

Atherosclerotic Narrowing of the Left Main Coronary Artery

A Necropsy Analysis of 152 Patients with Fatal Coronary Heart Disease and Varying Degrees of Left Main Narrowing

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SUMMARY Histologic sections of the left main (LM) and the other three major coronary arteries were studied in 152 patients. The lumen of the LM in 35 patients was >75% narrowed; in thirty, 50–75%; and in 87, <50% narrowed. The patients with >75% narrowing were younger. Angina pectoris and hyperlipoproteinemia, specifically type II, were more common ($P < 0.02$) and acute transmural and healed subendocardial myocardial infarcts were less frequent ($P < 0.05$) in the patients with >75% LM narrowing than in

those with <50% narrowing. Of the three other major coronary arteries, the average number narrowed in the patients with >75% LM narrowing was 2.9; in those with 50–75% LM narrowing, 2.7, and in those with <50% LM narrowing, 2.4. Of the 35 patients with >75% LM narrowing, 33 had >75% luminal narrowing of each of the other three major coronary arteries. Narrowing of the LM, therefore, indicates severe narrowing of usually all major coronary arteries.

SEVERAL ANGIOGRAPHIC STUDIES focusing on the significance of 50% or greater narrowing of the left main (LM) coronary artery have appeared during the past four years.^{1–13} None of these studies, however, compared the various cardiac observations in the patients with severe LM coronary narrowing by angiography to observations in patients with lesser degrees of LM narrowing. Necropsy studies focusing on the LM coronary artery in patients with coronary heart disease have not appeared. This report attempts to fill this void by describing certain clinical and morphologic findings in 152 necropsy patients with symptomatic coronary heart disease and varying degrees of narrowing of the LM coronary artery. Observations in the patients with severe (>75%) LM narrowing are compared to those in patients with lesser degrees of LM narrowing.

Methods

In this laboratory the major extramural coronary arteries of patients with ischemic heart disease are subserially sectioned in the following manner.¹⁴ The arteries are excised from the heart intact, fixed in formalin, decalcified, cut at 5 mm intervals, processed in alcohol and xylene, and two histologic sections are prepared from each 5 mm segment. One section is stained by hematoxylin-eosin and the second by Movat's stain. The coronary arteries in approximately 250 patients with ischemic heart disease have been prepared now in this manner. The sections from these 250 patients were re-examined and those patients in whom sections were available for re-examination of all four major coronary arteries were included in this study. On the basis of histologic study of the cross-sections of left main coronary artery, the patients were divided into three groups, each determined by the maximal degree of LM narrowing: 1) >75% cross-sectional area narrowing; 2) 50–75% narrowing; and 3)

<50% narrowing. The clinical and necropsy records of the patients with adequate sections of all four major coronary arteries were then examined. Patients with significant valvular or congenital heart disease or nonatherosclerotic type coronary disease, for example, coronary embolism, were excluded from this study.

A total of 152 patients with adequate sections of each of the four major coronary arteries and without associated heart disease, other than systemic hypertension, were found and form the study group for this analysis.

Results

Of the 152 patients, the cross-sectional area of the lumen of the LM coronary artery was >75% narrowed in 35 patients (23%), 50–75% narrowed in 30 patients (20%), and <50% narrowed in 87 patients (57%) (tables 1 and 2).

Clinical Findings (table 1)

The average age of the 35 patients with >75% LM narrowing was lower (53 years) than in either of the two groups with lesser degrees of LM narrowing (both 59 years). The sex ratio was similar in all three groups (males: females = 3:1). The frequencies of histories of acute myocardial infarcts which healed, congestive cardiac failure and diabetes mellitus were similar in all three groups. The frequency of angina pectoris, however, differed significantly ($P < 0.02$) between those with severe LM narrowing and those without: 66% in the group with >75% and 40% in the group with <50% LM narrowing. Serum cholesterol and triglyceride levels were available in 83 of the 152 patients. (Most of these determinations were done in the Laboratory of the Molecular Disease Branch of the National Heart and Lung Institute formerly under the direction of Doctors Donald S. Fredrickson and Robert I. Levy.) Hyperlipoproteinemia was significantly ($P < 0.01$) more frequent in the patients with >75% LM narrowing than in those with <50% LM narrowing (43% to 16%). Of the 22 patients with type II hyperlipoproteinemia, 11 (50%) had >75% LM narrowing, and of the 12 patients with type IV, three had >75% LM narrowing. Death in all 152 patients was related to ischemic heart disease. Death occurred during or within three days

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TABLE 1. *Clinical Observations in Ischemic Heart Disease with Varying Degrees of Left Main Coronary Narrowing (152 Necropsy Patients)*

	Degree of left main narrowing			Totals
	>75%	50-75%	<50%	
Number patients	35	30	87	152
Ages (years); range (avg.)	28-80 (53)	29-91 (59)	26-85 (59)	26-91 (57)
Males: females	25:9	20:10	68:19	113:38
Angina pectoris	23 (66%)*	15 (50%)	35 (40%)*	73 (48%)
Clinical acute MI → healed	16 (46%)	11 (37%)	33 (38%)	60 (40%)
Systemic hypertension	16 (46%)	12 (40%)	55 (62%)	83 (54%)
Diabetes mellitus	8 (23%)	11 (37%)	28 (32%)	47 (31%)
Normal lipoprotein pattern	10 (29%)	7 (23%)	17 (20%)	34 (22%)
Unknown lipoprotein pattern	10 (29%)	15 (50%)	56 (64%)	81 (53%)
Hyperlipoproteinemia	15 (43%)*	8 (27%)	14 (16%)	37 (25%)
Type II	11 (31%)*	3 (10%)	8 (9%)	22 (14%)
Type III	1 (3%)	0	2 (2%)	3 (2%)
Type IV	3 (9%)	5 (17%)	4 (5%)	12 (8%)
Cause of death				
Acute MI	12 (34%)*	13 (43%)	49 (56%)*	74 (49%)
Sudden (coronary)	8 (23%)	7 (23%)	24 (28%)	39 (25%)
Coronary bypass operation	8 (23%)	5 (17%)	4 (5%)	17 (11%)
Congestive heart failure	1 (3%)	3 (10%)	3 (3%)	7 (5%)
LV aneurysmectomy	0	0	3 (3%)	3 (2%)
Cardiac catheterization	3/15 (3%)	0	1/17 (1%)	4/32 (3%)
Non-cardiac	3 (9%)	2 (7%)	3 (3%)	8† (5%)

*Comparison between patients with >75% to those with <50% left main narrowing is significant ($P < 0.05$).

†Seven of these 8 patients had previous clinical evidence of ischemic heart disease.

Note: The percentages refer to the number of patients present in a particular vertical column and they are not applicable horizontally. Abbreviations: MI = myocardial infarction; LV = left ventricle.

after cardiac catheterization in three (20%) of 15 patients with >75% LM narrowing, and in one (6%) of 17 with <50% narrowing of the LM coronary artery. Of the 17 patients who died during or shortly after a coronary operation, eight had >75% narrowing of the LM coronary artery.

Necropsy Findings (table 2)

The 35 patients with >75% narrowing of the LM had significantly ($P < 0.01$) more narrowing of the other three

major coronary arteries than did the patients with <50% narrowing of the LM: an average of 2.9 of the right, left anterior descending and left circumflex compared to 2.4. In the 35 patients with >75% LM narrowing, 94% had >75% narrowing of each of the other three major coronary arteries, whereas 53% of the group with <50% LM narrowing had similarly severe disease. The group with 50 to 75% narrowing of the LM fell midway between the other two groups in severity of atherosclerotic narrowing of the other

TABLE 2. *Necropsy Observations in Ischemic Heart Disease with Varying Degrees of Left Main Coronary Narrowing (152 Necropsy Patients)*

	Degree of left main narrowing			Totals
	>75%	50-75%	<50%	
Number patients	35	30	87	152
Coronary arteries				
LAD >75% narrowed	35 (100%)	30 (100%)	72 (83%)	137 (90%)
LC >75%	33 (94%)*	23 (77%)	66 (76%)*	122 (80%)
Right (Rt) >75%	34 (97%)*	28 (93%)	65 (75%)*	127 (84%)
LAD, LC & Rt >75%	33 (94%)*	23 (77%)	46 (53%)*	102 (67%)
Avg. no. of LAD, LC, & Rt >75% narrowed	2.9*	2.7	2.4*	2.5
Myocardium				
Acute MI	15 (43%)*	17 (57%)	56 (64%)*	88 (58%)
Transmural	11 (31%)*	11 (31%)	54 (62%)*	76 (50%)
Subendocardial	4 (11%)	6 (20%)	2 (2%)	12 (8%)
Healed MI	22 (63%)	20 (67%)	52 (60%)	94 (62%)
Transmural	9 (26%)	12 (40%)	36 (42%)	57 (38%)
Subendocardial	13 (37%)*	8 (27%)	16 (18%)*	47 (31%)
Heart weight (g)				
Range	300-600	300-640	300-750	300-750
Average M:F	416:353	489:403	479:423	467:401
M >400	15/25 (60%)	16/21 (76%)	55/66 (83%)	86/112 (77%)
F >350	6/8 (75%)	5/9 (56%)	13/18 (72%)	24/35 (69%)

*Comparison between patients with >75% to those with <50% left main narrowing is significant ($P < 0.05$).

Note: The percentages refer to the number of patients in a particular vertical column and they are not applicable horizontally. Abbreviations: F = female; M = male; LAD = left anterior descending; LC = left circumflex; MI = myocardial infarction.

three major extramural coronary arteries. No patient had total occlusion (100% narrowing) of the LM coronary artery. The frequency of transmural left ventricular myocardial scars was similar in the three groups; in contrast, subendocardial scars were significantly ($P < 0.05$) more frequent in the 35 patients with $>75\%$ LM narrowing compared to the 87 with $<50\%$ LM narrowing (37% to 18%). Acute myocardial infarcts of the transmural type (not of the subendocardial type) were significantly ($P < 0.01$) less frequent in the patients with $>75\%$ LM narrowing compared to those with $<50\%$ LM narrowing (31% to 62%). Sections of the four major coronary arteries in one patient with severe narrowing of the LM are shown in figure 1.

Comments

The first two studies,^{1,2} both appearing in 1972, on patients with 50% or greater narrowing of the left main (LM) coronary artery by angiography emphasized a high frequency in these patients of severe angina pectoris, particularly crescendo and rest types, a high frequency of a highly positive exercise test, an increased mortality during or shortly following both cardiac catheterization and aorto-coronary bypass procedures, and a generally poor prognosis (table 3). Subsequent studies³⁻¹³ of patients with 50% or greater narrowing of the LM coronary artery by angiography (summarized in table 3) demonstrated a poorer prognosis in the patients with 50% or greater LM narrowing managed medically than in those treated by aorto-coronary bypass operations, but an increased mortality during or shortly after cardiac catheterization has not been confirmed. It is now generally recognized that there are no clinical parameters which indicate "significant" LM coronary narrowing. Indeed, coronary angiography is the only means of

clinically diagnosing "significant" LM coronary narrowing.

The observations (summarized in table 3) on patients with 50% or greater narrowing of the LM coronary artery by angiography were not compared to findings in patients with $<50\%$ narrowing of the LM coronary artery. Naturally the frequency of angina pectoris was high (94%) (table 3) in these patients because this symptom was the one usually prompting the angiographic study. The present study, however, does show that among necropsy patients with coronary heart disease, the frequency of angina pectoris is significantly ($P < 0.02$) higher in those with $>75\%$ LM narrowing than in those with $<50\%$ LM narrowing (66% to 40%).

Death during or shortly after cardiac catheterization occurred in three of 15 patients (20%) with $>75\%$ LM narrowing in the present necropsy study and in only one of 17 patients (6%) with $<50\%$ LM narrowing. In contrast, death during or shortly after cardiac catheterization (angiography) occurred in 18 (3%) of the 561 patients reported with 50% or greater narrowing of the LM by angiography (table 3). More recent studies^{5, 8-13} of patients with $>50\%$ LM narrowing by angiography have not shown an increased mortality during cardiac catheterization in these patients (table 3).

The mortality during or shortly after aorto-coronary bypass operations in the patients with significant LM narrowing may be higher than in the patients with lesser degrees of LM narrowing. Of the 235 reported patients with 50% or greater narrowing of the LM coronary artery by angiography and in whom this procedure was performed (table 3), 30 (13%) died during or in the early postoperative period. In the present necropsy study, of the 17 patients who underwent aorto-coronary bypass operations, eight had $>75\%$ LM narrowing and four had $<50\%$ LM narrowing.

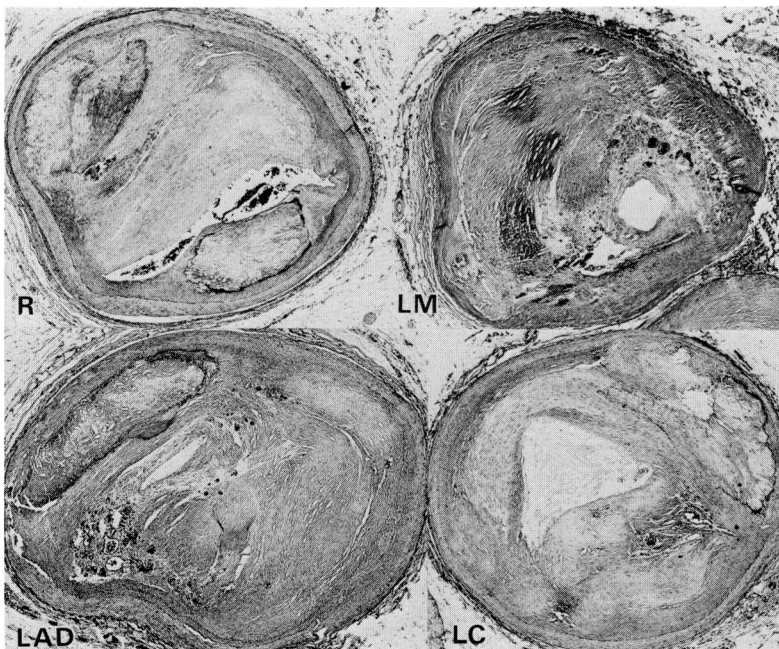


FIGURE 1. Photomicrographs of histologic sections of coronary arteries in a 57-year-old man (A72-78) who died 24 hours after aorto-coronary arterial bypass operation for severe angina pectoris. All four major coronary arteries were $>75\%$ narrowed by atherosclerotic plaques. The section of right (R) coronary artery is approximately 3 cm from its aortic ostium. The sections of the left anterior descending (LAD) and left circumflex (LC) are immediately distal to their origins from the left main (LM). Movat stains (R, LC and LAD); hematoxylin and eosin stain (LM); $\times 24$ (R and LC); $\times 27$ (LM); $\times 31$ (LAD).

TABLE 3. Observations in Reported Patients with 50% or Greater Narrowing of the Left Main Coronary Artery by Angiography

	Cohen and Gorlin ¹¹ (1972 + 1975)	Lavine et al. ⁵ (Dec 1972)	Zeft et al. ⁸ (Jan 1974)	Khaja et al. ⁵ (Aug 1974)	Lim, Proudfit Sones ⁹ (Aug 1975)	De Mott et al. ¹⁰ (Aug 1975)	Talano et al. ¹² (Aug 1975)	Sung et al. ¹³ (Aug 1975)	Totals
Degree of CA narrowing	50% or >	70% or >	75% or >	50% or >	50% or >	50% or >	>50%	50% or >	—
Number of patients	73	30	56	28	141	58	145	30	561
Angina pectoris	68(93%)	27(90%)	56(100%)	28(100%)	120(85%)	55	141(97%)	30(100%)	525(94%)
Congestive heart failure	4(5%)	—	3(5%)	5(18%)	13(9%)	—	—	—	25/298(8%)
LV contractility	43(59%)	24/29(86%)	34(61%)	17(60%)	52/119(44%)	—	110(76%)	27(90%)	327/480(68%)
Abnormality in other 3 CAs (Rt., LAD, LC)	49(67%)	29(97%)†	53(95%)†	18(64%)	71(50%)	28(49%)	140(97%)	27(90%)	540(96%)
2 vessel	14(19%)	0	—	10(36%)	41(29%)	18(31%)	—	2(7%)	—
1 vessel	4(6%)	1	—	0	25(18%)	10(17%)	—	—	—
0 vessel	6(8%)	0	3(5%)	0	4(3%)	2(2%)	5(3%)	1(3%)	21(4%)
% of all patients undergoing CA angiography	4%¶	—	2%	—	6%	2%	—	—	4%
Ages: range (avg.)	32-75(52)	40-70(54)	39-66(55)	34-64(53)	26-72(52)	—	—(55)	40-71(54)	26-75(53)
M:F	61:12	25:5	47:9	22:6	133:8	—	126:19	20:10	434:69(6:1)
Hypertension	—	—	—	—	48(34%)	16	—	9(30%)	73/229(32%)
Hypercholesterolemia	—	13§	—	—	—	14	—	10(33%)	46/100(46%)
OMI (history)	—	19(63%)	—	11(39%)	—	11	—	17(57%)	113/332(34%)
OMI (ECG)	26(36%)	19(63%)	—	—	40	12	—	—	69/229(30%)
Normal ECG	—	2(7%)	—	—	55	14/19(74%)	—	—	62/79(79%)
Abnormal stress ECG	34/42(81%)	7(23%)**	—	14/18(77%)	—	12(21%)	—	—	19/88(22%)
Calcium in LM CA	—	3(10%)	—	—	—	—	5(3%)§§	0	18/561(3%)
Deaths peri-catheterization	6††	—	0	—	3‡‡	—	10/89(11%)	1/19(5%)	30/235(13%)
Deaths peri-CABP	—	2/18(11%)	6(11%)	7/25(28%)***	—	4/28(14%)†††	—	—	—

*75% or greater narrowing in 25 of the 28 patients. †Height of the 30 had total occlusion of the right coronary artery and >70% of the left main. ‡Two percent in 1964-71 series and 8% in 1971-73 series. § >275 mg/100 ml. **Image intensification fluoroscopy. ††Only 1 death in last 41 studies. ‡‡All before 1967. §§In 83 angiographic procedures. §§§No deaths in last 18 months. ***Three of the 7 deaths also had ventricular aneurysmectomy. †††Only 1 death in last 24 patients.

Abbreviations: CA = coronary artery; CABP = coronary-artery-bypass operation; F = female; LAD = left anterior descending; LC = left circumflex; LM = left main; LV = left ventricular; M = male; OMI = old myocardial infarction; Rt = right.

These numbers also suggest that mortality from this procedure is increased in the individuals with greater LM narrowing. Despite its probable higher mortality, this operation has usually achieved striking symptomatic benefit to the patients with both severe and less severe LM narrowing, and also survival is prolonged in the patients with significant LM narrowing by angiography compared to those treated medically.¹⁰⁻¹³

An observation in the present study, not commented on in previous angiographic studies (table 3), is the increased frequency of type II hyperlipoproteinemia among the patients with >75% LM narrowing compared to the patients with <50% LM narrowing. Of our 22 patients with documented type II hyperlipoproteinemia, 11 (50%) had >75% LM narrowing; of the 12 with type IV, 25% had similar LM narrowing, and of the 34 patients with known normal lipoprotein patterns, 29% had >75% LM narrowing. Hypercholesterolemia has been mentioned in three previous studies of patients with LM narrowing by angiography of 50% or greater:^{2, 10, 13} of 100 patients with >50% LM narrowing by angiography and serum cholesterol determinations, 46% had elevated (>265 mg/100 ml) levels (table 3). It is likely that most of these 46 patients also had type II hyperlipoproteinemia.

More severe atherosclerosis in the ascending portion than in the descending portion of aorta has been observed in patients with the homozygous variety of type II hyperlipoproteinemia.^{15, 16} It is our impression that the amount of atherosclerosis in the ascending aorta also is greater in patients with the heterozygous form of type II hyperlipoproteinemia compared to patients with type IV hyperlipoproteinemia or to patients with normal lipoprotein patterns.^{15, 16} In the heterozygous patients, however, the atherosclerosis in the ascending aorta is not nearly as extensive as in the abdominal aorta.^{15, 16} Whenever the ascending aorta is involved by atherosclerotic plaques, it would appear reasonable that extension into the proximal portions of the coronary arteries would be more frequent. Of our 22 patients with type II hyperlipoproteinemia, one was a homozygote and both his LM and proximal right coronary arteries were narrowed >75%.^{15, 16} Severe (>75%) narrowing of the LM coronary artery also was present in 10 of the 21 patients with the heterozygous form of type II hyperlipoproteinemia.

All previous angiographic studies on patients with >50% LM coronary narrowing have demonstrated extensive disease in one or more of the other three major coronary arteries¹⁻¹³ (table 3). Most commonly, significant lesions were demonstrated in the left anterior descending, followed by left circumflex and, lastly, the right coronary artery. It is most unusual for a significant lesion to be present in only one of the other three major coronary arteries when the LM is significantly narrowed, and it is very rare for the LM to be the only major artery significantly involved. Indeed, in only 21 (4%) of the 561 reported patients with 50% or greater LM narrowing by angiography was the LM the only major coronary artery involved (table 3). None of our patients studied at necropsy had severe coronary narrowing limited to the LM. Of our 35 patients with >75% LM narrowing, 94% also had >75% narrowing of the right, left anterior descending

and left circumflex coronary arteries. In contrast, of the 87 patients with <50% LM narrowing, 53% had >75% narrowing of each of the other three major coronary arteries. Thus, marked narrowing of the LM coronary artery is indicative of severe, diffuse coronary atherosclerosis, and may account for the poor prognosis of these patients.¹⁷

Myocardial damage is frequent in patients with significant LM coronary arterial narrowing. Among the previously reported patients with 50% or greater narrowing of the LM by angiography (table 3), 327 (68%) of the 480 patients with left ventricular angiography had either focal or diffuse abnormalities in left ventricular contraction. Among our 152 necropsy patients, 94 (62%) had subendocardial or transmural left ventricular scars; the percent with transmural scars was not significantly different among the three groups but the percent with subendocardial scars was significantly greater in the patients with >75% LM narrowing compared to the patients with <50% LM narrowing (37% to 18%). In contrast, acute myocardial infarcts (myocardial necrosis contrasted to fibrosis) were observed in 88 (58%) of the 152 patients and the percent with transmural necrosis was significantly less among the patients with >75% LM narrowing contrasted to the patients with <50% LM narrowing. Overt chronic congestive cardiac failure was present in 25 (8%) of the 298 patients previously reported with LM narrowing of 50% or greater by angiography (table 3), and it was severe in 5% of our necropsy patients, not significantly different in any of the three groups.

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Influence of Dobutamine on Regional Myocardial Blood Flow and Ventricular Performance During Acute and Chronic Myocardial Ischemia in Dogs

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SUMMARY The data from this study document that dobutamine is a powerful inotropic agent in anesthetized dogs with acute myocardial ischemia and in awake, unsedated ones with chronic myocardial infarction. Dobutamine significantly increases heart rate at relatively small doses in anesthetized dogs with acute myocardial ischemia but considerably larger amounts of dobutamine are required to significantly increase heart rate in awake, unsedated dogs with myocardial infarction. Dobutamine also significantly increases regional myocardial blood flow to all areas of the heart at 20 μ g/kg/min in both anesthetized dogs with acute myocardial ischemia and awake, unsedated ones with myocardial infarction. However, in anesthetized dogs 20 μ g/kg/min of dobutamine

significantly increases epicardial ST-segment elevation during acute myocardial ischemia. Propranolol prevents the inotropic and chronotropic effects of dobutamine in both anesthetized and awake, unsedated dogs. This study suggests that during experimental acute myocardial ischemia dobutamine given at doses that significantly increase heart rate and contractility may increase the extent of myocardial damage. The data also suggest that this agent should be of value in the setting of severe myocardial depression without associated severe coronary artery disease to increase cardiac contractility at doses that do not markedly alter heart rate. The hemodynamic and coronary blood flow effects of dobutamine in patients with and without severe coronary artery disease should be evaluated.

DOBUTAMINE HAS RECENTLY been shown to be a powerful inotropic agent in experimental animals, and its chronotropic effect seems minimal.^{1,2} This drug might be more useful in treating "low output" states in patients with ischemic heart disease than certain other currently existing medications that are known to adversely effect the extent of myocardial damage.³ The crucial factor is its relative influence on several different parameters including contractile state, left ventricular volume, heart rate, and regional myocardial blood flow. Thus if dobutamine's major influence is to increase contractility and/or heart rate, then one would expect it to have an adverse effect on the extent of myocardial damage during myocardial ischemia. On the other hand, if dobutamine produces a greater effect on coronary blood flow and especially flow to the ischemic area than on contractility then it will either not extend, or might

even reduce the extent of myocardial damage during myocardial ischemia. The present study was designed to test the influence of dobutamine on contractility, regional myocardial blood flow, and heart rate in anesthetized dogs with acute myocardial ischemia and in awake, unsedated dogs with chronic myocardial infarction.

Methods

Anesthetized Dog Studies

Mongrel dogs were anesthetized with Nembutal (30 mg/kg), intubated and ventilated with a Harvard respirator, using a gas mixture of 95% oxygen and 5% carbon dioxide. The chest was opened through a median sternotomy, the proximal left anterior descending coronary artery (LAD) was freed and a reversible ligature placed around it. Left ventricular systolic pressure and the maximal rate of pressure rise (LV dp/dt) were measured through a short, wide-bore Y-shaped metal cannula inserted through the apex of the left ventricle. LV dp/dt was measured by continuously differentiating left ventricular systolic pressure. LV dp/dt/P was computed from the maximal rate of left ventricular pressure rise divided by developed pressure during isovolumic systole.⁴ Proximal aortic pressure was measured through a short, wide-bore polyethylene catheter inserted into the aortic arch through the left carotid artery. Epicardial ST-segments were measured in the anesthetized animals using a rounded, smooth tip electrode attached to

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