Effects of Reperfusion on Arrhythmias and Death After Coronary Artery Occlusion in the Rat: Increased Electrical Stability Independent of Myocardial Salvage

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Objectives. This study sought to delineate salvage-dependent from salvage-independent coronary reperfusion in acute myocardial infarction and the effects on spontaneously occurring arrhythmias and arrhythmic death in rats.

Background. Reperfusion of the infarct-related artery might increase electrical stability independently of salvage of ischemic myocardium.

Methods. In 98 conscious rats the electrocardiogram was monitored by telemetry for 48 h after MI, and all episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF) were analyzed. Reperfusion at 45 min (RP45) (n = 15), 90 min (RP90) (n = 18) and 180 min (RP180) (n = 30) min was compared with respect to the post-reperfusion periods.

Results. RP45, RP90 and RP180 reduced the incidence of VT by 93%, 98% and 88% and VF by 89%, 97% and 92%, respectively (all p < 0.01 vs. CAO). The all-cause mortality rate was reduced from 47% (CAO) to 8% (RP45, p < 0.05) and 0% (RP90, p < 0.01); after RP180 it was 17% (CAO 42%, p = 0.08). All reperfusion regimens reduced arrhythmic deaths: 47% to 8% (RP45, p < 0.05), 47% to 0% (RP90, p < 0.01) and 42% to 8% (RP180, p < 0.05). Infarct size was identical to that during CAO (49 ± 10% [mean ± SD]) and RP180 (49 ± 10%), whereas preferentially epicardial salvage occurred at RP45 (36 ± 8%, p < 0.001) and RP90 (38 < 10%, p < 0.001).

Conclusions. Early and late reperfusion reduce the incidence and duration of VT and VF in conscious rats with acute MI. Thereby, arrhythmia-related mortality is improved through the prevention of fatal VF episodes. Thus, reperfusion increases the electrical stability of the heart independently of myocyte salvage, as proposed by the open artery hypothesis.

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In the treatment of acute myocardial infarction (MI) a fundamental concept has evolved wherein the occluded infarct-related artery (IRA) is reperfused as early as possible. This treatment strategy originated from the discovery that the time-dependent “wavefront of ischemic cell death” can be interrupted by timely reperfusion of the coronary artery (1,2), thereby limiting myocardial necrosis, resulting in an improvement of left ventricular function and prognosis.

Despite the demonstration of the validity of these concepts, it has become apparent that the benefits of reperfusion therapy exceed the improvements in survival that can be attributed to augmentation of left ventricular function, leading to the “open artery hypothesis” (3). Even beyond the potential for myocardial salvage, reperfusion of the IRA can exert important beneficial effects on infarct expansion and scar formation (4), ventricular dilation and dysfunction (5) as well as on the “electrical stability” (5,6) of the myocardium. The latter mechanism might be of major prognostic importance because cardiac death from malignant ventricular arrhythmias has been found to be a major mechanism of death after hospital discharge in patients without reperfusion therapy.

The present study was designed to test the effects of reperfusion on electrical stability in conscious rats during the first 2 days after acute MI. As a variable of electrical stability, we analyzed the complete arrhythmia profile during this 48-h period with respect to episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF) and related these findings to mortality and infarct size. To dissociate the effects of myocardial salvage from factors that are independent of reperfusion-mediated reductions in infarct size, we studied the impact of coronary artery reperfusion in the rat after three different durations of ischemia compared with permanent coronary occlusion: reperfusion after 1) 45 min, with significant myocardial salvage (4); 2) 90 min, with a limited reduction in infarct size (4); and 3) 180 min, a time beyond the potential for myocardial salvage (4).
Infarct sizing. For deaths that occurred before reperfusion, Alcian blue dye was injected into the ascending aorta to outline the size of the occluded zone. Because, on average, 80% to 90% of this nonperfused area becomes necrotic in the rat model (10), infarct size for these early deaths was assessed as 0.8 × Nonperfused zone. The left ventricle was hand cut into four to six slices parallel to the base, which were then photographed after dye injection or tissue staining, depending on the time of death. All other deaths occurred >3 h after ligation, and these hearts were stained by incubating the tissue slices in 1% triphenyltetrazolium chloride (TTC) for 10 to 15 min at 37°C and pH 7.8. (11), bathed for 5 to 15 min in formal saline (4% formaldehyde) to enhance color contrast, fixed in formalin and processed for routine histologic analysis. From each slice, a 7-µm section was mounted and stained with hematoxylin-eosin. Infarct size was based on the TTC measurements, except for a few specimens that showed poor color discrimination after TTC staining, in which case infarct size was obtained from tissue stained with hematoxylin-eosin.

The lengths of necrotic (or nonperfused) tissue and noninfarcted (or dye perfused) myocardium for both the endocardial and epicardial surfaces of each slice were determined by planimetry of the projected and magnified (×10) photographic or histologic slides. The length of the infarction and the total circumference of each slice for the endocardial and epicardial surfaces were numerically summed separately. The ratio of these sums defined the infarct size for each of the myocardial surfaces, which were then averaged and expressed as a percentage to give total infarct size. The transmurality of an infarction was expressed as the ratio of the epicardial infarct size to the endocardial infarct size.

Arrhythmia analysis. The acquired single-lead ECG tracings were displayed and analyzed off-line in a semiautomated fashion, as previously reported (7). Every RR interval corresponding to a heart rate <300 beats/min, or every run of three or more RR intervals corresponding to a heart rate >500 beats/min, was evaluated individually. All arrhythmic events were classified by the observer according to the guidelines provided by “the Lambeth conventions” (12). VT was defined as ≥4 consecutive ventricular premature beats. Whenever possible, VT and VF were tabulated separately, although both arrhythmias can convert several times into each other during one arrhythmic episode without a clear-cut interface. VF was defined as a signal that changed from beat to beat in rate and configuration or where individual QRS-deflections could not easily be distinguished from one another (12).

The prevalence of VT and VF with certain time period was defined as the proportion of animals that were affected by VT or VF relative to all animals alive at the beginning of this period. For both VT and VF, the number of episodes was counted as a measure of arrhythmia incidence and for episodes that lasted >1 s, the durations were measured. Fatal VF was assigned a duration of 111 s, the longest observed nonfatal VF episode.

To compare the number as well as the sum of the durations of VF and VT episodes between groups, the data were

**Methods**

**Experimental infarction.** Three- to 6-month old female Wistar rats were used in these experiments, which were performed in accordance with protocols approved by the institutional animal management program. A total of 146 rats were prospectively assigned to either permanent coronary artery occlusion (CAO) (n = 48) or reperfusion at 45 min (RP45) (n = 29), 90 min (RP90) (n = 29) or 180 min (RP180) (n = 40). More rats were assigned to CAO and RP180 because we expected a higher mortality in these two groups, and it was our intention to detect even a small difference between CAO and late reperfusion. The final study groups included animals that had a technically successful infarct procedure and an endocardial infarct size ≥30% to select moderate to large infarctions. Endocardial infarct size was used as a selection criterion for all four groups because endocardial necrosis is well established by 45 min after coronary artery ligation in the rat (4). As in previous studies (7), a few animals (9 of [6%] 146) with extensive perfusion defects (>60%) that died in early pump failure were excluded.

**Study protocol.** The telemetry data were acquired and analyzed by using a previously described technique (7). Under ether anesthesia, an electrocardiographic (ECG) radiotransmitter was subcutaneously implanted, and the continuously emitted digitized biopotential signal was fed into a personal computer. Within 2 days after transmitter implantation, a 24-h baseline ECG was recorded. After allocation to one of the four experimental groups, the infarct procedure was performed directly on the receiver unit while the ECG was continuously recorded. After allocation to one of the four experimental groups, the infarct procedure was performed directly on the receiver unit while the ECG was continuously recorded. After a left-sided thoracotomy, the proximal left coronary artery was occluded by a modification of a previously described method using ether anesthesia (8). In the CAO experimental groups, the infarct procedure was performed in accordance with protocols approved by the institutional animal management program. Three- to 6-month old female rats were used in these experiments, which were performed in accordance with protocols approved by the institutional animal management program. A total of 146 rats were prospectively assigned to either permanent coronary artery occlusion (CAO) (n = 48) or reperfusion at 45 min (RP45) (n = 29), 90 min (RP90) (n = 29) or 180 min (RP180) (n = 40). More rats were assigned to CAO and RP180 because we expected a higher mortality in these two groups, and it was our intention to detect even a small difference between CAO and late reperfusion. The final study groups included animals that had a technically successful infarct procedure and an endocardial infarct size ≥30% to select moderate to large infarctions. Endocardial infarct size was used as a selection criterion for all four groups because endocardial necrosis is well established by 45 min after coronary artery ligation in the rat (4). As in previous studies (7), a few animals (9 of [6%] 146) with extensive perfusion defects (>60%) that died in early pump failure were excluded.

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To compare the number as well as the sum of the durations of VF and VT episodes between groups, the data were

<table>
<thead>
<tr>
<th>Abbreviations and Acronyms</th>
<th>Description</th>
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<tr>
<td>CAO</td>
<td>coronary artery occlusion</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram, electrocardiographic</td>
</tr>
<tr>
<td>IRA</td>
<td>infarct-related artery</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<tr>
<td>RP45, RP90, RP180</td>
<td>reperfusion at 45, 90 and 180 min, respectively</td>
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<tr>
<td>TTC</td>
<td>triphenyltetrazolium chloride</td>
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<tr>
<td>VF</td>
<td>ventricular fibrillation</td>
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<tr>
<td>VT</td>
<td>ventricular tachycardia</td>
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expressed as mean values/h. To account for the censoring effect associated with differential survival, we normalized the arrhythmia frequencies and durations by dividing the absolute number of episodes and their summed durations by the actual survival time or “time at risk” for experiencing an arrhythmia. We measured this time at risk in 30-min increments to avoid an overrepresentation of the arrhythmia severity in animals that died after only a few minutes into the time period of interest. For the analysis within a given time period, the arrhythmia data for each animal were divided by the number of 30-min blocks of time at risk within the period. The arrhythmia frequencies and durations were expressed in episodes/h per animal and s/h per animal, respectively.

Statistical analysis. We used the chi-square test to compare between-group categoric variables. Because most of the continuous variables that describe arrhythmia frequency or duration are not normally distributed, we compared these end points by Kruskal-Wallis analysis of variance on ranks with a Dunn test for between-group comparisons. Ischemia/necrosis-induced arrhythmias and deaths in the rat occur in a time-dependent pattern and are concentrated mainly within the first 9 h after MI, and thus the statistical comparison of arrhythmia end points between groups was restricted to this time period. Between-group infarct sizes were compared by analysis of variance. A p value <0.05 was considered significant. Results are presented as mean ± SD, unless otherwise specified.

Results

Of the 146 rats that were entered into the protocol, 98 had an endocardial infarct size >30%, 92 of which (94%) had complete arrhythmia profiles: 34 (CAO), 27 (RP180), 17 (RP90) and 14 (RP45). In a few rats (6 of [5.9%] 98), technical problems prevented the acquisition of a high quality ECG signal over the entire study period. All 98 animals were included in the mortality analysis: 35 (CAO), 30 (RP180), 18 (RP90) and 15 (RP45). The remaining 48 animals were excluded from final analysis for the following reasons: endocardial MI size <30% (too distal or incomplete ligation) (CAO 3 of 48, RP180 2 of 40, RP90 3 of 29, RP45 5 of 29); no MI (CAO 2 of 48, RP180 1 of 40, RP90 1 of 29, RP45 3 of 29); extensive MI with acute pump failure (CAO 3 of 48, RP180 2 of 40, RP90 3 of 29, RP45 1 of 29); surgical complications (CAO 3 of 48, RP180 5 of 40, RP90 4 of 29, RP45 5 of 29); unreliable tissue staining (CAO 2 of 48, RP180 5 of 40, RP90 2 of 29, RP45 5 of 29).

In addition to 2,352 h of baseline recording before infarction, we recorded and analyzed the continuous ECG for 3,208 h. Overall, we found 13,595 VT episodes and 953 VF episodes after MI. VF frequently occurs as a self-limited arrhythmia in the rat with myocardial ischemia/necrosis, and despite nonsustained VF episodes with durations of up to 111 s, only 26 (2.7%) of 953 of the VF episodes were sustained and, thus, fatal arrhythmias. During the baseline period before infarction, we found no episodes of VF and only rare episodes of brief, nonsustained VT (7).

Arrhythmias. After permanent CAO, we found a high prevalence of VT and VF. In the CAO group, 33 (97%) of 34 of all rats experienced at least one episode of VT, and in 26 (76%) of 34, one or more episodes of VF occurred. Overall, there were 10,081 episodes of VT and 552 episodes of VF in this group of 34 animals during the first 2 days after MI. Of these 10,633 arrhythmic events, 10,377 (98%) occurred during the first 9 h after occlusion, most of which occurred from 1.5 to 9 h after MI (Fig. 1). Therefore, the following analysis details the effects of reperfusion on this malignant arrhythmogenic phase.

Incidence and duration. The incidence and summed durations of all VT and VF episodes in the postreperfusion time periods were significantly reduced by all three reperfusion
regimens compared with those during CAO (Table 1, Fig. 1). The magnitude of this antiarrhythmic effect of reperfusion can be illustrated by calculating the reduction in the incidence and duration of VT and VF relative to that during CAO: RP45, RP90 and RP180, respectively reduced 1) the incidence of VT by 93%, 98% and 88%; 2) the incidence of VF by 89%, 97% and 92%; 3) the summed durations of all VT episodes by 93%, 99% and 94%; and 4) VF duration by 84%, 99% and 94%.

**Time course.** The antiarrhythmic effects of reperfusion were observed almost immediately after restoration of coronary blood flow (Fig. 1) and was true for early as well as late reperfusion. Because these reperfusion times fall into phases of low (RP45), intermediate (RP90) or high (RP180) spontaneous ectopic activity after MI, the rapid appearance of the antiarrhythmic effect was independent of the level of spontaneous arrhythmic activity at the time of reperfusion.

**Mortality.** The mortality time course was related to the post-MI arrhythmia profile, with 64% (21 of 33) of all deaths occurring between 1.5 and 9 h after MI, the most severe arrhythmogenic period (Table 2). All 21 deaths were related to an episode of VF. These fatal arrhythmias consisted of either sustained VF or a combination of nonsustained VF and VT or bradycardic rhythms.

**Postreperfusion mortality.** During CAO, the mortality rate between 45 or 90 min and 48 h after MI was 47% (16 of 34). There was a striking difference in mortality during the post-reperfusion time periods compared with that after CAO (Table 2, Fig. 2), with only 1 death (1.8% of 12, p < 0.05) during RP45 and no deaths during RP90 (0 of 16, p < 0.01). There was a trend (p = 0.086) toward a decrease in mortality after RP180 (4.17% of 24) compared with that after CAO (42% [13 of 31], p < 0.05) (Fig. 2).

The only two deaths that occurred >10 h after MI were at 22 and 23 h during RP180 and were observed and classified as pump failure deaths.

**Infarct size.** During CAO, 49 ± 10% of left ventricular circumferences became infarcted. RP45 or RP90 resulted in a smaller infarct size: 36 ± 8% and 38 ± 10%, respectively (p < 0.01 vs. CAO; p = NS for RP45 vs. RP90) (Table 3). As expected, late reperfusion (RP180) did not salvage myocardium, and infarct size was 49 ± 10% (p < 0.01 vs. RP45 or RP45). Although the main effect of early reperfusion (RP45, RP90) was reflected in a lesser epicardial infarct size, significant salvage of endocardium was also found. Nevertheless, both groups showed a marked reduction in infarct transmurality, indicating salvage predominantly of the epicardium.

**Discussion**

We studied the effects of early coronary artery reperfusion, which is associated with significant salvage of ischemic myocytes, and late reperfusion, wherein the restoration of patency is relatively independent of a reduction in myocardial necrosis, on spontaneously occurring arrhythmias and arrhythmic deaths in conscious and unrestrained rats. The major finding of our

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**Table 1.** Episodes and Duration of Arrhythmia for Three Reperfusion Regimens Versus Permanent Occlusion

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Episodes/h of VF</th>
<th>Episodes/h of VT</th>
<th>Duration of VF (s/h)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CAO</td>
<td>RP180</td>
<td></td>
</tr>
<tr>
<td>RP45</td>
<td>2.8 ± 3.3</td>
<td>0.3 ± 1.1</td>
<td>15.5 ± 9.7</td>
</tr>
<tr>
<td>RP90</td>
<td>3.3 ± 4.1</td>
<td>0.1 ± 0.3</td>
<td>14.4 ± 1.2</td>
</tr>
<tr>
<td>RP180</td>
<td>3.9 ± 5.8</td>
<td>0.3 ± 0.9</td>
<td>11.9 ± 1.3</td>
</tr>
</tbody>
</table>

*p < 0.01, †p < 0.001 versus coronary artery occlusion (CAO). Data presented are mean value ± SD. RP45, RP90, RP180 = reperfusion after 45, 90 and 180 minutes, respectively; VF = ventricular fibrillation; VT = ventricular tachycardia.

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**Table 2.** Mortality After Myocardial Infarction for Permanent Occlusion and Three Reperfusion Regimens

<table>
<thead>
<tr>
<th>Time After MI</th>
<th>CAO (n = 35)</th>
<th>RP180 (n = 30)</th>
<th>RP90 (n = 18)</th>
<th>RP45 (n = 15)</th>
</tr>
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<tbody>
<tr>
<td>0–45 min</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>45–90 min</td>
<td>0</td>
<td>0</td>
<td>2 (11%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>90–180 min</td>
<td>3 (9%)</td>
<td>6 (20%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>180 min–48 h</td>
<td>13 (37%)</td>
<td>4 (13%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data presented are number (%) of rats. Abbreviations as in Table 1.
The reduction of ventricular remodeling has been proposed by Kim and Braunwald (5) as the main mechanism by which late reperfusion without myocardial salvage improves electrical stability. The distorted left ventricular geometry after MI, with muscle fiber disarray and pathologic distribution of wall stress (20), can lead to increased dispersion of refractoriness and slow conduction, promoting arrhythmogenesis (21). The prevention or regression of these changes in geometry might therefore result in an increased electrical stability.

Although the exact mechanism of action by which reperfusion evokes these beneficial antiarrhythmic effects cannot directly be assessed by our study, several important characteristics of this phenomenon can be inferred from our data.

**Time course of post-MI arrhythmias.** We previously showed (7) that in rats with acute MI, two distinctly active arrhythmogenic periods develop (0 to 0.5 h [period I] and 1.5 to 9 h after MI [period II]), each followed by a quiescent phase of low ectopic activity. When this time-dependent occurrence of ischemia/necrosis-induced VT and VF in the CAO group is compared with that after reperfusion, the rapid onset of an antiarrhythmic effect becomes evident (Fig. 1). Because RP45 occurs in a phase of low spontaneous ectopic activity, and RP90 occurs just at the beginning of the second arrhythmogenic period, the time course of the antiarrhythmic effect is difficult to estimate. In contrast, the rapid onset of the antiarrhythmic effect can be more readily observed with RP180 because the level of spontaneous ectopic activity reestablishing patency has almost reached its peak, which occurs during the fourth and fifth hour after MI (7). Indeed, late reperfusion rapidly altered the course of the ongoing second arrhythmogenic period and prevented the occurrence of further arrhythmias. Notably, these reperfusion times fall into different stages of the electrophysiologic evolution of the infarct zone (22), supporting the concept that the observed antiarrhythmic effects of reperfusion are largely independent of the electrophysiologic status of the reperfused tissue. The salvage of ischemic myocytes could play a role in RP45 and, to a limited extent, in RP90, but is not a prerequisite for the observed suppression of arrhythmias in RP180, in which there is no substantial salvage of myocytes.

Except for some early deaths during the first arrhythmogenic phase, most deaths during CAO occurred in relation to an episode of fatal VF during the second arrhythmogenic phase, after which there was no difference in mortality between reperfused and CAO rats, aside from two pump failure deaths in the RP180 group. These two late deaths (22 and 23 h) provide additional evidence in favor of the hypothesis that the suppression of fatal VF episodes represents the main mechanism by which reperfusion improves survival in rats. Both deaths occurred at a time when we had not observed a death in any of the other groups. One explanation for this finding is that with permanent occlusion, these animals would most likely have died of an arrhythmia during the second arrhythmogenic period, but late reperfusion at 3 h improved electrical stability immediately despite the failure to salvage myocardium. This antiarrhythmic effect might have allowed these animals, both with extensive infarctions (57% and 64%), to survive the second arrhythmogenic period, but it also exposed them to the risk of dying of pump failure during the subsequent electrically quiescent hours. Baughmann et al. (23) also found a delayed mortality in conscious dogs reperfused after 1 or 3 h of ischemia, with no difference in MI size compared with that after permanent occlusion.

**Infarct size.** Most experimental work relevant to this field has been done in the dog, which has a highly variable coronary anatomy with large variations in collateral flow. The resulting wide range of infarct sizes and transmurality mandates the use of large sample sizes to show the effects of reperfusion on infarct size. Nonetheless, most studies have used relatively small groups of animals, and the observed reductions of arrhythmias (6,19) or mortality (23) after early reperfusion were attributed to a salvage-independent mechanism (5) because infarct size was not different among reperfused and permanently occluded groups.

A major objective of the present study was to clearly delineate salvage-dependent from salvage-independent mechanisms with respect to their effects on electrical stability during the acute phase of MI. In accordance with the time-dependent wave front phenomenon of ischemic cell death, the extent of
primarily epicardial salvage declined with RP45 and RP90. With early reperfusion an epicardial rim of viable tissue was salvaged, which might have facilitated more homogeneous electrical activation of the ventricle in addition to the mechanical advantage provided by a preserved muscle layer covering the necrotic tissue. In contrast, there was no salvage of myocardium when RP180 was compared with CAO: Infarct size was virtually identical in both groups. Therefore, mechanisms other than myocardial salvage must have been involved in the antiarrhythmic effect of reperfusion.

**Mortality.** Despite compelling evidence that reperfusion improves survival beyond the potential for myocardial salvage (5), it remains difficult in the clinical setting to assess reperfusion-related myocardial salvage or to clearly dissociate the effects of reperfusion from those of other variables, such as left ventricular function, that have a strong impact on survival.

In a study of reperfusion after 1 to 2 and 6 to 8 h of ischemia in rats, Boyle and Weisman (24) found no effects on mortality with either reperfusion regimen compared with permanent occlusion, although reperfusion caused a significant reduction in infarct expansion and left ventricular remodeling despite a similar infarct size in the three groups. However, only the reperfused animals underwent a second thoracotomy, which might have eliminated a possible survival benefit in these groups. In our study, early and late reperfusion significantly reduced the incidence of fatal arrhythmias, an effect that could clearly be dissociated from the occurrence of myocardial salvage. Because >90% of all deaths were related to an episode of VF, the main mechanism by which early as well as late reperfusion improved survival during the second arrhythmogenic period was the effective suppression of potentially fatal VF episodes.

**Other mechanisms.** The electrical stability of the myocardium is also strongly influenced by the balance between the sympathetic and parasympathetic components of the autonomic nervous system. MI can alter the control of vagal tone, as reflected by a diminished heart rate variability or baroreflex sensitivity, which has been linked to an increased risk of arrhythmias and sudden death after MI (25). Moreover, vagal activation can have a significant antifibrillatory effect, preventing fatal VF episodes (26). Recently, Mortara et al. (27) reported that patients with a patent IRA had significantly less depression of baroreflex sensitivity after MI than patients with a permanently occluded vessel. This effect was largely independent of left ventricular function, suggesting a salvage-independent role of reperfusion for the electrical stability of the myocardium. Recently reported findings from the Global Utilization of Streptokinase and t-PA [tissue plasminogen activator] for Occluded Coronary Arteries (GUSTO) database (28) showed that heart rate variability is depressed during the first 48 h after MI, and the severity of this alteration is inversely related to the time to reperfusion and to 30-day mortality. The lack of a strong correlation between the depression of heart rate variability and ejection fraction in that study supports the concept of a salvage-independent role of electrical stability as a prognostic index after MI. These are the first clinical data showing that the failure to achieve electrical stability within hours after MI can have important prognostic implications. In conscious rats during the early hours after CAO, we found a significant reduction in heart rate variability, which recovered to pre-MI values within 3 weeks, except for those animals that developed severe left ventricular dysfunction and heart failure (29). On the basis of these findings, it appears that modification of autonomic tone, reflected in variables of heart rate variability, may have an impact on electrical stability and thereby on post-MI mortality in the rat infarct model.

**Study limitations.** Although it was possible to show that reperfusion reduced the incidence of fatal VF episodes in our model, the present study does not provide evidence concerning the precise electrophysiologic mechanisms responsible for this effect. Likewise, we cannot reject the hypothesis that this phenomenon is mainly secondary to a rapid reperfusion-induced reversal of arrhythmogenic alterations in the structure and geometry of the infarcted ventricle (5) because we obtained no data on infarct expansion or early remodeling in this study.

Furthermore, our experimental data apply only to the first 48 h after MI, corresponding to the first few days after MI in humans, whereas some of the clinical variables discussed (13,14,17,27) were obtained during the subacute or chronic post-MI phase.

Because the rats were awake at the time of reperfusion, no direct assessment of actual blood flow in the IRA could be obtained. However, the reproducible ECG changes after suture removal, together with the uniform reductions in infarct size, indicate instantaneous and sustained reperfusion with the technique used.

**Clinical implications.** These data support the clinical strategy to open an IRA, even beyond the time window for potential myocardial salvage. In addition to the well-established beneficial effects of such an approach on post-MI ventricular remodeling, recent clinical data show a powerful salutary effect of reperfusion on variables of electrical stability (13,14,17). The decision to reopen such an occluded IRA is usually guided by the presence of viability or ischemia in the dependent myocardium. This approach could be modified by integrating variables of electrical stability, such as late potentials or heart rate variability, into the decision process. This practice would help to select patients at increased risk of future arrhythmic events who might benefit most from an increase in electrical stability after reperfusion of the IRA, independent of any myocardial salvage.

**Conclusions.** The present experimental data provide new evidence that reperfusion can improve arrhythmia-related mortality by the prevention of fatal VF episodes in a conscious rat infarct model independently of myocyte salvage, as proposed by the open artery hypothesis.

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References


