Expansion of Acute Myocardial Infarction: An Experimental Study

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SUMMARY Expansion (regional dilatation and thinning) of acutely infarcted myocardium in man has been shown to correlate with overall cardiac dilatation and rupture. We studied gross and histopathologic features and the time course of expansion in rats. Infarcts were produced in 84 rats by ligation of the left coronary artery and studied at 1, 2, 3, 4, 5 and 7 days. All hearts were prepared by potassium diastolic arrest, gel diastension and fixation. Expansion was graded 0 to +: 1+, mild thinning of infarcted wall; 2+, mild thinning and dilatation; 3+, moderate thinning and dilatation; and 4+, marked thinning and dilatation. There were 80 transmural infaracts, and 66% showed expansion; 36 of 80 (45%) were graded 1–2+ and 17 of 80 (21%) 3–4+. None of the four exclusively nontransmural infaracts showed expansion.

Expansion was present in 61% of transmural infarcts at 1–2 days, in 65% at 3–4 days and in 80% at 5–7 days. The percentage of rats with severe (3–4+) expansion increased markedly over this period, from 0% at 1–2 days to 23% at 3–4 days to 65% at 5–7 days. Histopathologic infarct evolution was roughly twice as rapid as that of humans; 5–7-day-old infarcts showed well-developed granulation tissue.

Thus, expansion can be produced in an animal model. A critical infarct size of 17% appeared necessary for significant (> 1+) expansion, and the degree of expansion correlated with infarct size. Although this phenomenon begins early after infarction, it extent progresses over days, making interventions to interrupt its development feasible.

STUDIES of myocardial infarction have generally paid little attention to the gross topographic changes early after infarction or to the consequences of these changes.1,2 Infarct expansion, defined as regional thinning and dilatation of the infarct zone, is a gross topographic change that occurs early after acute myocardial infarction in humans3 and is associated with a poor clinical prognosis.4 Pathologic studies show that severe expansion occurs most commonly in transmural and first myocardial infaracts.4 The process occurs within days of myocardial infarction, before resorption of necrotic tissue has occurred,1 and appears to be a major factor in overall acute cardiac dilatation and cardiac rupture after infarction.5

The present study was designed to develop an experimental model of infarct expansion, and to use this model to investigate the time course of expansion and its correlation with the size and histopathology of the infarct.

Materials and Methods

Infarct Model

Infarcts were produced by left coronary artery ligation in female Sprague-Dawley rats weighing 220–300 g, as previously described.6–9 The rats were anesthetized with sodium methohexital (Brevital), 35 mg/kg, administered intraperitoneally. A left thoracotomy was performed in the fifth or sixth intercostal space. The rats were given intermittent positive-pressure ventilation with 95% O2 and 5% CO2. A pericardiotomy was performed and the left main coronary artery was occluded by snaring and tying a band of myocardium 2–3 mm to the left of the aorta and ligating it with 5-0 silk sutures. Because the left main coronary artery is an intramyocardial structure,6 the snared myocardium did not always include a coronary artery. The rats in which ligation was unsuccessful served as controls. The chest was closed with a 4-0 silk pursestring suture, and 100,000 U of benzathine penicillin (Bicillin) were administered intramuscularly. The rats were awake within 5–30 minutes postoperatively.

The rats were fed standard rat chow. At 1, 2, 3, 4, 5 or 7 days, the rats were given intraperitoneal heparin and anesthetized with methohexital. The hearts were excised and immediately immersed in cold 30-mM KCl to achieve diastolic arrest. Failure to arrest the heart in a specific phase of the cardiac cycle results in uncontrolled changes in topography, i.e., the ratio of wall thickness to cavity size.

To preserve topographic relationships after fixation, the atria were removed and a warm liquid gel was injected into the left and right ventricles through the atrioventricular valves. The hearts were then immersed in cold 20% formalin to solidify the gel rapidly and fixed in formalin for at least 24 hours. The fixed hearts were sliced transversely, parallel to the atrioventricular groove, in 2-mm sections from apex to base and prepared for histologic examination. All sections were stained with hematoxylin and eosin and Verhoff van Geissen stains.

Data Analysis

All histologic slides were reviewed for the transmural extent of necrosis, polymorphonuclear response, resorption of dead myocardial cells and presence of granulation and scar tissue. Infarct size was assessed as follows. The histologic sections were projected on a sheet of paper at ×10 magnification and
Infarcted and noninfarcted areas were traced. The areas of the traced images were determined by planimetry using a digitizing computer program (Hewlett-Packard 9810A calculator with a 9864A digitizer). The mass of infarcted and noninfarcted myocardium per kg body weight was calculated by multiplying cross-sectional area times slice thickness. Because resorption of tissue affects the measurement of infarct size in later infarcts, we calculated the amount of infarcted myocardium in all infarcts as:

$$100\% \times \left(1 - \frac{\text{noninfarcted LV mass/kg body weight}}{\text{control LV mass/kg body weight}}\right)$$

Twenty control rats were used to establish norms of LV mass, corrected for body weight. This method has been used for older infarcts. If infarct size were calculated by expressing infarcted mass as a percentage of total LV mass for each rat, any resorption of infarcted tissue would lead to an underestimation of infarct size. Our method of calculating infarct size, based on the mass of residual uninfarcted myocardium, is not affected by resorption.

Expansion was graded as 0; 1+, mild thinning of infarcted zone; 2+, mild thinning and dilatation; 3+, moderate thinning and dilatation; and 4+, marked thinning and dilatation. All rats were graded independently by two observers who were unaware of the time after coronary ligation. Several grades of expansion are shown in figure 1.

Results

Infarcts Studied

One hundred thirty-seven rats underwent attempted coronary ligation; 16 (12%) died immediately after operation, 11 (8%) within 24 hours, and six (4%) later than 24 hours. None of the six late deaths appeared related to cardiac complications and only one of these six rats had a myocardial infarction. The remaining

FIGURE 1. (A) A moderate-size 2-day-old infarct (arrows) involving the posterolateral wall. The normal left ventricular (LV) contour is preserved. The inflammatory response can be seen surrounding the necrotic fibers. Residual gel is present in the left ventricular cavity. (B) A large 2-day-old infarct that involves the LV free wall and shows 2+ expansion. The infarcted wall is thinned and there is regional dilatation of the left ventricular cavity. (C) A large 7-day-old infarct of the free wall that shows severe (4+) expansion, a paper-thin wall and marked cavity dilatation. Granulation tissue surrounds the residual core of necrotic myocardium. All sections were stained with hematoxylin and eosin; original magnification x 8.
104 rats were included in this study. Rats that did not have infarcts served as controls. Infarcts were successfully induced in 84 rats (81%). Eighty infarcts (95%) were transmural, defined as those in which any area of the infarct was full thickness. Four infarcts were nontransmural. The location of the infarcted myocardium always involved a portion of the LV free wall and did not involve the septum, except occasionally in the apical slice. Postmortem examination of the position of the ligature showed that smaller infarcts are created when branches of the left coronary, rather than the main stem of the left coronary artery, are occluded. There was a wide range of infarct sizes (fig. 2). Four infarcts in figure 2 were plotted as negative values; this is a result of the method used for calculating infarct size. These four rats had small infarcts and larger than average hearts, and their noninfarcted myocardial mass exceeded the mean control myocardial mass. Although this resulted in an inappropriately low value for infarct size in these rats, the aggregate effect on mean infarct size in each group was balanced by the small number of rats that had smaller hearts and large infarcts. The advantage of this method, that it is unaffected by tissue resorption, makes it an accurate way of assessing mean infarct size in large numbers of animals at varying times after infarction.

Transmurality

The four nontransmural infarcts showed no expansion. In contrast, 53 of 80 transmural infarcts (66%) showed at least 1+ expansion. Six of the transmural infarcts had only small areas of transmurality, with a rim of preserved epicardium surrounding most of the infarct (fig. 3); none of these six expanded.

Time Course

Figure 4 shows expansion as a function of time. Expansion was present in 61% of the rats at 1–2 days, 65% at 3–4 days and 80% at 5–7 days. The extent of expansion increased markedly over this period. Marked expansion (3–4+) was present in no rats at 1–2 days, 23% at 3–4 days and 65% at 5–7 days. The infarct size was similar at each time (table 1); thus, a sampling error of differing infarct size does not explain this progression.

Infarct Size

To determine how infarct size affects expansion, we looked at the degree of expansion as a function of infarct size independent of age (fig. 2). There is a significant positive relationship of infarct size with expansion ($r = 0.592$, $p < 0.001$ by linear regression). Larger infarcts are more likely to expand. Although there is a significant relationship between infarct size and degree of expansion, there is also a large amount of variability, suggesting that other factors contribute to expansion. Infarcts as large as 56% of the left ventricle did not expand, and infarcts as small as 28% of the left ventricle showed severe (3–4+) expansion. Figure 2 shows that only infarcts involving more than 17% of the left ventricle showed more than 1+ expansion.

Histopathologic Changes

Twenty-four hours after left coronary artery ligation, infarcted myocardium was readily identifiable by
hypereosinophilia and early loss of nuclei. By 48 hours there was a moderate polymorphonuclear inflammatory response at the margins of the infarct. By 3 days, there was a large zone of residual necrotic cells surrounded by an inflammatory response with mixed polymorphonuclear and mononuclear cells. By 5 days, rich granulation tissue was present, with a residual central area of necrotic cells. By 7 days, there was decreased cellularity and early formation of scar tissue. In no heart with myocardial infarction was there evidence of infarct extension.

Discussion

Early after acute myocardial infarction, gross topographic alterations in the left ventricle may become evident, including regional dilatation and thinning of the acutely infarcted tissue. Infarct expansion can be recognized by two-dimensional echocardiography in humans within 3 days after myocardial infarction and correlates with increased mortality. In pathologic studies, expansion of some degree has been shown to occur in 72% of patients with transmural myocardial infarction and to be predictive of myocardial rupture. Expansion seems to represent the pathophysiologic basis of a spectrum of related events, including overall cardiac dilatation, aneurysm formation and cardiac rupture.

Using the rat coronary artery ligation model of acute infarction, we produced predominantly transmural infarcts. Infarct expansion was detectable as early as 24 hours after myocardial infarction, when histologically only the earliest changes of necrosis were evident. Thus, expansion had developed before any resorption of necrotic myocardium had occurred. A similar proportion of rats showed expansion at 1 day and at 1 week which suggests that expansion is declared early. Early expansion of the infarct may result from stretching of necrotic fibers and perhaps from intramural rupture.

The degree of expansion increased with time: marked (3-4+) expansion was present in 65% of rats at 5-7 days, compared with 23% at 3-4 days and none at 1-2 days. Histologically, resorption of necrotic tissue occurred as the degree of expansion was increasing.

The histopathologic changes after acute myocardial infarction develop roughly twice as fast in rats as they do in humans. There are gross changes within 24 hours, including pallor and thinning of the infarcted zones. Granulation tissue is present at 5 days and healing is complete in rats by 21 days, in contrast to 2 weeks and 6 weeks, respectively, in humans.

Infarct size appears to be an important determinant of expansion. Infarct size can be difficult to quantify accurately. Depending on the method of measurement used, infarct size calculations can be influenced by the amount of infarcted myocardium, the extent of resorption, the amount of granulation and scar tissue, the amount of hypertrophy of noninfarcted myocardium and the degree of expansion. Infarct circumference measurements are likely to overestimate, and direct infarct mass measurements may underestimate, true infarct size. In the rat, in which resorption occurs earlier than in humans or in dogs, it is especially important to correct for these processes in determining infarct size. We therefore measured infarct size by comparing the amount of remaining normal myocardium to a norm established for the LV myocardial mass. Although this method does not take into account hypertrophy of noninfarcted myocardium that might occur days to weeks after coronary ligation, the fact that the sizes of infarcts of different ages did not differ significantly (table 1) suggests that such an error was not introduced.

Although infarct size correlates with degree of expansion, there is variability in this relationship; some

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**Table 1. Relation of Mean Infarct Size to Time After Infarction**

<table>
<thead>
<tr>
<th>Days after infarction</th>
<th>1 (n = 10)</th>
<th>2 (n = 19)</th>
<th>3 (n = 17)</th>
<th>4 (n = 20)</th>
<th>5 (n = 9)</th>
<th>7 (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean infarct size (%)</td>
<td>39 ± 5.6</td>
<td>28 ± 4.8</td>
<td>38 ± 4.6</td>
<td>33 ± 3.6</td>
<td>31 ± 11</td>
<td>37 ± 5.2</td>
</tr>
</tbody>
</table>

Not statistically significant by analysis of variance. Abbreviation: LV = left ventricle.

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**Figure 4. Relation of the degree of expansion to the time after infarct. Expansion occurs early: 76% of infarcts expanded at 1 week had done so by 1-2 days. The degree of expansion increases during the first week after infarction.**

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infarcts involving as much as 56% of the left ventricular mass showed no expansion. Therefore, infarct size alone is not highly predictive of the degree of expansion in individual cases, and hemodynamic and metabolic factors may play a role. Noncontracting necrotic myocardium bulges in systole\cite{1, 12} and is subjected to continued intermittent high pressures during systole; this stress might further stretch and deform the weakened tissue. Thus, the determinants of the tensile properties of the wall and of wall stress are important factors affecting the degree of expansion. Increased stress on the infarcted wall might increase the degree of expansion. Also, as suggested by our data, a thin rim of preserved myocardium may alter the properties of the infarcted wall enough to resist significant expansion.

Transmurality has been suggested to be necessary for significant expansion in human infarcts.\cite{6, 7} This is clearly shown in the present histopathologic studies, in which no nontransmural infarct expanded, whereas a large percentage of transmural infarcts expanded significantly. Additionally, however, the extent of transmurality was an important determinant of expansion: None of the six infarcts that were large but only focally transmural showed expansion.

If early thinning and dilatation did not occur after myocardial infarction, the process of remodeling with resolution of necrotic tissue, laying down of granulation tissue and scar formation would probably result in a healed area that was somewhat thinned but generally preserved normal LV contour. Indeed, this occurred in 20% of the infarcted rat hearts at 5–7 days. Preservation of the normal LV contour, for any given infarct size, is probably hemodynamically advantageous. Dyssynergic areas increase ventricular volume and diameter and waste a large part of the total left ventricular stroke volume and work, placing an increased hemodynamic and metabolic burden on the remaining myocardium.\cite{12, 11} Expansion increases functional infarct size. The hemodynamic impairment probably depends more on this functional infarct size than on the actual amount of infarcted myocardium.

Our data suggest that transmurality and a critical infarct size are prerequisites of significant expansion, and that infarct size correlates with degree of expansion in rats. The presence of previous infarcts correlates negatively with expansion in humans.\cite{5} However, the other pathophysiologic factors affecting the extent of expansion — structural, metabolic or hemodynamic — are unknown. This model can be used to investigate further the factors that lead to infarct expansion and to assess the hemodynamic alterations that occur as a result. It also provides the opportunity to study the effect of interventions designed to decrease the degree of expansion.

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References

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