The Signal-Averaged Electrocardiogram and Ventricular Arrhythmias After Thrombolysis for Acute Myocardial Infarction

GIOIA TURITTO, MD,* ANNA LISA RISA, MD, EGIDIO ZANCHI, MD, PIER LUIGI PRATI, MD
Rome, Italy

The prevalence of an abnormal signal-averaged electrocardiogram (ECG) and ventricular arrhythmias on 24 h ambulatory electrocardiography was evaluated in 118 patients 13 ± 2 days after acute myocardial infarction. Group 1 (46 patients) underwent intravenous thrombolysis within 6 h of the onset of symptoms, whereas Group 2 (72 patients) did not. An abnormal signal-averaged ECG was seen in 15% of patients in Group 1 and 21% of those in Group 2 (difference not significant).

The number of ventricular premature complexes/h was lower in Group 1 than in Group 2: 2.58 ± 1.63 versus 7.91 ± 10.75 (p < 0.01). However, complex arrhythmias (≥10 ventricular premature complexes/h or ventricular tachycardia) were equally common in Groups 1 and 2 (20% versus 22%, respectively). Their prevalence was similar in patients with or without an abnormal signal-averaged ECG (29% versus 18%, respectively, in Group 1 and 27% versus 21%, respectively, in Group 2). Comparison between patients with (n = 26) or without (n = 20) angiographic patency of the infarct-related coronary artery after thrombolysis showed no significant difference in the prevalence of an abnormal signal-averaged ECG (8% versus 25%, respectively) and complex ventricular arrhythmias (19% versus 20%, respectively).

These data suggest that thrombolysis does not affect the prevalence of complex ventricular arrhythmias and an abnormal signal-averaged ECG or their relation after acute myocardial infarction.

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Methods

Study patients. Patients were included in this study if they fulfilled the following criteria: 1) a diagnosis of acute myocardial infarction based on the presence of typical chest pain for >30 min not relieved by sublingual nitrates, >1 mm of ST elevation in two or more adjacent leads on the admission ECG, with subsequent development of Q waves or persistent (>24 h) ST-T changes and an increase in serum enzymes (creatine kinase and its MB isoenzyme); 2) absence of prior myocardial infarction according to history and ECG; 3) QRS duration <120 ms, with absence of bundle branch block pattern and QT prolongation on the 12 lead ECG; and 4) survival to completion of the protocol. A total of 118 consecutive patients admitted to our hospital between January and November 1989 met the inclusion criteria and entered the study. Among them, 46 patients who were hospitalized within 6 h of the onset of symptoms and without contraindications to it received thrombolytic therapy by intravenous route; the remaining 72 patients did not receive this treatment because of their late hospital arrival (n = 67), or the occurrence of cardiogenic shock (n = 2), prolonged cardiopulmonary resuscitation (n = 1) or recent gastrointestinal bleeding (n = 2). Agents used for intravenous throm-
bolysis were urokinase (2 million U over 60 min) in 35 patients, streptokinase (1.5 million U over 60 min) in 4 patients and recombinant tissue-type plasminogen activator (100 mg over 180 min) in 7 patients.

Study design. All patients had a 24 h ambulatory ECG before discharge 13 ± 2 days after the index infarction and after withdrawal of all therapy for ≥24 h. No patients received a beta-adrenergic blocker throughout the study period. Except for 1 patient who developed recurrent sustained ventricular tachycardia and was treated with amiodarone after recording the signal-averaged and ambulatory ECG, the only antiarrhythmic drug used during the study was lidocaine, which was given to 14 patients during the first 5 days after infarction. The signal-averaged ECG was recorded within 24 h of the ambulatory ECG in all patients.

Signal-averaged ECG. Recordings were performed with the Arrhythmia Research Technology model 1200 EPX unit using previously reported techniques (7). The ECG was recorded during sinus rhythm with standard bipolar orthogonal X, Y and Z leads. Signals were amplified, averaged and filtered with a bidirectional filter at frequencies of 25 to 250 Hz. The filtered leads were combined into a vector magnitude \( \sqrt{X^2+Y^2+Z^2} \). A computer program algorithm determined the onset and offset of the QRS complex and calculated total QRS duration, duration of low amplitude signals <40 \( \mu \)V, root mean square voltage of the total QRS complex and root mean square voltage of signals in the last 40 ms of the QRS complex (RMS40). Recordings with a noise level ≥1 \( \mu \)V were rejected. Between 200 and 400 complexes were usually averaged to reach this end point noise level. An abnormal signal-averaged ECG was defined as a recording showing one or more of the following abnormalities: total QRS duration >115 ms, duration of low amplitude signals >32 ms, root mean square voltage of signals in the last 40 ms of the QRS complex <25 \( \mu \)V (8). Late potentials were defined as signals with abnormal root mean square voltage of signals in the last 40 ms of the QRS complex.

Ambulatory ECG. A two channel, 24 h ECG was recorded with the Avionics model 445 portable unit and analyzed with the Avionics model 660B replay unit. Arrhythmia detection and interpretation were performed by three of the investigators (G.T., A.L.R., E.Z.). The number and configuration of ventricular premature complexes and the prevalence of polymorphic ventricular premature complexes, couplets, nonsustained ventricular tachycardia (three or more ventricular premature complexes, lasting <30 s at a rate of >100/min) and sustained ventricular tachycardia (≥30 s) were assessed. Complex ventricular arrhythmias were defined as frequent ventricular premature complexes (≥10/h) or ventricular tachycardia, or both (9).

Cardiac catheterization. All 46 patients subjected to thrombolysis underwent cardiac catheterization 10 ± 5 days after infarction. All had given written informed consent to an ongoing protocol on the effects of thrombolysis, as approved by our institution. In the group not treated with thrombolysis, 39 of the 72 patients underwent cardiac catheterization 12 ± 4 days after infarction because of the presence of early postinfarction angina (n = 8), left ventricular failure (n = 3), non-Q wave myocardial infarction (n = 12) or at the request of their attending physician (n = 16). Selective coronary angiograms were recorded in multiple views; the left ventriculogram was recorded in the right anterior oblique view. Left ventricular ejection fraction was calculated according to the area-length method. Left ventricular wall motion abnormalities, defined as the presence of segmental akinesia or dyskinesia, were evaluated using a five segment model that divided the ventricular outline into anterobasal, anterolateral, apical, inferior and posterobasal segments (10).

ECG location of myocardial infarction. This was related to coronary anatomy and left ventricular wall motion as follows (11–14):

- **Anterior infarction** (including anterior, anteroseptal, anterolateral and lateral locations on the 12 lead ECG) was related to disease in the left anterior descending coronary artery and wall motion abnormalities in the anterobasal, anterolateral and apical segments.
- **Inferior infarction** (including inferior, inferoposterior, posterior and inferolateral locations on the 12 lead ECG) was related to disease in the circumflex or right coronary artery and wall motion abnormalities in the inferior and posterobasal segments.

Definitions. The following definitions were adopted:

- **Successful thrombolysis**: patency of the infarct-related coronary artery with grade ≥2 flow in the Thrombolysis in Myocardial Infarction trial classification (14).
- **Collateral circulation**: opacification of the artery distal to a stenotic or occluded segment by branches from other major coronary arteries (modified by Elayda et al. [15]).

Statistical analysis. Patients were separated into two groups according to whether they did or did not receive intravenous thrombolytic therapy. Group 1 consisted of patients subjected to thrombolysis, and was further divided into two subgroups based on the success (Group 1A) or failure (Group 1B) of thrombolysis. Group 2 included patients who did not undergo thrombolysis. Patients from both groups characterized by patency or occlusion of the infarct-related coronary artery were pooled together for further analysis. Student’s \( t \) test and chi-square analysis, with Yates’ correction for continuity or Fisher’s exact test where appropriate, were used for comparisons. A p value <0.05 was considered statistically significant. Continuous variables were expressed as mean values ± 1 SD.

Results

Comparison of patients with or without thrombolysis (Table 1). Patients who received thrombolysis (Group 1) were
not significantly different from patients who did not (Group 2) with regard to age, gender distribution, type and location of myocardial infarction, maximal increase in serum cardiac enzymes and prevalence of ventricular fibrillation during hospitalization. An abnormal signal-averaged ECG was recorded in 22 (19%) of the 118 study patients, with no significant difference between Groups 1 and 2 (15% versus 21%, respectively). No significant differences were found between Groups 1 and 2 in terms of the prevalence of prolonged QRS duration, prolonged low amplitude signal duration and late potentials, singly or in combination, or the mean value of any of the signal-averaged ECG variables. An abnormal signal-averaged ECG was slightly more frequent in patients with inferior than anterior infarction (19% versus 10% in Group 1 and 24% versus 18% in Group 2, respectively). However, comparison of the signal-averaged ECG data according to the site of infarction did not reveal any significant differences between groups.

Complex ventricular arrhythmias on the ambulatory ECG were observed in 25 (21%) of the 118 study patients, with no significant difference between Groups 1 and 2 (20% versus 22%, respectively). No significant differences were found between Groups 1 and 2 in terms of the prevalence of any of the index arrhythmias (frequent, polymorphic or repetitive ventricular premature complexes or ventricular tachycardia). However, the mean hourly number of ventricular premature complexes was lower in Group 1 than in Group 2 (p < 0.01). Complex ventricular arrhythmias were equally common in patients with or without an abnormal signal-averaged ECG in both groups. In fact, they were present in 29% of patients in Group 1 and 27% of patients in Group 2 who had an abnormal signal-averaged ECG, as well as in...
Comparison of patients with or without successful thrombolysis (Table 2). Thrombolysis was successful in restoring patency of the infarct-related coronary artery in 26 patients (Group 1A), but failed to do so in 20 patients (Group 1B). Left ventricular ejection fraction was higher \((p < 0.05\), whereas akinesia or dyskinesia in the infarcted area and collateral circulation to the infarct-related vessel were less common \((p < 0.001\) in the presence (Group 1A) than in the absence (Group 1B) of successful thrombolysis. Signal-averaged ECG abnormalities tended to be less frequent in Group 1A than Group 1B, but none of the observed differences reached statistical significance. In contrast, both the mean root mean square (RMS) voltage of the total QRS complex and root mean square voltage of signals in the last 40 ms of the QRS complex (RMS40) were significantly higher in Group 1A than Group 1B. No significant differences were found between Groups 1A and 1B in terms of the prevalence of complex ventricular arrhythmias (19% versus 20%, respectively) or any of the index arrhythmias. Conversely, the mean hourly number of ventricular premature complexes was lower in Group 1A than Group 1B \((p < 0.01\). In Group 1A, complex ventricular arrhythmias were seen in no patients with an abnormal signal-averaged ECG and in 21% of patients with a normal signal-averaged ECG; in Group 1B, they were noted in 40% of patients with an abnormal signal-averaged ECG and in 13% of patients with a normal signal-averaged ECG (differences not significant).

Comparison of patients with or without patency of the infarct-related coronary artery (Table 3). To assess if patency of the infarct-related artery, whether mediated by thrombolysis or not, influenced the signal-averaged ECG and the prevalence of complex ventricular arrhythmias, the characteristics of 42 patients with patency of the infarct-related artery (26 from Group 1A and 16 from Group 2) were compared with those of 33 patients with occlusion of the infarct-related artery (20 from Group 1B and 13 from Group 2). This analysis showed no significant differences in the prevalence of abnormal signal-averaged ECG variables, although a trend existed toward a lesser prevalence of abnormalities in the group with than in the group without patency of the infarct-related artery. Moreover, the mean root mean square voltage (RMS) of the total QRS complex and the last 40 ms (RMS40) of the QRS complex were significantly higher in the former than the latter group, thus duplicating a finding observed when comparing Groups 1A and 1B (patients with or without patency of the infarct-related artery associated with thrombolytic therapy). Similarly, no significant differ-
Table 3. Characteristics of 75 Patients With or Without Patency of the Infarct-Related Coronary Artery After Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Patency of the Infarct-Related Coronary Artery (n = 42)</th>
<th>Occlusion of the Infarct-Related Coronary Artery (n = 33)</th>
<th>p Value</th>
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<tr>
<td>Ambulatory ECG data</td>
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<tr>
<td>VPCs/h (n)</td>
<td>3.16 ± 6.15</td>
<td>6.39 ± 7.00</td>
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<td>Frequent VPCs (%)</td>
<td>3 (7)</td>
<td>5 (15)</td>
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<tr>
<td>Polymorphic VPCs (%)</td>
<td>6 (14)</td>
<td>6 (18)</td>
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<tr>
<td>Couplets (%)</td>
<td>1 (2)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Nonsustained VT (%)</td>
<td>5 (12)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Sustained VT (%)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Complex ventricular arrhythmias (%)</td>
<td>7 (17)</td>
<td>6 (18)</td>
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<tr>
<td>Signal-averaged ECG data</td>
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<td></td>
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<tr>
<td>QRS duration (ms)</td>
<td>99 ± 14</td>
<td>106 ± 18</td>
</tr>
<tr>
<td>LAS40 (ms)</td>
<td>24 ± 10</td>
<td>29 ± 14</td>
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<tr>
<td>RMS QRS (μV)</td>
<td>140 ± 50</td>
<td>104 ± 38</td>
</tr>
<tr>
<td>RMS40 (μV)</td>
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<td>47 ± 27</td>
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<td>Prolonged QRS duration (%)</td>
<td>4 (10)</td>
<td>7 (21)</td>
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<tr>
<td>Prolonged LAS40 (%)</td>
<td>5 (12)</td>
<td>9 (27)</td>
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<tr>
<td>Late potentials (%)</td>
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<td>8 (24)</td>
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<tr>
<td>Abnormal signal-averaged ECG (%)</td>
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<td>1 abnormal variable (%)</td>
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<td>2 abnormal variables (%)</td>
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</tr>
<tr>
<td>3 abnormal variables (%)</td>
<td>3 (7)</td>
<td>5 (15)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

ences were found in the prevalence of complex ventricular arrhythmias between patients with or without patency of the infarct-related artery, although the mean hourly number of ventricular premature complexes was lower (p < 0.05) in the former group.

Discussion

Several large studies (16–25) have investigated the prevalence and significance of late potentials on the signal-averaged ECG (16–20) and of complex ventricular arrhythmias on the ambulatory ECG (21–25) after myocardial infarction; however, most of these studies were performed before the advent of the thrombolytic era (16,21–25), or the number of patients subjected to thrombolysis was not reported (17–20) or was too small to draw meaningful conclusions (3,26). Thus, an assessment of the frequency of late potentials and ventricular arrhythmias after thrombolysis was overdue.

Thrombolysis and the signal-averaged ECG. Reports (3,4) on the signal-averaged ECG in patients with or without thrombolytic treatment have produced conflicting results. Gang et al. (4) performed a signal-averaged ECG within 48 h of admission in 44 patients with and 62 patients without thrombolytic treatment and found abnormal variables in 2 (5%) and 14 (23%) patients, respectively. This difference was statistically significant (p = 0.01). An abnormal signal-averaged ECG was associated with future arrhythmic events when observed in the late hospital period (6 to 30 days after infarction) rather than in the early phase (0 to 5 days after infarction) (27); thus, the findings of Gang et al. (4) may not be relevant to long-term prognosis of postinfarction patients. Furthermore, in their study, the signal-averaged ECG repeated before discharge remained abnormal in 2 (5%) patients with and in only 11 (18%) patients without thrombolysis (difference not significant).

In our present study, we report the results of signal-averaged ECGs performed 13 ± 2 days after myocardial infarction in a series of 118 patients treated with or without intravenous thrombolysis within 6 h of the onset of symptoms and with angiographic control of achieved reperfusion. A threefold conclusion may be drawn from our data: 1) Thrombolysis favorably influenced some signal-averaged ECG variables, namely, root mean square voltage of the total QRS complex and root mean square voltage of the last 40 ms of the QRS complex. In fact, these indexes were significantly higher in the presence than in the absence of successful thrombolysis, possibly a reflection of reduced loss of myocardial mass as a result of necrosis. Thus, they may be helpful in estimating myocardial salvage after thrombolysis in a manner analogous to QRS scoring systems based on the surface ECG (28,29). 2) Conversely, no significant differences in the prevalence of an abnormal signal-averaged ECG were observed between patients with or without
thrombolysis, although there was a tendency toward fewer abnormal signal-averaged ECG variables in the group with than in the group without successful thrombolysis. 3) This result was independent of the effect of thrombolysis on left ventricular function because an abnormal signal-averaged ECG was equally common in patients with or without akinesis or dyskinesia in the infarcted area. The latter finding duplicates that of Gomes et al. (30), who documented no correlation between the signal-averaged ECG and left ventricular ejection fraction and wall motion abnormalities in a group of 50 postinfarction patients. It may be speculated that late potentials arise from viable myocardium interspersed in the infarct-related artery was a spontaneous event rather than an effect of thrombolysis. Thus, any intervention to reduce the extent of myocardial infarction and wall motion abnormalities may not be expected to modify the substrate for late potentials on the signal-averaged ECG.

**Thrombolysis and ventricular arrhythmias.** The immediate arrhythmogenic effects of thrombolysis have been well recognized; in contrast, its delayed effects are less well characterized (5,6). One study (5) suggested that ventricular arrhythmias after thrombolysis-induced reperfusion were limited to the early phase after treatment and were rare before hospital discharge; however, a control group was not available in this investigation. Theroux et al. (6) reported a significant reduction in the number and frequency of ventricular premature complexes/24 h in a large group of patients treated with intravenous streptokinase, as compared with a control group. On the contrary, the prevalence of ventricular tachycardia was not altered by thrombolysis. The 24 h ambulatory ECGs were performed after hospital discharge, 42 ± 72 days after the index infarction (6).

We, too, observed a decrease in the number of ventricular premature complexes after thrombolysis; however, we were unable to show any changes in the prevalence of complex ventricular arrhythmias. Differences in the time of recording the ambulatory ECG and the definition of complex ventricular arrhythmias may partially explain discrepancies between our results and those of Theroux et al. (6). We chose to record the ambulatory ECG 13 ± 2 days after infarction because most studies (21-24) of the prognostic significance of ventricular arrhythmias in survivors of myocardial infarction derived their data from ambulatory ECGs performed 10 to 11 days after the index event or before discharge. Complex ventricular arrhythmias increased substantially on later recordings (9,27,32), but their prognostic value remains to be established. Similarly, our definition of frequent ventricular premature complexes was based on the results of the Multicenter Post-Infarction Research Trial (21), which demonstrated that ventricular premature complexes carried a high risk for cardiac death when their number was ≥10/h. The lack of a net antiarrhythmic efficacy of thrombolytic therapy observed in our study is not surpris-


