Thrombolytic Therapy can Reduce the Arrhythmogenic Substrate After Acute Myocardial Infarction
— A Study Using the Signal-Averaged Electrocardiogram, Endocardial Catheter Mapping and Programmed Ventricular Stimulation —

Junichi Akiyama, MD; Kazutaka Aonuma, MD; Akihiko Nogami, MD*; Michiaki Hiroe, MD*; Fumiaki Marumo, MD*; Yoshito Iesaka, MD**

Thrombolytic therapy improves survival after acute myocardial infarction (AMI) primarily by preserving left ventricular function. Its influence on the arrhythmogenic substrate remains uncertain. To investigate the electrophysiologic effects of thrombolytic therapy, signal-averaged electrocardiography, endocardial catheter mapping and programmed stimulation were performed in 93 consecutive patients with their first AMI who underwent thrombolytic therapy. Early reperfusion was achieved in 75 patients (group 1), but not in 18 patients (group 2). The incidence of the signal-averaged electrocardiogram abnormality was 11% in group 1 (8 of 75 patients) and 33% in group 2 (6 of 18 patients) (p<0.02). Catheter mapping detected delayed endocardial electrograms in 30 group 1 patients and 10 group 2 patients (p=NS). The spatial distribution of these electrogams was smaller, and the longest duration of endocardial electrograms was shorter in group 1 than in group 2 (p<0.01). Sustained monomorphic ventricular tachycardia was induced less commonly in group 1 (20%) than in group 2 (44%) (p<0.05). In conclusion, thrombolytic therapy can reduce the arrhythmogenic substrate and improve electrical stability after AMI. This antiarrhythmic effect may contribute, in part, to the improved survival of patients treated with thrombolytic drugs. (Jpn Circ J 1999; 63: 838–842)

Key Words: Myocardial infarction; Thrombolytic therapy; Ventricular arrhythmias

Thrombolytic therapy has been shown to improve survival after acute myocardial infarction (AMI) primarily by decreasing infarct size and consequently preserving left ventricular function.1–6 This mortality benefit has been reported to be greater than would be expected solely from the improvement of left ventricular function.4,5 Some authors suggested that enhancement of electrical stability might contribute to the lower mortality,6,7 but there is controversy about the electrophysiologic effects of early reperfusion achieved by thrombolytic therapy.8–20

To evaluate electrical stability after myocardial infarction, several clinical techniques have been developed. The signal-averaged electrocardiogram (ECG)21–31 and endocardial catheter mapping32–37 are performed to detect delayed ventricular activation, which is required for the development of reentry. The induction of sustained monomorphic ventricular tachycardia by programmed ventricular stimulation is known to be one of the most useful predictors of future arrhythmic events.24,29–31,38–40

Previous studies, however, have used only one or two noninvasive methods, such as the ambulatory or the signal-averaged ECG, to evaluate the electrophysiologic effects of thrombolytic therapy.9–16 In the present study, using the signal-averaged ECG, endocardial catheter mapping and programmed ventricular stimulation together, we investigated the electrophysiologic effects of early reperfusion achieved by thrombolytic therapy in patients who had recovered from their first AMI.

**Methods**

*Study Patients*

The study group comprised 93 consecutive patients (80 men and 13 women; mean [± SD] age, 59.6±9.8 years; range, 39–75) who were admitted to hospital within 6h after the onset of the symptoms of their first AMI. The diagnosis of AMI was based on the typical chest pain lasting more than 30min, ST elevation of more than 2mm in at least 2 ECG leads and an increase in serum creatine kinase MB isoenzyme. Patients older than 75 years old, with bundle branch block, atrial fibrillation or with contraindications to thrombolytic therapy were excluded. All patients underwent emergency coronary angiography using the Judkins technique. All of the patients were shown to have a culprit coronary artery with grade 0 or 1 flow of the Thrombolysis in Myocardial Infarction (TIMI) trial classification.41 They received intracoronary urokinase (960,000 units over 40min) or recombinant tissue-type plasminogen activator (100mg over 40min). Before the study, all patients gave informed, written consent. The Clinical Research Committee of the hospital approved the study protocol.
Antiarrhythmic Effects of Early Thrombolysis

deflection of the electrogram. A late electrogram was
of each electrogram was measured; the duration (in ms)
the distal electrode pairs with the amplifier bandpass of
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defined as
length method. Significant coronary artery stenosis was
raphy in the right anterior oblique projection using the area-
ular ejection fraction was calculated from left ventriculog-
angiography 26±5 days after the onset of AMI. Left ventric-
Calcium antagonists, nitrates or angiotensin-converting
catheter mapping and contrast angiography as a series
Cassidy et al.34 Bipolar electrograms were recorded from
guidance according to a mapping scheme described by
left ventricular endocardium under biplane fluoroscopic
CA, USA) introduced percutaneously into the femoral
Cardiac Catheterization and Angiography
filtered QRS complex <20
or the root mean square voltage of the last 40 ms of the
criteria were fulfilled: the filtered QRS duration >114 ms,
Late potentials, the duration of the terminal low amplitude
ings from the individual lead. Three parameters, the filtered
signals for the 3
frequencies of 40–250 Hz. The filtered signals for the 3
Using orthogonal bipolar X, Y and Z leads, signals from
1200 EPX unit in all patients in the fourth week after
rhythm with the Arrhythmia Research Technology model
1200 EPX unit in all patients in the fourth week after
admission, according to the method described by Simson.21 Using orthogonal bipolar X, Y and Z leads, signals from 200 to 250 beats were amplified, digitized and averaged to reduce the noise level below 0.5 μV. We used a bidirec-
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frequencies of 40–250Hz. The filtered signals for the 3
leads were combined into a vector magnitude obtained by
taking the square root of the sum of the squares of the read-
ings from the individual lead. Three parameters, the filtered
QRS duration, the duration of the terminal low amplitude
signal of less than 40
QRS duration, the duration of the terminal low amplitude
represent delayed ventricular activation, which was
required for the development of reentrant ventricular tachy-
cardia.38 We examined the presence of, and the spatial and
temporal distribution of, late electrograms.

Programmed Ventricular Stimulation
All patients underwent programmed ventricular stimula-
tion in the fasting, non-sedated state 32±5 days after the
onset of AMI. Two 6F quadripolar electrode catheters were
inserted percutaneously into the right femoral vein, advanced under fluoroscopic guidance and positioned at the right ventricular apex and outflow tract to perform programmed stimulation and to record local endocardial electrograms. Right ventricular sites were paced at twice diastolic threshold with 1 ms of pulse width and at 2 different
basic drive cycle lengths (600 and 400 ms), and up to 3
extrastimuli were delivered sequentially until ventricular refractoriness was reached. The endpoint of the study was
the induction of sustained ventricular tachycardia or
completion of the stimulation protocol. Sustained ventricu-
lar tachycardia was defined as ventricular tachycardia
lasting more than 30s or requiring a prompt termination
because of hemodynamic deterioration. Nonsustained
ventricular tachycardia was defined as ventricular tachycar-
dia with 10 or more repetitive responses that terminated
spontaneously within 30s. Ventricular tachycardia with a
constant cycle length, configuration and axis was defined as
monomorphic, and ventricular tachycardia with a changing
pattern of cycle length, configuration and axis as polymor-
phic.39 We considered the induction of sustained monomor-
phic ventricular tachycardia as significant, because inducible sustained monomorphic ventricular tachycardia is thought to be a useful predictor of arrhythmic events
after myocardial infarction.24,29–31,38–40

Follow-up
Patients were treated with β-adrenergic antagonists, calcium antagonists, nitrates or angiotensin-converting
enzyme inhibitors at the discretion of the attending physi-
cian. Antiarrhythmic drugs were not given to any patients
regardless of the results of programmed ventricular stimu-
lation. After discharge, patients were evaluated every
month at the outpatient clinic of the hospital.

Statistical Analysis
Continuous values were expressed as mean±1 standard
deviation. Unpaired Student’s t test and chi-square test

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**Table 1** Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=75)</th>
<th>Group 2 (n=18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.5±9.9</td>
<td>60.0±9.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>64/11</td>
<td>16/2</td>
<td>NS</td>
</tr>
<tr>
<td>MI site (ant/inf)</td>
<td>44/31</td>
<td>6/12</td>
<td>NS</td>
</tr>
<tr>
<td>Peak CK (IU/L)</td>
<td>306±2375</td>
<td>203±971</td>
<td>NS</td>
</tr>
<tr>
<td>Peak CK-MB (IU/L)</td>
<td>351±314</td>
<td>249±132</td>
<td>NS</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td>1.4±0.7</td>
<td>1.3±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56.8±12.5</td>
<td>53.8±13.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; ant, anterior; inf, inferior; CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme; LVEF, left ventricular ejection fraction.

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**Table 2** Results of the Signal-Averaged Electrocardiogram, Endo-
Cardial Catheter Mapping and Programmed Ventricular Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=75)</th>
<th>Group 2 (n=18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late potentials</td>
<td>8 (11%)</td>
<td>6 (33%)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Catheter mapping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late electrograms</td>
<td>30 (40%)</td>
<td>10 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Percent distribution of late electrograms</td>
<td>12.1±2.8%</td>
<td>34.1±22.3%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
| Longest duration of endo-
cardial electrograms (ms) | 98.8±13.2 | 140.8±26.6 | <0.01 |
| Inducible SMVT | 15 (20%)      | 8 (44%)       | <0.05   |

SMVT, sustained monomorphic ventricular tachycardia.

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Signal-Averaged Electrocardiogram
A signal-averaged ECG was obtained during sinus
rhythm with the Arrhythmia Research Technology model
1200 EPX unit in all patients in the fourth week after
admission, according to the method described by Simson.21 Using orthogonal bipolar X, Y and Z leads, signals from 200 to 250 beats were amplified, digitized and averaged to reduce the noise level below 0.5 μV. We used a bidirec-
tional Butterworth filter, setting a bandpass filter at
frequencies of 40–250Hz. The filtered signals for the 3
leads were combined into a vector magnitude obtained by
taking the square root of the sum of the squares of the read-
ings from the individual lead. Three parameters, the filtered
QRS duration, the duration of the terminal low amplitude
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represent delayed ventricular activation, which was
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cardia.38 We examined the presence of, and the spatial and
temporal distribution of, late electrograms.

Cardiac Catheterization and Angiography
All 93 patients underwent cardiac catheterization and
angiography 26±5 days after the onset of AMI. Left ventricu-
lar ejection fraction was calculated from left ventriculog-
raphy in the right anterior oblique projection using the area-
length method. Significant coronary artery stenosis was
defined as≥75% reduction of luminal diameter.

Endocardial Catheter Mapping
Endocardial catheter mapping was performed prior to
cardiac catheterization and contrast angiography as a series
of consecutive studies. Antiarrhythmic drugs, including
β-adrenergic antagonists, were discontinued for at least 5 half
lives before catheter mapping and were withheld until
programmed ventricular stimulation was completed. Using
a 6F deflectable quadripolar electrode catheter with a 5-mm
interelectrode spacing (EP Technologies, Inc, Sunnyvale, CA, USA) introduced percutaneously into the femoral
artery and advanced into the left ventricle, we mapped the
left ventricular endocardium under biplane fluoroscopic
guidance according to a mapping scheme described by
Cassidy et al.34 Bipolar electrograms were recorded from
the distal electrode pairs with the amplifier bandpass of
30–500Hz and at a paper speed of 100mm/s. The duration
of each electrogram was measured; the duration (in ms)
was defined as the time from the beginning to the end of
the deflection of the electrogram. A late electrogram was
defined as an electrogram that had a delayed, fractionated
component with an amplitude of 0.5mV or less after the
rapid deflection.35 Late electrograms were considered to
correspond to delayed ventricular activation, which was
required for the development of reentrant ventricular tachy-
cardia.38 We examined the presence of, and the spatial and
temporal distribution of, late electrograms.

Follow-up
Patients were treated with β-adrenergic antagonists, calcium antagonists, nitrates or angiotensin-converting
enzyme inhibitors at the discretion of the attending physi-
cian. Antiarrhythmic drugs were not given to any patients
regardless of the results of programmed ventricular stimu-
lation. After discharge, patients were evaluated every
month at the outpatient clinic of the hospital.

Statistical Analysis
Continuous values were expressed as mean±1 standard
deviation. Unpaired Student’s t test and chi-square test
were used. A p value <0.05 was considered statistically significant.

**Results**

**Patient Characteristics (Table 1)**

No patients died or suffered spontaneous ventricular tachycardia or aborted sudden death during the hospitalization. None of the patients underwent coronary angioplasty or bypass surgery because of medically refractory postinfarction angina before the completion of the study protocol. Among the 93 patients, 75 patients had the culprit artery recanalized by thrombolytic therapy, with coronary blood flow of TIMI grade 2 or 3 (group 1). Early reperfusion was not achieved (TIMI grade 0 or 1) in the other 18 patients (group 2). There were not any significant differences in age, gender distribution, infarction sites, peak creatine kinase level, peak creatine kinase MB isoenzyme level or the number of diseased vessels between the 2 groups. Left ventricular ejection fraction was higher in group 1, but the difference between the groups was not statistically significant.

**Incidence of Late Potentials (Table 2)**

There was a significant difference in the incidence of late potentials between the groups. Only 8 patients (11%) in group 1 had positive late potentials, compared with 6 (33%) in group 2 (p<0.02).

**Endocardial Catheter Mapping (Table 2)**

We performed catheter mapping to record electrograms at least 2 sites in each region of the anterior, lateral, infero-posterior and septal walls. Accordingly, 8–12 sites were mapped in every patient. The number of total mapped sites was 9.5±1.1 in group 1, and 10.0±1.3 in group 2 (p=NS). Late electrograms were recorded in at least one endocardial site in 30 (40%) of the group 1 patients and in 10 (56%) of the group 2 patients (p=NS). However, the number of sites where late electrograms were recorded was smaller in group 1 (1.2±0.4) than in group 2 (3.5±2.4) (p<0.01).

As for the spatial distribution of late electrograms, we used the percent distribution of late electrograms. This was significantly smaller in group 1 (12.1±2.8%) than in group 2 (34.1±22.3%) (p<0.01).

With regard to the temporal distribution of late electrograms, we used the longest duration of endocardial electrograms, including late electrograms. This was significantly shorter in group 1 (98.8±13.2 ms) than in group 2 (140.8±32.6 ms) (p<0.01).

**Programmed Ventricular Stimulation (Table 2)**

Sustained monomorphic ventricular tachycardia was induced in 15 (20%) group 1 patients and in 8 (44%) group 2 patients. The incidence of inducible sustained monomorphic ventricular tachycardia was significantly lower in group 1 than in group 2 (p<0.05).

**Follow-up**

All patients were followed up at the outpatient clinic of the hospital (follow-up period: group 1, 6–25 months, 16.4 months on average; group 2, 6–23 months; 14.9 months on average). No patients in group 1 experienced sudden death or spontaneous ventricular tachycardia, although 2 patients in group 2 had arrhythmic events during the follow-up period (ventricular tachycardia in one patient and unexpected sudden death without chest pain in another) (p<0.05). Moreover, 4 group 1 patients and 2 group 2 patients were hospitalized for worsening heart failure (p=NS). Ischemic events were documented in 11 group 1 patients and 1 group 2 patient (p=NS).

**Discussion**

The present study, using together the signal-averaged ECG, endocardial catheter mapping and programmed ventricular stimulation, demonstrated that early reperfusion achieved by thrombolytic therapy in AMI reduced the incidence of late potentials, the spatial and temporal distribution of delayed ventricular activation and the incidence of inducible sustained monomorphic ventricular tachycardia. These results suggest that early reperfusion can reduce the arrhythmogenic substrate in patients with AMI.

**Experimental and Histopathological Studies of Early Reperfusion**

Experimental studies of canine myocardial infarction model showed that early reperfusion produced histologically heterogeneous infarcts and increased electrical instability. However, in the study of Karagueuzian et al, the extent of infarcts in reperfused dogs was not significantly smaller than that in dogs without reperfusion. In fact, dogs with obviously smaller infarcts produced by reperfusion did not have ventricular tachycardia induced by programmed stimulation. In autopsy findings of patients with AMI who died after thrombolytic therapy, hemorrhagic infarction was frequently observed, but histological heterogeneity was not examined. Thus, whether thrombolytic therapy makes infarcts heterogeneous and increases electrical instability remains to be determined in both experimental and clinicopathological studies.

**Early Reperfusion and the Signal-Averaged Electrocardiogram**

There are several clinical studies concerning the effects of thrombolytic therapy on the signal-averaged ECG. As Winters et al pointed out, there were considerable differences in the study design and methods among those studies: the interval from the symptom onset to the thrombolytic therapy, the thrombolytic agents administered, the definition of vessel patency, the time for recording a signal-averaged ECG, signal-averaging techniques and the definition of abnormal results of the signal-averaged ECG. Despite these differences, most reports, as well as ours, suggest that thrombolytic therapy could reduce the incidence of late potentials in the signal-averaged ECG. The lower success rate of thrombolyis in the study of Turitto et al might mask the beneficial effects of thrombolysis.

**Endocardial Catheter Mapping, Programmed Ventricular Stimulation and Early Reperfusion**

Because activation of the anterior segments of the left ventricle is earlier than that of the inferoposterior segments delayed activation originating in the anterior segments may be obscured within the QRS complex. Therefore, patients with anterior myocardial infarction are less likely to demonstrate late potentials in the signal-averaged ECG. In fact, it was reported that the incidence of

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positive late potentials was greater in patients with inferior myocardial infarction than in patients with anterior myocardial infarction.\(^9\) For this reason, although they are invasive, endocardial catheter mapping and programmed ventricular stimulation are thought to be able to evaluate the effects of thrombolytic therapy on an electrophysiologic substrate more accurately than the signal-averaged ECG.

Thus far, a few investigations have evaluated electrical instability after thrombolysis using programmed ventricular stimulation.\(^{17-20}\) Kierschot et al showed sustained monomorphic ventricular tachycardia was less commonly induced in patients treated with thrombolytic agents (29%) than in control patients (67%).\(^9\) In a study of high-risk patients with a transmural anterior myocardial infarction, thrombolytic therapy significantly improved electrical stability and reduced the incidence of arrhythmic events (sudden death or spontaneous ventricular tachycardia) despite the absence of improvement of left ventricular function.\(^9\) Our present study showed similar results: sustained monomorphic ventricular tachycardia was induced only in 20% of patients with successful thrombolytic therapy, but in 44% of patients with failed thrombolysis. McComb et al reported that thrombolytic therapy did not influence the incidence of inducible sustained ventricular tachycardia.\(^5\) However, their protocol of programmed stimulation was less aggressive than ours or those of other studies, and the incidence of inducible sustained ventricular tachycardia was rather low (22%) in their study.

The present study is the first that introduced endocardial catheter mapping to investigate the effects of thrombolysis on delayed ventricular activation. Untereker et al revealed that patients with healed myocardial infarction and recurrent sustained ventricular tachycardia had a significantly longer duration of endocardial electrograms and wider areas in which late electrograms were recorded than patients without recurrent ventricular tachycardia, and that the temporal and spatial distribution of delayed ventricular activation in patients with myocardial infarction might be associated closely with the development of ventricular tachycardia.\(^5\) Our present study demonstrated that early reperfusion reduced both the spatial and temporal distribution of delayed ventricular activation and the incidence of inducible sustained monomorphic ventricular tachycardia in patients with their first AMI but no clinical ventricular tachycardia.

### Study Limitations

The study population was relatively small because of the invasiveness of much of the study protocol. However, both groups had comparable clinical and angiographic variables. Endocardial catheter mapping in sinus rhythm, although perhaps appropriate for patients with a history of clinical ventricular tachycardia, has not been validated for post-infarction patients without clinical arrhythmias. We did not evaluate the collateral vessels. The possibility that the presence of collaterals might influence the effects of early thrombolysis on electrical substrates cannot be excluded. In spite of early reperfusion, group 1 did not have significantly better left ventricular ejection fraction than group 2. This might be attributable to the inclusion of TIMI grade 2 flow after thrombolytic therapy in successful early reperfusion. However, our results showing that thrombolytic therapy significantly improved ventricular electrical stability without preserving left ventricular function might support the observation that the mortality benefit brought about by thrombolytic therapy is greater than would be expected solely from the improvement of ventricular function.\(^5\)

### Conclusions

In this relatively small study population, early reperfusion achieved by thrombolytic therapy significantly reduced an arrhythmogenic substrate and improved ventricular electrical stability in patients with a first AMI. These antiarrhythmic effects of thrombolytic therapy may contribute, in part, to the improved prognosis of patients treated with thrombolytic drugs.

### References


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