Expansion of Acute Myocardial Infarction: Its Relationship to Infarct Morphology in a Canine Model

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SUMMARY Regional dilation (expansion) of newly infarcted myocardium has been associated with increased mortality. To study this entity further, and to define the relationship of expansion to infarct morphology, infarcts were created in 44 open-chest dogs by a coronary ligation and coronary embolization method. Twenty-one transmural and 18 nontransmural infarcts of 1 to 11 days of age were studied. Infarct expansion was quantified by comparison of lengths of infarct and noninfarct containing segments of transversely sliced hearts. Five dogs died less than 6 hours after infarction and showed no evidence of expansion. Of those surviving more than 24 hours, 17 had infarct expansion and 22 did not. In the latter group, four infarcts were transmural and 18 were nontansmural; in the former, all 17 infarcts with expansion were transmural. Infarct thinning for the 17 infarcts with expansion was significantly greater than that observed in the nontransmural infarcts or the nonexpanded transmural infarcts (P < 0.001). Of the 21 transmural infarcts, the largest infarct without expansion was 10.8%, and the smallest infarct with expansion was 11.3% of left ventricular weight. Among infarcts with expansion, there was a poor correlation between the extent of expansion and infarct size (r = 0.19). A significant inverse relationship (P<0.02) was observed, however, between the extent of expansion and postinfarct survival for the transmural infarcts. Although infarct expansion occurred only in transmural infarcts exceeding a critical but relatively small threshold of injury, the absence of a further relationship between transmural infarct size and extent of expansion suggests that other anatomic, metabolic, or hemodynamic factors affect the development of acute infarct expansion.

PATHOLOGICAL and clinical studies in humans have demonstrated early alterations in left ventricular topography in approximately one-third of patients who died as a result of acute myocardial infarction (Hutchins and Bulkley, 1978; Eaton et al., 1979). These topographic alterations, referred to as infarct expansion, are characterized by dilation and thinning of the infarcted zone. Such changes have been observed to appear clinically as early as 3 days after myocardial infarction, and to progress over days to weeks with no evidence to suggest more recent myocardial necrosis or infarct extension. This process appears to be associated with deterioration in cardiac function and increased mortality (Eaton et al., 1979), and may be important in the developments of cardiac rupture (Schuster and Bulkley, 1979) and late aneurysm formation. Studies in the human have suggested that certain morphological features, including transmural necrosis and infarct size, may be determinants of the development of expansion.

The purpose of this study was to evaluate the relationship of the morphological features of transmural necrosis, infarct size, and infarct location to the development of infarct expansion in an animal model. Because conventional canine infarcts created by isolated coronary ligation produce few transmural infarcts, a model using embolic occlusion of the coronary bed was developed for the present study. This ensured a predictable number of animals with transmural as well as subendocardial necrosis.

Methods

Preparation of Infarcts in Canine Hearts

Forty-four adult mongrel dogs of both sexes, weighing 20–25 kg, were anesthetized with intravenous pentobarbital (30 mg/kg) and ventilated mechanically. Hearts were exposed through intercostal thoracotomy incisions and either the left anterior descending or circumflex coronary arteries were identified and isolated with silk suture. Infarcts were prepared by two methods to ensure a range of subendocardial and transmural infarcts: (1) The isolated ligation group consisted of 20 dogs in which suture ligation alone was used to create the infarct. (2) The embolic occlusion group consisted of 24 dogs in which 0.5–0.7 ml of a biologically inert, non-resorbable, polysulfide polymer (Omniflex, Coe Laboratories) was injected immediately after ligation into the arterial lumen. This polysulfide ma-
terial sets to a soft, rubbery consistency at body temperature and embolizes into small intramural coronary branches.

Systemic blood pressure, heart rate, and ECG were monitored in each dog for the 2 hours immediately following coronary occlusion, and severe ventricular arrhythmias appearing during this time were treated with intravenous lidocaine and D.C. countershock. At the end of this time, thoracotomy incisions were closed and physiological intrapleural pressure was restored prior to discontinuation of mechanical ventilation. The dogs were returned to the kennel for observation.

**Post-Infarction Management**

After infarction, animals were maintained on the standard kennel diet. No efforts were made to manage clinical signs of heart failure pharmacologically. Of the 24 dogs in the embolic occlusion group, all dogs surviving 7 days were killed within the next 4 days with an intravenous pentobarbital overdose. The 20 dogs in the isolated ligation group were arbitrarily separated into two groups. One group of 13 dogs was selected for study 2 days after infarction, for comparison with dogs from the embolic occlusion group dying early after infarction. The remaining seven dogs from the isolated ligation group were killed 7 days after infarction for comparison with those dogs from the embolic occlusion group having longer post-infarction survival.

**Postmortem Evaluation of Canine Hearts**

After death, the animals’ hearts were removed, the chambers perfused with formalin, packed with gauze, and immersed in a formalin bath for a minimum of 24 hours. In all hearts, for quantification of the degree of expansion, the atria and atrioventricular valves were removed, leaving only the right and left ventricular walls and septum. The midpoint of the septum was identified by linear measurement, and the perpendicular bisector of the left ventricular free wall as well as its interpolated course along the endocardial surface of the left ventricular wall and septum were marked with indelible ink. Each heart then was sliced into transverse sections which were 1 cm thick. Intersections of the septal bisector on the left ventricular free wall and septal endocardial surfaces divided each transverse section into an anterior and posterior segment (Fig. 1). The transverse section containing the greatest percent of infarcted tissue was selected for each heart, and the lengths of the endocardial margins for the anterior and posterior segments, as defined by the points of intersection of the septal bisector, were measured. An index of expansion then was determined for each heart as follows: expansion index = (endocardial length of the infarct-containing segment/endocardial length of the noninfarcted segment). Thus the transverse slices of the left ventricle having been divided into anterior and posterior segments, a transverse section from a heart containing an infarct in the circumflex distribution had an expansion index defined as: length of the posterior segment/length of the anterior segment. For infarcts in the vascular distribution supplied by the left anterior descending coronary artery, the expansion was defined as: length of the anterior segment/length of the posterior segment.

For each heart, infarct expansion was considered present if the expansion index for the selected transverse slice was greater than 2 SD beyond the mean expansion index determined for five noninfarcted dog hearts (0.99 ± 0.05, mean ± SD) using the expansion index randomly selected for either the anterior or posterior vascular distribution for each of the five hearts. Thickness of the infarcted and adjacent noninfarcted ventricular wall was measured for each transverse slice selected from each heart. Infarct size expressed as a percentage of total left ventricular weight was determined by planimetry of weighed transverse slices using a model 9810A Hewlett-Packard calculator and 9864A digitizer. Representative portions from each heart were collected and prepared for histological examination.

**Statistical Analysis**

For comparison of expanded and nonexpanded hearts in regard to infarct size and wall thinning, the unpaired t-test was applied. To test for a significant correlation between infarct size and the extent of expansion, comparison was made using two-variable, least squares linear regression analysis (Snedecor and Cochran, 1967). For all transmural infarcts, survival time following infarction was compared to the extent of infarct expansion adjusted for infarct size by multiple variable regression analysis (BMDP 1R, UCLA, 1977). All values were expressed as mean ± SD.
Results

Post-Infarction Survival

Of the 24 dogs in the embolic occlusion group, five dogs (all with left anterior descending coronary occlusions) died suddenly, probably from arrhythmias, during the first 6 hours after occlusion. At 6 hours, morphological changes of infarction were not apparent histologically or by gross examination of the heart, and these animals were excluded from further analysis. Of the remaining 19 dogs in this group, nine (47%) had left anterior descending and 10 (53%), circumflex artery occlusion; 10 (five left anterior descending and five circumflex infarctions) survived fewer than 7 days following infarction (Table 1). All 10 dogs had clinical signs of poor recovery after infarction, including poor feeding, tachypnea, labored respirations, and decreased spontaneous ambulation. The remaining nine dogs from the embolic occlusion group survived at least 7 days after infarction and were killed. One of the 20 dogs in the isolated ligation group died approximately 44 hours after infarction. Twelve of the remaining dogs were studied at 2 days, and seven at 7 days, as described previously.

Statistically significant differences were not observed between the embolic occlusion and isolated ligation groups in regard to heart rate or arterial blood pressure over the 2 hours of monitoring following infarction.

Pathology of Infarcts

In the embolic occlusion group, each of the 19 dogs surviving at least 24 hours after infarction had evidence of transmural infarction defined as necrosis through the full thickness of the ventricular wall (Fig. 2). Infarct size ranged from 2 to 27% of total left ventricular weight with a mean value of 16.5 ± 5.8%. Among the 20 dogs from the isolated ligation group, 18 had infarcts which were nontransmural, with sizes ranging from 2 to 24% of left ventricular weight with a mean value of 5.8 ± 6%. Fourteen of these infarcts were in the left anterior descending vascular distribution and four were in the circumflex distribution. The remaining two infarcts in the isolated ligation group were transmural infarcts in the left anterior descending vascular distribution with sizes of 17.8% and 14.1%.

Histology of Transmural and Subendocardial Infarcts

Transmural infarction was evident in all 19 of the dogs with embolic occlusion. On histological examination, the injection mass producing the infarct was evident in the epicardial coronary and in the intramural arteries and small arterioles (Figs. 2 and 3). Capillaries were not filled by the gel. The bulk of the necrotic myocardium showed coagulation-type necrosis and thin wavy fiber change was common (Bulkey, 1979). The two transmural infarcts produced by snare ligation showed a similar histological picture with the bulk of dead tissue showing coagulation necrosis. Of the 17 nontransmural infarcts, contraction band necrosis comprised over half of the injury (Fig. 4) with the central core of the infarct showing coagulation necrosis. Towards the epicardium there was considerable interdigitation of islands of normal myocardium with zones of tissue showing contraction band necrosis. Within 2 days, inflammatory cells infiltrated the edge of the infarct zone and were especially prominent in the epicardium. Organization of the infarct with replacement by scar tissue was evident in some portions of the myocardium by day 11. On the edge of the infarct, focal areas of contraction band or reperfusion necrosis were evident.

Infarct Expansion

Using the expansion index defined above, 15 of the transmural infarcts from the embolic occlusion group showed expansion in one or more transverse sections through the area of infarction. In addition, the two transmural infarcts from the isolated ligation group showed expansion (Table 2). The expansion index for this group of 17 hearts, each with an individual index greater than 1.09, was 1.34 ± 0.17 with a range of 1.12 to 1.96. Seven of these infarcts were in the distribution of the circumflex coronary artery and 10 were in the distribution of the left anterior descending artery. The five dogs from the embolic occlusion group that died within 6 hours after infarction showed no evidence of infarct expansion (expansion index = 1.01 ± 0.04) (Fig. 5).

The remaining 22 dogs included 18 with subendocardial and four with transmural infarctions. None showed evidence of infarct expansion (expansion index = 0.99 ± 0.04). Two of the four transmural infarcts in this group were in the circumflex and two were in the left anterior descending vascular distribution. These four transmural infarcts ranged in size from 2% to 10.8% (mean, 5.4%), and the subendocardial infarcts ranged from 2% to 24%
FIGURE 2  Shown in A is a transverse section through a heart with an embolic occlusion infarct. The white polysulfide is evident in the epicardial and intramural coronary arteries (arrow) in the distribution of the transmural infarct which is 3 days old. Thinning and regional dilation is evident in the infarct zone. In B is a histological section of myocardium from a dog with an embolic infarct. The polysulfide material (arrow) is seen within and occluding an intramural coronary artery. The myocardial fibers were densely eosinophilic, and even at this magnification the loss of myocardial cell nuclei is evident. A leukocytic infiltration, evident around the blood vessel, was extensive at the margin of the infarct. A histological section from an embolic infarct which is 11 days old is shown in C. Necrotic myocardial fibers (myo) are surrounded by granulation tissue, lymphocytes, and macrophages. One arteriole containing the occlusive polymer is evident (arrow) (hematoxylin and eosin, each, 120X). LV = left ventricle; RV = right ventricle.

FIGURE 3  Histological sections of dog myocardium one (A) and four (B) days after the polysulfide injection was made into the left anterior descending coronary artery. Small coronary arteries and arterioles are occluded by the dark staining mass. The myocardium in B, taken at the same magnification as A, shows persistent thin wavy fiber change (12) which may be a histological sign of ischemic injury which has been identified in humans, and which appears to develop within hours of clinical evidence of myocardial infarction. This change may not be specific for infarction (hematoxylin and eosin, 120X).
(mean, 5.8%) with three of them exceeding 11% of left ventricle.

Thus, infarct expansion did not develop in any subendocardial infarct within the range of sizes studied, even in the largest infarct involving 24% of the left ventricle, but was observed in 17 of the 21 transmural infarcts (81%) created by both infarction techniques. Approximately equal frequencies of expansion were observed in transmural infarcts in both circumflex and left anterior descending vascular distributions (80% and 81%, respectively). Statistically significant differences were not observed between the nine left anterior descending and eight circumflex infarctions in regard to infarct size (16.5 ± 3.5%, left anterior descending, vs. 20.6 ± 5.7%, circumflex, 0.05 < \( P < 0.10 \)), or the extent of expansion (1.53 ± 0.3, left anterior descending, vs. 1.29 ± 0.16, circumflex, 0.05 < \( P < 0.10 \)).

In each of the 17 transmural infarcts with expansion, ventricular wall thinning was observed in the infarcted areas in which regional dilation was present (Figs. 2, 5, and 6). Among the infarct expansion group, the wall involved by infarction had thinned to a mean value of 0.66 ± 0.15 cm compared to mean wall thickness of adjacent noninfarcted myocardium of 1.06 ± 0.18 cm (\( P < 0.001 \)). Hence, infarcted walls thinned by approximately 38%. In contrast, there was no significant thinning of the infarcted zone relative to the noninfarcted zone for the 18 subendocardial infarcts (1.11 ± 0.2 cm, in-

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<th>Table 2 Comparison of Infarcts with and without Expansion</th>
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<td>Transmural infarcts</td>
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<td>Infarct size (mean % LV weight ± se)</td>
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<td>Expansion index (mean ± se)</td>
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* Includes two infarcts from the isolated ligation group.
† \( P > 0.001 \).
Infarct expansion: To illustrate infarct expansion in the sagittal plane, a longitudinal section through a normal dog heart (A) and one with a transmural infarct (arrow) produced by embolic coronary occlusion (B) was made. Disproportionate dilation and thinning of anteroseptal and apical left ventricle leading to overall cavity dilation is evident in this infarct at 2 days in this plane as well. LA = left atrium; LV = left ventricle; mv = mitral valve; PM = papillary muscle; RV = right ventricle.

Farct, vs. 1.15 ± 0.24 cm, noninfarct, NS) or in the four transmural infarcts without expansion (0.98 ± 0.17 cm, infarct, vs. 1.03 ± 0.19, noninfarct, NS).

Relationship of Expansion to Infarct Size in Transmural Infarction

The 17 transmural infarcts with expansion were significantly larger than the four transmural infarcts without expansion (P < 0.001) (Table 2). In Table 3, these 21 transmural infarcts are shown separated into three groups according to infarct size. In the three infarcts that were less than 10% left ventricular weight, no expansion was observed. Four out of five (80%) of the infarcts ranging from 10 to 15% of left ventricular weight showed evidence of expansion. All 13 transmural infarcts greater than 15% left ventricular weight showed expansion. From these observations, it appears that transmural infarcts in this canine model have a critical threshold of infarct size in the range of 10 to 15% of left ventricular weight required for the development of infarct expansion. When this threshold was exceeded, infarct expansion occurred in a majority of cases. In this study, the smallest infarct with expansion was 11.3%, and the largest without expansion was 10.8%.

Figure 7 shows the relationship of the degree of infarct expansion to infarct size in the 17 transmural infarcts in which expansion developed. Although all 17 infarcts exceeded the apparent threshold of approximately 11% infarct size, there was no further statistically significant relationship between the degree of infarct expansion and the size of the infarct (r = 0.19). Of note is the broad range of infarct expansion (1.15 to 1.96) over a relatively narrow range of infarct sizes (15 to 18%, respectively) with the largest infarcts of 26.8% and 27% at the moderately low range of the expansion scale (1.3 and 1.2, respectively).

Survival among Animals with Transmural Infarction

Twenty of the 21 dogs with transmural infarction survived from 24 hours to 7 days after thoracotomy. (One of the 21 transmural infarcts was in a dog from the isolated ligation group which was killed at 2 days by study design and was, therefore, excluded from survival analyses.) By two-variable least squares linear regression analysis, there was a significant inverse correlation between post-infarction survival during the first week and the extent of expansion (r = 0.63, P < 0.01). To adjust for effects
EXPANSION vs. INFARCT SIZE

FIGURE 6 Correlation of infarct size and expansion for the 17 infarcts that expanded. On the ordinate is expansion expressed as the expansion index; on the abscissa is infarct size expressed as a percent of left ventricular weight. The r value is 0.19.

on survival resulting from differences in infarct size among the transmural infarcts, multiple variable regression analysis was performed (Fig. 7). This also revealed a close correlation between the extent of expansion and survival during the first week following infarction (P < 0.02). Specifically, the shortest survival during the first 7 days after infarction was seen in those animals having the greatest degree of infarct expansion measured after death.

Discussion

Acute infarct expansion has been studied clinically and pathologically in humans (Hutchins and Bulkley, 1978; Eaton et al., 1979). To test the notion that the specific morphological variables of infarct size, infarct location, and transmural vs. subendocardial necrosis are important in the development of acute regional ventricular dilatation, the present study of acute canine infarction was undertaken. Two infarct models were used in this study to mimic the types of infarcts seen in humans. Because collateral blood flow in the dog is well developed, the coronary snare ligation model most often produces nontransmural infarcts, which frequently have a hemorrhagic appearance, and histologically show a large component of contraction band or reperfusion necrosis in addition to the core of coagulation necrosis (Fig. 4); the coronary ligation infarcts in dogs are similar to nontransmural human infarcts. In contrast the embolic occlusion model was designed to occlude intramyocardial vessels and limit collateral flow to produce consistently transmural, pale, nonhemorrhagic infarcts (Fig. 2), comprised mostly of coagulation necrosis (Mallory et al., 1939) and more akin to the human transmural infarct. We used these two infarct models and were able to study transmural and subendocardial infarcts of varying size (2 to 27 of left ventricular weight), location, and age.

The results of this study indicate that transmural necrosis of the infarct is a major determinant of infarct expansion. Expansion of the acute infarct

TABLE 3 Infarct size and Expansion in Transmural Infarcts

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FIGURE 7 Correlation of post-infarct survival and the extent of expansion for the 20 dogs with transmural infarcts that were not killed before 7 days after coronary occlusion. Shown is the equation for the relationship between survival and the extent of expansion, adjusted for differences in infarct size by multiple regression analysis, where Y = survival in days, X1 = infarct size, and X2 = extent of expansion expressed as the expansion index.
zone was observed in 80% of the transmural, but in none of the 18 nontransmural infarcts. Infarct expansion caused disproportionate, regional dilation of the infarcted myocardium of up to 96% compared to noninfarcted segments, and an average wall thinning of almost 40%. Even among the largest of the nontransmural infarcts, regional cardiac dilation and thinning did not occur, findings compatible with the human studies (Hutchins and Bulkley, 1978; Eaton et al., 1979). That transmural necrosis appears to be a virtual requisite for infarct expansion suggests that viable epicardial myocardium is important in preserving cardiac shape; normal epicardial muscle may prevent stretching and possibly intramural rupture that can occur when transmurally necrotic myocardium bulges dyssynergically with systole.

Infarct size is another determinant of infarct expansion. Expansion was detected to some degree in every transmural infarct exceeding an apparent "critical size" of 11%. Beyond this threshold, however, there was no further relationship between the extent of expansion and size. For example, within the narrow range of infarct sizes of 15 to 18%, disproportionate dilation of the ventricular segment containing the infarct ranged from 15 to 96%. Thus, infarct size influences which infarcts expand, but other factors must control the extent to which this process develops. At the present time, one can only speculate as to what the latter factors may be; however, metabolic conditions, hemodynamic events including pressure and heart rate, and possibly intrinsic structural differences in both the infarcted and noninfarcted tissue seem likely candidates.

Infarct location is another structural factor which may, in part, affect the extent to which infarct expansion occurs. In the present study, infarcts of both the anterior and posterior left ventricular wall were prepared, but a significant difference in the development or extent of expansion between these two sites could not be identified. The near equal frequency of expansion in the canine anterior and posterior infarcts differs somewhat from the human studies identifying this event more commonly and to a greater extent in the anterior and anteroseptal wall (Hutchins and Bulkley, 1978; Eaton et al., 1979). In the dog, however, a larger myocardial bed is supplied by the circumflex coronary artery than in the human. That the anterior left ventricular wall may be more susceptible to the development of expansion after transmural infarction is at least suggested here, insofar as the posterior transmural infarcts tended to be larger ($P < 0.10$) but anterior infarcts showed a greater extent of expansion ($P < 0.10$).

It now is recognized widely that infarct size is important to outcome after infarction (Page et al., 1971; Sobel et al., 1972), and effort over the past decade has been directed to the reduction of infarct size by therapeutic intervention. Since infarct expansion increases the percent of left ventricular circumference involved by infarct, it effectively increases functional infarct size without changing total mass of infarcted tissue. Also, the net cardiac dilation resulting from regional dilation can only be detrimental to overall left ventricular performance, especially in an oxygen-limited heart. It would follow, therefore, that for a given mass of infarcted myocardium, expansion should be associated with a poorer outcome. Findings in this study on dogs are compatible with this notion, as there was a significant inverse relationship between extent of expansion and length of post-infarction survival, a correlation which remained significant when adjusted for differences in infarct size (Fig. 3).

The early time course of infarct expansion needs further definition. Although the fixed morphological changes characterizing infarct expansion appears to take up to 24 hours to develop, functional shape alterations resulting from acute transmural ischemia may be the first step in the genesis of expansion. Forty-five years ago, Tennant and Wiggers (1935) showed that acute coronary ligation could cause a regional bulge in the ischemic myocardium, and that this regional dyskinesia was reversible after several minutes. More recent evidence for functional expansion in the setting of transient ischemia has been provided by Apstein et al. (1979) who have shown early, reversible wall thinning as a component of the acute cardiac failure caused by total global ischemia in an isolated perfused rabbit heart. With transient transmural ischemia, myocardial shape should recover with restoration of function. However, if the ischemic myocardium goes on to infarction, dyskinesia can only persist and likely lead to irreversible thinning and dilation of the affected area. This infarct expansion may be one cause of the thin wavy fiber change (Bouchardy and Majno, 1974) noted histologically (Fig. 3). During this early stage of infarction, function may in large part be determining structure, and factors such as intracavitary pressure and volume, and adrenergic tone probably have an effect on the extent of reshaping of the infarcted segment. After 2 days, as the necrotic myocardial tissue softens, the inflammatory process heightens, and variable amounts of edema and reperfusion occur, these additional tissue properties may well become important to the development of infarct expansion.

Although we have yet to determine when infarct expansion becomes irreversible, our data suggest that this occurs after 6 but within the first 24 hours, and continues to progress with time. Thus, permanent remodeling of the heart due to acute infarction is occurring at a time after the ischemic event has occurred but in time for clinical recognition and possible interventions.

In summary, this study demonstrates the occurrence of infarct expansion in a canine model, shows...
the dependence of this phenomenon on transmural necrosis and a critical infarct size, and suggests a detrimental effect of expansion on survival. In addition, the effect of other factors upon the development of infarct expansion is strongly suggested by the variability of the relationship between extent of expansion and infarction once a critical infarct size is exceeded. Through use of the experimental infarct model developed for this study, a systematic approach may now be undertaken to elucidate the individual and collective contributions which metabolic and hemodynamic factors, differences in inflammatory and healing processes, and other such variables may have on the development of infarct expansion.

Acknowledgments

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