No-Reflow Phenomenon Persists Long-Term After Ischemia/Reperfusion in the Rat and Predicts Infarct Expansion

Thorsten Reffelmann, MD; Sharon L. Hale, BS; Joan S. Dow, BS; Robert A. Kloner, MD, PhD

Background—No-reflow after reperfusion therapy for myocardial infarction is a strong predictor of clinical outcome. But its fate on a long-term basis and potential significance for infarct healing are not yet known.

Methods and Results—Twenty-nine female Fisher rats were subjected to 60 minutes of coronary occlusion followed by reperfusion. At 4 weeks, 15 survivors were euthanized after measurement of regional myocardial blood flow (radioactive microspheres) and in vivo staining of perfused tissue (0.5 mL 50% Unipere blue IV). Infarct size (34.3±3.4%), scar thickness (1.19±0.10 mm), and infarct expansion index (0.51±0.04) were assessed from histological sections (2 additional exclusions because of failed occlusion). Regional myocardial blood flow in the reperfused infarct was reduced significantly compared with noninfarcted tissue (1.98±0.47 versus 4.55±0.86 mL · min⁻¹ · g⁻¹, P<0.003, apical slice, and 1.77±0.44 versus 5.34±0.38 mL · min⁻¹ · g⁻¹, P<0.0001, second slice), accompanied by a striking reduction of perfused capillaries within the infarct (n=23±4 versus 163±8 in the noninfarcted tissue, P<0.0001, microscopically assessed as capillaries containing blue particles per high-power field). Macroscopically, no-reflow areas were visible in 9 of 13 hearts. The number of perfused capillaries within the infarct correlated significantly with infarct expansion index (r=−0.76, P<0.003), infarct thickness (r=0.60, P<0.03), and the ratio of infarct to septum thickness (r=0.74, P<0.004).

Conclusions—The no-reflow phenomenon persists for 1 month after reperfusion and predicts worse scar thinning and infarct expansion. Thus, one might shift the “open-artery” hypothesis downstream to an “open-microvessel” hypothesis, relating infarct healing, infarct expansion, and outcome to the completeness of microvascular reperfusion above and beyond epicardial artery patency. (Circulation. 2003;108:2911-2917.)

Key Words: blood flow □ infarction □ microcirculation □ remodeling □ echocardiography

The term “no-reflow,” first used to characterize distinct zones of reduced tissue perfusion and capillary damage after temporary coronary artery occlusion in animal models,1–2 has recently been extended to clinical observations of compromised myocardial reflow on the microvascular level after reperfusion therapy for acute myocardial infarction.3–5 By definition, it describes compromised tissue perfusion despite restoration of epicardial vessel patency. Experimental animal studies2–6,7 and clinical investigations4–5 consistently demonstrated a close correlation between zones of microvascular obstruction and myocardial necrosis. In long-term studies, the incidence and extent of early no-reflow proved to be a strong predictor of persistent contractile dysfunction,8,9 worse left ventricular (LV) remodeling and dilatation,10 and complications and worse clinical outcome.10,11

The fate of no-reflow zones beyond observation periods of more than the initial 2 days after reperfusion in animal studies is not yet known,12 however, and results from clinical investigations are contradictory.4,13–15 Hence, the question of whether compromised tissue perfusion is an independent predictor or even a causal factor for unfavorable outcome after myocardial infarction is of utmost diagnostic and therapeutic interest, especially if compromised tissue perfusion persisted during the period when infarct healing and structural remodeling take place.

In the present study, we provide evidence for long-term persistence of microvascular obstruction in a rat model of coronary artery occlusion and reperfusion. Furthermore, we investigated whether the degree of capillary patency 4 weeks after temporary coronary artery occlusion might correlate with indices of infarct expansion. We examined whether this delayed reflow, even when related primarily to scar perfusion, might have an impact on remodeling, which may reflect the pathological basis for the unfavorable prognostic implications of the no-reflow phenomenon.

Methods

The experiments were conducted in accordance with the national and institutional guides for the care and use of laboratory animals.

Surgical Procedures

Twenty-nine female Fisher rats (body weight, 170 to 240 g; Charles River, Wilmington, Mass) were anesthetized with ketamine (75
mg/kg IP) and xylazine (5 mg/kg IP). After intubation and initiation of ventilation (room air; Harvard Apparatus Rodent Ventilator, model 683), the chest was infiltrated with bupivacaine (0.1 mg/kg), the thorax opened (at the fourth intercostal space), and the pericardium excised. A stitch was taken around the left coronary artery (4-0 suture with an atraumatic needle). A snare formed by the 2 ends of the suture threaded through a length of tubing was tightened for 60 minutes and reopened. Approximately 15 minutes after reflow, the animals received an injection of 0.05 mL of Iscove’s modified DMEM into the epicardial surface of the previously ischemic tissue, avoiding major vessels, because these animals served as a control group for another study. After closure of the chest, application of buprenorphine (0.02 mg/kg SC) and 10 mL/kg saline (SC), and weaning from the respirator, the rats were placed on a heating pad while recovering from anesthesia.

After 28±0.4 days, the surviving rats were reanesthetized and ventilated as described above. A catheter was inserted into the carotid artery and into the jugular vein, and regional myocardial blood flow (RMBF) was measured. Approximately 1.5 minutes after in vivo staining of perfused myocardial tissue, the deeply anesthetized rats were euthanized with 2 mEq KCl, and the hearts were removed and pressure-fixed (see below).

**Echocardiography**

Using inhalative anesthesia (1% to 4% isoflurane in 1 L/min oxygen), echocardiography was performed before surgery and 7.2±0.2 and 26.4±0.3 days after infarction. 2D and M-mode echocardiographic images of a short-axis view on the midpapillary level were recorded with a 7.5-MHz pediatric transducer connected to an echocardiographic imaging unit (Hewlett Packard, Sonos 1000 Ultrasound System). Wall thickness and LV diameters in diastole and systole were measured from M-mode recordings according to the leading-edge method. Fractional shortening (%) was calculated as (LVdsystole−LVdias)÷LVdias. Diastolic and systolic LV areas were planimetrized from 2D recordings. Area ejection fraction (area EF, %) was calculated as (LVarea systole−LV area diastole)/LV area diastole. All values were averaged over 3 consecutive cycles.

**LV Volume Measurements**

After removal of the heart from the thorax, the LV was cannulated retrogradely via the ascending aorta. By connecting the cannula to a column of 10% formalin (pressure equal to 13 cm H2O column), the heart was fixed at a constant intraventricular pressure. LV volumes were assessed by filling the cavity with distilled water and weighing (average of 3 measurements).

**Macroscopic Assessment of No-Reflow**

Before the animal was euthanized at the end of the protocol, 0.5 mL DMEM into the epicardial surface of the previously ischemic tissue, avoiding major vessels, because these animals served as a control group for another study. After closure of the chest, application of buprenorphine (0.02 mg/kg SC) and 10 mL/kg saline (SC), and weaning from the respirator, the rats were placed on a heating pad while recovering from anesthesia.

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**Macroscopic Assessment of No-Reflow**

Before the animal was euthanized at the end of the protocol, 0.5 mL 50% Unipure blue (Ciba Geigy), a suspension of blue particles, was injected intravenously to stain perfused myocardial tissue. The formalin-fixed hearts were cut transversely into 5 slices and photographed under water. The epicardial and endocardial contour and the area not stained by the blue dye, defined as macroscopic no-reflow, were traced manually from projected slides. After computerized planimetry, the macroscopic area of no-reflow was expressed as a percentage of the weight of the whole heart.

**Infarct Size, Wall Thickness, and Infarct Expansion Index**

Histological sections (5 μm) cut from the apical part of the third heart slice after processing and paraffin embedding were stained with hematoxylin and eosin (HE). The following parameters were determined after manual tracing of projected HE slides and computerized planimetry: infarct size: total length of the scar as a percentage of the LV circumference averaged over the endocardial and epicardial tracing; the thickness of the infarct and the septum averaged from 3 measurements (margins and center of infarct and septum, respectively); the ratio of LV cavity area to total LV area to quantify LV dilation; and infarct expansion index: ratio of septum to scar thickness multiplied by this ratio of LV dilation.16

**Measurement of RMBF**

Before injection of the blue dye during the 4-week surgical procedure, approximately 500 000 radioactive microspheres labeled with either 141Ce or 103Ru were injected into the LV. Simultaneously, a reference blood sample was withdrawn from the arterial catheter at a rate of 0.443 mL/min.

The macroscopically visible infarcted tissue and a noninfarcted tissue piece were dissected carefully from the apical and second slices. Tissue and blood sample radioactivity was counted in a multichannel pulse-height analyzer (model ND62, Nuclear Data). RMBF was calculated after correction for background as the ratio of counts in the tissue and the reference blood sample multiplied by 0.443 mL/min and divided by the weight of the tissue.

**Quantification of Tissue Perfusion**

As an estimate of perfused capillaries, the number of capillaries containing blue particles was counted in 3 high-power fields (40-fold microscopic magnification) within the scar tissue and within the noninfarcted tissue of the histological (HE) slides. Counts are expressed as perfused capillaries per high-power field.

**Control Experiments: Early Reflow**

To ensure restored epicardial vessel patency in our model, RMBF was measured in 6 additional rats subjected to the same surgical procedure 15 minutes after reopening of the snare (60 minutes of occlusion). Thereafter, 0.6 to 0.8 mL thioflavin S (4% solution in saline, Sigma) was injected intravenously to stain perfused tissue, and after reocclusion, 1 mL blue dye was injected to delineate the area at risk. Heart slices were photographed as described above and also under an ultraviolet light (365-nm wave length, Spectroline model ENF 280 C, Spectronics). The heart was cut into tissue samples stained by the blue dye and not stained by the blue dye to...
Correlation of Various Parameters of Cardiac Performance and LV Remodeling With the Number of Perfused Capillaries in the Infarct

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean±SEM</th>
<th>Range</th>
<th>Correlation With Perfused Capillaries in the Infarct</th>
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<td>Echocardiography 1 week after myocardial infarction</td>
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</tr>
<tr>
<td>LV diameter (diastole), mm</td>
<td>6.78±0.24</td>
<td>5.36–8.42</td>
<td><strong>r = −0.05, ( P &lt; 0.08 )</strong></td>
</tr>
<tr>
<td>LV area (diastole), mm²</td>
<td>23.4±0.6</td>
<td>19.8–26.5</td>
<td><strong>r = −0.12, ( P &lt; 0.09 )</strong></td>
</tr>
<tr>
<td>FS, %</td>
<td>31.7±2.7</td>
<td>21.3–52.7</td>
<td><strong>r = −0.18, ( P &lt; 0.05 )</strong></td>
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<tr>
<td>EF, %</td>
<td>53.8±3.1</td>
<td>36.8–79.0</td>
<td><strong>r = −0.12, ( P &lt; 0.07 )</strong></td>
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<tr>
<td>Anterior wall thickness (diastole), mm</td>
<td>1.22±0.04</td>
<td>0.91–1.36</td>
<td><strong>r = −0.08, ( P &lt; 0.09 )</strong></td>
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<tr>
<td>Echocardiography 4 weeks after myocardial infarction</td>
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<tr>
<td>LV diameter (diastole), mm</td>
<td>7.26±0.18</td>
<td>6.50–8.03</td>
<td><strong>r = −0.13, ( P &lt; 0.07 )</strong></td>
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<tr>
<td>LV area (diastole), mm²</td>
<td>23.6±1.2</td>
<td>19.1–34.5</td>
<td><strong>r = 0.40, ( P &lt; 0.19 )</strong></td>
</tr>
<tr>
<td>FS, %</td>
<td>31.9±1.5</td>
<td>24.0–40.8</td>
<td><strong>r = −0.08, ( P &lt; 0.07 )</strong></td>
</tr>
<tr>
<td>EF, %</td>
<td>53.3±2.9</td>
<td>37.3–69.2</td>
<td><strong>r = −0.14, ( P &lt; 0.06 )</strong></td>
</tr>
<tr>
<td>Anterior wall thickness (diastole), mm</td>
<td>1.15±0.04</td>
<td>0.96–1.36</td>
<td><strong>r = −0.31, ( P &lt; 0.03 )</strong></td>
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<tr>
<td>Postmortem analysis</td>
<td></td>
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<tr>
<td>LV volume, ( \mu L )</td>
<td>288±16</td>
<td>207–391</td>
<td><strong>r = 0.09, ( P &lt; 0.78 )</strong></td>
</tr>
<tr>
<td>Infarct size, %</td>
<td>34.3±3.4</td>
<td>9.4–56.7</td>
<td><strong>r = 0.22, ( P &lt; 0.48 )</strong></td>
</tr>
<tr>
<td>Infarct thickness, mm†</td>
<td>1.19±0.10</td>
<td>0.71–1.73</td>
<td><strong>r = 0.60, ( P &lt; 0.03 )</strong></td>
</tr>
<tr>
<td>Infarct thickness/septum thickness†</td>
<td>1.0±0.1</td>
<td>0.61–1.53</td>
<td><strong>r = 0.74, ( P &lt; 0.004 )</strong></td>
</tr>
<tr>
<td>LV cavity area/LV total area</td>
<td>0.49±0.01</td>
<td>0.42–0.56</td>
<td><strong>r = −0.28, ( P &lt; 0.36 )</strong></td>
</tr>
<tr>
<td>Infarct expansion index</td>
<td>0.51±0.04</td>
<td>0.30–0.83</td>
<td><strong>r = −0.76, ( P &lt; 0.003 )</strong></td>
</tr>
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</table>

FS indicates fractional shortening; EF, ejection fraction.

*Significant difference.
†In sham animals (surgery without occlusion of the coronary artery, \( n = 6 \)), thickness of the free LV wall was 1.36±0.05 mm, and thickness of the septum was 1.10±0.05 mm.

Statistical Analyses

RMBF and the number of perfused capillaries in the normal and infarcted tissue were compared by a paired \( t \) test. Echocardiographic parameters were compared by a 1-way ANOVA for correlated measurements, followed by Tukey’s post hoc test. Multiple regression analysis was performed with Pearson’s minimal square method with subsequent ANOVA testing for significance. Values are expressed as mean±SEM. A probability value of \( P < 0.05 \) was considered statistically significant.

Results

Mortality and Exclusions

Fourteen of 29 animals died before completing the study, primarily (12 rats) during the first 4 hours after myocardial infarction. Two animals were excluded because of failed coronary occlusion. Data are presented for the remaining 13 rats. Two measurements of absolute RMBF were not included because of technical difficulties.

Echocardiographic Parameters

Compared with baseline echocardiography before myocardial infarction, fractional shortening and area EF were decreased significantly 1 week after myocardial infarction, with no further decrease in the 4-week examination (Figure 1). LV dimensions, as derived from M-mode and from 2D echocardiographic images, demonstrated significant LV dilation within the first week after myocardial infarction, accompanied by a significant reduction in systolic thickening of the anterior wall (+70±5% at baseline, +28±7% at 1 week, and +33±8% at 4 weeks; \( P < 0.01 \)).

Infarct Size, Wall Thickness, Infarct Expansion Index, and LV Volumes

Histological analysis revealed fibrous scar formation with a small rim of viable cardiomyocytes (≈4 to 6 layers) adjacent to the endocardium and a variable number of salvaged myocytes in the epicardial portion of the sections. Infarct size, expressed as percent of total circumference, averaged 34.3±3.4% (Table) and correlated inversely with scar thickness (1.19±0.10 mm, \( r = −0.51, \( P < 0.08 \)). Infarct expansion index (0.51±0.04) did not correlate significantly with infarct size (\( r = 0.26, \( P < 0.39 \)).

Postmortem measured LV volumes correlated significantly with the diastolic area derived from 2D echocardiography at the 4-week follow-up (\( r = 0.62, \( P < 0.03 \)) and with the ratio of LV dilation (LV cavity area/total LV area, \( r = 0.65, \( P < 0.02 \)), confirming the validity of both parameters for assessing increased LV volumes.

RMBF, Macroscopic No-Reflow, and the Number of Perfused Capillaries

In the analyzed tissue of both the apical slice and the second slice, RMBF was significantly lower in the infarcted–reperfused tissue compared with the noninfarcted myocardium (Figure 2). RMBF in the remote basal part of the septum
amounted to 4.80±0.45 mL · min⁻¹ · g⁻¹ after 4 weeks. Macroscopic no-reflow, visible in 9 of 13 hearts, averaged 0.9±0.3% of the total heart weight (Figure 3A).

Parallel to the striking reduction of RMBF within the infarct, a highly significant reduction of the number of perfused capillaries (14±2% of noninfarcted control) in the scar was present (Figures 2 and 3). Regions of reduced capillary density were closely associated with the spatial distribution of scar tissue, and within the scar tissue, the capillary density was nearly equally distributed.

**Correlation Analysis Between Tissue Perfusion and Cardiac Performance**

The number of perfused capillaries per high-power field correlated significantly with infarct expansion index, as a consequence of its close relationship with the ratio of infarct to septum thickness (Figure 4, Table). Parameters of LV dilation, regardless of whether derived from echocardiography, postmortem morphometry, or direct LV volume measurements, did not correlate significantly with tissue perfusion, nor did parameters of systolic contractile performance.

**Control Experiments: Early Reflow**

RMBF in 6 control animals subjected to 60 minutes of coronary occlusion and 15 minutes of reperfusion amounted to 3.28±1.34 mL · min⁻¹ · g⁻¹ in the risk area and 2.24±0.45 mL · min⁻¹ · g⁻¹ in the nonischemic tissue, indicating hyperemic early reflow. Figure 5 shows the distribution of fluorescence after staining of perfused tissue with thioflavin S compared with the risk area.
fluorescence covers large parts of the risk area with small hypofluorescent zones, indicating initially successful reperfusion, with the demarcation of small zones of early no-reflow (Figure 5).

Discussion

This study provides evidence for persistence of the no-reflow phenomenon in the rat over a period of 4 weeks after reperfused myocardial infarction, as evidenced by reduced RMBF and the dramatic reduction of capillaries perfused with blue particles after in vivo staining. Interestingly, tissue perfusion in these reperfused infarcts was less compromised compared with a permanent occlusion infarct, as measured recently in a separate study. Using the same technique (n=17), RMBF in this permanent occlusion infarct was 0.72±0.14 mL·min⁻¹·g⁻¹ in the apical heart slice (P<0.003 versus 1.98±0.47 mL·min⁻¹·g⁻¹ in the present study), the macroscopic perfusion defect 3.0±0.6% of the heart (P<0.005 versus 0.9±0.3% in the present study), and the number of blue capillaries was 12±1 per high-power field (P<0.003 versus 23±4 in the present study; infarct expansion, 0.83±0.06 versus 0.51±0.04, P<0.0003), indicating that tissue perfusion after permanent coronary artery occlusion is even more compromised.

Furthermore, in the present study, a significant correlation between the extent of no-reflow after 4 weeks and thinning of the infarcted wall was demonstrated, resulting in a strong correlation with infarct expansion index.

Fate of No-Reflow Over Time

To the best of our knowledge, the maximum observation period with respect to anatomic assessment of no-reflow in animal models of coronary occlusion and reperfusion is 48 hours after reflow in the dog. Within the first hours of reperfusion, microvascular reperfusion injury may lead to a significant expansion of anatomic no-reflow. In clinical studies, a quantitative contribution of reperfusion injury within the early stages after reperfusion therapy is a matter of debate.

However, beyond that acute phase, the fate of compromised tissue perfusion in animal studies is not known. Clinical investigations using contrast echocardiography and MRI were in part contradictory.

In the present study, we provide evidence for persistent myocardial blood flow reduction in the infarcted tissue accompanied by a striking decrease of perfused capillaries after 4 weeks, a period in which major steps in infarct healing have taken place. Our findings therefore show for the first time in this experimental model that no-reflow persists for at least 1 month after reopening of the epicardial coronary artery.

Infarct Healing and Infarct Expansion

In the rat, significant infarct expansion occurs beyond the first 2 days after myocardial infarction, along with qualitative and quantitative reorganization and healing of the infarcted tissue. However, the extent and degree of these processes are not invariably determined by the initial ischemic burden: reperfusion too late to salvage jeopardized myocardium attenuated or prevented LV dilation, scar thinning, and infarct expansion in several animal models and clinical investigations. In addition, experimental animal studies demonstrated that pharmacological interventions might modify the

Figure 4. Multiple linear regression analysis revealed a significant inverse correlation between number of perfused capillaries in infarct zone (abscissa) and infarct expansion index (left), which was a consequence of positive correlation with thickness of infarct (middle) and ratio of infarct to septum thickness (right).

Figure 5. Control experiments to ensure epicardial vessel patency. Top, Risk area is delineated by staining with blue dye after reocclusion. Bottom, At 15 minutes after reopening of occlusion, staining of reperfused tissue by fluorescent dye thioflavin S demonstrates reperfusion of risk area with small zones of hypofluorescence, indicating early no reflow.
process of infarct healing, resulting in either improved or exacerbated infarct expansion, scar thinning, or ventricular dilation.

Hence, a potential influence of the completeness of tissue perfusion on the process of infarct healing seems to be reasonable. In the present study, the number of perfused capillaries in the scar was correlated significantly with the thickness of the infarct and the calculated infarct expansion index, supporting a potential role of tissue perfusion for the healing process. Because the number of perfused capillaries did not correlate with echocardiographic or postmortem parameters of LV dilation, the correlation with infarct expansion reflects primarily the relationship with scar thinning.

Early mortality in the present investigation was relatively high (48%), which in theory could mean that some animals with the highest amount of necrosis were unintentionally excluded from the analysis. However, average infarct size and scar thickness and expansion index were similar to data obtained after 90 minutes of ischemia and 6 weeks of reperfusion in a previous study from our laboratory, which also demonstrated significantly worse scar thinning and infarct expansion in a permanent occlusion model. Therefore, tissue perfusion might determine infarct expansion and scar thinning beyond the beneficial effects of restoration of epicardial artery patency.

Shifting the “Open Artery” Hypothesis Downstream: the “Open Microvessel” Hypothesis

The initial hypothesis that reperfusion is beneficial even if achieved too late to salvage significant amounts of myocardium was based on several reports of improved survival after late coronary artery reperfusion that was not associated with improved LV contractile function.

The mechanisms believed to be responsible were beneficial effects on infarct healing with reperfusion, leading to firmer and thicker scars and less infarct expansion, with the blood-filled vasculature as a “scaffolding” that supports surrounding necrotic myocardium.

At the present time, when reperfusion therapy has become the pivotal therapeutic goal in acute myocardial infarction, one might define an “open-microvessel” hypothesis. Wu et al. were the first to report prognostic significance of microvascular obstruction, assessed by contrast MRI, even after statistical control for infarct size. The presence of microvascular obstruction was associated with fibrous scar formation, thinner ventricular walls, and greater rise in end-diastolic LV volumes.

Our present study may provide a pathoanatomic substrate of these prognostic implications, demonstrating that compromised tissue perfusion persists over the initial time of infarct healing and that the degree of compromised tissue perfusion is associated with scar thinning and infarct expansion. As a consequence, increased microvascular perfusion might favorably influence the healing process and alter inflammatory reactions, or the blood-filled vasculature might simply exhibit a buttressing effect.

Hence, the open-microvessel hypothesis would mean that improvement of microvascular perfusion confers additional benefit beyond the benefit resulting from late reperfusion.

In patients showing no-reflow after reperfusion therapy for acute myocardial infarction, some differences from our experimental rat model, such as a variable amount of epicardial salvage or additional effects of distal embolization, are to be considered. Nonetheless, therapeutic interventions aimed at preventing or attenuating no-reflow might improve infarct healing, leading to thicker scars and less infarct expansion. Indeed, the correlation between capillary patency and infarct expansion suggests that delayed reflow has an impact on remodeling even in the chronic stage.

Conclusions

In this rat model of 60 minutes of coronary artery occlusion and reperfusion, tissue perfusion on the microvascular level was still compromised after 4 weeks, as evidenced by reduced RMBF and lower numbers of perfused capillaries within the infarct. The close correlation of the degree of tissue perfusion and infarct thinning and infarct expansion in the chronic stage might provide the pathoanatomic basis for the prognostic implications of no-reflow. Improved infarct healing might be a corollary of enhanced tissue perfusion and hence an attractive target for future therapeutic interventions.

Acknowledgments

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