Predictive value of ventricular arrhythmias for patency of the infarct-related coronary artery after thrombolytic therapy

A Jacob Six, J Hans Louwerenburg, J Herre Kingma, Etienne O Robles de Medina, Norbert M van Hemel

Abstract
In animal studies reperfusion of coronary arteries is commonly accompanied by ventricular arrhythmias. It is not certain, however, whether ventricular arrhythmias can be used as a reliable non-invasive marker of reperfusion in humans. Two-channel Holter recordings were obtained from the start of an intravenous infusion of streptokinase until coronary angiography (2-8 (2-7) hours (mean (SD)) afterwards) in 57 patients with acute myocardial infarction of less than four hours who were generally not treated with antiarrhythmic drugs. Ventricular arrhythmias occurred in 21 (37%) of the 57 patients; accelerated idioventricular rhythm in 13 patients and non-sustained ventricular tachycardia in 15 patients. Seven patients had both accelerated idioventricular rhythm and non-sustained ventricular tachycardia. Coronary angiography showed a patent infarct-related vessel in 12 (92%) of the 13 patients with accelerated idioventricular rhythm (95% confidence interval 66 to 99%), in 22 (50%) of the 44 patients without accelerated idioventricular rhythm (95% CI 34 to 66%), in 11 (73%) of the 15 patients with non-sustained ventricular tachycardia (95% CI 45 to 92%), and in 23 (55%) (95% CI 39 to 71%) of the 42 patients who did not have non-sustained ventricular tachycardia. Seventeen (81%) of the 21 patients with accelerated idioventricular rhythm, or non-sustained ventricular tachycardia, or both, had a patent infarct-related vessel (95% CI 58 to 94%) as did 17 (47%) of the 36 patients with no ventricular arrhythmia (95% CI 29 to 65%).

In patients with accelerated idioventricular rhythm after thrombolysis the infarct-related vessel is almost certain to be patent; but the infarct-related coronary artery can still be patent when no arrhythmia is seen.

Because intravenous thrombolytic agents are increasingly used to treat acute myocardial infarction non-invasively determined indices of reperfusion are needed. Ventricular arrhythmias are regarded as a reliable sign of reperfusion in most, but not all, laboratory animals. In humans, however, some of the arrhythmias seen in the first hours after the onset of infarction can be attributed to the inherent electrical instability of the ischaemic myocardium and not to reperfusion. To investigate the difference between "infarction arrhythmias" and "reperfusion arrhythmias", we need to measure the patency rate of the infarct-related coronary artery and disorders of the heart rhythm within a well-defined interval.

We therefore determined the predictive value of ventricular arrhythmias for patency of the infarct-related vessel in patients with acute transmural infarction by monitoring the heart rhythm with Holter recording from the start of streptokinase administration until angiographic visualisation of the infarct-related vessel up to four hours later (that is, the study period).

Patients and methods

PATIENTS
Fifty seven patients with acute myocardial infarction were treated with intravenous streptokinase. We studied male and female patients below the age of 71 years with symptoms of acute myocardial infarction for less than four hours and ST segment elevation of >1 mm in at least two leads of the standard 12 lead electrocardiogram. We excluded patients with a history of abnormal bleeding, use of anticoagulant drugs, recent surgery (<2 weeks), previous cerebral haemorrhage or injury, impaired renal function (serum creatinine concentration >300 μmol/l), systolic blood pressure >200 mm Hg, diastolic >120 mm Hg, severe heart failure with pulmonary congestion on admission, any malignancy (except those of the skin), or previous treatment with streptokinase.

All patients were informed of the treatment and its potential risks and were asked for consent. β Blockers were used on the day before or on the day of admission by 10 patients and calcium antagonists by six patients. During the study period 10 patients were treated with atropine for bradycardia or atrioventricular conduction disturbances. Lignocaine was given to five patients, in two by continuous infusion after an episode of ventricular fibrillation before admission to the coronary care unit. In the three other patients lignocaine was given as a bolus injection at home by the general practitioner for unknown reasons, probably extrasystoles.

TREATMENT
Twenty patients were treated as part of a
dose-ranging trial of streptokinase, in which they received a one hour infusion of 200 000 IU (n = 4), 750 000 IU (n = 6), 1 500 000 IU (n = 5), or 3 000 000 IU (n = 5) of streptokinase (KabiLab). Twenty four other patients were treated with 1 500 000 IU of intravenous streptokinase plus oral or intravenous captopril (Capoten) in an attempt to diminish reperfusion damage of the myocardium, as described elsewhere.

Thirteen other patients were given 30 000 IU of intravenous streptokinase only. The infusion was stopped if allergic reactions, bleeding complications, or a fall in blood pressure developed. Steroids, antiarrhythmic drugs, or salicylates were not used routinely. Analgesic drugs and nitrates were given freely. Coronary angiography was performed within four hours of the streptokinase infusion.

CORONARY ANGIOGRAPHY
Coronary cineangiography was performed by the Judkins approach. Immediately after the introduction of a sheath in the femoral artery, patients were given 5000 IU of heparin. Furthermore, each patient was treated with 2.5 mg isosorbide dinitrate sublingually. The right coronary artery was usually filmed in two projections and the left coronary artery in at least three views. All coronary angiograms were independently analysed by cardiologists who specialised in coronary angiography. The perfusion of the infarct-related vessel was classified according to the thrombolysis in myocardial infarction (TIMI) study group: patency was defined as TIMI perfusion class II or III.

HOLTER RECORDINGS
A two-channel Holter recorder was connected to the patient immediately on admission. Soon after infusion of streptokinase began. Recording continued until angiography of the infarct-related vessel was completed. All recordings were manually analysed on a beat-to-beat basis (paper speed 25 mm/s) by one experienced cardiologist (JHL) and all arrhythmias detected were recorded on paper.

DEFINITIONS OF ARRHYTHMIAS
Accelerated idioventricular rhythm was defined as the occurrence of at least three consecutive uniform complexes of ventricular origin with a frequency of 60 to 100 beats/minute. Non-sustained ventricular tachycardia was defined as at least three consecutive ventricular complexes with a frequency of more than 100 beats/minute, for <30 seconds. Sustained ventricular tachycardia was defined as a ventricular tachycardia lasting 30 seconds or more.

Table 1 Characteristics and incidence of ventricular arrhythmias in 57 patients who were treated with intravenous streptokinase for acute myocardial infarction

<table>
<thead>
<tr>
<th>AIVR</th>
<th>ns-VT</th>
<th>AIVR, ns-VT, AIVR and ns-VT</th>
<th>No arrhythmias</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>13 (10-8)</td>
<td>15 (8-7)</td>
<td>21 (9-4)</td>
<td>44 (9-3)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>76 (88)</td>
<td>81 (82)</td>
<td>83 (82)</td>
<td>81 (78)</td>
</tr>
<tr>
<td>Anterior wall infarction (%)</td>
<td>54 (59)</td>
<td>57 (59)</td>
<td>50 (56)</td>
<td>49 (50)</td>
</tr>
<tr>
<td>Duration of symptoms (min)</td>
<td>151 (54)</td>
<td>148 (59)</td>
<td>143 (59)</td>
<td>147 (50)</td>
</tr>
<tr>
<td>Interval between SK infusion and rhythm disturbance (min)</td>
<td>105 (74)</td>
<td>98 (75)</td>
<td>101 (75)</td>
<td>77 (56)</td>
</tr>
<tr>
<td>Patency (%)</td>
<td>92 (73)</td>
<td>81 (73)</td>
<td>86 (73)</td>
<td>60 (60)</td>
</tr>
</tbody>
</table>

AIVR, accelerated idioventricular rhythm; ns-VT, non-sustained ventricular tachycardia; SK, streptokinase.

STATISTICAL ANALYSIS
Continuous distributed values are given as the mean (SD). Sensitivity was defined as the percentage of patients with an open vessel with the rhythm disturbance under examination. Specificity was defined as the percentage of patients with an occluded vessel who did not have that rhythm disturbance. The results are given with 95% confidence intervals.

Results
Table 1 shows the characteristics of patients with various rhythm disturbances. Ventricular arrhythmias occurred in 37% (21/57) of the patients: accelerated idioventricular rhythm in 13 patients and non-sustained ventricular tachycardia in 15 patients. Both accelerated idioventricular rhythm and non-sustained ventricular tachycardia occurred in seven patients. Sustained ventricular tachycardia and ventricular fibrillation were never recorded.

Patency of the infarct-related vessel was seen in 92% (12/13) of patients with accelerated idioventricular rhythm and 50% (22/44) of those without; and in 73% (11/15) of the patients with non-sustained ventricular tachycardia and 55% (23/42) of those without ventricular tachycardia. The infarct-related vessel was patent in 81% (17/21) of the patients with accelerated idioventricular rhythm or non-sustained ventricular tachycardia or both. Forty seven per cent (17/36) of patients without ventricular arrhythmia had patent vessels. Six of the seven (86%) patients who had both accelerated idioventricular rhythm and non-sustained ventricular tachycardia had patent vessels.

Both patients who had an episode of ventricular fibrillation before admission to the hospital had patent infarct-related coronary arteries as did 70% (7/10) of patients who were treated with atropine for bradycardia. In those without bradycardia, patency was seen in 57% (27/47).

Table 2 shows the sensitivity, specificity, and the predictive value of the occurrence of various rhythm disturbances for patency.
Reperfusion arrhythmias

Table 2  Sensitivity, specificity, and predictive values of the occurrence of various rhythm disturbances for patency of the infarct-related coronary artery of 57 patients, of whom 34 had a patent vessel (numbers in parentheses are 95% confidence intervals)

<table>
<thead>
<tr>
<th>Arrhythmia</th>
<th>Number of patients with rhythm disturbances</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Predictive value of positive test (%)</th>
<th>Predictive value of negative test (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIVR</td>
<td>13</td>
<td>39</td>
<td>96</td>
<td>92</td>
<td>50</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>15</td>
<td>32</td>
<td>83</td>
<td>73</td>
<td>45</td>
</tr>
<tr>
<td>AIVR or non-sustained VT or both</td>
<td>21</td>
<td>50</td>
<td>83</td>
<td>81</td>
<td>53</td>
</tr>
<tr>
<td>AIVR and non-sustained VT</td>
<td>21</td>
<td>7</td>
<td>96</td>
<td>86</td>
<td>44</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>2</td>
<td>6</td>
<td>100</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>10</td>
<td>21</td>
<td>87</td>
<td>70</td>
<td>43</td>
</tr>
</tbody>
</table>

AIVR, accelerated idioventricular rhythm; VT, ventricular tachycardia.

Discussion
Necrosis and/or ischaemia of myocardial cells may initiate abnormal ventricular depolarisations which are currently thought to be triggered by reentry or triggered activity.11-15 Ventricular rhythm disturbances, however, may also be caused by reperfusion and in such cases reentry or enhanced automaticity may play a role.16

REPERFUSION ARRHYTHMIAS IN ANIMALS
An interesting aspect of reperfusion arrhythmias is the existence of an apparent species specificity. In some laboratory animals the occurrence of arrhythmias can be considered as a reliable non-invasive sign of reperfusion.7-6 Ventricular tachycardias and fibrillation are often seen in dogs,46 pigs, and rats immediately after reperfusion, though this is less common in cats.5

REPERFUSION ARRHYTHMIAS IN HUMANS
We obtained Holter recordings in a well-defined period of the acute infarction: from shortly before the start of thrombolytic therapy to the primary end point of the study (the injection of contrast agent into the infarct-related coronary artery). We emphasise that our patients were generally not treated with antiarrhythmic drugs. It seemed that accelerated idioventricular rhythm gave the highest scores in predicting the outcome of angiography. Accelerated idioventricular rhythm predicted patency in 92% of patients; but on the other hand, its absence predicted a permanent occlusion in only 50%. So this arrhythmia has a very high specificity (96%) and a poor sensitivity (35%) as a non-invasive index of patency. It should also be noted that coronary angiography is only a "snapshot"; it does not exclude intermittent occlusion and recanalisation.11 None the less, it is the best diagnostic tool for recording the coronary anatomy that is clinically available.

Sustained ventricular tachycardia or ventricular fibrillation did not occur during the period of investigation. However, before the period of investigation two patients with patent vessels had ventricular fibrillation, which suggests that there may be a relation between the occurrence of ventricular fibrillation and patency, but this sample size is too small to draw any conclusions.

Non-sustained ventricular tachycardia was slightly more common than accelerated idioventricular rhythm (15 patients v 13 patients, respectively), but non-sustained ventricular tachycardia has both a poorer specificity (83%) and sensitivity (32%) than does accelerated idioventricular rhythm.

COMPARISON WITH OTHER STUDIES
Large controlled trials showed that life threatening arrhythmias were less common in patients after thrombolytic therapy than in control groups.18-20 Furthermore, Theroux and coworkers showed that the number of ventricular extrasystoles per hour during the first 24 hours of infarction was significantly less after thrombolysis than after conservative treatment.20

Arrhythmias during intracoronary streptokinase administration in humans have been described (specifically) in three studies,22-24 which, unfortunately, are difficult studies to compare for the following reasons. First, the definition of "reperfusion arrhythmias" differed from study to study. Secondly, in such a type of investigation, arrhythmias that were less relevant to the course of action in the coronary care unit (such as accelerated idioventricular rhythm) were often ignored. For instance, in our study, we found that the routine records of rhythm kept by the nursing staff were not complete: seven of the 13 episodes of accelerated idioventricular rhythm that were found on the Holter recordings were not recorded. This may partly explain why other studies did not show that rhythm disturbances in routine rhythm strip recordings were predictive for patency.1 Thirly, the incidence of reperfusion arrhythmias may be different with intracoronary and intravenous streptokinase administration. Also, routine administration of antiarrhythmic drugs may influence the incidence of arrhythmias; indeed in the studies described by Goldberg et al and Miller et al patients were routinely treated with lignocaine.25 23

TIME OF REPERFUSION
Animal studies showed that arrhythmias occur...
at the time of reperfusion. So rhythm recordings can be used to calculate the interval from the onset of symptoms until reperfusion. This is a non-invasive method of calculating the total period of tissue anoxia. Such information may be of great value when the effects of thrombolytic drugs administered at different rates of infusion are compared. It cannot be obtained by angiography or other non-invasive methods such as enzyme studies.25

CLINICAL IMPLICATIONS

In view of the results of the TIMI II study of the therapeutic strategy after thrombolytic therapy, does information on patency have any practical consequence?26 There were no clear benefits with either invasive or conservative management of patients after thrombolytic therapy, regardless of whether or not recanalisation was achieved. Nevertheless, the presence of accelerated idioventricular rhythm is highly predictive of patency and easy to record. This may make it a useful method for calculating the total anoxia period, so it seems sensible to instruct the nursing staff on the importance of this arrhythmia.

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18 GISSI. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;ii:397-402.