

Myocardial Infarct Size and Location in Relation to the Coronary Vascular Bed at Risk in Man

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SUMMARY Recent infarcts were compared with the anatomic boundaries of the involved vascular bed in human hearts to determine the amount and location of necrosis in relation to the myocardium at risk. The coronary arteries were injected with BaSo₄ in 18 human hearts with 3–16-day-old infarcts. Thin (3–4-mm) slices were cut at 10–15-mm intervals, photographed, x-rayed and used for histologic analysis. Infarct outlines were traced from gross photographs using histologic confirmation of infarct boundaries, and the vascular bed was independently traced from the x-rays. Ischemic bed size and infarct size were then calculated by computerized planimetry. Infarct size ranged from 13–72% of the left ventricle (mean $30 \pm 3.6\%$) and was linearly related to the size of the occluded vascular bed ($r = 0.93$). However, the infarcts were always smaller than the occluded beds. They involved 50–88% of the ischemic bed (mean $69 \pm 3.0\%$) due to variation in the transmural extent of necrosis. A lateral zone of viable muscle within the ischemic bed was present but consistently narrow (mean 1.7 ± 0.3 mm) so that the infarcts involved $93 \pm 2.3\%$ of the width of the bed at risk. Thus, ischemic bed size is a major determinant of infarct size in fatal human infarcts. When natural limitation of infarct size occurs, it is due primarily to limitation of the transmural extent of necrosis.

INTERVENTIONS designed to limit infarct size after coronary occlusion are being closely examined. Fundamental to this goal is the presence of ischemic but reversibly injured cells that would eventually die without therapy. The exact location of these cells within the distribution of an occluded coronary artery in animal models remains controversial.^{1–16} Classically, this myocardium at risk for infarction has been considered to be in a concentric peripheral zone of intermediate ischemia surrounding a severely ischemic core.¹ Recent studies in dogs suggest, however, that at the subendocardial lateral border of an infarct the transition from well-perfused to severely ischemic tissue is sharp.^{2, 3} Reimer et al.^{4, 5} have demonstrated that cell death in an evolving acute canine myocardial infarct progresses in a transmural wave front over a period of 3–6 hours, but that the subendocardial, lateral boundaries of the infarct are established within the first 40 minutes. Variation among dogs in the size of completed infarcts after permanent coronary occlusion is a function of the size of the anatomic vascular bed and of the transmural extent of the infarct within this area at risk. Variation among dogs in the transmural extent of infarction is primarily a function of the amount of collateral blood flow supplying the subepicardial myocardium.⁵

Although other authors concluded that human infarcts are usually smaller than the ischemic area at risk,^{17–20} the anatomic relationship between an infarct and the vascular bed at risk in man has not been well studied.²¹ The present study was done to compare, by detailed postmortem gross, histologic and radiographic analysis, the size and location of acute infarcts

with the anatomic distribution of the occluded coronary artery in human hearts. We were particularly interested in the amount of viable myocardium that remained at the lateral border of the anatomic vascular bed at risk.

Materials and Methods

The human hearts used in this study were collected from 1970–1979 in the Duke University Pathology Department. Hearts were included in the study if (1) the infarct was 3–16 days old, (2) the infarct was non-circumferential, (3) there was no old infarct in the vascular bed of the recent infarct, (4) the infarct was not a perioperative infarct associated with coronary bypass surgery, and (5) adequate materials remained from the initial study of the heart done at the time of autopsy. Infarcts more than 3 days old were selected so that infarct boundaries would be sharply defined. Old infarcts were eliminated to avoid underestimation of infarct size because of shrinkage that occurs with organization and fibrosis.²²

To define the vascular bed that had been at risk of infarction, relative to the actual infarct which occurred, serial sections of the coronaries were examined at 2-mm intervals and the location of acute or chronic stenoses and/or occlusions were carefully mapped. The approximate location of the critical coronary lesion was identified by noting the point of origin of major coronary branches and noting whether myocardium supplied by such branches was included in the infarct. The most severely stenotic point in this general segment of the involved vessel was considered to be the critical lesion. The myocardium at risk then was defined as all that myocardium in the anatomic distribution of the involved vessel(s) distal to this critical lesion(s).

The coronary arteries had all been injected at their origins with a suspension of barium sulphate and gelatin, and anteroposterior and lateral x-rays of the whole heart had been taken (fig. 1). The ventricles then

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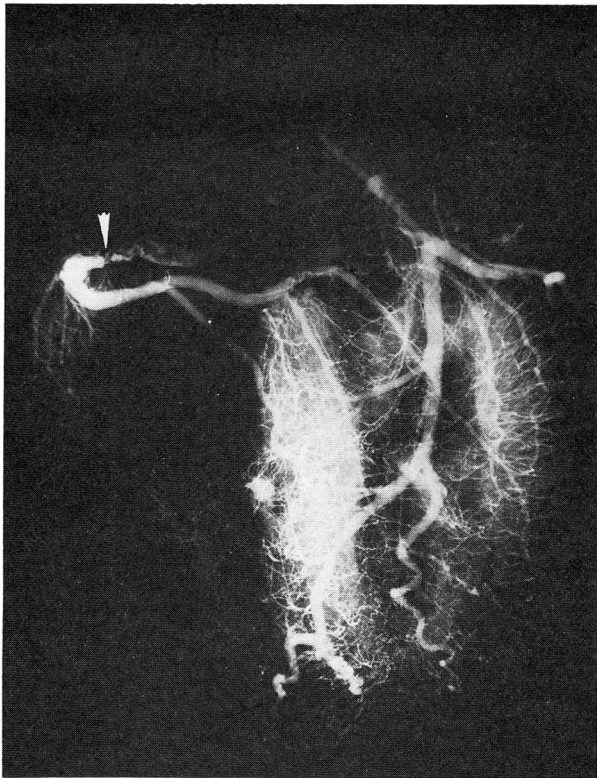


FIGURE 1. An x-ray (anteroposterior view) showing the location of a right coronary lesion associated with a posterior infarct. All coronary arteries were injected with barium sulfate.

were cut into four or five cross sections (fig. 2) that were photographed (fig. 3A) and x-rayed. Sections 3–4 mm thick were then cut just above or below the photographed surface and were x-rayed (fig. 3B) and processed for circumferential histologic analysis.

The gross photographs were enlarged and traced and the tracings duplicated. The infarct was drawn on one copy of the tracing based on gross and histologic analysis. All of the infarcts were recent or organizing infarcts (as defined by the criteria for inclusion). Thus, all of the infarcts contained a central core of coagulation necrosis and a peripheral zone that varied, according to the age of the infarct, from necrotic muscle with an acute inflammatory infiltrate to granulation tissue with early collagen deposition. Thus, the boundaries of these infarcts, although often irregular or patchy, were sharply defined from adjacent surviving myocardium. Any myocytolysis or any very acute necrosis associated with the patient's agonal course was not considered to be part of the infarct in question.

The coronary vascular bed distal to the critical lesion was independently drawn on a second copy of the tracing based on thin section x-rays. Gross material, x-rays of the whole heart, and thick section x-rays were used to identify the proximal source of intramyocardial penetrating arteries. We found that horizontal sections 3–4 mm thick were thin enough to avoid the apparent overlap between vascular beds that occurs on x-rays of thicker sections, and provided op-

timum detail to allow determination of the boundaries between vascular beds.

In the free wall we did not routinely observe intramyocardial collateral connections between adjacent vascular beds. In the septum, however, there were frequent intramyocardial connections between the septal branches of the anterior descending and the right coronary arteries that often made determination of septal boundaries difficult. In cases where such collaterals were present, we chose the most narrow point of the connecting vessel as the vascular bed boundary.

The tracings of the infarct and vascular bed were superimposed (fig. 4) to make one composite tracing on which the distribution of the vascular bed and infarct could be compared. Infarct size and vascular bed size were determined for each heart, using computerized planimetry of the tracings of each slice as defined by Ideker et al.²⁸ These results are expressed as percents of the left ventricle. The circumferential dimensions of the infarct and vascular bed were measured one-third of the distance between endocardium and epicardium in subendocardial infarcts and midway between the endocardium and epicardium in infarcts involving more than half of the wall thickness. The width of the infarct in the lateral dimension was calculated as a percent of the width of the vascular bed at risk. In addition, the lateral dimensions of viable myocardium within the vascular bed were measured.

All data are expressed as the mean $\pm$ SEM. Statistical comparison between groups was done using the nonpaired *t* test.

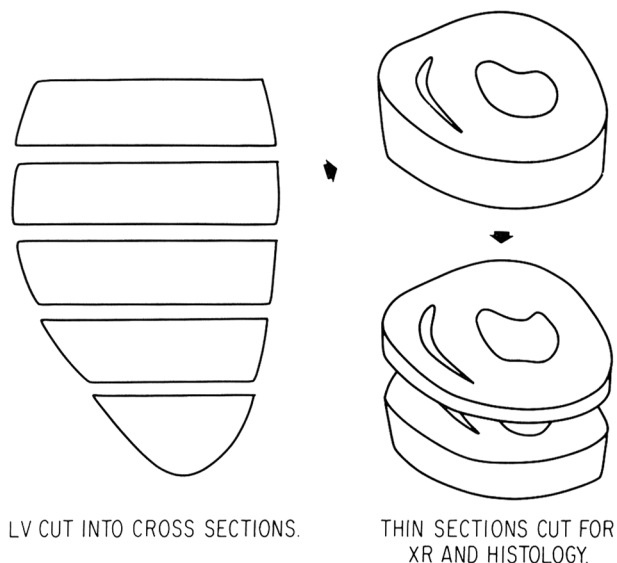


FIGURE 2. Diagram of the way in which the hearts were sectioned. The left ventricle (LV) of each heart was divided into four or five horizontal cross sections that were photographed and x-rayed. Three- to 4-mm-thick sections were then cut just above or below the photographed surface and were x-rayed and processed for circumferential histological analysis. Thus, the gross and microscopic analysis of the infarct and the x-ray determination of the vascular bed boundaries were all taken from the same thin section.



FIGURE 3. (A) Gross photograph of a thick cross section and (B) x-ray of a thin slice for the same heart as in figure 1. The border of the right coronary bed is indicated by the black line in A. The boundaries of the vascular bed are shown by the white lines in B.

Results

Description of Hearts

Ninety-nine infarcts 3–16 days old were identified. Of these, 18 were used in this study (fig. 5). The others were eliminated: 17 were circumferential, 37 had old infarcts in the same vascular region, 11 were associated with coronary bypass surgery and in 16, adequate gross materials were no longer available.

Of the 18 hearts studied, 15 involved the myocardium in the distribution of a single coronary artery. Of these, four hearts had infarcts in the circumflex (LCC) vascular bed, three had infarcts in the right coronary (RC) bed, and eight had infarcts in the anterior descending (LAD) bed. Three of the 18 hearts had an infarct that involved myocardium supplied by more than one major coronary artery (table 1). Thus, critical lesions were identified in 22 coronary arteries. Eight of these arteries were occluded by acute thrombi, one by an embolus, and one by intramural hemorrhage into a plaque. Eight of these 10 vessels with acute occlusions had already been narrowed $\geq 90\%$ by preexisting atherosclerosis. Six arteries had old occlusions, and

six had subtotal stenosis (five $\geq 95\%$ and one 85%) but neither recent nor old total occlusion.

The severity of disease in the other major coronary arteries was also recorded for each heart. Severe disease was defined as 85% or greater stenosis of the lumen based on cross-sectional area. (This corresponds to a 75% narrowing of the vessel diameter, commonly considered to indicate severe disease in angiographic studies.) Six hearts had one-vessel disease, six had two-vessel disease and six had three-vessel disease. Eight hearts had an old infarct in a vessel bed separate from the one containing the acute infarct.

There was a wide variation in how well the occluded vascular beds filled with BaSO_4 . In the infarcted region, 10 hearts had good perfusion in all major vessels, three hearts had poor perfusion and the other five had intermediate degrees of filling. In the hearts in which the vessel bed to be studied was poorly perfused, determination of the vascular bed was made largely from the distribution of the vessels in the nonoccluded areas. The adjacent vessel beds were always well perfused, so the boundaries between vascular beds still

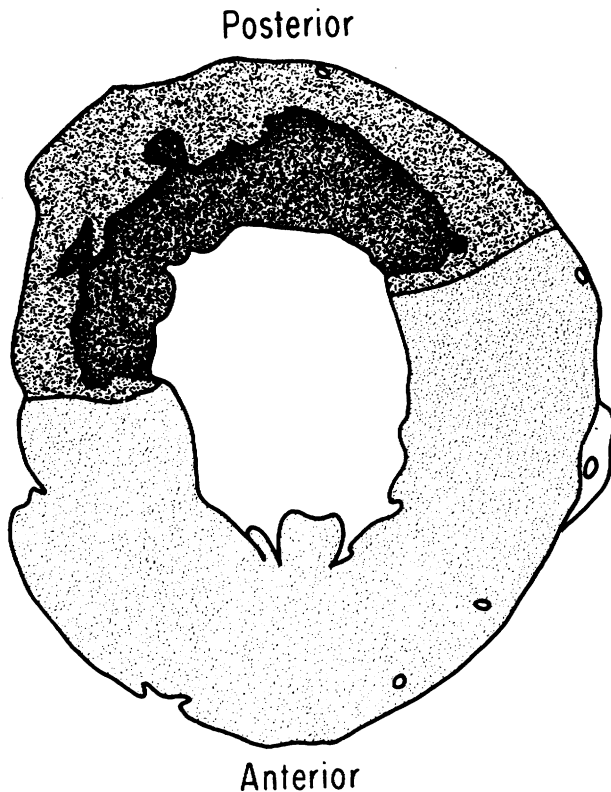


FIGURE 4. Superimposition of tracings of the infarct and the vascular bed for determination of vessel bed size, infarct size and measurements of the lateral dimensions. The lateral border of viable muscle between the lateral extent of the infarct and the vessel bed was measured in mm.

could be accurately defined. There was no difference in the size of the border zone measured in hearts with well filled and poorly filled vessels.

Vascular Bed Size and Infarct Size

The size of the vascular bed at risk and infarct size were calculated for each heart and were expressed as a percentage of the total LV myocardium (table 1). The vascular bed that was considered to be the myocardium potentially at risk of infarction was that myocardium in the anatomic distribution of vessels distal to the critical lesions, as defined above. The size of the

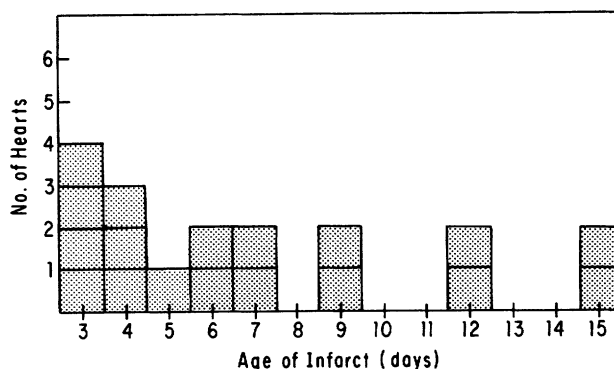


FIGURE 5. The ages, based on clinical history and confirmed by histology, of the 18 infarcts used in this study.

vascular bed at risk ranged from 21–83% of the left ventricle (average $42 \pm 3.9\%$). Infarct size ranged from 13–72% of the LV (average $30 \pm 3.6\%$). The average infarct size was closely related to the vascular bed size at risk ($r = 0.93$) (fig. 6). Thus, in these fatal human infarcts, the vessel bed size was a major determinant of infarct size.

Lateral Border Width

The average width of the lateral border of viable muscle was calculated as the difference between the lateral edge of the necrosis and the lateral border of the vascular bed. One hundred twenty-eight borders were measured in the 18 hearts. The average border size for each heart (table 1) was used to calculate a mean for all hearts of 1.7 ± 0.3 mm. The circumferential width of the infarcts averaged $93 \pm 2.3\%$ of the width of the bed at risk. In all but four hearts (nos. 5, 6, 8 and 13), the width of the infarct was greater than 92% of the width of the bed at risk. Thus, in these infarcts the lateral border was small. However, in case 5, the infarct was nearly transmural but the lateral dimension showed a much larger border zone. In this case, the width of the infarct measured at two levels was only 64% of the vascular bed width. This larger border of viable myocardium was supplied by a single penetrating coronary artery and was on only one side of the infarct. The other side of this infarct had a typically small border zone. Aside from this exception, the lateral border of viable muscle was equally narrow in small and large vascular beds and did not differ between RC, LAD or LCC infarcts. Because large collateral connections were frequently observed in the septum between the septal perforating branches of the LAD and the RC we expected to see a larger border for the septal boundaries of LAD and RC infarcts. However, comparison of the septal boundaries with the free wall boundaries showed no difference (fig. 7).

Variation of Infarct Size Within the Vascular Bed at Risk

The amount of vascular bed infarcted ranged from 50–88% (average $69 \pm 3.0\%$) (table 1). Thus, the amount of viable muscle within the occluded vascular bed ranged from 12–50% (fig. 8). The lateral border of viable muscle was small; thus, the variation in infarct size was largely due to variation in the transmural extent of the infarct. The natural variation among hearts in the transmural extent of the infarct may have been due to variation in collateral blood flow. However, we could not estimate the number or size of collateral connections from the postmortem angiograms because of intrinsic variation among hearts in the degree of small vessel filling. There was no relationship between the variation in the transmural extent of the infarct and the presence or absence of complete coronary occlusion, the general severity of coronary disease, or the presence of an old infarct in an adjacent vascular bed. However, the number of hearts in this study may have been too small to detect such relationships.

TABLE 1. *Ischemic Vascular Bed Size, Infarct Size and the Width of Viable Muscle at the Lateral Margins of the Infarct but Within the Occluded Vascular Bed. Patients are Ranked According to Increasing Vascular Bed Size*

Pt	Vascular beds involved	Critical coronary lesions (% narrowing)†	Ischemic bed size (% of LV)	Infarct size (% of LV)	Infarct size (% of ischemic bed)	Average border width (mm)
1	LCC	100	21	13	62	-0.6
2	RC	95	24	15	63	2.0
3	LCC	0 + 100 (E)	26	13	50	0.5
4	LAD	85	29	18	62	2.4
5	LCC	100	29	17	59	4.8
6	LAD	100	31	17	55	2.7
7	RC	90 + 10 (T)	34	22	65	1.0
8	RC	95 + 5 (T)	37	20	54	3.3
9	LAD	95 + 5 (T)	38	31	82	1.3
10	LAD	100	39	26	67	1.0
11	LCC	95 + 5 (T)	43	37	86	0.6
12	LAD	95 + 5 (IMH)	43	36	84	0.3
13	LCC/LAD*	95 + 5 (T)/95/95	50	34	68	3.5
14	LAD	75 + 25 (T)	52	46	88	1.4
15	LAD	90 + 10 (T)	54	45	83	1.0
16	RC/LAD	95/100	65	37	57	2.6
17	LAD	100	66	40	61	2.8
18	LAD/LCC	95/95 + 5 (T)	83	72	87	0.7
Mean			42	30	68	1.7
± SEM			± 3.9	± 3.6	± 3.0	± 3.0

*The infarct in case 13 involved the LCC, optional diagonal, and first diagonal branch of the LAD artery.

†The first numbers listed under critical coronary lesions indicate old atherosclerotic narrowing. Superimposed narrowing by acute lesions are indicated in the 10 arteries in which acute occlusions were observed.

Abbreviations: LV = left ventricle; LCC = left circumflex coronary artery; RC = right coronary artery; LAD = left anterior descending coronary artery; E = embolus; T = thrombus; IMH = intramural hemorrhage.

Discussion

Infarct Size as a Function of the Anatomic Vascular Bed at Risk

The anatomic region supplied by an occluded artery defines the area potentially at risk of infarction. Through a series of experimental studies in dogs^{5, 6} we have shown that this anatomic vascular bed is a major determinant of infarct size in untreated animals. Much of the variability in infarct size among animals with occlusion of a given coronary artery is due to variation in the size of the vessel bed. Because the vascular anatomy cannot be altered by therapy it is a constant predictive index of infarct size in studies of potentially protective therapies and can be used to improve the accuracy of such studies.

One of the aims of the present study was to determine to what extent the geometry and size of human infarcts are related to the involved vascular bed apparently at risk. The boundaries of the involved vascular bed were determined from x-rays of serial cross sections of the ventricles after postmortem coronary injection with barium sulfate suspensions. Similar techniques have been used by others.^{7, 24-27} The

study demonstrated a close linear correlation between infarct size and the size of the vascular bed. Thus, in humans as in dogs, ischemic bed size is a major determinant of infarct size.

Location of Human Myocardial Infarcts in Relation to the Vascular Bed at Risk

In this study, infarct size, as a percent of the vascular bed at risk, ranged from 50-88%. Thus, a widely variable proportion of the occluded vascular bed, ranging from 12-50%, remained viable after completion of the infarcts. Theoretically, the variation of the percent of the vascular bed infarcted could have been due to variation in either the transmural or lateral dimensions of the infarcts within the occluded vascular beds. However, we found that, in general, the variation in the percent of the vascular bed infarcted was due to variation in the transmural extent of the infarct. With one exception, the lateral boundary of the infarct closely approximated the lateral extent of the vascular bed. Thus, the average lateral border of viable muscle within the anatomic vascular bed at risk was only 1.7 ± 0.3 mm and the lateral width of the in-

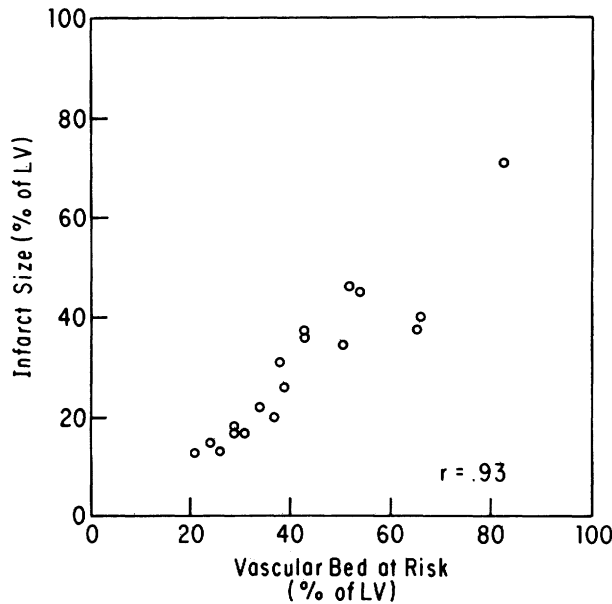


FIGURE 6. Infarct size vs the size of the vascular bed at risk ($r = 0.93$), indicating that in these fatal human infarcts the size of the vascular bed at risk was a primary determinant of infarct size. LV = left ventricle.

infarct averaged $93 \pm 2.3\%$ of the width of the vascular bed.

These results may not be representative of all human infarcts for two reasons. First, this was an autopsy study of recent infarcts, all of which were fatal. Presumably, these infarcts were larger, on the

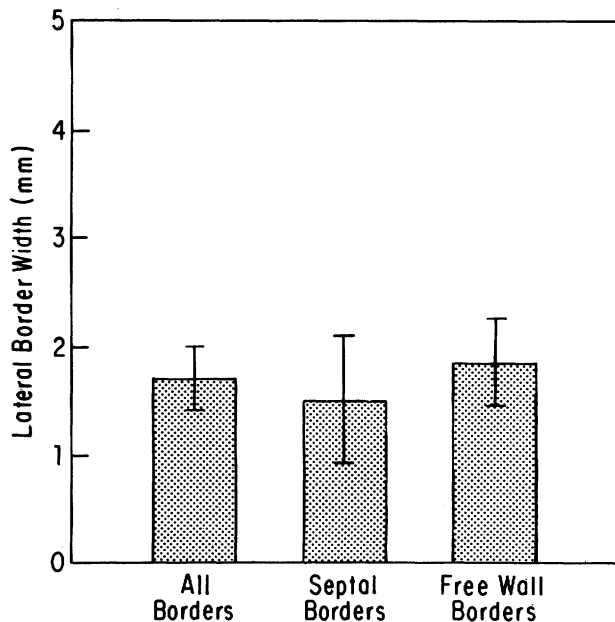


FIGURE 7. Histogram showing that the lateral border of viable muscle in fatal human infarcts is small for both septal and free wall borders. The lateral border of viable muscle remaining in the vascular bed averaged 1.7 ± 0.4 mm. The width of the infarct in the lateral dimension averaged $93 \pm 2\%$ of the width of the vascular bed in the lateral dimension.

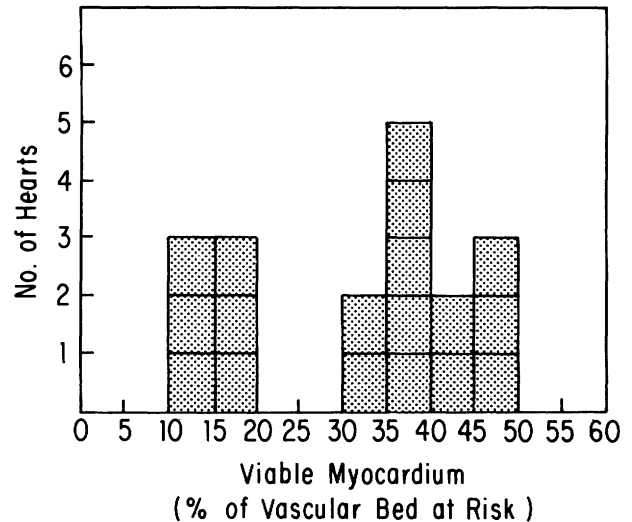


FIGURE 8. The amount of myocardium that was not infarcted within the vascular bed distal to the occlusion. The amount of viable myocardium ranged from 12–50% of the vascular bed and was primarily located in the subepicardial region.

average, than nonfatal infarcts. Nevertheless, the proximity of the lateral boundaries of the infarcts to the boundaries of the vascular bed at risk was similar in the smallest and largest infarcts in the present study. The major differences between small and large infarcts were the size of the vascular bed at risk and the transmural extent of the infarcts in these beds. Second, in hearts with very extensive coronary disease and multiple collateral interconnections, it seems likely that some areas of myocardium would have been perfused by collateral arteries rather than the coronary artery that was anatomically distributed to the region. Thus, an occlusion of one vessel could cause infarction in collateral-dependent areas beyond the boundaries of its anatomic distribution. This is the most likely explanation for the three infarcts in the present study that involved more than one coronary vascular bed (cases 13, 16 and 18). Even in these cases, the lateral boundaries of the infarct approximated the lateral boundaries of the combined vascular beds. Nevertheless, in hearts with extensive collateralization, the actual source of myocardial perfusion may have no obvious relationship to the anatomic distribution of the coronary arteries. In such hearts, the myocardium at risk would not be determinable. Such complicated hearts were not encountered in the present study, probably because of our exclusion criteria. Infarcts were excluded if they were circumferential or if both old and recent infarcts co-existed in the same anatomic distribution.

Thus, the results of the present study should be viewed as most applicable to patients who are relatively early in the course of their clinical coronary disease and in whom local myocardial perfusion is still determined by the anatomic distribution of the major arteries.

Our observations from this select group of patients

parallel the observations of several authors regarding the geometry of completed infarcts in dogs.^{5, 15, 16} Reimer and Jennings showed that infarcts induced by proximal circumflex ligations in open-chest dogs varied in size from 64–92% (mean $79 \pm 2.6\%$) of the ischemic vascular bed at risk, which, in turn, averaged 41% of the LV.⁵ All infarcts extended to within 1–2 mm of the lateral boundaries of the ischemic bed as identified by dye injection, but varied in their transmural extent. Vokonas et al.,¹⁶ also assessed the lateral dimensions of infarcts in relation to the area of ischemia 24 hours after occlusion of a small branch of the circumflex artery. They reported an average infarct width of 10.9 mm within ischemic regions that averaged 15.3 mm in width. Thus, the average lateral border zone was 2.2 mm wide. However, because these infarcts were small, the lateral border zone made a larger contribution to the natural salvage of myocardium within the ischemic region than was the case in the present study or in canine studies using more proximal occlusions.

In contrast, Jugdutt et al.⁷ found an average lateral border zone of 6–7 mm after occlusion of the LCCA in the dog when the vessel bed at risk was defined by postmortem angiograms. While their average risk region was 40% of the left ventricle, the infarct size was only 23% of the area at risk. The reason for these differences are not known.

Other authors have found wider lateral border zones with intermediate depletion of creatine kinase after experimental myocardial infarction.^{28, 29} However, Factor et al.¹⁴ reported that the boundary between adjacent vascular beds, although sharply defined, is irregular, with peninsulas of viable and necrotic myocardium. They demonstrated that intermediate enzyme levels could be accounted for as mixtures of nonischemic and ischemic tissue.¹⁵

The relative constancy of the lateral subendocardial boundaries of infarcts may be due to a sharp gradient of collateral blood flow at the lateral boundaries between nonoccluded and occluded vascular beds. In dogs, demonstrable collateral anastomoses are present principally between epicardial branches of the coronary arteries; intramyocardial arterioles and capillaries between adjacent beds do not connect.³¹ When appropriate techniques have been used in microsphere flow studies to correct for sampling contamination, i.e., admixtures of ischemic and nonischemic myocardium, the lateral subendocardial boundary between nonischemic and severely ischemic myocardium has been sharp.² Thus, the collateral flow responsible for the salvage of myocardium reaches the occluded vascular bed via epicardial connections. The penetrating arteries are functionally and anatomically end arteries.^{15, 31} In contrast, intramural and subendocardial collateral anastomoses have been observed in human hearts in addition to subepicardial anastomoses.^{19, 20} Nevertheless, collateral circulation, whether epicardial or intramural, did not usually limit the lateral extent of human infarcts in the present study. The exception to this was in heart 5, which had

a large average lateral border zone. The large lateral border zone was on one side of the infarct in the distribution of a single epicardial branch. Presumably, this epicardial branch received collateral flow that was not distributed evenly to the remainder of the occluded vascular bed, and resulted in lateral salvage of myocardium.

Although a broad lateral border of viable muscle was the exception, a fairly constant narrow lateral border of viable muscle was observed in this study (average 1.7 mm) and in dog studies.⁵ This may have been because of the limited ability of oxygen and substrates to diffuse through the tissue from the nonischemic to the ischemic regions, rather than to any gradient of collateral blood flow. Diffusion between the ventricular lumen and the ischemic region often preserves the viability of a layer of 6–10 cells immediately beneath the endocardium in both canine and human infarcts. Such beneficial diffusion presumably could occur at the lateral boundaries of an infarct as well.

Border Zones and the Salvage of Myocardium

The term border zone has become a confusing and controversial term in recent years, partly because it has been used to denote different entities by various authors. We⁵ and Fishbein et al.⁸ used the term, in relation to the potential limitation of infarct size by therapy, to refer to myocardium that is sufficiently ischemic to become lethally injured in the absence of therapy, but is still viable and thus potentially salvageable when therapy is initiated.

Other authors have used the term to refer to areas on the margins of evolving infarcts showing intermediate severity of ischemia (levels of collateral blood flow) or intermediate severity of cellular injury.^{9–12} To what extent such areas represent mildly ischemic and potentially salvageable myocardium vs contaminated samples consisting of mixtures of nonischemic and severely ischemic myocardium is controversial.^{13, 14}

Authors who have looked at completed infarcts have used the term border zone in reference to mixtures of viable and necrotic myocardium on the edges of the infarct. Again, the extent to which such mixtures are due to truly intermediate degrees of ischemic injury vs a complex interdigitation of nonischemic-viable and ischemic-necrotic muscle is controversial.^{14, 15}

In the present study we examined fully developed infarcts and identified the location of myocardium within the occluded vascular bed that nevertheless survived the acute event. This definition of border zone is similar to that of other investigators who have evaluated the geometry of completed infarcts with respect to the region of ischemia.^{7, 18} The remaining viable myocardium survived even though no therapies were specifically directed toward limiting infarct size. Thus, by definition, these border zones of viable muscle were outside any region that could have been salvaged by therapy. Because the present study in-

volved completed infarcts, any border zone of myocardium that might have been salvaged by therapy was not identified. Conversely, the viable myocardium within the vascular bed may well have been at high risk of death had the oxygen supply/metabolic demand balance deteriorated, either through spontaneous hemodynamic complications or because of ill-advised therapy. Nevertheless, all infarcts in this study were smaller than the involved vascular bed, indicating that a variable portion of the ischemic myocardium survived without specific therapy. In this sense, natural limitation of infarct size invariably occurred.

The reason for the variation among human infarcts in the transmural extent of necrosis has not been established. This variation could be due to a variation in metabolic demand and/or collateral blood flow within the subepicardial zone of the ischemic region. We could not estimate the number or size of collateral connections in these human hearts and could not assess the potential role of collateral connections in limiting the transmural extent of necrosis in human infarcts. However, in dogs, the transmural extent of a fully developed canine infarct has correlated closely with the amount of collateral blood flow available to the subepicardial region during the first 3 hours after coronary occlusion.⁶ A close correlation between the amount of necrosis and blood flow has also been observed in individual samples of the infarcted region.³⁰ The variation in the transmural extent of necrosis not accounted for by collateral flow may be due to variation in metabolic demand.

Potential for Therapeutic Limitation of Infarct Size in Man

The present study provides no direct data regarding the potential for therapeutic limitation of human myocardial infarcts. However, these data, in conjunction with animal studies, permit speculation. In the present study, the lateral boundaries of infarcts were set by the boundaries of the occluded vascular beds. The width of viable but ischemic myocardium at these boundaries was small and relatively invariable. Thus, lateral limitation of infarct size was rare in this series. In contrast, the transmural extent of infarction was variable, suggesting that the epicardial boundaries of an infarct may be more readily limited by therapeutic interventions.

Studies of evolving canine infarcts reperfused at various times after coronary occlusion demonstrated a wave front progression of cell death that began in the subendocardial myocardium and spread into the subepicardial region as the duration of ischemia was prolonged.^{4, 5} Reperfusion at 40 minutes resulted in subendocardial infarcts but salvaged much of the subepicardial half of the ischemic region. However, even after this relatively brief period of ischemia, necrosis developed to within 1–2 mm of the lateral boundary of the occluded vascular bed, i.e., equivalent to permanent infarcts.⁵ Thus, the lateral boundaries of the infarct were set by the vascular bed boundaries within the first 40 minutes of ischemia, so that reperfusion at this time did not limit the lateral dimension of the in-

farct. On the other hand, the final transmural extent of canine infarcts was not reached until 3–6 hours after coronary occlusion because some subepicardial salvage was still demonstrable by reperfusion at 3 hours.

Whether a similar transmural wave front progression of cell death occurs in evolving human infarcts has not been established, but seems likely. Primates, like dogs, have a transmural gradient of collateral blood flow,³² with greatest flow in the subepicardial region, and when viable myocardium occurs within the occluded vascular bed of human hearts, it is located predominantly in the subepicardial region. If human infarcts do evolve with a transmural progression of cell death, it seems likely that successful limitation of infarct size with most therapies would occur by conversion of a potentially transmural infarct into a more subendocardial infarct. However, in humans, it is also possible that the time course for cell death in the lateral dimension is longer than in dogs so that salvage at the lateral boundaries of an infarct might occur with a therapeutic agent such as hyaluronidase which could increase diffusion through ischemic tissue.³³ If lateral salvage can be achieved in human infarcts, it should be readily detectable by postmortem studies. Because a lateral border zone is consistently narrow in untreated infarcts, the boundaries of the occluded vascular bed could be used to predict the lateral width of the infarct, and clinically relevant lateral salvage would be evident.

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