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Lateral Border Zone: Quantitation of Lateral Extension of Subendocardial Infarction in the Dog

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This study was undertaken to quantitate the lateral extension that occurs concomitantly with the transmural extension of a subendocardial infarction. A subendocardial infarct was produced in 12 dogs by a 40 minute temporary coronary artery occlusion. Infarct extension was induced 7 days later by permanent occlusion of the same vessel. Regional myocardial blood flows confirmed that ischemia had been produced with both coronary artery occlusions. The vascular boundaries between the normally perfused and ischemic beds were defined by perfusion with different-colored Microfil solutions. The extent of subendocardial infarction and subsequent transmural and lateral extensions were assessed by point counting of histologic specimens.

The initial temporary occlusion produced a 30.0 ± 4.2% transmural infarct and the subsequent permanent occlusion a 29.2 ± 3.5% transmural extension in a risk region of 39 ± 4 g. Lateral extension was not measured in four dogs because the initial subendocardial infarct was patchy with markedly irregular lateral borders. In eight dogs the size of the measured lateral infarct extension from each lateral margin from two histologic sections was 0.63 ± 0.013 cm^2. The area of both lateral extensions was 1.7 ± 0.1% of the cross-sectional area of its risk region as determined by planimetry. Using a model of the risk region; the mass of the lateral extension was estimated to be 1.4 ± 0.3 g or 3.5 ± 0.6% of the region at risk.

Thus, at the lateral margin of a subendocardial infarct there is a border zone that is small relative to the size of the region at risk and infarcted myocardium. This border zone is not a site at which a significant volume of myocardium can be salvaged or into which significant extension can occur.

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The border zone of a myocardial infarct may be considered to be that region of myocardium adjacent to necrotic or irreversibly damaged myocardium which is less ischemic and thus potentially viable. The subendocardium is more vulnerable than the subepicardium to ischemic necrosis, not only because of its greater reduction in systolic blood flow (1) but also because of factors independent of blood flow (2). The extent to which the infarct spreads across the wall from endocardium to epicardium depends on the duration of ischemia and the tissue blood flow during this period (3,4). Thus, a border zone exists at the epicardial aspects of the subendocardial infarct. In contrast, the existence of a lateral border zone is controversial. If it exists, its size would theoretically depend on the extent of intramyocardial vascular connections and the degree of diffusion from normally perfused adjacent myocardium.

In our laboratory, we were unable to demonstrate the existence of either a lateral gradient in creatine kinase depletion (5) or a histologic (6) border zone after 24 hours of myocardial ischemia after coronary artery occlusion. Therefore, we undertook a study to determine whether a lateral border zone exists at the lateral edge of a subendocardial infarct produced by transient coronary occlusion and reperfusion, and whether this viable myocardium lateral to the infarct would survive additional ischemia, that is, whether lateral extension of an infarct can occur.

Methods

Production of subendocardial infarction and infarct extension. A small subendocardial infarct was produced by temporary coronary artery occlusion. In 12 open chest dogs anesthetized with pentobarbital (25 mg/kg body weight) and ventilated with 100% oxygen, the left anterior descending coronary artery distal to the first large diagonal branch was

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temporarily occluded with silk thread for 40 minutes and then released. This has been shown to produce a subendocardial infarct involving 28 to 38% of the transmural myocardium (3,4). After the 40 minutes of coronary occlusion, a nylon snare was loosely passed under the left anterior descending artery at the site of the temporary occlusion, both ends were threaded through polyethylene tubing and the distal ends of both the tubing and thread were implanted subcutaneously in the chest wall. After 7 days, the subcutaneous snare and tubing were exposed under local anesthesia and light sedation. Infarct extension was produced by firm tension applied to the left anterior descending coronary artery snare for 24 hours before the dog was killed. Five additional dogs were not included in the study; four developed ventricular fibrillation during or immediately after the temporary coronary occlusion and one did not survive the second, or permanent, occlusion.

Definition and quantitation of region at risk. The region at risk and normal zones were defined using different-colored Microfil solutions (Canton Bio-Medical Products, Inc.) (7) injected simultaneously under similar pressures into the cannulated left anterior descending and left main coronary arteries under general anesthesia. Microfil is a silicone rubber compound that has a low viscosity, fills the capillary microcirculation and gels in situ. The different colors were apparent on the gross cross sections and on histologic sections using epiillumination.

The hearts were fixed in 3.7% formaldehyde, the free wall of the right ventricle and both atria were removed and the left ventricle was sectioned in 1 cm layers perpendicular to the long axis. The transmural sections from each heart were weighed and photographed and perimeters of the two Microfil-defined zones (risk region and normal zone) were determined by planimetry. The weight of the risk region in each ring was determined by multiplying the weight of the ring by the average fractional area of the upper and lower surfaces of that ring occupied by the risk region. The total mass of the risk region was calculated as the sum of the mass of the risk regions of each ring. The most basal ring or rings closest to the site of the left anterior descending coronary artery ligation contained an epicardial region at risk (because of the obtuse angle made by the perforating coronary arteries), and the apical ring frequently contained a circumferential risk region. These rings were, therefore, not analyzed further. There were four or five intervening rings from each heart; two nonadjacent rings were used for histologic examination and two other rings were used for measurement of regional blood flow. The transmural thickness of the risk region was measured in three places from each ring and averaged.

Histology and quantitation of transmural infarction. Two rings were paraffin-embedded and sectioned, stained with hematoxylin-eosin and examined histologically. The two myocardial rings were entirely sectioned circumferentially and that portion containing infarct was divided into three parts: 1) a central and two lateral areas with the latter including grossly identifiable infarct, 2) normal myocardium, and 3) the lateral border region. The 7 day old infarct was readily distinguished from the more recent 24 hour infarct extension. The healing subendocardial infarct (8 days old) was characterized by hypereosinophilia and hemorrhagic contraction band necrosis, which is associated with reperfusion infarcts (8), and demonstrated organizing granulation tissue and chronic inflammation (9). Infarct extension, which was 24 hours old, showed characteristic hypereosinophilic hyaline degeneration and a polymorphonuclear infiltrate.

The extent of transmural infarction and transmural infarct extension was calculated using a method of point counting in a 10 mm wide zone in the section containing central infarct, but not through the anterior papillary muscle (10). Sections were placed in a photographic enlarger, magnified eight times and photographed on print paper. Point counting was performed by overlaying the print with a transparent sheet having a grid of 2.5 mm per horizontal and vertical line. The total number of points per grid crossings falling on the subendocardial infarct, transmural infarct extension and noninfarcted myocardium was counted from sections from the two nonadjacent rings separated by 2 to 3 cm and was expressed as a percent of the total number of counts in this central zone. Because the transmural percent of these three measurements was not significantly different for each animal, the results for each parameter were averaged before the mean was taken. The depth in millimeters of the subendocardial infarct was approximated by measuring its extent from the photomicrographs. The measurements were made at six points: from the middle of the central and two lateral edges of each section, avoiding the anterior papillary muscle, and from two nonadjacent rings.

Quantitation of lateral infarct extension. Because the lateral margins of the subendocardial infarct were frequently irregular, a simple method of quantitation of lateral extension was not readily evident. In addition, the curvature of the epicardial surface of the infarct often made identification of extension as being in either a lateral or an epicardial direction difficult to ascertain. We therefore derived two methods to estimate its size. The region lateral to the subendocardial infarct (Fig. 1) was defined by an area whose borders were the subendocardium, the lateral vascular boundary and two drawn lines. One line (AB) was circumferentially parallel to the subendocardium at a distance between the endocardium and epicardium corresponding to the average depth of the central portion of the infarct, and another (BC) radially on the shortest distance between endocardium and epicardium intersecting line AB at the lateral margin of the subendocardial infarct. The area of lateral extension was calculated by point counting the new (24 hour) infarct within this defined region, and was also ex-

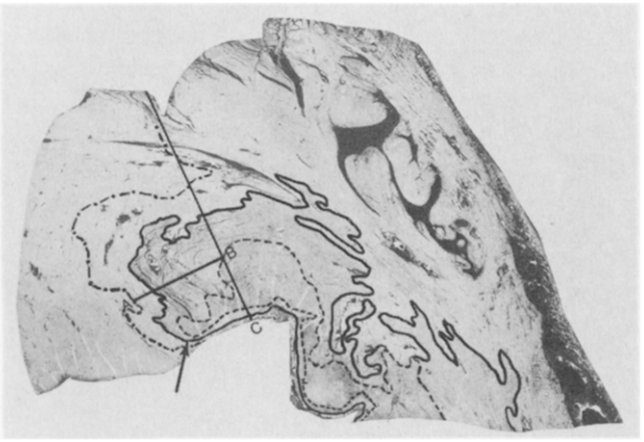


Figure 1. Representative example of a photographically enlarged histologic section from the lateral border demonstrating the patterns of old and new infarction and the method employed to define a lateral region at risk. The histologic features of the tissue cannot be appreciated at this magnification, but they were confirmed by examination of the same slide under the microscope and transposing the findings to the photographic print. Epiillumination was used to define the two Microfil-perfused vascular territories. The 7 day old subendocardial infarction is outlined by **dashes** (– – –), the 1 day old acute infarct extension is outlined by the irregular **solid line** (——) and the vascular boundary of the region at risk is outlined by **dots and dashes** (–•–•). The **arrow** points to the most lateral aspect of the 7 day old subendocardial infarct. Note that acute infarct extension occurs predominantly in an epicardial direction, with small zones of subendocardial and lateral extension. For explanation of line AB and BC, see Methods section in text. All magnifications and marking lines shown in subsequent Figures 3 and 4 are identical to Figure 1 (histologic section enlarged × 8, reduced by 50%).

pressed as a percent of the Microfil-defined region at risk, as determined by planimetry of the ventricular rings.

The lateral extension and preserved zones were also estimated in millimeters by measuring the shortest distance at four equidistant points between the old and new infarcts on their respective lateral margins to the vascular boundary defined by Microfil. There was no difference in the transmural dimension of the muscle in the lateral infarct zone compared with the adjacent normal zone, but we cannot exclude the possibility that this was due to a combination of contracture of the old infarct and swelling of the recent infarct extension. However, no correction was made for any shrinkage of tissue that may have occurred during the processing of tissue for histologic study.

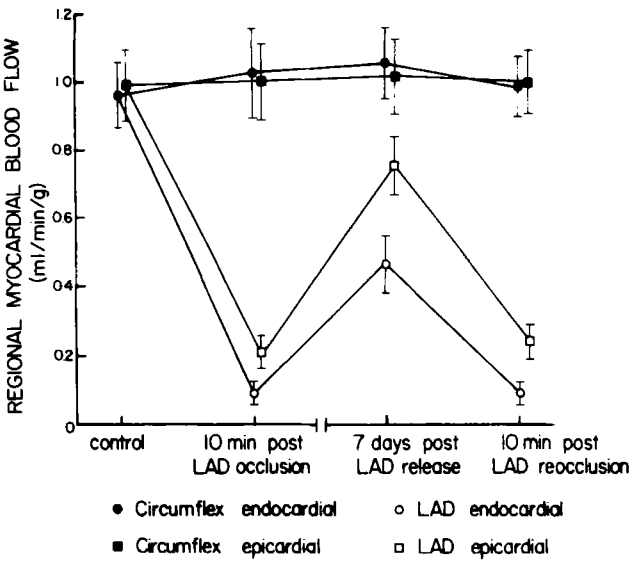
Regional blood flow determinations. Regional blood flow measurements were determined by the injection of 2×10^6 microspheres labeled with radionuclides (3M Company, 9 μ diameter, cerium-141, chromium-51, niobium-95, strontium-85) into the left atrium and constant withdrawal of blood samples from the aorta (11). Microspheres were injected before and 10 minutes after temporary left anterior descending coronary artery occlusion on the first day of the study, and before and 10 minutes after permanent occlusion on the seventh day. Approximately 2 to 4 g samples from the infarct center and normal tissue of two nonadjacent rings were excised and divided into inner and outer halves. Blood flows were calculated using gamma spectrometry and computer separation of energy spectra of different radionuclides (10). Blood flow measurements were corrected for apparent microsphere loss or possible tissue swelling or contracture that may have occurred in the region supplied by the left anterior descending coronary artery after the first occlusion of this artery (12), but not for measurements made after the second occlusion on the seventh day.

Statistics. Quantitated results were expressed as the mean and standard error of the mean. Differences in depth, thickness or percent of infarction were compared by a paired t test for pairs of measurements and by two-way analysis of variance for nonpaired measurements. A value of $p > 0.05$ was considered not significant.

Results

Regional blood flows. The results of regional blood flows in the normal and ischemic zones in the 12 dogs are shown in Figure 2. Forty minute temporary left anterior descending coronary artery occlusion resulted in a marked reduction of subendocardial blood flow in the region at risk. After 7 days

Figure 2. Regional myocardial blood flow measurements (mean and standard error of the mean) in samples of myocardium from the endocardial and epicardial halves of the left ventricle supplied by the circumflex and left anterior descending (LAD) coronary arteries. Radionuclide-labeled microspheres for measurement of regional myocardial blood flow were injected during a control period before occlusion of the left anterior descending coronary artery, 10 minutes after its occlusion (temporary), during reperfusion 7 days after the occlusion was released and 10 minutes after the second (permanent) occlusion.



JACC Vol. 5, No. 5
May 1985:1125–31

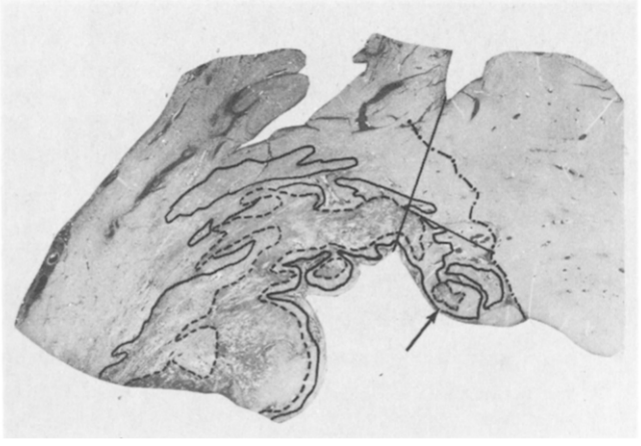
of reperfusion, regional blood flow had increased toward normal levels. The second and permanent occlusion of the left anterior descending coronary artery resulted in a degree of ischemia similar to that of the first occlusion. The regional blood flows were equivalent to control values in the nonischemic regions.

Quantitation of infarct size. The mean weight of the left ventricle in the 12 dogs was 128 ± 5 g, and the region at risk weighed 39 ± 4 g (30% of the left ventricular weight) and was 1.11 ± 0.05 cm thick.

Histologic quantitation of the infarct by point counting from the infarct center revealed that the 40 minute temporary left anterior descending coronary artery occlusion produced a subendocardial infarct that involved 30.0 ± 4.2% of the myocardium in this region. Permanent occlusion of this artery resulted in infarct extension that involved an additional 24.6 ± 3.5% of myocardium toward the epicardium and 4.6 ± 0.2% of myocardium toward the endocardium in the central zone of the infarct. The depth of the subendocardial infarct was larger in the central section (3.8 ± 0.3 mm) than in the anterolateral edge (3.5 ± 0.4 mm) or the anteromedial edge (3.2 ± 0.3 mm), but this difference was not significant.

Lateral infarct extension. This could be quantitated in only 8 of the 12 dogs. Representative examples of the histologic features of this region and the corresponding measured zones are shown in Figures 1 and 3. In the remaining four dogs, the lateral margin of the subendocardial infarct was markedly irregular and appeared patchy on histologic sections, thus precluding quantitation of the lateral extension employing the methods of this study (Fig. 4).

Figure 3. Example of lateral extension in which the subendocardial infarct is relatively homogeneous. A small "detatched" peninsula (**arrow**) is present in the lateral region, but it is not intercepted by line AB. Disregarding the peninsula leads to a somewhat greater amount of lateral infarct extension than had it been used as the lateral most point of measurement. Despite this possible overestimation of lateral extension, most of the extension occurs in an epicardial direction. See Figure 1 for explanation of marking lines.



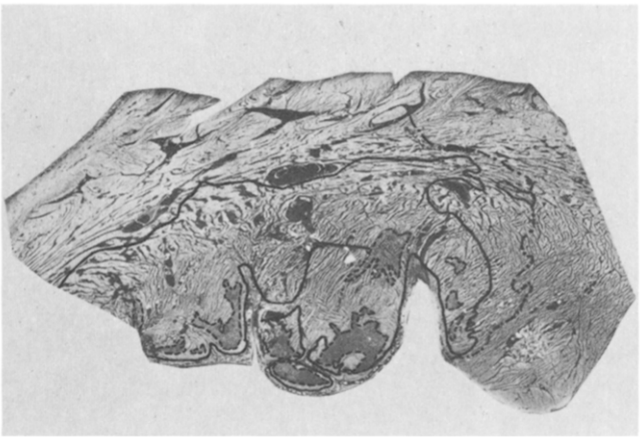


Figure 4. Example of one of the four infarcts that could not be quantitated for lateral extension by the methods of this study because the initial subendocardial infarct was patchy and irregular. Note that if the discontinuous islands represent peninsulas of a continuous infarct, then the pattern of predominantly epicardial extension is similar to the previous examples. See Figure 1 for explanation of marking lines.

Area of lateral extension. The transmural surface area of the region at risk from the two nonadjacent rings used for histologic study was 7.5 ± 0.7 cm^2. The area lateral to the subendocardial infarct (defined by the vascular margin, the subendocardium and two lines defining the depth and lateral margin of the subendocardial infarct) was 0.153 ± 0.028 cm^2 for each lateral margin (0.172 ± 0.039 cm^2 for the anteromedial and 0.134 ± 0.016 cm^2 for the anterolateral margin); however, 0.032 ± 0.008 cm^2 of old subendocardial infarct was also present in this zone (0.037 ± 0.010 cm^2 on the anteromedial and 0.027 ± 0.003 cm^2 on the anterolateral side). Acute infarct extension into this region measured 0.064 ± 0.013 cm^2 (42% of the area of this region) (0.057 ± 0.010 cm^2 on the anteromedial and 0.071 ± 0.025 cm^2 on the anterolateral side). Thus, lateral infarct extension involved 55.8 ± 6.3% of each lateral region at risk, but only 1.7% of the risk region of the sections in which they were studied. The mean lateral extension was 3.2 ± 0.7 mm, and the preserved myocardium lateral to the infarct extension was 1.4 ± 0.4 mm.

Total mass of lateral extension. An attempt was made to quantitate the total mass of lateral extension from measurements made on the histologic sections and the gross cross-sectioned rings. The mass of the risk region was accurately determined from the planimetrically determined areas of the photographs of each myocardial ring and its weight. For the purposes of estimating the size of lateral extension, it was assumed that the risk region can be approximated by an unrolled flat slab with a square surface. The length of the four lateral sides of this slab was calculated from the mass (39 ± 4 g) and the mean thickness of the risk region (1.11 ± 0.05 cm). The volume of infarct extension was calculated for the lateral sides of this slab by multiplying

the side length (5.38 ± 0.30 cm) by the mean lateral extension area (0.064 ± 0.013 cm^2, measured by point counting) four times. The mass of lateral extension calculated, assuming this model of a square slab of the risk region, was 1.4 ± 0.3 g, or 3.5 ± 0.6% of the region at risk.

Discussion

In this laboratory (5), we previously demonstrated the absence of a lateral border zone of a myocardial infarct by showing an equivalent or greater depletion of creatine kinase (CK) from the lateral region of the infarct compared with the infarct center. Subsequently, we showed (6) that the lateral border of the infarct abutted on the vascular boundary between ischemic and nonischemic myocardium. These findings were observed after 24 hours of ischemia, and the question has been raised whether a significant lateral border zone exists at an earlier stage of infarction (13,14). For a significant lateral volume of preserved myocardium to exist within the region at risk, one would have to postulate that its preservation is dependent on intramyocardial collateral circulation or diffusion of oxygen and metabolites from the normal zone. The presence of a noninterconnected coronary microcirculation composed of end capillary loops (7) and the relatively small size of a preserved layer of cells whose survival is dependent on diffusion (10) would suggest that the size of this region is not large.

In this dog model of subendocardial infarction after temporary coronary occlusion and subsequent infarct extension after permanent occlusion of the same vessel, we have demonstrated that infarct extension was predominantly in a transmural direction. We previously described the phenomenon of subendocardial infarct extension (10). In the present study, the extent of lateral extension was relatively small in comparison with the size of the risk region, whether this was measured in a single plane from histologic sections or calculated from a model of the risk region.

We could not measure lateral extension in 4 of the 12 dogs because the initial subendocardial infarct was patchy with markedly irregular lateral borders. Subsequent acute infarction did not extend throughout this border region containing "islands" of healing necrotic myocardium, but rather the new infarct followed the patchy geographic pattern of the original process. As we have shown previously (15), such islands of necrosis represent peninsulas that protrude in three dimensions from the central infarct, but that appear as islands when viewed in two dimensions. Thus, the size of the lateral border zone and lateral infarct extension could not be quantitated in these four dogs.

Border zone. Several investigators have described a sizable lateral border zone on the basis of intermediate levels of several variables measured in the region lateral to the central ischemic zone compared with the normally perfused myocardium. The conclusion that a lateral border zone exists has been made on the basis of analysis of the epicardial electrogram (16–18), microsphere-measured regional blood flow (19,20), histochemical staining for dehydrogenase enzymes (13,21) and autoradiographic studies (22) from this area. This is in contrast to investigators who have discounted the presence of a lateral border zone by using methods that have corrected for interdigitating normal tissue when measuring CK depletion (5) or regional blood flow (23). By employing microsampling techniques with microelectrodes (24), NAD fluorescence (25) or regional blood flows measured with microspheres (26), a number of studies (13,16–26) have identified either sharp or gradual changes in a measured variable between an intensely ischemic and normal zone, but they have not necessarily defined a change between viable myocardium and myocardium destined to die because of irreversible cell injury.

Reimer and Jennings (4) described a 1 to 2 mm lateral border zone; that is, necrosis was observed to extend to within 1 to 2 mm of the lateral margins of the circumflex coronary artery bed whether necrosis was produced by a 40 minute or a longer occlusion of that vessel. Transmural necrosis was slightly more extensive in the central than in the lateral region. Lee et al. (27) described a lateral preserved region of 1.7 mm for human postmortem material. However, the same criticism can be made of this latter study as of our earlier study (6), in that these specimens were from infarcts that were at least 3 days old with 50 to 88% transmural infarction, which does not exclude the possibility of a larger lateral preserved zone at an earlier stage of infarction.

Alteration of infarct size in lateral direction. Jugdutt et al. (28) showed that the size of infarcts could be increased in dogs pretreated with indomethacin. The increase in infarct size took place by extension both at lateral and subepicardial margins. Thus, lateral extension could occur because of a significant rim of uninfarcted myocardium within the region at risk at the lateral margin. These investigators were able to demonstrate salvage of a substantial border zone, both laterally and epicardially, when dogs were pretreated with ibuprofen (29) or nitroglycerin (30).

Ertl et al. (31) reported that 6 hours of ischemia resulted in myocardial necrosis that was confined to and involved 93 to 96% of the risk region when the latter was defined in vivo after 15 minutes ischemia using an autoradiographic technique. However, when the risk region was measured postmortem with a Monastral dye method, the risk area was 33% larger, reflecting the risk region in the absence of collateral vessels. If the risk area did in fact change, it could do so only in a lateral direction; these investigators attributed the consequent large, laterally preserved region to collateral blood flow supplying the lateral region at risk. The size of this region and its collateral blood flow, but not the flow in the central ischemic region, could be increased by an angiotensin-converting enzyme inhibitor (31).

It has been suggested (32) that a functional rather than an anatomic risk zone exists and that it varies with time

after the onset of coronary artery occlusion. It also has been reported (33) that the ultimate size of an infarct may be larger than the risk region defined at 30 minutes. This implies lateral extension of an infarct into the normal zone and alterations of the risk region. The minor degree of lateral extension described in our report is evidence against this idea. Our results support the concept that the risk region is fixed and is determined by the anatomic pattern of the coronary microcirculation at the lateral border.

Critique of present study. The question is frequently raised whether reperfusion of ischemic myocardium during evolution of acute myocardial infarction may increase the infarct size because of consequent vascular necrosis. It has been convincingly shown that early reperfusion decreases the ultimate size of infarction (3,4,34). Furthermore, hemorrhagic necrosis characteristic of reperfusion is observed to occur well within the border of the necrotic myocardium (35) and in areas where blood flow has been reduced to less than 15% of control (35).

In our study, we have used the hematoxylin and eosin staining method to identify microscopically necrotic tissue by hyaline degeneration and hypereosinophilia. Although this method depends on necrotic tissue taking up a stain, it is the generally accepted standard by which myocardial infarction can be diagnosed histologically after 24 hours of evolution.

We believe that our histologic methods, combined with delineation of the microvasculature, are precise within certain limits. The dimensions of infarct extension have been taken from histologic sections and thus in a single, two-dimensional plane. If the sections were not perpendicular to the vascular boundary, the measurements made in this study overestimate their size. An accurate quantitation of the infarct and its extension can only be made by using tedious serial histologic sections and three-dimensional reconstruction of the entire risk region. The presence of edema in the acutely extended infarct, which was 24 hours old at the time of the histologic study, may have disporportionately increased the dimensions of the infarct extension.

To quantitate the lateral extension, we have used the point counting method for measuring the transmurality or depth of the infarct center. We have employed this measurement laterally to draw the circumferential line (AB, Fig. 1) parallel to the endocardium at the depth of the subendocardial infarct. As the infarct tended to slope slightly toward the endocardium from the center, our method of analysis will slightly exaggerate the dimensions of the lateral extension. Because of the irregular curvature of the endocardium, it is not always possible to determine precisely whether extension of the infarct is occurring in an epicardial or lateral direction. We have artificially constructed intercepts with the endocardial surface and the 7 day old infarct thickness (determined centrally) to define the lateral region. Therefore, even with the quantitative methods in the present study, at best we can only approximate the direction of extension. Illustration of the new and old infarct in individual specimens ultimately may be more informative than quantitation of group patterns for determining whether significant lateral extension occurs.

In an attempt to quantitate the mass of lateral infarct extension, we have developed a model of the risk region which has a square epicardial and endocardial surface. However, if this surface were circular or ellipsoid, the estimated mass of lateral infarct would have been smaller, but would have been larger if its surface were serpiginous.

Conclusion. A border zone does exist at the lateral margin of a subendocardial infarct. This region is small and it is not a site at which a significant mass of myocardium can be salvaged or into which significant extension can occur. This conclusion is not surprising when it is considered that collateral blood flow is distributed by way of epicardial collateral vessels rather than intramyocardial vascular connections from the normal to the risk region.

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