Effects of Reperfusion after Coronary Artery Occlusion on Post-infarction Scar Tissue


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SUMMARY. Early reperfusion after a coronary occlusion may reduce myocardial infarct size, but late reperfusion into necrotic myocardium may alter post-infarction healing. In rabbits, we compared 1- or 3-week-old scars resulting from permanent coronary occlusion to those resulting from a 1- or 3-hour occlusion followed by reperfusion. Reperfusion at 1 hour post-occlusion did not affect scar mechanical properties assessed at 1 week post-infarction, but at 3 weeks post-infarction, these scars had a tensile strength significantly lower than those not reperfused (78 ± 11 vs. 158 ± 15 g/mm$^2$, $P < 0.001$). They also were composed of a mixture of fibrous tissue (58 ± 8%) and myocytes (43 ± 8%) with a hydroxyproline content of 23 ± 2.5 mg/g dry weight. The nonreperfused scars had a higher proportion of fibrous tissue (73 ± 3%) by histological evaluation and a 35% higher hydroxyproline content (31 ± 2 mg/g dry weight, $P < 0.001$) than the scars reperfused after 1 hour. In contrast, 3-week-old scars resulting from late' reperfusion at 3 hours post-occlusion were similar to nonreperfused scars in fibrous tissue composition and hydroxyproline content. Nonetheless, the tensile strength of these scars reperfused 3 hours post-occlusion was significantly less than that of the nonreperfused scars (72 ± 5 vs. 158 ± 15 g/mm$^2$, $P < 0.001$). The lower tensile strength was associated with a lower collagen cross-link density in this reperfused group of scars. At physiological stress levels (approximately 3 g/mm$^2$), all groups of reperfused and nonreperfused scars had similar mechanical properties in terms of natural strain, stiffness, creep, and stress relaxation. Thus, although the reperfused scars ruptured more easily at high stresses, when assessed at physiological stresses their mechanical properties were not significantly different from those of nonreperfused scars. (Circ Res 57: 562-577, 1985)

TIMELY reperfusion of acutely ischemic myocardium can reduce infarct size and preserve left ventricular (LV) function (Ginks et al., 1972; Jarmakani et al., 1976; Reimer et al., 1977; Markus et al., 1981; Mathey et al., 1981; Connelly et al., 1982; Smalling et al., 1983). However, in the clinical setting, the timing of reperfusion with thrombolytic therapy is often uncertain, since the onset of ischemia is frequently difficult to define precisely, and the speed with which reperfusion can be achieved is variable. Even under optimal clinical circumstances, reperfusion usually does not prevent all myocardial necrosis. Thus, reperfusion may occur in a region which is partially or completely necrotic, and the effect of such 'late' reperfusion on the healing and repair process is unknown.

A myocardial infarct initially undergoes resorption and healing with predominantly leukocytic and histocytic infiltration followed by formation of granulation tissue with fibroblast proliferation and collagen deposition, leading to scar formation (Karsner et al., 1916; Mallory et al., 1939; Fishbein et al., 1978). The reentry of arterial blood during the early phase of this process has the potential to influence the speed of healing and/or the quality of scar that is formed (Rona and Kahn, 1969; Shetlar et al., 1979; Roberts et al., 1983). Early reperfusion of necrotic myocardium may predispose it to ventricular rupture (Lewis et al., 1969; Bates et al., 1977; Rasmussen et al., 1979) or may negatively influence scar formation by washing out a factor, such as lactate, which stimulates collagen synthesis (Comstock and Udenfriend, 1970), or an extracellular enzyme, such as lysyl oxidase, necessary for collagen fiber cross-linking (Prockop et al., 1979a, 1979b). However, reperfusion might also speed myocardial healing by providing cofactors necessary for collagen synthesis and scar organization (e.g., oxygen, vitamin C, calcium, iron) (Rona and Kahn, 1969; Prockop et al., 1979a, 1979b).

The mechanical properties of scars formed after a myocardial infarction can influence overall ventricular performance. A stiff, noncompliant scar is more beneficial than an elastic, compliant scar, which absorbs a greater fraction of the mechanical work generated by the non-infarcted myocardium and which may predispose to aneurysm formation (Hood et al., 1970; Forrester et al., 1972; Gaasch et
al., 1976; Glantz and Parmley, 1978; Grossman and Barry, 1980). The viscoelastic properties of the scar tissue may also influence aneurysmal bulging and increase compliance in the damaged myocardium (Forrester et al., 1972; Gaasch et al., 1976; Vokonas et al., 1976).

We tested the hypothesis that reperfusion alters post-infarction healing. Groups of rabbits were subjected to either permanent coronary occlusion or transient coronary occlusion of 1 or 3 hours followed by reperfusion. Previous work demonstrated that a 1-hour occlusion resulted in transmural infarction in the rabbit (Connelly et al., 1982). At 7 and 21 days post-infarction, the scars were excised and assessed for tensile strength, mechanical properties, collagen content, collagen cross-link density, cellular composition, and histological characteristics and maturation of the scar tissue. The present study demonstrates that reperfusion results in scar tissue that has less of a post-infarction increase in tensile strength than scars from nonreperfused infarcts. The lower tensile strength was associated with a lower collagen content when reperfusion occurred relatively "early" (at 1 hour post-occlusion) and with a decrease in collagen cross-link density when reperfusion occurred relatively "late" (3 hours after occlusion). Nonetheless, myocardial scar tissue formed in the infarcted-reperfused region had adequate tensile strength at both 1 and 3 weeks post-infarction to withstand intra-left ventricular (LV) pressures without apparent danger of rupture.

**Methods**

**Surgical Preparation**

One hundred and thirty-eight New Zealand white male rabbits (1.5–2.0 kg) were anesthetized with sodium thio-ental (2.5 mg/kg) and subjected to tracheostomy. The animals were ventilated on a Harvard Apparatus respirator, while a left thoracotomy was performed on a sterile field. The heart was suspended in a pericardial cradle and the large marginal branch of the circumflex coronary artery was identified (Connelly et al., 1982). The animals were randomized into one of three groups: (1) permanent coronary occlusion; (2) 1-hour coronary occlusion and reperfusion; or, (3) 3-hour coronary occlusion and reperfusion.

**Connective Tissue Biochemical Analysis**

Scar collagen content was assessed by two independent methods. First, a colorometric determination was used for measuring the hydroxyproline content in all tissue samples (Bergman and Loxley, 1969; Zwolinski et al., 1976). Second, in a smaller group of scars, amino acid analysis of samples selected for lysine-derived cross-link determinations was performed; this method also yielded hydroxyproline values in these samples. In the calculation of collagen content, it was assumed that hydroxyproline accounts for 8.23% by weight of collagen.

Insoluble elastin in the scar tissue samples was prepared according to the method of Lansing et al. (1952).

To assess scar cross-link content, nine samples of scar from the permanent occlusion group, and seven samples of scar from the group reperfused after 3 hours of occlusion were analyzed for lysine-derived cross-link density in the collagen molecule. Lyophilized samples of scar tissue were homogenized extensively in 4°C water with a motorized glass homogenizer. Each scar homogenate was divided into aliquots for separate determinations of total amino acid content, alka-linsoluble elastin content, total α-amino-adipic acid β-semi-aldehyde and aldol condensation product, then lyophilized.

**Amino Acid Analysis**

Total amino acid composition of the scar tissue samples, hence, total protein, hydroxyproline, and desmosine content, was determined by analysis on a Beckman model 119CL amino acid analyzer equipped with a model 126 data system after hydrolysis in 6 N HCl at 110°C in vacuo for 24 hours.

**NaB\(^{3}\)H\(_4\) Reduction and Cross-link Analysis**

We reduced scar tissue aliquots with NaB\(^{3}\)H\(_4\) before hydrolysis in order to quantify both α-aminoadipic acid β-semi-aldehyde—a precursor to the lysine-derived cross-links, and the aldol condensation product—an intramolecular cross-link of collagen and an intermolecular cross-link in elastin formed from two residues of the semialdehyde. Reduction with NaB\(^{3}\)H\(_4\) converts the semialdehyde and the aldol to the more stable compounds of hydroxyorniine and the reduced aldol product (Aldol), respectively, allowing quantification (Lent et al., 1969). A tritium label is introduced into each of the structures during this reaction, facilitating identification and quantification (Blumenfeld and Gallop, 1966).
Mechanical Properties

The post-infarction scar was analyzed in terms of tensile strength by stretching scar strips until rupture occurred. The calculation of tensile strength was complicated by the fact that the cross-sectional area decreased as the scar strip was being stretched. Therefore, we assumed that the cross-sectional area at the point of rupture, i.e., the stress at rupture for derivation of tensile strength. The stresses required to rupture the scars greatly exceeded physiological values (see below). The stress-strain relationship was also determined for groups of scar strips at stress levels within the physiological range (Fig. 1).

Rupture Threshold

- The excised scar was placed in oxygenated Krebs-Henseleit solution at room temperature. For mounting in the scar-stretching apparatus, a vertical strip of central scar tissue approximately 3.5 mm wide was excised. The lateral edges of each strip were formed by two parallel razor blade cuts to keep the strip width uniform along the length of the strip. There was some variation in scar thickness along the length of the strip due to natural variations in scar tissue formation. To account for this, the width and thickness of the scar strip were measured at its upper, middle, and lower regions with either a Vernier caliper or a Gaertner cathetometer, and the cross-sectional areas were calculated. The adjacent scar, not included in the central strip, was preserved in 4% formalin for subsequent histological examination.

The excised scar strip then was clamped between the two jaws of an Instron material-testing device, consisting of a force-transducer with an attached strip chart recorder. The clamps were placed on the scar tissue, excluding the scar-muscle junction from mechanical analysis. A previous study showed that this device can measure the tensile strength of scar tissue from a healing wound (Williams and Harrison, 1977). After the scar strip was secured and its resting length (L₀) measured, the jaws were separated at a speed of 5 cm/min until scar rupture occurred. Each scar was stretched along its vertical axis to minimize any anisotropic differences among different scars. Tensile strength was determined by recording the force/cross-sectional area at the point of rupture, i.e., the stress at which the scar strip tore apart. Care was taken not to damage the tissue when it was clamped in the jaws; data from strips which tore in the region of the jaws were not used.

The calculation of tensile strength was complicated by the fact that the cross-sectional area decreased as the scar strip was being stretched. Therefore, we assumed that the volume of the scar strip remained constant, and calculated the cross-sectional area at the time of rupture from measurement of the initial scar dimensions and the measured

Phasic Physiologic Stretch

![Figure 1](http://circres.ahajournals.org/)

**FIGURE 1.** Schematic representation of apparatus for measuring scar elasticity and strength. Upper section illustrates the phasic physiological stretch over the stress range of 0–3 g/mm². Lower section illustrates the continuous stretch to the point of rupture for derivation of tensile strength.
change in length at the time of rupture. By measuring width and thickness in three different regions, we could utilize the initial cross-sectional area closest to the point of rupture of the strip. The cross-sectional area at the time of rupture was determined by the following formula:

\[ \text{volume}_{\text{R}} = \text{volume}_{\text{o}} \]
\[ \text{CSR} = \frac{\text{CS}_{\text{o}} \times \text{L}_{\text{o}}}{(\text{L}_{\text{o}} + \Delta \text{L})} \]

where \( \text{volume}_{\text{R}} \) = volume at rupture; \( \text{volume}_{\text{o}} \) = initial volume; \( \text{CS}_{\text{o}} \) = initial cross-sectional area; \( \text{CS}_{\text{R}} \) = cross-section at rupture; \( \text{L}_{\text{o}} \) = initial length; \( \Delta \text{L} \) = change in length.

The \( \Delta \text{L} \) was recorded by the strip chart tracing, which was directly linked to the amount of jaw separation.

**Scar Stiffness, Stress-Relaxation, and Creep**

In a separate series of infarcted hearts, excised scars were placed in oxygenated Krebs-Henseleit solution at 37°C and cut in two vertical strips along the base-to-apex axis (Fig. 2). The adjacent scar region not included in the vertical strips was weighed and frozen for hydroxyproline assay.

The excised scar strips were attached by spring clips to an apparatus usually used for papillary muscle studies and recently adapted for the assessment of passive mechanical properties of pericardial strips (Wiegner and Bing, 1981). This apparatus incorporated a computer-controlled servo-system capable of setting force and length. The length measurement was made on the second strip, the creep values after the stress-strain measurement on the first strip from each scar, the creep values were obtained. Creep, the time-dependent elongation of a material held at a constant force (Mirsky, 1976; Wiegner and Bing, 1981), was measured. After the stress-strain measurement on the first strip from each scar, the strip was adjusted from \( \text{L}_{\text{o}} \) to a length at which the stress was about 3.0 g/mm² (approximating peak systolic wall stress). Force was measured continuously for 5 minutes after the length increment. After the stress-strain measurement was made on the second strip, the creep values were obtained. Creep, the time-dependent elongation of a material held at a constant force (Mirsky, 1976; Wiegner and Bing, 1981), was measured by increasing the force rapidly, from near zero to 15 g, and maintaining that force for 5 minutes while continuously sampling the length of the strip.

After mechanical measurements, one scar strip was saved in 4% formalin for histological analysis, and the other was frozen for hydroxyproline assay.

**Stress-Strain Relationship**

The excised strips were stretched and released at a constant velocity (usually 12 or 16 mm/sec) so as to cycle force between 0 and approximately 15 g at a frequency of 4 cycles/sec. The stretch rate of 4 Hz simulated the normal heart rate of the rabbit (200-300 beats/min). We imposed a maximum force of 15 g (approximately 3 g/mm²) to the excised strips to approximate the peak systolic force to which the scar would be exposed in vivo. For a typical scar strip, a stretching force of 15 g would be approximately equivalent to a left ventricular pressure of 180 mm Hg (see Appendix).

Under computer control, the stretch and release cycles were continued for 30 seconds, while being recorded and stored in a digital computer (Nova 2) for later analysis.

Force was expressed as Eulerian stress \( (\sigma) \) and length as a natural strain \( (\epsilon) \).

\[ \sigma = \frac{\text{force}}{A_i} \]
\[ \epsilon = \ln \left( \frac{\text{L}}{\text{L}_0} \right) \]

where \( A_i \) = instantaneous cross-sectional area; \( \text{L} \) = instantaneous length; \( \text{L}_0 \) = zero-stress length. Natural strain for the force range was measured on both strips from each scar, and the values were averaged.

**Stiffness**

According to the method of Wiegner and Bing (1981), stiffness or tangent modulus \( (K) \) was derived at a given stress from the instantaneous slope of the curvilinear relationship between stress and strain. This value was calculated at stresses of 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 g/mm² by a moving ensemble-modified least-squares technique that fit a straight line through 20 points, 10 of which lay on either side of the point of force. \( K \) values at each stress level were averaged for both scar strips.

**Viscoelastic Properties**

The time-dependent decrease in force of a material held at a constant strain (Mirsky, 1976; Wiegner and Bing, 1981), stress-relaxation, was measured. After the stress-strain measurement on the first strip from each scar, the strip was adjusted from \( \text{L}_{\text{o}} \) to a length at which the stress was about 3.0 g/mm² (approximating peak systolic wall stress). Force was measured continuously for 5 minutes after the length increment. After the stress-strain measurement was made on the second strip, the creep values were obtained. Creep, the time-dependent elongation of a material held at a constant force (Mirsky, 1976; Wiegner and Bing, 1981), was measured by increasing the force rapidly, from near zero to 15 g, and maintaining that force for 5 minutes while continuously sampling the length of the strip.

After mechanical measurements, one scar strip was saved in 4% formalin for histological analysis, and the other was frozen for hydroxyproline assay.

**Statistical Measurements**

Measured values are expressed as the mean ± SE. Differences among groups were tested by one-way analysis of variance. When the analysis of variance showed a significant difference among groups, the unpaired Student's \( t \)-test was used to test the statistical significance of differences between specific mean values.

**Results**

**Infarct and Scar Size**

Our methodology produced post-infarction scars of a relatively standard size with comparable dimen-
sions among all groups. At 1 week post-infarction, the scar area measured on the endocardial surface was 179 ± 18 mm² in the permanently ligated group ($n = 5$) and 204 ± 20 mm² in the 1-hour occlusion + reperfusion group ($n = 6$; $P = $ not significant (NS)). At 3 weeks post-infarction, the endocardial scar surface areas were 134 ± 11 mm², 113 ± 15 mm², and 154 ± 14 mm², for the permanently occluded ($n = 21$), 1-hour occlusion + reperfusion ($n = 14$), and the 3-hour occlusion + reperfusion groups ($n = 15$), respectively ($F = 2.1611$, $P = $ NS).

Ultimate scar thickness was not affected by reperfusion at 3 hours post-occlusion; at 3 weeks post-infarction, both the permanently occluded group and the 3-hour occlusion + reperfusion group had scars that were approximately 33% thinner than the normal LV wall. However, reperfusion at 1 hour post-occlusion resulted in scars thicker than those resulting from permanent occlusion or reperfusion at 3 hours post-occlusion. The scars resulting from 1 hour of occlusion and reperfusion were as thick as the normal LV wall (Table 1).

**Scar Cellular Composition**

Figure 3 and Table 2 contain a summary of the histological results. The group reperfused at 1 hour post-occlusion had twice as many surviving myocytes as the other groups (Fig. 3). No difference was found in myocyte or fibrous tissue content between the permanently occluded group and the group reperfused 3 hours post-occlusion.

The distribution of surviving myocytes was qualitatively different among the groups. In the permanently occluded group, as well as in the group reperfused 3 hours post-occlusion, surviving myocytes were found only at the subepicardial and subendocardial edges of the scar. In contrast, in the group reperfused at 1 hour post-occlusion, myocytes were frequently found in the mid-myocardial region and were scattered throughout the scar. In some areas, these myocytes appeared as peninsulas or islands surrounded by a dense collagen matrix. Although these myocytes appeared to be viable on PTAH staining, most appeared to be abnormal, with disordered and hyperextended myofibrils (Fig. 4).

**TABLE 1**

<table>
<thead>
<tr>
<th>Days Post-MI</th>
<th>Perm</th>
<th>3R</th>
<th>1R</th>
<th>Myo†</th>
<th>($F$, $P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Width of excised scar strip (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3.50 ± 0.38</td>
<td>3.95 ± 0.31</td>
<td>3.42 ± 0.22†</td>
<td>$F = 1.4068$</td>
<td>$P = $ NS</td>
</tr>
<tr>
<td>$n = 7$</td>
<td></td>
<td>$n = 7$</td>
<td>$n = 13$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>3.33 ± 0.15</td>
<td>3.34 ± 0.16</td>
<td>3.55 ± 0.22</td>
<td>3.42 ± 0.22†</td>
<td>$F = 0.297$</td>
</tr>
<tr>
<td>$n = 26$</td>
<td></td>
<td>$n = 16$</td>
<td>$n = 13$</td>
<td></td>
<td>$P = $ NS</td>
</tr>
<tr>
<td><strong>Thickness of excised scar strip (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2.60 ± 0.27</td>
<td>3.05 ± 0.37</td>
<td>3.09 ± 0.25†</td>
<td>$F = 1.9193$</td>
<td>$P = $ NS</td>
</tr>
<tr>
<td>$n = 7$</td>
<td></td>
<td>$n = 7$</td>
<td>$n = 13$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>2.05 ± 0.08*</td>
<td>2.055 ± 0.10*</td>
<td>2.88 ± 0.21</td>
<td>3.09 ± 0.25†</td>
<td>$F = 12.766$</td>
</tr>
<tr>
<td>$n = 26$</td>
<td></td>
<td>$n = 16$</td>
<td>$n = 13$</td>
<td></td>
<td>$P &lt; 0.001$</td>
</tr>
</tbody>
</table>

Post-MI = postmyocardial infarction; Perm = permanent ligation; 3R = 3 hours occlusion + reperfusion; 1R = 1 hour occlusion + reperfusion; Myo = non-infarcted myocardial strip from LV free wall. All values are mean ± SEM.

* $P < 0.001$ vs. 1R or Myo; $P = $ NS for Perm vs. 3R, 1R vs. Myo.
† Same control group used for comparison at 7 and 21 days.
‡ $F = $ variance ratio from analysis of variance.
Connelly et al./Post-infarction Scar Properties

TABLE 2
Mean Scores of Histological Grading at 3 Weeks Post-Infarction

<table>
<thead>
<tr>
<th></th>
<th>Perm (n = 14)</th>
<th>3 R (n = 11)</th>
<th>1 R (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis*</td>
<td>3.2 ± 0.2</td>
<td>3.4 ± 0.2</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>Fat†</td>
<td>0.6 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>Mononuclear cells†</td>
<td>0.7 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>Abnormal myocytes</td>
<td>1.4 ± 0.3</td>
<td>1.6 ± 0.3</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>Normal myocytes</td>
<td>1.5 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>2.4 ± 0.3</td>
</tr>
</tbody>
</table>

All values represent the mean ± SEM of score given on a scale of 0–4, with 0 = absent, 1 = minimal, 2–3 = intermediate, and 4 = prominent, see Table 1 for abbreviations (n).

* P < 0.1, † P ≤ 0.01, ‡ P ≤ 0.025, by x² analysis.

Scar Strength

Relatively high forces and stresses were required to produce scar rupture in all groups (Fig. 5). At 1 week post-infarction, there was no significant difference in tensile strength or total force borne (Table 3) between scars resulting from permanent occlusion and those resulting from occlusion with reperfusion at 1 hour post-occlusion. Both types of scars had twice the tensile strength and force-bearing capacity of non-infarcted excised strips of cardiac muscle.

However, at 3 weeks post-infarction, an effect of reperfusion on scar strength was evident (Fig. 5; Table 3). The permanently occluded group had scars with 2½ times the tensile strength of either reperfused group; total force-bearing capacity was also greater in the permanently occluded group (Table 3). There was no significant difference in tensile strength or force-bearing capacity between infarcts reperfused at 1 and 3 hours post-occlusion. Between 1 and 3 weeks post-infarction, the permanently occluded group underwent a markedly greater increase in scar strength than the 1-hour occlusion and reperfusion group. The tensile strength of the permanently occluded group tripled; that of the reperfused group increased by only 40% during the same 2-week period. Total force-bearing capacity increased by 230% in the permanently occluded group compared to 150% in the 1-hour occlusion + reperfusion group (Table 3).

Although the reperfused scars ruptured at significantly lower stress values than the permanently ligated scars at 3 weeks post-infarction, the reperfused scars withstood forces of 70–75 g/mm² before rupture. In the rabbit, an intraventricular pressure of 180 mm Hg would produce a wall stress of approximately 3 g/mm² in the scar region (Appendix). Thus, the reperfused scars had the strength to withstand greater than approximately 3000 mm Hg before rupturing. Late reperfusion therefore did not appear to increase the risk of scar rupture within the physiological stress range, when assessed at 1 or 3 weeks post-infarction.

Scar Collagen (Hydroxyproline) Content

At 1 week post-infarction, the hydroxyproline content per gram dry weight of scar as determined by colorometric analysis was virtually identical in

FIGURE 4. Photomicrograph at 3 weeks post-infarction of scar tissue reperfused after 1 hour of occlusion. 120× magnification of a section from the mid-wall of the scar. Residual disordered and hyper-extended myofibrils are within the collagen matrix.
the permanently occluded group and in the group reperfused at 1 hour post-occlusion. In both groups, hydroxyproline content was 5-fold greater than the non-infarcted ventricular tissue (Fig. 6). At 3 weeks post-infarction, the hydroxyproline content in the permanently occluded group and in the group reperfused at 3 hours post-occlusion was 10 times that of normal myocardium; the group reperfused at 1 hour post-occlusion had significantly less hydroxyproline on a gram per dry weight basis than the other two scar groups ($P < 0.05$) (Fig. 6). Thus, at 3 weeks post-infarction, the group differences in hydroxyproline content were proportional to the fraction of the scar consisting of fibrous tissue on histological examination (Fig. 3). In other words, when hydroxyproline content was normalized to the scar's fraction of fibrous tissue, there were no statistical differences among the groups (Table 4). Similarly, when total hydroxyproline content per scar was calculated, there also were no significant differences among the groups (Table 4). These data indicate that the decrease in hydroxyproline content per gram dry

Table 3

<table>
<thead>
<tr>
<th>Days</th>
<th>Perm</th>
<th>3R</th>
<th>1R</th>
<th>Myo</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>275 ± 63*</td>
<td>308 ± 44*</td>
<td>126 ± 24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$n = 5$</td>
<td>$n = 6$</td>
<td>$n = 6$</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>638 ± 76††</td>
<td>341 ± 36‡‡</td>
<td>488 ± 55‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$n = 13$</td>
<td>$n = 8$</td>
<td>$n = 7$</td>
<td></td>
</tr>
</tbody>
</table>

Perm = scars from permanent occlusion; 3R = scars from 3 hours of occlusion + reperfusion, 1R = scars from 1 hour of occlusion + reperfusion, Myo = non-infarcted myocardial strip from LV free wall. Values represent the total force on the excised scar strip at the moment of rupture. The data are not normalized for cross-sectional area. Strip width was similar in all groups, but scar thickness varied. All values are in grams, mean ± SEM, (n).

* $P \leq 0.05$ vs. Myo, † $P \leq 0.001$ vs. Myo, ‡ $P \leq 0.01$ vs. 3R, §§ $P \leq 0.05$ vs. 1R.
weight in the 1-hour occlusion and reperfusion group reflects the greater number of residual surviving myocytes in that group, and does not indicate a decrease in collagen content of "pure" scar tissue.

The differences in tensile strength among the scar groups (Fig. 5) were not proportional to hydroxyproline content (Fig. 6). The most striking disparity between tensile strength and hydroxyproline content came from a comparison at 3 weeks post-infarction of the permanently occluded group and the group reperfused at 3 hours post-occlusion. Both of these groups had the same hydroxyproline content per gram dry weight (Fig. 6) and the same percentage of scar tissue on histological examination (Fig. 3), but the permanently occluded group had 2½ times the tensile strength of the reperfused groups (Fig. 5). This observation suggests that reperfusion may have altered the scar organization and/or the connective tissue cross-linking, resulting in a scar with a lesser tensile strength, compared to the nonreperfused scars. Therefore, these two groups were analyzed with respect to their collagen cross-link contents.

### Collagen Cross-link Analysis

As shown in Table 5, there is no significant difference in total protein content, hydroxyproline (collagen) content, or elastin content between the scars from the permanent occlusion group and those resulting from 3 hours of occlusion with reperfusion. To assess the content of connective tissue cross-links in the scar samples, hydroxyxylolueine, the reduced form of the allysine cross-link precursor, aldol, the condensation product of two allysine residues, and desmosine, the final stable cross-link in elastin, were measured as described in Methods. Connective tissue cross-link content in collagen and/or elastin is expressed relative to scar total protein and also scar total hydroxyproline.

Table 5 shows that the aldol condensation product was significantly lower in the reperfused scar tissue than in the nonreperfused scars when expressed either per milligram total protein or per microgram hydroxyproline. The hydroxyxylolueine content in the reperfused group had a nonsignificant trend toward a value lower than that of the permanently occlusion group.
occluded group. There was a very small amount of elastin relative to the scar collagen content and no significant difference in elastin content between the reperfused and nonreperfused groups.

Figure 7 demonstrates a good correlation between tensile strength and counts/min aldol/μg OH-Pro (r = 0.734, P < 0.05). It can also be seen from this figure that the reperfused scars have lower mean values of tensile strength and aldol content than the nonreperfused scars.

Stress-Strain Properties at Physiological Stress Levels

The rupture studies reported above required that relatively high stress values be imposed on the scar strips and that measurements be recorded at relatively low sensitivity. Accordingly, a different series of experiments was performed to assess scar properties with loading conditions in the physiological stress range and with measurements made at high sensitivity. These studies all were performed 3 weeks post-infarction.

The amounts of strain required to achieve stress levels from 0.5-3.0 g/mm² at a frequency of 4 Hz are reported in Table 6 for both the stretch and release phases of the cycle. All scar strips exhibited typical stress hysteresis, i.e., for a given stress, the strain was greater during the release phase than during the stretch phase of the cycle.

A comparison of the stress-strain curves for the stretch phase of the cycle for the three scar groups is presented in Figure 8. This figure represents stresses and strains that would be imposed on the strips if they were in the ventricular wall during a cardiac cycle from end diastole to a peak systole of 150 mm Hg. The change in strain over this stress cycle for the myocardial strips (0.093 ± 0.006, n = 7) was significantly greater than the change in strain in tissue after a permanent occlusion (0.059 ± 0.006, n = 12), tissue reperfused after 3 hours of occlusion.
Myocardial strip from LV free wall.

...non-infarcted myocardial strip from LV free wall.

...ischemic region. This increase in strain of approximately 40% from end diastole to peak systole in ischemic regions after coronary occlusion dyskinetic or aneurysmal bulging of an ischemic region. This increase in strain of approximately 10% from end diastole to peak systole in these strips is within the range (4-11%) found by other investigators who measured systolic segment length changes in ischemic regions after coronary artery occlusion in dogs (Theroux et al., 1974; Heyndrickx et al., 1975).

The lesser degree of strain in the scar groups represents the stiffening of the tissue as healing occurs (Hood et al., 1970; Theroux et al., 1977; Roan et al., 1979). Our data suggest that the amount of aneurysmal bulging should decrease by approximately 40% between the immediate post-occlusion period and at 3 weeks post-infarction. This is in agreement with the findings of Roan et al. (1979), who showed that aneurysmal bulging (as measured by net systolic wall thinning) decreased by 44% between 24 hours and 1 week after coronary occlusion in dogs.

Stiffness (Scar Tissue)

The greater degree of strain during systole which occurred in myocardial strips represents acute post-occlusion dyskinetic or aneurysmal bulging of an ischemic region. This increase in strain of approximately 10% from end diastole to peak systole in these strips is within the range (4-11%) found by other investigators who measured systolic segment length changes in ischemic regions after coronary artery occlusion in dogs (Theroux et al., 1974; Heyndrickx et al., 1975).

The lesser degree of strain in the scar groups represents the stiffening of the tissue as healing occurs (Hood et al., 1970; Theroux et al., 1977; Roan et al., 1979). Our data suggest that the amount of aneurysmal bulging should decrease by approximately 40% between the immediate post-occlusion period and at 3 weeks post-infarction. This is in agreement with the findings of Roan et al. (1979), who showed that aneurysmal bulging (as measured by net systolic wall thinning) decreased by 44% between 24 hours and 1 week after coronary occlusion in the dog.

Stiffness values (K), which represent the tangents to the stress-strain curves at different stress levels, are presented in Table 7 and Figure 8. Because of the presence of stress-hysteresis, the K values were higher during the release phase of the cycle than during the stretch phase (Table 7). There were no significant differences among K values for the scar groups at any stress. At all stress levels, the three scar groups had K values significantly greater than the myocardial strips.

When the stiffness coefficient or the slope of the K values per unit of stress (Fig. 8B) is calculated, the result is comparable to the β-coefficient of the monoexponential fit of the stress-strain curve (Fig. 8A). These values are reported in Table 8.

Scar viscoelastic properties were not influenced by reperfusion. There were no statistical differences between reperfused and nonreperfused scars in creep or stress-relaxation measured over a 5-minute period (Fig. 9). For assessment of stress-relaxation, the length of the strip was increased from resting length by a step change to that length which achieved a stress of 3.0 g/mm². The decline in stress...
was logarithmic over 5 minutes, and stress decreased to 35% of its initial value in all scar groups (Fig. 9). For assessment of creep, the strip was subjected to a step increase in stress from zero by 3.0 g/mm². The increase in strain was logarithmic over the 5-minute interval, and strain increased by 6% of its initial value in all scar groups (Fig. 9). Creep was greater and stress-relaxation was less in the excised myocardial strips than in any of the scar groups.

**Discussion**

Our experiments were designed to assess possible deleterious or beneficial effects of reperfusion on the postinfarction healing process. Usually, a myocardial infarction begins out-of-hospital, and minutes to hours elapse before an occluded coronary artery can be reperfused. In this context, reperfusion may reduce infarct size, but rarely does it completely prevent myocardial necrosis. If reperfusion occurs after the injury has become irreversible throughout the ischemic region, no “salvage” can be accomplished. Thus, in most cases, reperfusion occurs in a region of myocardium that is either partially or wholly necrotic. Impaired healing of such necrotic myocardium may predispose to ventricular rupture or to the development of an excessively elastic scar region, which can decrease overall pump efficiency by absorbing systolic mechanical energy generated by the remaining noninfarcted contracting region. A strong, noncompliant postinfarction scar produces the best results in terms of overall ventricular function for a given infarct size (Hood et al., 1970; Diamond and Forrester, 1972; Covell and Ross, 1973; Gaasch et al., 1976; Grossman and Barry, 1980).

Our methodology was designed to impose reperfusion on myocardium that had already become necrotic because of prolonged ischemia. The rate of myocardial necrosis after coronary occlusion in the rabbit is considerably faster than in the dog or in man. We showed previously in rabbits that a 1-hour coronary occlusion produced a transmural infarction, whereas shorter occlusion periods produced subendocardial infarcts when assessed by gross inspection of the tissue slices after nitroblue tetrazolium staining (Connelly et al., 1982). Therefore, in our initial series of experiments, reperfusion was instituted after a 1-hour occlusion, and scar properties were assessed at 1 and 3 weeks post-infarction. We were surprised to find histologically a relatively large number of surviving myocytes intermixed with collagenous scar tissue throughout the thickness of the scar (Figs. 3 and 4). This finding suggests that...
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The tensile strength of the myocardial strips as well as all of the scar groups appeared more than adequate to withstand rupture (Fig. 5). An intraventricular pressure of 180 mm Hg in the rabbit heart should produce a wall stress of approximately 3 g/mm² (see Appendix). The isolated muscle strips did not tear apart until a stress greater than 20 g/mm² was applied. At 1 week post-infarction, scars from both the reperfused and permanently occluded groups required a stress of 50 g/mm² to rupture. At 3 weeks post-infarction, the scars from both reperfused groups could withstand 70 g/mm²; the scars in the permanently occluded group required 160 g/mm² to rupture. Thus, the post-infarction healing process produced scar tissue with an extraordinary reserve in tensile strength relative to imposed physiological stresses. These results are consistent with our previous observation (Lerman et al., 1983) that isolated hearts can withstand pressures above 500 mm Hg beforerupturing when a fluid-filled latex balloon was expanded within the left ventricular chamber. Reperfusion clearly affected tensile strength (Fig. 5), but tensile strength remained well above physiological stress levels in the reperfused groups. These results suggest that reperfusion has no physiologically significant effect on 1- or 3-week-old scar tissue rupture threshold, even though the mechanical properties of the scars were clearly altered by reperfusion.

Since wall thinning occurs during post-infarction healing, assessment of in vivo scar strength requires consideration of both tensile strength and the total force-bearing capacity of the scar, which is independent of cross-sectional area. Theoretically, a post-infarction increase in tensile strength (force per cross-sectional area) could be influenced by a decrease in scar cross-sectional area if marked thinning occurred; in such a circumstance, the total strength of the scar could decrease despite an increase in tensile strength. However, analysis of the total force-bearing capacities of the excised scar strips (Table 3) resulted in the same major conclusions as analysis of the tensile strength data (Fig. 5). At 1 week post-infarction, the scar strips were significantly stronger than the normal myocardial strips, and there was no significant difference between the permanently occluded and reperfused groups. At 3 weeks post-infarction, the permanently occluded group had doubled in total scar strength relative to its 1-week post-infarction value (Fig. 5).
despite significant scar thinning between 1 and 3 weeks in this group (Tables 1 and 3). At 3 weeks post-infarction, scar strips from the permanently occluded group were significantly stronger, in terms of total load-bearing capacity, than either reperfused group (Table 3).

Whereas both "early" (1 hour post-occlusion) and "late" (3 hours post-occlusion) reperfusion resulted in 3-week post-MI scars with less tensile strength than after a permanent coronary occlusion, different mechanisms may be responsible for the lesser tensile strength in the early and late reperfusion groups. The lower tensile strength in the early reperfusion group was associated with less scar collagen content per gram dry weight as assessed both biochemically (Fig. 6) and histologically (Fig. 3); the lower collagen content in this early reperfusion group was probably related to the greater number of surviving myocytes (Fig. 3). In contrast, late reperfusion did not decrease scar collagen content by either histological or biochemical assessment (Figs. 3, 6). However, collagen cross-link density was significantly reduced in the late reperfused group (Fig. 7; Table 5), suggesting that this was the mechanism for this group's lower tensile strength.

Collagen and elastin fibers derive their tensile strength from inter- and intramolecular cross-links. It has been shown that a reduction in cross-link density may reduce the tensile strength of connective tissues (Chen and Postlethwait, 1964; Prockop et al., 1979a, 1979b). Our data (Table 5) indicate that, at 3 weeks post-myocardial infarction, both scars resulting from permanent occlusion or 3 hours of occlusion and reperfusion had the same hydroxyproline content (implying the same collagen content), the same elastin content, and the same hydroxyproline content per microgram hydroxyproline. However, aldol content was significantly reduced in the scars reperfused after 3 hours of occlusion. Aldol is an intramolecular cross-link in collagen. Aldol formation results from the conversion of two allysine residues in the N-terminal telopeptide region of two a-chains. It may also serve as a precursor or component of more complex intermolecular cross-links (Kang et al., 1969; Franzblau et al., 1970; Robins et al., 1973). Aldol is also a cross-link in elastin, as well as a precursor to the desmosine cross-links of elastin. Thus, the lower tensile strength of the reperfused scars may in part be related to the decreased amount of the aldol cross-link. It should be pointed out that there are other cross-links of collagen which were not measured in this study (Bailey et al., 1974; Eyre and Oguchi, 1980), and which also could be potentially affected by reperfusion.

The mechanism by which reperfusion resulted in a decrease in aldol cross-link content was not addressed in our experiments. It is necessary for newly synthesized collagen or elastin molecules to aggregate, align properly, and form insoluble aggregates in order for the enzyme lysyl oxidase to catalyze the oxidation of lysyl and hydroxylysyl residues to make cross-links (Siegel, 1976; Narayanan et al., 1978). Most collagens aggregate to form fibrils; however, the thickness of the fibers, mode of aggregation, and association with non-collagenous materials differs with collagen types. Wiegner and Bing (1981) have shown that collagen fiber alignment in pericardial strips can affect their mechanical properties. Thus, reperfusion may have the potential to interfere with collagen aggregation through steric alignment alterations, thereby decreasing the amount of cross-link formation. Another possibility is that reperfusion may alter the mean activity of lysyl oxidase during the 3-week post-infarction period, since it is an extracellular enzyme. Alternatively, the lysyl oxidase activity might be unaffected, but the ability of the allysine residues to form complex cross-links might be inhibited through the introduction of metabolites. This is seen in tissues treated with penicillamine (Siegel, 1977).

There are some important limitations to our conclusion that reperfusion does not reduce post-infarct scar strength in a physiologically significant way. First, we deliberately excluded the myocardial-scar junction when testing the isolated scar strips. Since our intent was to test tissue that was as homogeneous as possible, we assessed tissue strips that came only from within the borders of the healed infarct or from non-infarcted myocardium. Therefore, the results may not be applicable to the infarct border region where post-infarction rupture can occur (Lewis et al., 1969) and where in vivo stress may be particularly high (Bogen et al., 1980). Second, our earliest studies were carried out 1 week post-infarction. It is therefore possible that we missed an earlier time in the healing phase when reperfusion may have had a transient but greater effect on the mechanical properties of the healing infarct. The absence of observed spontaneous rupture in either the reperfused or permanently occluded groups argues against such a possibility, but it cannot be completely excluded, since not all spontaneous deaths were autopsied.

The post-infarction scars were significantly stiffer than the acutely ischemic myocardial strips (Fig. 8B). This result is not surprising, as other workers have previously demonstrated that post-myocardial infarct healing increases ventricular chamber stiffness (Hood et al., 1970; Gaasch et al., 1976; Mirsky, 1976; Glantz and Parmley, 1978; Lerman et al., 1983).

Parmley et al. (1973) examined the passive length-tension characteristics of human ventricular aneurysms from resected ventricles and related the in vitro characteristics to degree of paradoxical systolic expansion in vivo. They measured stiffness in fibrous, fibrous and muscular, and muscular aneurysms and found that with increasing muscular involvement in the aneurysm, the stiffness decreased and the systolic expansion increased. They concluded that conversion of an acute muscular infarct-
tion to a completely fibrous scar is mechanically advantageous to the ventricle, whereas a mixed fibrous and muscle scar was coincident with decreased function.

Laird and Vellekoop (1971) attempted to evaluate the passive elastic properties of the damaged myocardium from 4 hours to 10 days post-infarction in rabbits. A force elongation test was performed on non-reperfused infarcts, and stiffness was evaluated from the exponential stress-strain curve. However, they found no increase in stiffness over the time period studied as the non-reperfused infarct healed.

In our studies, reperfusion did not significantly influence scar stiffness within the range of physiological stress values. At 3 weeks post-infarction, there was no significant difference in stiffness among the different post-infarction scar groups (Fig. 8B), despite the differences in histological composition (Fig. 3) and collagen content (Fig. 6).

Some investigators have suggested that changes in viscoelasticity post-infarction may influence aneurysm formation in the damaged tissue (Theroux et al., 1974; Gaasch et al., 1976; Vokonas et al., 1976; Rankin et al., 1977). Vokonas et al. (1976) suggested that early segment length changes following coronary occlusion may be related to segmental viscoelastic properties, i.e., a "plastic deformation" and aneurysm formation attributable to creep of the cardiac tissue. Their study was done 6 hours post-infarction, before any connective tissue replacement had occurred, and thus they were observing essentially irreversibly damaged cardiac muscle.

In our studies, the 3-week-old scar tissue exhibited less creep than the myocardial strips (Fig. 9). The decrease in creep between the myocardial strips and the post-infarction scars indicates that progressive healing reduces creep, and this may be related to the progressive decrease in aneurysmal dilation observed in the infarcted region during the initial few weeks post-infarction (Theroux et al., 1977; Roan et al., 1979).

On the other hand, the post-infarction scars had a greater stress-relaxation than the myocardial strips (Fig. 9). Thus, relative to muscle, the scars had a greater resistance to elongation (i.e., they had less creep), but they had less ability to maintain a passive imposed stress (i.e., they had more stress-relaxation). Reperfusion had no effect on creep or stress-relaxation.

Reperfusion has previously been implicated in altering the healing process after myocardial infarction by affecting granulation tissue formation (Rona and Kahn, 1969; Althaus et al., 1977; Shetlar et al., 1979; Roberts et al., 1983). However, Fishbein and associates (1981) found that reperfusion had no effect on wall thickness, hemorrhage, granulation tissue formation, or inflammation at 1 week. Reperfusion has also been associated with changes in the occurrence of aneurysm. Althaus et al. (1977) found a decreased incidence of aneurysmal dilation with reperfusion, while Rona and Kahn (1969) found an increased incidence of aneurysm in their perfused infarcts.

Our study focused on the effects of reperfusion on the mechanical properties of post-infarction scars. This study is the first to show that reperfusion does not alter the healing process as defined by the elastic and viscoelastic properties of post-infarction scars when they are assessed in a physiological stress range at 1 and 3 weeks post-infarction. However, reperfusion reduced scar strength by 50% relative to non-reperfused scars in terms of tensile strength and total load-bearing capacity; nonetheless, supra-physiological stresses were necessary to cause rupture in both the permanently occluded and reperfused groups, as both types of scars were much stronger than normal myocardium.

Appendix

Definitions

Creep
Time-dependent elongation of a material held at a constant force.

Elastic Hysteresis
On decreasing load, the stress-strain curve is not retraced, despite being restored to its original length.

Tangent Modulus (\(K\))
Measure of stiffness, slope of line relating stress to strain.

Tensile Strength
Force at point of rupture divided by the cross-sectional area.

Strain
(Eulerian): \(\ln (L/Lo)\). An indication of the deformation of a material produced by the application of a stress.

Stress
Force per unit of cross-sectional area.

Stress-Relaxation
Time-dependent decay in stress of a material held at a constant elongation or length.

Law of LaPlace
\[
\text{Pressure} = \frac{\text{stress} \times \text{radius}}{2 \times \text{thickness}}
\]

Units: \(g/mm^2\)

Derivations (pressure)
\[
\begin{align*}
1 \text{ mm Hg} &= 1.36 \text{ g/cm}^2 \\
1 \text{ mm Hg} &= 0.0136 \text{ g/mm}^2
\end{align*}
\]
Derivations (radius)

<table>
<thead>
<tr>
<th>Volume = 4/3(π)r³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume = 0.8 ml (end-diastolic volume in rabbit) (Apstein and Ogilby, 1980)</td>
</tr>
<tr>
<td>radius³ = 0.8 ml</td>
</tr>
<tr>
<td>radius = 0.191</td>
</tr>
<tr>
<td>radius = 0.576 cm</td>
</tr>
</tbody>
</table>

Derivations (thickness)

| Thickness of average scar = 0.233 cm (n = 56) |
| Thickness of average LV free wall = 0.310 cm (n = 13) |
| Therefore: LV wall stress at 90 mm Hg systolic pressure = 0.0136 g/mm²/mm Hg X (90 mm Hg) X 0.576 cm |
| = 1.5 g/mm² in scar region |
| = 0.0136 g/mm²/mm Hg X (90 mm Hg) X 0.576 cm |
| = 1.1 g/mm² in normal LV wall |

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INDEX TERMS: Myocardial infarction • Ventricular rupture • Infarct healing • Myocardial scar • Ventricular aneurysm • Myocardial collagen • Myocardial hydroxyproline • Reperfusion
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