Relationship between no reflow and infarct size as influenced by the duration of ischemia and reperfusion

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Reffelmann, Thorsten, Sharon L. Hale, Guohu Li, and Robert A. Kloner. Relationship between no reflow and infarct size as influenced by the duration of ischemia and reperfusion. Am J Physiol Heart Circ Physiol 282: H766–H772, 2002. First published October 4, 2001; 10.1152/ajpheart.00767.2001.—No reflow after acute myocardial infarction is an important predictor of infarct size and clinical outcome. However, the exact relationship between no reflow and infarct size remains to be determined, particularly because no reflow may progress during the time course of reperfusion. Control groups of five previous protocols using the anesthetized, open-chest rabbit model of coronary artery occlusion and reperfusion were retrospectively analyzed with respect to the correlation between regional myocardial blood flow (RMBF; radioactive microspheres) and infarct size (triphenyltetrazolium chloride) in the course of reperfusion. After 30 min of occlusion, reflow (defined as the ratio of RMBF in the risk area divided by the nonischemic area) declined from hyperemic values after 30 min of reperfusion (reflow ratio: 1.33 ± 0.81; RMBF in the risk area at the same time point: 2.25 ± 1.04 ml·g⁻¹·min⁻¹) to 0.47 ± 0.22 after 120 min and 0.46 ± 0.13 after 180 min of reperfusion. After 120 min of ischemia, reflow at 30 min of reperfusion was 0.49 ± 0.24 and deteriorated by 120 min of reperfusion (0.26 ± 0.15). In every group, there was a strong correlation between infarct size and reflow (correlation coefficients: −0.62 to −0.82). The lines of regression for the groups with assessment of RMBF after 120 or 180 min of reperfusion were nearly identical regardless of the duration of ischemia. Thus microvascular reperfusion injury led to a striking decrease in RMBF within the first 2 h of reperfusion, with infarct size as the major determinant of reflow at a given time point of reperfusion.

myocardial blood flow; rabbit; microvasculature

AFTER TEMPORARY CORONARY ARTERY OCCLUSION, reperfusion to the previously ischemic tissue may remain incomplete despite complete reopening of the epicardial artery, due to microvascular damage. This "no-reflow" phenomenon is characterized by decreased resting myocardial blood flow, ultrastructural vascular alterations, and distinct areas of hypoperfusion (11, 12). The degree of no reflow worsens with longer durations of ischemia (12); however, a further progression of no reflow with ongoing reperfusion seems to be characteristic (2). This increasing impairment of myocardial reflow during reperfusion can be interpreted as a form of reperfusion injury at the microvascular level. In clinical studies, compromised tissue perfusion and distinct areas of microvascular hypoperfusion after successful thrombolysis or primary angioplasty for acute myocardial infarction were demonstrated as well. Recent investigations using the Thrombolysis in Myocardial Infarction (TIMI) grading of myocardial perfusion by coronary angiography (16) or myocardial contrast echocardiography (8, 19) revealed evidence for a close relationship among the incidence or degree of no reflow and clinical outcome, myocardial viability, and left ventricular function at follow-up. In addition, some clinical investigations provided evidence for a progression of microvascular damage with ongoing reperfusion by measurement of intracoronary flow velocities (10) or coronary venous flow (14) after reperfusion therapy for acute myocardial infarction.

However, the exact relationship between the amount of no reflow, as influenced by different durations of ischemia and reperfusion, and myocardial infarct size remains to be determined in both clinical and experimental animal studies. In the present analysis, control experiments of five protocols were retrospectively grouped to gain insight into the relationship between no reflow and myocardial infarct size and to determine to what degree this relationship depends on the duration of ischemia and reperfusion.

METHODS

Animal preparation. All experiments were conducted in accordance with the institutional and national Guide for the Care and Use of Laboratory Animals (17). Animals that served as control groups for other protocols were analyzed retrospectively for the current study.

New Zealand White rabbits, weighing between 2.0 and 3.6 kg, were anesthetized with an intramuscular injection of ketamine (400 mg) and xylazine (200 mg). After the rabbits were shaved, tracheotomy or endotracheal intubation was followed by mechanical ventilation using room air enriched with 1.5 l/min oxygen. Initial tidal volumes were adjusted after thoracotomy. Fluid-filled catheters were inserted into

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the jugular vein and carotid artery for additional intravenous anesthesia (pentobarbital, as needed) and continuous monitoring of arterial blood pressure. After a thoracotomy via the fourth intercostal space and pericardial incision, a major branch of the circumflex coronary artery was encircled by a suture. The two ends of the suture were threaded through a piece of plastic tubing, forming a snare. Thereafter, a fluid-filled catheter was inserted into the left atrial appendage and fixed by a clamp. Rectal temperature was monitored, and a heating pad was used to maintain body temperature. After registration of baseline parameters, the coronary artery was occluded by tightening the snare for either 30 or 120 min. Reperfusion was then allowed by release of the coronary occlusion. At different time points, regional myocardial blood flow (RMBF) was measured by intra-atrial injection of radioactively labeled microspheres (see Regional myocardial blood flow). At the end of reperfusion, the coronary artery was reoccluded, and 4 ml of 50% Uniprerse blue (Ciba-Geigy; Hawthorne, NY) were injected into the left atrial appendage. The rabbits were euthanized by an intravenous overdose of xylazine followed by 12 mg of potassium chloride (intratrarial).

Assessment of ischemic risk area and infarct size. After removal of the right ventricle and the major vessels, the left ventricle was transversely sliced into six to eight sections and photographed. The slices were incubated in 1% triphenyltetrazolium chloride for 15 min and rephotographed. After projection of the slides, the contour of each slice, the risk area, visualized as tissue not stained by the blue dye, and the area of necrosis (not stained by triphenyltetrazolium) were traced manually. After computerized planimetry, the percentages of the risk area and necrotic area were multiplied by the weight of the slice; the risk area was expressed as a percentage of the weight of the left ventricle, and the area of necrosis was expressed as a percentage of the risk area.

Regional myocardial blood flow. RMBF was measured by intra-atrial injection of ~500,000 microspheres per measurement labeled with 99mniobium, 141cerium, or 103ruthenium. Simultaneously, a reference blood sample was withdrawn through the arterial catheter at a rate of 2.06 ml/min. At the end of the protocol, the hearts were cut into samples stained by 1% triphenyltetrazolium. Tissue and blood sample radioactivity was counted using a multichannel pulse-height analyzer.

In the groups with 30 min of occlusion, mean infarct size was 72 ± 10% and 68 ± 12% in groups IV and V, respectively (Fig. 2). Pairwise comparison of the groups with equal duration of ischemia did not reveal significant differences; however, all comparisons between the individual groups. The duration of coronary occlusion and reperfusion, as well as the different time points for measurement of RMBF, are indicated. Animals in group II received a continuous saline infusion during the reperfusion period at a rate of 0.103 ml·kg⁻¹·min⁻¹, because this group served as a control group for a drug study. For the same reasons, an intravenous bolus of saline was given in group III at 20 min of occlusion.

Statistical analysis. The measured parameters are expressed as means ± SD. To assess whether the groups are comparable with respect to baseline parameters, risk area, hemodynamics, and temperature, a one-way ANOVA for independent measurements was applied. RMBF at different time points and infarct size was analyzed by one-way ANOVA testing with subsequent Tukey's honestly significant difference post hoc test, provided that the P value revealed a significant difference among the groups. Correlation analysis between the amount of reflow and infarct size was performed using Pearson's correlation coefficient with subsequent ANOVA analysis for significance. A P value of <0.05 was considered statistically significant.

RESULTS

Comparison of the five groups. The five groups did not significantly differ with respect to body weight, heart rate, or systolic blood pressure at baseline and during occlusion (Table 2). In addition, hemodynamics at 30 min of reperfusion did not significantly differ among the groups with equal time of ischemia. However, the animals in group IV tended to have higher diastolic blood pressure at baseline and during early occlusion (Fig. 1). Importantly, the risk area was nearly equal in all the five groups. Rectal temperature in group V was slightly lower than in the other groups.

Hemodynamics. Figure 1 demonstrates blood pressure and heart rate during the experimental procedure in the five groups. In every group, coronary occlusion was followed by a marked decrease of blood pressure, and heart rate tended to increase slightly. Hemodynamics remained relatively stable until the end of the protocol.

Infarct size. In the groups with 30 min of occlusion, infarct size as a percentage of the risk area amounted to 36 ± 16%, 40 ± 17%, and 45 ± 14% (means ± SD) in groups I, II, and III, respectively. In the groups with 120 min of occlusion, mean infarct size was 72 ± 10% and 68 ± 12% in groups IV and V, respectively (Fig. 2). Pairwise comparison of the groups with equal duration of ischemia did not reveal significant differences; however, all comparisons between the individual groups

Table 1. Experimental protocol

<table>
<thead>
<tr>
<th>n</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
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<tbody>
<tr>
<td>Occlusion, min</td>
<td>8</td>
<td>8</td>
<td>12</td>
<td>8</td>
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<tr>
<td>Reperfusion, min</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>120</td>
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<tr>
<td>RMBF</td>
<td>180</td>
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<td>180</td>
<td>120</td>
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n, No. of animals. RMBF, time points when regional myocardial blood flow was measured.
with 30 min of occlusion versus 120 min of occlusion were significantly different. Hence, as expected, infarct size was larger with 120 min of ischemia than with 30 min of ischemia.

**RMBF at baseline and during occlusion.** Baseline RMBF, determined in group II, was 1.81 ± 0.37 ml·g⁻¹·min⁻¹ in the nonischemic area. RMBF during occlusion was determined in groups I, III, and IV and ranged between 0.02 ± 0.03 and 0.04 ± 0.02 ml·g⁻¹·min⁻¹ in the risk area, which is consistent with negligible collateral blood flow to the risk area in the rabbit heart. At the same time points, RMBF in the nonischemic tissue ranged between 1.47 ± 0.54 and 1.90 ± 0.61 ml·g⁻¹·min⁻¹.

**RMBF after reperfusion of a 30-min occlusion (groups I–III).** Mean RMBF in the risk area at 30 min of reperfusion was hyperemic in group I (30 min of occlusion) and amounted to 2.25 ± 1.04 ml·g⁻¹·min⁻¹ (RMBF in the nonischemic area: 1.80 ± 0.38 ml·g⁻¹·min⁻¹). But when RMBF was measured after 120 or 180 min of reperfusion (groups II and III), a marked decrease of tissue perfusion within the risk area was apparent (Fig. 2).

To account for a potential influence of coronary perfusion pressure at the different time points of reperfusion, “reflow” was calculated as the ratio of RMBF within the risk area divided by the RMBF in the nonischemic tissue as an indicator of the completeness of tissue reperfusion (Fig. 3). While this reflow ratio was 1.33 ± 0.81 after 30 min of occlusion and 30 min of reperfusion (group I), i.e., hyperemia compared with the nonischemic tissue, reflow was reduced to 0.47 ± 0.22 after 120 min of reperfusion (group II) with no further decrease after 180 min of reperfusion (0.46 ± 0.13, group III).

**RMBF after reperfusion of a 120-min occlusion (groups IV and V).** After 120 min of ischemia, RMBF after 30 min of reperfusion did not reach hyperemic values (0.65 ± 0.28 ml·g⁻¹·min⁻¹ in the risk area versus 1.43 ± 0.50 ml·g⁻¹·min⁻¹ in the nonischemic area) (Fig. 2). Average reflow was 0.49 ± 0.24 after 120 min of occlusion and 30 min of reperfusion (group IV; Fig. 3) and was further reduced after 120 min of occlusion and 120 min of reperfusion (0.26 ± 0.15, group V).

**Correlation between reflow and infarct size.** Correlation analysis between infarct size and the amount of reflow revealed a strong correlation in each of the five groups with the Pearson correlation coefficient ranging from −0.62 to −0.82 (Fig. 3). This correlation did not reach statistical significance in group II (P < 0.086) and group V (P < 0.065) but did in the other groups. Interestingly, the lines of regression were nearly equal for groups II, III, and V when RMBF was measured after 120 or 180 min of reperfusion, which on the one hand suggests that the amount of no reflow did not further deteriorate after 120 min of reperfusion, and on the other hand that the reduced reflow after longer times of occlusion but equal time of reperfusion was solely explained by the larger infarct size. RMBF after 30 min of reperfusion was characterized by a higher variability in both groups after 30 and 120 min of ischemia (groups I and IV). The lines of regression of groups I and IV had a steeper slope, and hyperemic reflow was predominantly apparent in the animals with small infarcts. Although the two lines of regression at 30 min of reperfusion differed more than the

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### Table 2. Comparison of the five groups

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
<th>P Values</th>
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<tr>
<td>Body weight, kg</td>
<td>2.38 ± 0.23</td>
<td>2.68 ± 0.28</td>
<td>2.65 ± 0.24</td>
<td>2.69 ± 0.16</td>
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<td>Heart rate, beats/min</td>
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<tr>
<td>Baseline</td>
<td>178.1 ± 18.1</td>
<td>174.3 ± 24.3</td>
<td>180.5 ± 9.5</td>
<td>186.3 ± 44.6</td>
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<tr>
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<td>174.4 ± 19.4</td>
<td>193.9 ± 33.3</td>
<td>182.3 ± 10.6</td>
<td>187.5 ± 32.0</td>
<td>185.8 ± 26.2</td>
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<tr>
<td>Groups I–III</td>
<td>178.8 ± 17.3</td>
<td>191.4 ± 35.0</td>
<td>181.8 ± 12.6</td>
<td>187.5 ± 10.4</td>
<td>204.4 ± 29.0</td>
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<td>Groups IV and V</td>
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<td>Systolic BP, mmHg</td>
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<td>Baseline</td>
<td>88.3 ± 14.0</td>
<td>89.8 ± 8.2</td>
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<td>105.5 ± 14.0</td>
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<td>69.8 ± 6.2</td>
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<td>82.8 ± 11.3</td>
<td>73.5 ± 16.2</td>
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<tr>
<td>Groups I–III</td>
<td>69.3 ± 6.4</td>
<td>74.0 ± 6.6</td>
<td>75.3 ± 7.0</td>
<td>65.5 ± 5.5</td>
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<td>Diastolic BP, mmHg</td>
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<tr>
<td>Baseline</td>
<td>65.8 ± 13.2</td>
<td>68.1 ± 11.8</td>
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<td>80.6 ± 14.8</td>
<td>59.7 ± 12.8</td>
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<tr>
<td>Occlusion</td>
<td>52.3 ± 5.6</td>
<td>54.6 ± 6.9</td>
<td>56.1 ± 7.8</td>
<td>65.3 ± 12.5</td>
<td>52.4 ± 11.8</td>
<td>0.044*</td>
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<tr>
<td>Reperfusion</td>
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<tr>
<td>Groups I–III</td>
<td>52.3 ± 6.9</td>
<td>58.3 ± 6.4</td>
<td>56.1 ± 6.0</td>
<td>44.5 ± 7.2</td>
<td>46.9 ± 11.7</td>
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<td>0.636</td>
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<td>39.1 ± 0.8</td>
<td>38.6 ± 0.3</td>
<td>38.8 ± 0.4</td>
<td>37.6 ± 0.8</td>
<td>0.001*</td>
</tr>
<tr>
<td>Occlusion</td>
<td>38.0 ± 0.5</td>
<td>39.0 ± 0.8</td>
<td>38.5 ± 0.2</td>
<td>38.9 ± 0.6</td>
<td>37.7 ± 0.8</td>
<td>0.001*</td>
</tr>
<tr>
<td>Risk area, % of LV</td>
<td>35.9 ± 10.4</td>
<td>36.9 ± 4.7</td>
<td>33.2 ± 8.2</td>
<td>34.4 ± 9.6</td>
<td>29.9 ± 11.2</td>
<td>0.571</td>
</tr>
</tbody>
</table>

Values are means ± SD. BP, blood pressure; reperfusion, data at 30 min of reperfusion. Reperfusion data were compared separately for the groups with 30 min of occlusion (groups I–III) and 120 min of occlusion (groups IV and V). P values were the result of a statistical comparison by one-way ANOVA. *Statistical significance, P < 0.05.
lines of regression in the groups with longer reperfusion, the amount of reflow after 30 min of reperfusion seemed to be mainly determined by infarct size as well.

DISCUSSION

The main results of this analysis are as follows. First, the amount of reflow to the previously ischemic myocardium after release of a coronary artery occlusion decreased with ongoing reperfusion and reached a stable value after 2 h of reperfusion. Second, the impairment of reflow was more pronounced after 2 h of ischemia than after 30 min of ischemia. Third, at every time point of reperfusion, there was a strong correlation between infarct size and the amount of reflow after both 30 and 120 min of ischemia. Finally, at 120 min of reperfusion, the depressed reflow after 2 h of ischemia compared with 30 min of ischemia seemed to be solely explained by the increased size of necrosis. Similarly, after 30 min of reperfusion, infarct size seemed to be the major determinant of reflow.

No reflow and experimental myocardial infarction. As demonstrated by Ambrosio et al. (2) in a canine model of myocardial infarction, anatomic no reflow increased more than twofold between 2 min and 3.5 h of reperfusion, which was accompanied by a parallel progressive decrease of RMBF. Interestingly, the progressive decline of regional blood flow in this study was predominantly observed in zones of low collateral blood flow.

The data presented in our rabbit model, which is characterized by negligible collateral flow, are consistent with these findings and extend the concept of microvascular reperfusion injury by specifying its time course and its relationship to different durations of ischemia and infarct size. While Ambrosio et al. (2) found an inverse correlation between the size of ana-
of reperfusion, the results of the present analysis provide evidence for a strong inverse correlation between reflow and infarct size at different time points of reperfusion and after different durations of ischemia. In addition, the increase in no reflow with longer times of ischemia is mainly explained by the increased infarct size notwithstanding the duration of coronary occlusion. As the susceptibility of the microvascular and cardiomyocytes to both the ischemic insult and reperfusion injury may be different (12), this relationship is not self-evident. On the other hand, the present analysis suggests that the marked progression of no reflow during reperfusion predominantly develops during the first 2 h of reperfusion, with no further deterioration with 3 h of reperfusion.

In this context, it should be emphasized that the no-reflow phenomenon is characterized by distinct areas of microvascular perfusion defects; therefore, the data on RMBF within the risk area in this study represent an average value of zones of no or low reflow and normal or even hyperemic regional flow. Hence, RMBF in the risk area is influenced by the size and uniformity of areas of no reflow as well as functional integrity and vasomotor tone in the rest of the previously ischemic tissue.

The mechanisms responsible for no reflow and its progression during reperfusion have not yet been fully elucidated, and a characterization of the time course of no reflow during reperfusion might help to estimate the importance of different potential mechanisms.

Ischemia-related morphological alterations of the microvascular bed, such as localized endothelial swelling or membrane-bound intraluminal bodies, may contribute to compromised blood flow, probably directly after release of the coronary occlusion (11). With ongoing reperfusion, leukocyte-mediated mechanisms, whether solely confined to mechanical plugging (6) or more likely underlying complex interactions with endothelial cells, platelets, and myocytes (20), have been put forward to explain the progression of microvascular damage during reperfusion. After 90 min of ischemia and 3 h of reperfusion in the canine model, Tanaka et al. (21) demonstrated a marked accumulation of neutrophils in the risk area and beneficial effects of anti-neutrophil treatment on blood flow at 45 min of reperfusion. However, accumulation of granulocytes in the risk area of dog hearts, characterized by higher collateral flow, may already commence during ischemia (5). Hence, the apparently parallel development of no reflow does not necessarily apply to the rabbit model with its lack of collateral flow. Reactive oxygen species (1, 13, 18), originating from leukocytes (4) or the xan-
thine-oxidase reaction (3), are considered to play a crucial role in microvascular reperfusion injury. Whether the development of tissue edema, which is considered to occur mainly within the first minutes of reperfusion, with subsequent compression of the microvasculature is significantly involved in the progression of microvascular injury during reperfusion appears to be doubtful (15).

**Microvascular reperfusion injury and infarct size in clinical studies.** Recent clinical studies (8, 16, 19) confirm a close correlation among no reflow after reperfusion therapy for myocardial infarction and myocardial viability, clinical outcome, and left ventricular function. Angiographic no reflow after coronary angioplasty for acute myocardial infarction, defined as TIMI grade 0–2 flow on the final coronary angiogram, was shown to be a strong predictor of adverse clinical outcome (16). Ito et al. (9) demonstrated sizable contrast defects by myocardial contrast echocardiography even with TIMI grade 3 flow after primary percutaneous transluminal coronary angioplasty (PTCA) for acute myocardial infarction, and recovery of regional contractile function was only observed in patients without perfusion defects. However, it still remains to be clarified whether the correlation between no reflow and clinical outcome simply reflects the size of the infarct or whether this correlation in addition is directly related to microvascular damage, which might impede infarct healing, promote ventricular remodeling, or potentially reduce collateral formation. A recent study (23) using magnetic resonance imaging for visualization of microvascular obstruction suggested that no reflow might be a prognostic predictor in addition to its relationship to myocardial viability.

Although some clinical studies (10, 14) have provided evidence for a deterioration of no reflow during reperfusion, its significance and time course are not well defined. A progressive decrease of coronary vein flow was demonstrated in 9 of 19 patients, after acute myocardial infarction, over the first 24 h (14). Intracoronary Doppler flow measurement demonstrated characteristic changes within the first 10 min after primary PTCA (10). Also, different or additional mechanisms of no reflow compared with animal models of mechanical coronary artery ligation and reperfusion have to be considered in the clinical situation, which is associated with atherosclerotic and thrombotic vascular alterations. In particular, coronary microembolization in acute myocardial infarction and unstable angina, or as a side effect of thrombolysis or primary PTCA, may significantly compromise microvascular perfusion (22).

The present analysis of regional myocardial flow after experimental infarction confirms a close correlation between the amount of necrosis and reflow, which parallels clinical observations. This relation seems to be present after different durations of ischemia and reperfusion. When the same time points of reperfusion are compared, the amount of reflow appears to be predominantly determined by infarct size regardless of the duration of ischemia.

**Limitations.** This analysis was performed retrospectively. Significant differences of diastolic blood pressure at baseline and during early occlusion, as well as temperature, are not reflected by corresponding differences of infarct size or RMBF but may weaken the analysis. Risk area, as one of the major determinants of infarct size in the rabbit, was nearly equal in the five groups.

The overall duration of reperfusion was 2 h in groups II and V but 3 h in the other groups. The determination of infarct size by triphenyltetrazolium staining may depend on the duration of reperfusion; however, average infarct size did not significantly differ from groups with identical duration of ischemia but longer duration of reperfusion in this set of data.

In conclusion, resting RMBF after temporary coronary artery occlusion and reperfusion was characterized by a progressive decrease within the first 2 h in the rabbit heart. The amount of reflow closely correlated with the amount of necrosis at any duration of reperfusion. This relation between infarct size and reflow at a given time point of reperfusion seems to be mainly determined by infarct size regardless of the duration of ischemia. These investigations parallel clinical observations that suggest a close relation between the incidence and amount of no reflow and myocardial viability, recovery of regional contractile function, and clinical outcome.

**REFERENCES**


