Reperfusion Arrhythmias after Thrombolysis∗
Electrophysiologic Tempest, or Much Ado about Nothing
Harlan M. Krumholz, M.D., and Ary L. Goldberger, M.D.

Arrhythmias that may accompany myocardial reperfusion have generated significant clinical interest. First, there were concerns, based on animal studies, that high-grade ventricular tachyarrhythmias would pose a serious threat following thrombolytic therapy to treat an evolving myocardial infarction. Second, lower-grade arrhythmias, such as accelerated idioventricular rhythm, were cited as useful, noninvasive markers of successful reperfusion. Critical review of the current data, however, indicates that arrhythmias following thrombolytic therapy for acute myocardial infarction are usually neither dangerous clinical events nor consistent markers of reperfusion.

Arrhythmias that may accompany myocardial reperfusion have generated interest and controversy. After a decade of experience with thrombolysis for acute myocardial infarction, sufficient evidence has emerged to conclude that, in patients, these arrhythmias are neither useful markers nor clinical threats. This brief review examines (1) the experimental association between myocardial reperfusion and arrhythmias; (2) the potential danger of reperfusion arrhythmias; (3) the claim that arrhythmias are useful markers of reperfusion; and (4) the vulnerability of patients who receive thrombolytic therapy to late arrhythmias.

Is There an Experimental Association between Myocardial Reperfusion and Arrhythmias?

In an early study of the effect of coronary occlusion on myocardial contraction in dogs, Tennant and Wiggers,1 in 1955, serendipitously noted an event that was unrelated to their primary investigation, but is now generally heralded as the first description of reperfusion arrhythmias. In a protocol that involved temporarily clamping coronary arteries for 1 min to 2 h, they noted that "during several experiments ventricu-

ular fibrillation occurred either before or just after the release of the clamp." Many subsequent studies have confirmed that arrhythmias are associated with both coronary occlusion and subsequent myocardial reperfusion.5-16 The most common reperfusion arrhythmias are ventricular tachycardia and ventricular fibrillation.

These animal studies also suggested some features that distinguish reperfusion arrhythmias from arrhythmias associated with acute coronary occlusion. Reperfusion arrhythmias typically occur suddenly and often deteriorate quickly into ventricular fibrillation, whereas arrhythmias due to coronary occlusion develop more gradually and less commonly evolve into ventricular fibrillation.5-7,11,12 Reperfusion arrhythmias in animal models have a different response to antiarrhythmic intervention as compared with ischemic arrhythmias. For instance, alpha-blockers are more effective in preventing arrhythmias during reperfusion, and beta-blockers are more effective in preventing arrhythmias during coronary occlusion.11

The mechanism of experimental reperfusion arrhythmias is controversial and unsettled.20-23 Ischemia produces a time-dependent decrease in ventricular action potential duration and amplitude, resting membrane potential, and maximal rate of rise of voltage of phase 0.7,8,14 Reperfusion may lead to marked regional variability in recovery of these abnormalities. This heterogeneity, in turn, may induce a differential return of excitability within a formerly ischemic area, thereby facilitating reentry.13,16,19 Other investigators have favored enhanced automaticity as the primary mechanism of reperfusion arrhythmias.19 Finally, triggered activity, possibly due to calcium overload, is a third potential mechanism.

It is also uncertain which changes at the cellular level are most responsible for the production of reperfusion arrhythmias. Putative factors include free radical generation, electrolyte alterations, α-adrenergic stimulation, elevated levels of cyclic adenosine monophosphate and products of glycolysis, and calcium overload.13,15,21-23 Nevertheless, despite a flurry of investigation, no single cellular perturbation has emerged as the primary instigator of reperfusion arrhythmias.

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DO DANGEROUS REPERFUSION ARRHYTHMIAS OCCUR IN HUMANS?

The induction of malignant reperfusion arrhythmias in animals has generated understandable concern about the potentially arrhythmogenic effect of thrombolytic therapy in humans during treatment of acute myocardial infarction. Early studies of thrombolytic therapy reported that arrhythmias following treatment were common, but the arrhythmias were less malignant than those previously reported in animal models.26,27

In 1983 Goldberg and colleagues27 reported an observational study of 21 patients with total occlusion of a coronary artery supplying the area of an evolving infarction who received intracoronary streptokinase. All of the patients received lidocaine as part of the protocol. This study was limited in several respects. The control group consisted of only 4 patients who had unsuccessful thrombolysis. In 14 cases, intra-aortic balloon counterpulsation was part of the protocol. The cardiac rhythm was displayed by continuous ECG monitoring, and no permanent record was made. Nevertheless, the study yielded an important result that would hold up to further study: successful thrombolysis did not routinely produce ventricular fibrillation or sustained ventricular tachycardia.

In 1986 the ISAM study,28 a randomized trial of intravenous streptokinase and placebo in 1,741 patients, reported rhythm disturbances that occurred within 3 h after the start of the study medication. None of the patients received lidocaine. The study found that the most dangerous arrhythmias did not occur more frequently with thrombolysis. In particular, there was no difference between the groups in the incidence of ventricular tachycardia greater than 120 beats/min, ventricular fibrillation, atrioventricular block, or asystole. Although the data on rhythm disturbances were obtained from nursing station monitors, the study is useful because the observers were blinded to the treatment. The imperfect method of collecting information about arrhythmias may have led to misclassification of innocuous arrhythmias, but probably not sustained tachyarrhythmias.

The large randomized trials of the efficacy of thrombolysis confirmed the findings of these early studies (Table 1). Neither the GISSI study, the ISIS-2 trial, nor the ASSET trial was able to show that ventricular fibrillation occurred more commonly in patients who received thrombolytic therapy.29-31 In fact, in these large studies, with over 34,000 patients, the incidence of ventricular fibrillation was slightly lower in the groups that received thrombolytic therapy. Currently, therefore, there is no firm support for the concern that malignant ventricular reperfusion arrhythmias typically accompany successful thrombolytic therapy. The importance of careful monitoring of patients receiving such therapy, however, is highlighted by the fact that all the clinical studies do report a small incidence of life-threatening arrhythmias, regardless of mechanism or association with thrombolysis. Nevertheless, there does not appear to be a need for special precautions with the use of thrombolytic therapy.

The reason for the apparent difference between the high-grade reperfusion arrhythmias in animals and humans is not known. The experiments typically involved open-chest anesthetized animals.22 Coronary artery occlusion in these experiments was performed most commonly for less than 1 h. The time of coronary occlusion affects the vulnerability of the myocardium to arrhythmias in many animal models.5,28 For example, in the isolated rat model, arrhythmias are most likely after intermediate periods of coronary occlusion (eg, 15 to 20 min but less likely after short (eg, 5 min) or long (30 min) periods. Therefore, the animal models do not simulate the usual clinical experience in which thrombolytic therapy is given hours after coronary occlusion. It should not be surprising, therefore, that clinical experience does not reflect laboratory findings.

Opie20 has suggested that the higher incidence of reperfusion arrhythmias in experimental studies, as compared with clinical investigations, may also be related to the faster rate of reperfusion in the animals. He attributes the accelerated reperfusion to (1) abrupt withdrawal of a mechanical obstruction; (2) the absence of baseline coronary artery disease in the animal model; and (3) the use of buffer solutions that remove platelets and neutrophils from the reperfusion solution, possibly lessening capillary plugging during ischemia and increasing reperfusion flow.32

Table 1—Incidence of Ventricular Fibrillation in Major Trials of Thrombolysis

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Thrombolytic Agent</th>
<th>Drug Group</th>
<th>Control Group</th>
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<tbody>
<tr>
<td>GISSI</td>
<td>11,712</td>
<td>Streptokinase</td>
<td>398/5,867 (6.6)</td>
<td>439/5,595 (7.5)</td>
</tr>
<tr>
<td>ISIS-2</td>
<td>17,187</td>
<td>Streptokinase</td>
<td>370/5,392 (4.3)</td>
<td>425/5,390 (4.9)</td>
</tr>
<tr>
<td>ASSET</td>
<td>5,006</td>
<td>Fibrinogen activator</td>
<td>94/2,512 (3.7)</td>
<td>116/2,490 (4.6)</td>
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*Values represent incidence of nonfatal ventricular fibrillation. This report also notes that no patients in the streptokinase group had ventricular arrhythmias leading to withdrawal of the drug infusion, but that 70 patients (1.2%) had unspecified ventricular arrhythmias "attributed" to the drug after the completion of the infusion.
ARE ARRHYTHMIAS THAT FOLLOW THROMBOLYTIC THERAPY USEFUL AS MARKERS OF SUCCESSFUL THROMBOLYSIS?

While dangerous ventricular tachyarrhythmias do not often complicate thrombolysis, other arrhythmias have been observed. In the study by Goldberg et al., the most common arrhythmia was accelerated idioventricular rhythm (AIVR), at a rate between 70 and 95 beats/min, which occurred in 10 of the 17 patients with successful thrombolysis. Other observational studies also reported a high incidence of AIVR with thrombolytic therapy. At least several groups reported severe bradycardia and hypotension (Bezold-Jarisch reflex) accompanying reperfusion of the right coronary artery, presumably associated with activation of inhibitory cardiac receptors with vagal afferents located predominantly in the inferoposterior wall of the left ventricle. The ISAM study compared the incidence of arrhythmias (detected with continuous ECG monitoring) in their streptokinase group and control group. In the first 3 h after the start of the study medication they found a significant increase in the incidence of bradycardia (<60 beats/min), ventricular ectopic beats (>10 beats/min), ventricular couplets, ventricular salvos (3 to 5 ventricular ectopic beats in a row), and ventricular tachycardia (<120 beats/min) among patients who received streptokinase. Since the patients in this study did not undergo angiography around the time of administration of the study medication, no comment could be made on the relation of these arrhythmias to perfusion status.

The apparent association of these lower-grade arrhythmias with thrombolysis suggested their utility as noninvasive clinical markers of successful thrombolysis. One study even incorporated the presence of

<table>
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<th>Study</th>
<th>Methods</th>
<th>Findings</th>
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<tr>
<td>Cereck and Hervat, 1985&lt;sup&gt;2&lt;/sup&gt;</td>
<td>23 patients given IV SK and 22 given saline evaluated by continuous ECG monitoring</td>
<td>Significantly more premature ventricular complexes (p&lt;0.01) and AIVR (p&lt;0.05) in SK group</td>
<td>Study not blinded; no HM; 6 patients (4 SK, 2 controls) received lidocaine</td>
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<td>Miller et al, 1986&lt;sup&gt;1&lt;/sup&gt;</td>
<td>52 patients given IC SK evaluated by IIM and angiography</td>
<td>Overall patency rate of 44%; no difference in arrhythmias between groups</td>
<td>Only 37 of 52 patients had adequate HM; small groups (7 17 without reperfusion, 8 with subtotal occlusion); all patients received lidocaine</td>
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<td>Cereck et al, 1987&lt;sup&gt;2&lt;/sup&gt;</td>
<td>40 patients given IV SK; 40 with clinical signs of reperfusion compared to those without signs of reperfusion; HM within 24 h of admission</td>
<td>More ventricular arrhythmias in patients with signs of reperfusion</td>
<td>Reperfusion assessed by clinical signs; control group only 4 patients; 1 patient received lidocaine</td>
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<td>Kircher et al, 1987&lt;sup&gt;2&lt;/sup&gt;</td>
<td>50 patients given IV SK or tPA evaluated by continuous ECG and angiography</td>
<td>Arrhythmias in 14 of 37 patients with reperfusion and 3 of 15 without reperfusion</td>
<td>Not blinded; no HM; no statistical analysis; no mention of antiarrhythmic therapy</td>
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<td>Califf et al, 1988&lt;sup&gt;2&lt;/sup&gt;</td>
<td>396 patients given IV tPA evaluated by continuous ECG and angiography</td>
<td>Overall patency rate of 75%; arrhythmias not associated with reperfusion</td>
<td>Not blinded; no HM; no mention of antiarrhythmic therapy</td>
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<td>Gore et al, 1988&lt;sup&gt;2&lt;/sup&gt;</td>
<td>67 patients given IC SK evaluated by continuous ECG and angiography</td>
<td>Arrhythmias not associated with reperfusion</td>
<td>Not blinded; no HM; all patients received lidocaine</td>
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<tr>
<td>Gorgels et al, 1988&lt;sup&gt;2&lt;/sup&gt;</td>
<td>87 patients given IC or IV SK evaluated by continuous ECG and angiography</td>
<td>Overall patency rate of 86%; AIVR occurred in 26 of 70 without reperfusion (p=0.027)</td>
<td>Not blinded; no HM; lidocaine given to 43 patients</td>
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<td>Solimene et al, 1988&lt;sup&gt;2&lt;/sup&gt;</td>
<td>20 patients given IC SK and 22 historical controls</td>
<td>No difference between groups in incidence or type of arrhythmia</td>
<td>Not blinded; no HM; no mention of antiarrhythmic therapy</td>
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<td>Burney et al, 1989&lt;sup&gt;2&lt;/sup&gt;</td>
<td>45 patients with MI, 225 given thrombolytic therapy; all evaluated by continuous ECG</td>
<td>No significant difference in arrhythmias between patients given and not given thrombolytic therapy</td>
<td>Not blinded; no HM; no mention of antiarrhythmic therapy</td>
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<tr>
<td>Nicolau et al, 1989&lt;sup&gt;26&lt;/sup&gt;</td>
<td>101 patients given SK evaluated by continuous ECG and angiography</td>
<td>Arrhythmias were 63% sensitive and 58% specific for a patent artery</td>
<td>Not blinded; no HM; angiography performed days after thrombolytic therapy; all patients given lidocaine</td>
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</table>

*Abbreviations: AIVR = accelerated idioventricular rhythm; HM = Holter monitoring; IC = intracoronary; IV = intravenous; MI = myocardial infarction; SK = streptokinase; tPA = tissue plasminogen activator*
"ectopic beats in late diastole, bouts of AIVR, or the disappearance of atrioventricular block" as one of the
criteria for assessing the efficacy of streptokinase.\textsuperscript{56} Reports that patients who failed thrombolytic therapy
might benefit from percutaneous transluminal coronary angioplasty gave impetus to the need for such a
marker.

At least 10 studies, summarized in Table 2, have evaluated the usefulness of arrhythmias following
thrombolytic therapy in predicting successful thrombolyis.\textsuperscript{30-46} The data from these studies have not
consistently shown a clinically useful predictive role for any arrhythmia. Unfortunately, the interpretation
of most of the data on arrhythmias as a marker of reperfusion is hampered by limitations in study de-
sign. Methodologic problems include lack of an appropriate control group, small number of patients, impre-
cise methods of determining reperfusion, inconsistent use of lidocaine, and the lack of quantitative methods
to monitor arrhythmias.

The absence of Holter monitoring is perhaps the most important problem that limits the validity of
most studies. Continuous ECG monitoring in which arrhythmias are visually analyzed in real time by
observers in close proximity to the patient precludes masking and may introduce significant bias into these
studies. Observers of the arrhythmias are likely to be aware of the patient's symptoms and ST-segment
changes and, in some cases, of their angiographic results. Knowledge of the patient's probable perfusion
status, therefore, may influence the observation of arrhythmias.

The TAMI trial of treatment of patients with intra-
venous tissue plasminogen activator is the largest
study to date specifically addressing the utility of
arrhythmias in predicting coronary artery patency
after thrombolytic therapy.\textsuperscript{44} The investigators, using continuous ECG monitoring of patients after
thrombolytic therapy and coronary angiography to assess vessel patency, found that neither ventricular tachy-
arrhythmias, ventricular fibrillation, atrioventricular block,
or sinus bradycardia was associated with a higher
rate of reperfusion (p = 0.71). In contrast, the resolu-
tion of pain (p = 0.0005) and the complete resolution
of ST-segment elevation (p<0.0001) were highly sig-
nificant predictors of coronary perfusion status. Cur-
rently, therefore, there is no consistent evidence to
support the use of arrhythmias as reliable markers of
successful thrombolysis.

ARE PATIENTS WHO RECEIVE THROMBOLYTIC THERAPY SUSCEPTIBLE TO "LATE" ARRHYTMIAS?

Once the acute period of reperfusion is over, patients
who have undergone successful thrombolytic therapy
may actually be less susceptible to arrhythmias. A
study from The Netherlands compared the inducibility
of ventricular tachyarrhythmias by programmed elec-
trical stimulation in 62 patients with myocardial in-
farction treated with thrombolytic therapy.\textsuperscript{46} Sustained
ventricular arrhythmias were less commonly induced
in patients with early reperfusion. Other investigators,
however, have found no difference in inducible ventr-
icular tachyarrhythmias in comparing patients with
successful and unsuccessful thrombolysis.\textsuperscript{46} Studies of
the signal-averaged ECG have suggested that throm-
bolysis either reduces or does not affect the incidence
of late potentials.\textsuperscript{36-70} Overall, these studies suggest
that thrombolytic therapy does not increase late sus-
cceptibility to arrhythmias and that, to the extent that
they limit infarct size, these agents may actually be
protective.\textsuperscript{31}

SUMMARY

Animal studies have shown consistently that high-
grade ventricular arrhythmias are associated with
abrupt reperfusion following mechanical coronary
occlusion. The clinical introduction of thrombolytic
therapy led to concerns that dangerous arrhythmias
might jeopardize some of the gains of thrombolysis.
At the same time there were hopes that certain
arrhythmias might provide a reliable, noninvasive
marker of successful thrombolysis. After a decade of
experience with thrombolytic therapy, it appears that
reperfusion arrhythmias are neither so frequent nor
so malignant as to negate the benefit of reperfusion,
nor are they sufficiently reliable markers of reperfu-
sion to merit special clinical attention. Furthermore,
patients who receive thrombolytic therapy are not
more susceptible to subsequent late arrhythmias.
Future studies will be needed to elucidate further the
mechanism of reperfusion arrhythmias in animals and
to delineate whether earlier administration of throm-
bolytic agents increases the likelihood of transient
electrical instability in patients.

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