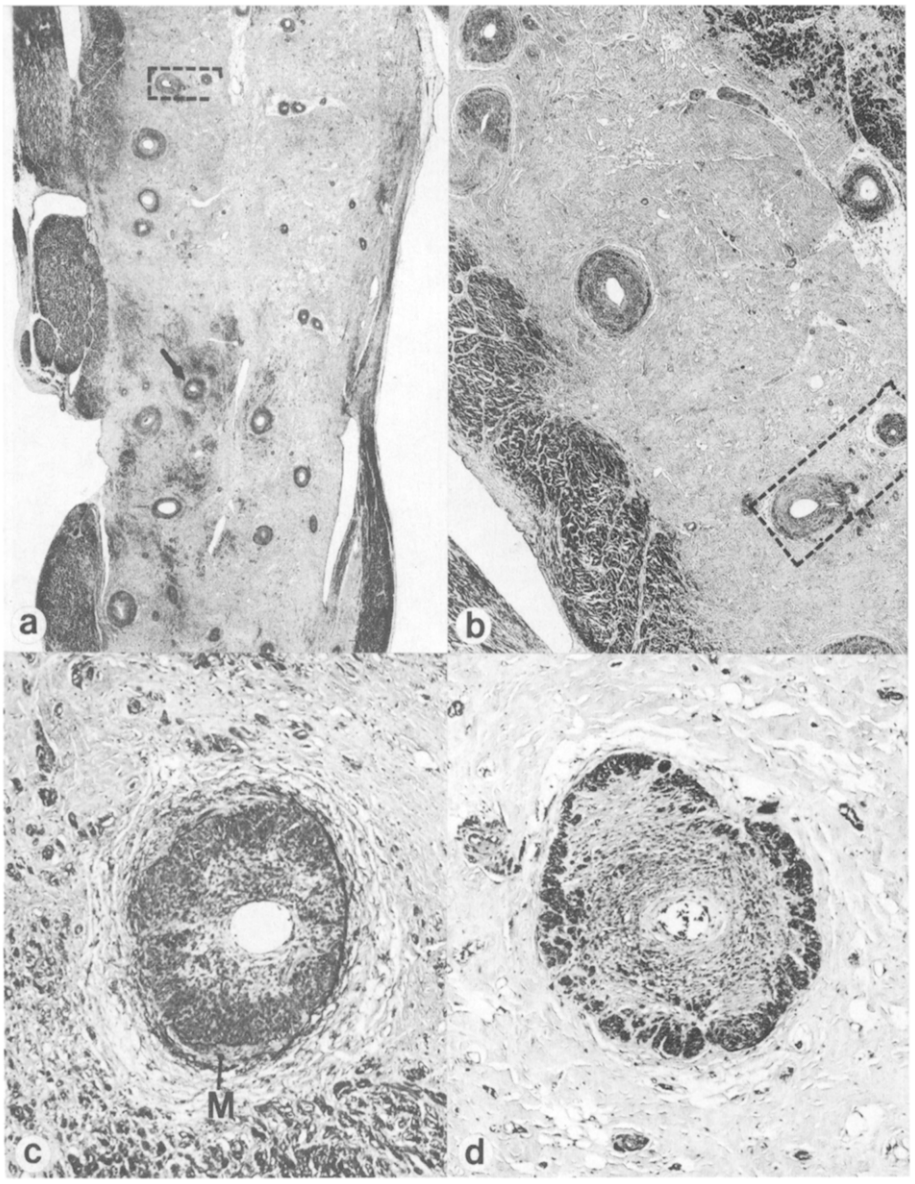


Figure 5. Four photomicrographs (**a to d**) showing substantial replacement scarring of the ventricular septum and abnormal intramural coronary arteries. **a**, Low power view showing transmural scarring of the septum and numerous altered intramural coronary arteries; some intramural coronary arteries have a thickened wall and narrowed lumen. Original magnification ×8. **b**, Higher power view of the septum shown in **a**; the two intramural coronary arteries within the **box** are indicated in a similar fashion in **a**. Original magnification ×20. **c**, High power micrograph of an abnormal intramural coronary artery surrounded by fibrous tissue that is designated by the **arrow** in **a**; luminal narrowing is due primarily to proliferation of intimal smooth muscle; the small medial (M) layer is evident at the periphery. Original magnification ×100. **d**, Abnormal intramural coronary artery in which luminal narrowing is due primarily to medial fibrous tissue proliferation. Original magnification ×100. All reduced by 26%.

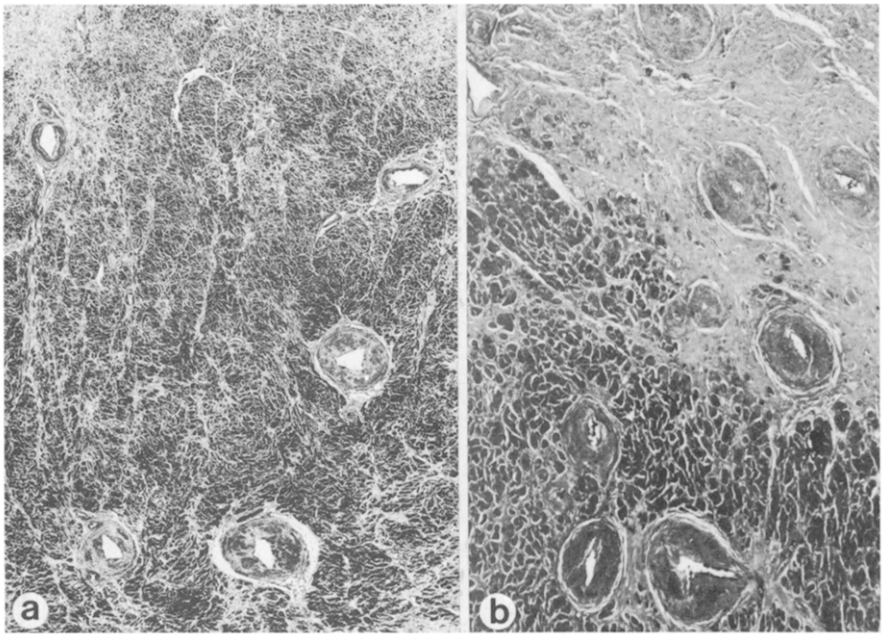


Figure 6. **a**, A portion of ventricular septum with only small patchy areas of fibrosis. Abnormal intramural coronary arteries are present in or near both scarred and nonscarred areas. Original magnification ×20. **b**, Area of left ventricular free wall in which numerous abnormal intramural coronary arteries are present in a region of scarring, as well as in an adjacent area of myocardium that is not scarred. Original magnification ×55. Both reduced by 26%.

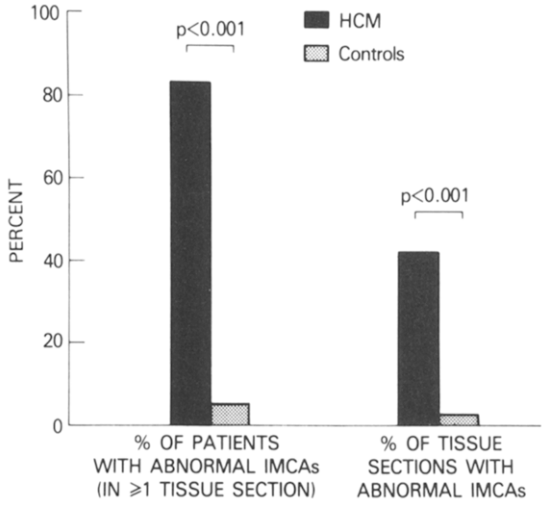


Figure 7. Prevalence of abnormal intramural coronary arteries (IMCAs) in patients with hypertrophic cardiomyopathy (HCM) and control subjects, and in tissue sections from these two groups of patients.

myopathy (2.1 ± 0.1) than in control patients (0.08 ± 0.03; $p < 0.001$) (Fig. 9; Table 3). Furthermore, in patients with hypertrophic cardiomyopathy, the magnitude of intramural coronary artery abnormalities was significantly greater in the ventricular septum than in the anterior free wall and greater in the anterior free wall than in the posterior free wall (Fig. 9).

Abnormal intramural coronary arteries were identified in the ventricular septum from three of the eight infants with hypertrophic cardiomyopathy. In two of these three infants numerous altered arteries had moderate to marked thickening of the vessel wall and luminal narrowing; in the remaining infant, milder arterial abnormalities were identified. Fibrosis was not associated with the abnormal arteries in the three infants.

Relation between abnormal intramural coronary arteries and myocardial fibrosis. In the 48 patients with hypertrophic cardiomyopathy, myocardial scarring was absent or mild in 102 tissue sections and moderate to severe in 42 sections. Abnormal intramural coronary arteries were significantly more common in those tissue sections with moderate or severe fibrosis (31 [74%] of 42) than in sections with no or mild fibrosis (31 [30%] of 102; $p < 0.001$) (Fig. 10). The association between altered intramural arteries and fibrosis was most significant in ventricular septal sections; abnormal arteries were present in 19 (90%) of 21 septal sections with moderate to marked fibrosis, but in only 14 (52%) of 27 septal sections with no or mild fibrosis ($p < 0.025$). In 24 of the 31 sections in which abnormal intramural coronary arteries and substantial fibrosis were present, a particularly close association between the two was apparent, with abnormal arteries located either within or at the margins of areas of replacement fibrosis (Fig. 5 and 6).

Transmural scarring was present in tissue sections from eight patients, including ventricular septum in seven and anterior free wall in one. In each of these sections, clusters of large numbers of abnormal intramural coronary arteries were present either within or adjacent to the scar (Fig. 5 and 6). Most of these arteries had a small, narrowed lumen, although in occasional vessels the arterial lumen appeared normal or even dilated. The relation between abnormal intramural arteries and myocardial fibrosis was not influenced by the age or sex of the patient. Of the six tissue sections with abnormal intramural coronary arteries in the control group, only one showed moderate fibrosis, while the remainder had either no or mild fibrosis.

Correlation of abnormal intramural coronary arteries with other clinical or morphologic findings. Various clinical, hemodynamic and morphologic findings in the 48 patients with hypertrophic cardiomyopathy were correlated with the prevalence and severity of abnormal intramural coronary arteries. There was no correlation between the occurrence or magnitude of intramural coronary artery abnormalities and age of the patient, sex distribution, presence or absence or severity of symptoms, mode of death (sudden versus chronic decompensation), left ventricular end-diastolic pressure, heart weight, ventricular septal thickness or septal to free wall thickness ratio. Although there was no statistically significant relation between the presence, absence or magnitude of left ventricular outflow obstruction and small artery abnormalities (in the 32 patients who underwent cardiac catheterization), the abnormal intramural coronary artery tissue section grade in patients with nonobstructive hypertrophic cardiomyopathy (2.8 ± 0.6) tended to exceed that of patients with obstructive hypertrophic cardiomyopathy (1.6 ± 0.4; $p < 0.2$). Altered arteries were present in each of the 15 patients with nonobstructive hy-

Figure 8. Distribution of abnormal intramural coronary arteries (IMCAs) in the left ventricle (LV) of patients with hypertrophic cardiomyopathy (HCM) and control subjects. ANT. FW = anterior free wall; POST. FW = posterior free wall; VS = ventricular septum.

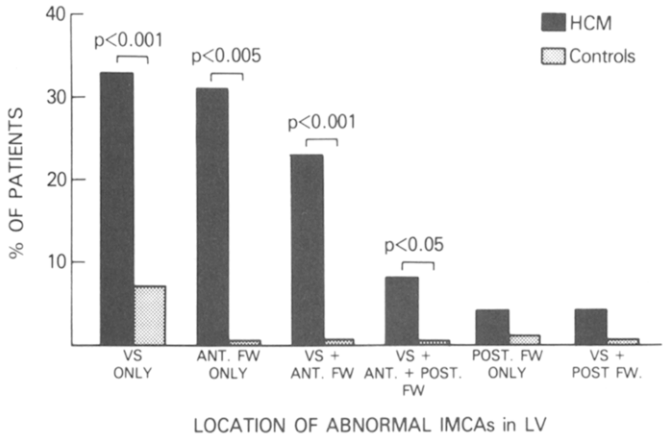


Table 4. Frequency of Abnormal Intramural Coronary Arteries in Patients With Hypertrophic Cardiomyopathy and Control Subjects

	Hypertrophic Cardiomyopathy	Control Group
No. of patients	48	68
Total no. of abnormal IMCAs	433	15
Avg. no. of abnormal IMCAs/tissue section	3.0 ± 0.7*	0.1 ± 0.05*
Maximal no. of abnormal IMCAs/tissue section	76	3
Avg. tissue section area (cm^2)†	3.5 ± 0.2*	2.3 ± 0.1*
Avg. no. of abnormal IMCAs/cm^2 of myocardium‡	0.9 ± 0.2*	0.04 ± 0.02*
IMCA tissue section grade§	2.1 ± 0.1*	0.08 ± 0.03*

*Comparison of these variables in patients with hypertrophic cardiomyopathy and control patients achieved statistical significance, $p < 0.001$. †Expressed here for ventricular septum, anterior free wall and posterior free wall combined. ‡Analysis of only those tissue sections with abnormal intramural coronary arteries. §Reflects the frequency as well as the severity of abnormal intramural coronary arteries; data presented here combine ventricular septal and both free wall tissue sections in each patient (see text for details). Avg. = average; IMCAs = intramural coronary arteries.

pertrophic cardiomyopathy and in 12 of 17 patients with obstructive hypertrophic cardiomyopathy.

Of the 48 patients with hypertrophic cardiomyopathy, 19 had experienced clinically significant and recurrent episodes of chest pain. Of these 19 patients, 15 (79%) had abnormal intramural coronary arteries in at least one tissue section; however, these altered arteries were also commonly identified in patients without chest pain (25 [86%] of 29). Furthermore, there was no relation between the occurrence of chest pain and the extent of myocardial fibrosis; chest pain was present in 12 (63%) of 19 patients with moderate to marked fibrosis and in 14 (48%) of 29 patients with no or mild fibrosis.

Interobserver variation. There was agreement between two observers with regard to the presence or absence of abnormal intramural arteries in 88% of observations (32 of 36 tissue sections analyzed).

Discussion

Occurrence and pathogenesis of abnormal intramural coronary arteries in hypertrophic cardiomyopathy. The findings of this study demonstrate that many patients (over 80%) with hypertrophic cardiomyopathy have structural abnormalities of the intramural coronary arteries. There was great variation in the magnitude of these abnormalities, which were striking in some patients and relatively mild in others. Altered intramural coronary arteries were most common in the ventricular septum, but were also frequently identified in the anterior or posterior left ventricular free wall. These

Figure 9. Semiquantitative expression of magnitude of intramural coronary artery (IMCAs) abnormalities in the 48 patients with hypertrophic cardiomyopathy (HCM) and 68 control patients. Tissue section grade utilized here takes into account both the *frequency* of abnormal intramural coronary arteries and the apparent *severity* of wall thickening and luminal narrowing (see text for details).

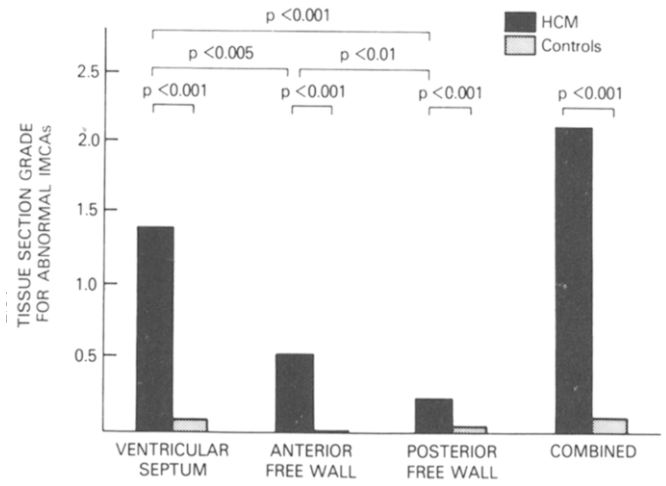
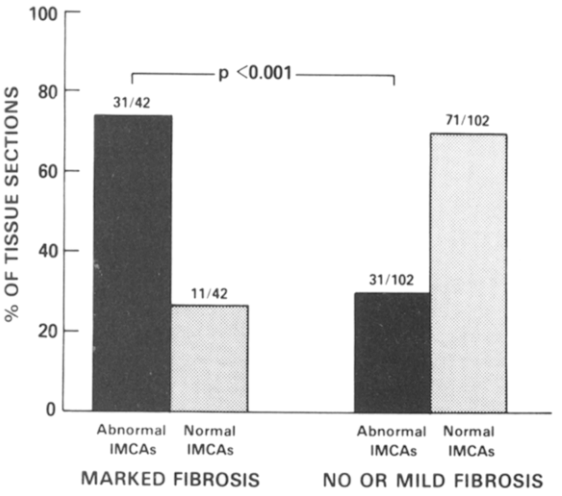


Figure 10. Relation between occurrence of abnormal intramural coronary arteries (IMCAs) and myocardial fibrosis in 144 tissue sections obtained from the ventricular septum and anterior and posterior left ventricular free walls in 48 patients with hypertrophic cardiomyopathy. Marked fibrosis includes those tissue sections graded as moderate or severe.



findings of abnormal intramural coronary arteries in hypertrophic cardiomyopathy are similar to those described in several patients by James and Marshall (22). The present study extends their observations, however, because our results allow a quantitative assessment of the prevalence, distribution and severity of these abnormal intramural coronary arteries in patients who died of hypertrophic cardiomyopathy, as well as in control patients with a variety of other cardiac diseases.

Our findings indicate that the presence of abnormal intramural coronary arteries is not unique for hypertrophic cardiomyopathy; such vessels were also present in a few control patients with a variety of cardiac diseases characterized by left ventricular hypertrophy. However, the altered intramural coronary arteries identified in our control patients were much less frequent and less severe than those observed in patients with hypertrophic cardiomyopathy. In particular, their prevalence was much lower in patients with systemic hypertension and in patients with valvular aortic stenosis. Because these latter diseases lead to a pressure load on the left ventricular myocardium, this finding indicates that myocardial wall stress alone is not sufficient to produce these abnormal intramural arteries in the frequency with which they are found in hypertrophic cardiomyopathy. In addition, our observations that intramural coronary artery abnormalities were equally severe in patients with and without left ventricular outflow obstruction and the lack of relation between left ventricular wall thickness and frequency or location of abnormal intramural coronary arteries, further substantiate the conclusion that these abnormal arteries are not solely related to elevated intramyocardial wall tension. Although we have no definitive data that define the pathogenesis of the abnormal intramural coronary arteries present in most patients with hypertrophic cardiomyopathy, the fact that these altered arteries cannot be ascribed to high ventricular pressures suggests that they may constitute an independent marker of hypertrophic cardiomyopathy and a component of the cardiomyopathic process, which may be present at birth (three of the eight infants with hypertrophic cardiomyopathy we studied had abnormal intramural coronary arteries). On the other hand, it is possible that in some patients these abnormal intramural arteries arise secondary to substantial or transmural fibrous tissue formation, as a form of neovascularization.

Abnormal intramural coronary arteries in other diseases. Previous investigators (26,27,31–37) have reported alterations in small left ventricular intramural coronary arteries (as well as in small arteries in the sinoatrial and atrioventricular nodes) similar to those described in this report. These observations, made primarily in patients with diseases *other than hypertrophic cardiomyopathy,* included systemic or metabolic diseases in which hypertrophy was absent or mild, such as diabetes mellitus (26), progressive muscular dystrophy (27), Friedreich's ataxia (27,31), scleroderma (32), homocystinuria (33) and the Marfan syndrome (27). Abnormal intramural coronary arteries have also been described in a diverse group of primary cardiovascular diseases with or without left ventricular hypertrophy such as tunnel subaortic stenosis (34), primary pulmonary hypertension (27), Newfoundland dogs (35,36) with discrete fibrous subaortic stenosis, newborns with aortic or pulmonic atresia (37) and the syndrome of congenital deafness, syncope and sudden death associated with QT interval prolongation (27). In addition, small arteries with similar morphologic features have been observed to be limited to the specialized sinoatrial or atrioventricular conduction tissue of apparently healthy young individuals (including competitive athletes) who died suddenly and either had left ventricular hypertrophy (38) or had no gross evidence of structural heart disease (39,40). Although none of these studies attempted to quantitate the frequency and severity of altered intramural coronary arteries, it is our impression (based on a review of the published papers) that these arteries occurred in relatively small numbers, and therefore did not constitute the widespread and potentially significant lesion that we observed in most patients with hypertrophic cardiomyopathy.

Considerations regarding control subjects. The control group assembled for this study was comprised of patients with a normal heart, dilated cardiomyopathy and acquired heart disease associated with increased left ventricular pressure, mass, or both (for example, systemic hypertension, aortic valve disease and coronary heart disease). Therefore, this particular control group was designed to reflect a population of adult patients with heart diseases that are relatively common in cardiologic practice. As a result, many of the congenital cardiac or systemic diseases in which abnormal intramural coronary arteries have occasionally been reported (as described earlier) are not represented. However, it was not our intention in this investigation to suggest that abnormal intramural coronary arteries are more common in hypertrophic cardiomyopathy than in *any* other cardiac or systemic disease. Our study design permits only an assessment of the relative frequency of these altered arteries in hypertrophic cardiomyopathy as compared with other common cardiac diseases associated with left ventricular hypertrophy.

Relation between abnormal intramural coronary arteries and myocardial fibrosis. In our study there was no clear relation between the presence of abnormal intramural coronary arteries and the clinical history of chest pain in patients with hypertrophic cardiomyopathy. Whereas about 80% of patients who had chest pain had altered intramural coronary arteries, about 85% of patients who had no chest pain also showed abnormal intramural coronary arteries. It is conceivable that this lack of specificity of abnormal intramural arteries for patients with chest pain may be due in part to the fact that clinical assessment of chest pain in a retrospective analysis such as ours is a difficult and subjec-

tive judgment. In addition, "silent" ischemia has now been well documented in patients with coronary artery disease (41), and there is no reason to assume that this phenomenon would be less common in hypertrophic cardiomyopathy. Most importantly, however, our study identified an important association between abnormal intramural coronary arteries and objectively determined evidence of severe prolonged ischemia, that is, myocardial fibrosis. Altered intramural coronary arteries were more commonly present near or within areas of substantial fibrosis, and clusters of increased numbers of these arteries were often identified in transmural scars. In our view, this finding suggests that the intramural coronary artery abnormalities identified in hypertrophic cardiomyopathy are of pathophysiologic significance. We hypothesize that abnormal narrowed small arteries compromise coronary blood flow, resulting in myocardial ischemia which, if prolonged and severe, produces myocardial necrosis and fibrous tissue formation.

Conclusions. The "small vessel" intramural coronary artery disease identified in this study (in patients with and without left ventricular outflow obstruction) constitutes a common morphologic component of the disease process in patients with hypertrophic cardiomyopathy. The presence of abnormal intramural coronary arteries in some infants who died of hypertrophic cardiomyopathy implies that these abnormal arteries may be present from birth as part of the developmental abnormality in hypertrophic cardiomyopathy. The association of altered intramural arteries with myocardial fibrosis suggests that these vessels may contribute to the formation of myocardial fibrosis.

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