Frequency of Predischarge Ventricular Arrhythmias in Postmyocardial Infarction Patients Depends on Residual Left Ventricular Pump Performance and Is Independent of the Occurrence of Acute Reperfusion

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Objectives. To test whether acute reperfusion of the infarct-related vessel after an acute myocardial infarction is associated with a subsequent reduction in spontaneous ventricular arrhythmias that is independent of ventricular ejection fraction, 1,944 patients from the GISSI-2 study population were studied. The patients were selected on the basis of a first myocardial infarction and the availability of two-dimensional echocardiographic ejection fraction and data on the number of premature ventricular contractions per hour on Holter monitoring.

Background. It has been suggested that postthrombolytic reperfusion of the culprit vessel may be associated with an increased electrical stability of the infarcted heart, irrespective of its residual pump performance.

Methods. The predischarge relation between ejection fraction and number of premature ventricular contractions per hour was plotted according to the occurrence (1,309 patients) or not (635 patients) of acute reperfusion, identified noninvasively according to the modifications of the ST segment in serial electrocardiograms obtained in the first 24 h after infarction.

Results. The frequency of premature ventricular contractions increased in a linear fashion with decreasing ejection fraction in both cohorts ($p < 0.005$ and $p < 0.0001$); however, there was no significant difference between the slopes and the intercepts of the two regression lines, so that the relation between ejection fraction and number of premature ventricular contractions per hour could be adequately described by a single equation: y (number of premature ventricular contractions) $= 33.0 - 0.42x$ (ejection fraction) ($r = -0.107$, $p < 0.0001$). The results were the same even when differences between group characteristics were accounted for in a multiple regression model.

Conclusions. It is concluded that 1) the number of premature ventricular contractions per hour after an acute myocardial infarction is dependent in a linear, inverse fashion on the residual ventricular ejection fraction, and 2) this relation is independent of the occurrence of reperfusion in the acute phase of infarction.

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Although the extent of necrosis and the condition of the noninfarcted myocardium (i.e. residual left ventricular function) should be considered the ultimate determinants of prognosis in patients after a myocardial infarction, alternative mechanisms have been proposed to explain the frequent discrepancies between survival and left ventricular function data that have been reported in many trials devoted to

thrombolysis (1). In particular, it has been suggested that postthrombolytic reperfusion of the infarct-related vessel may be associated with a decreased incidence of inducible and spontaneous ventricular arrhythmias that is independent of ventricular ejection fraction (2). Such a result would depend on an increased electrical stability of the reperfused infarcted heart, probably mediated by the reduced incidence of late potentials, coupled with the more homogeneous ventricular activation provided by a patent culprit vessel (3–5).

However, there is some doubt about the electrophysiologic mechanisms involved because restoration of patency could create a border zone of necrotic and live tissue that would produce rather than minimize the substrate for ventricular reentry (6–8). Alternatively, the electrical stability of the heart might be improved through the potentially beneficial impact of reperfusion on infarct size and ventricular remodeling (9) because chamber dilation would increase the inducibility of arrhythmias (10). If this were the case,

then the beneficial effect of a patent vessel on ventricular ectopic activity would be merely secondary to the limiting effects of reperfusion on infarct size and on preservation of left ventricular function and topography (11,12).

It was the purpose of the present study to test, in the population of the GISSI-2 trial (13), the hypothesis that reperfusion of the infarct-related vessel in the acute phase of a first myocardial infarction is associated, at comparable levels of ejection fraction, with a predischarge incidence of premature ventricular contractions that is lower than that in patients who do not experience reperfusion in the acute phase. We anticipated 1) that the number of premature ventricular contractions per hour is dependent in a linear, inverse fashion on the residual ventricular ejection fraction, and 2) that this relation is independent of the occurrence of reperfusion in the acute phase of the illness.

Methods

The design and method of the GISSI-2 trial have been described in detail elsewhere (13). Briefly, GISSI-2 was a controlled, multicenter open trial, with central randomization and a 2 × 2 factorial design. Half of the patients were allocated randomly to treatment with streptokinase (1.5 million U intravenously) and half to alteplase (100 mg intravenously). Half of the patients were also allocated randomly to treatment with subcutaneous heparin (12,500 U) twice daily, starting 12 h after the infusion of the thrombolytic drug (13).

Electrocardiography. A standard 12-lead electrocardiogram (ECG) plus leads V_3R and V_4R, recorded at entry and after 4 h and read centrally by four cardiologists unaware of the treatment allocation were used to develop noninvasive criteria for detection of acute reperfusion. In particular, the difference between the sum of ST segment elevations in the different leads at randomization and after 4 h was calculated and the rate of decrease assessed. A percent decrease ≥50% was taken to indicate acute reperfusion (14).

Two-dimensional echocardiography. An in-hospital two-dimensional echocardiographic examination was performed approximately 2 weeks after admission, with use of parasternal, apical and subcostal views, and images were stored on videotape. Ejection fraction was computed as usual from calculated volumes obtained from an apical four-chamber view using either the area-length method or the modified Simpson rule. Ejection fraction was computed locally at the discretion of those centers able to provide confident assessment of this variable using the two chosen methods for volume calculation.

Holter monitoring. Predischarge 24-h ambulatory ECG (Holter) monitoring was performed after washout of antiarrhythmic and beta-adrenergic blocking agents, whenever this was deemed feasible by the attending physician. The Holter recordings were performed and analyzed by each of the participating centers. Premature ventricular complexes were quantified according to their mean frequency per hour.

Quality control. Central quality control of echocardiograms and Holter monitoring was ensured by a staff of experienced cardiologists who had no knowledge of study treatments and who checked a randomly selected sample of ~10% of all examinations done by each laboratory. Quality control was meant to verify the correct assignment of patients to subgroups according to ejection fraction ≤35% or >35% and <10 ≥ 10 premature ventricular contractions/h. Data concerning the overall proportion of agreement were adjusted for the agreement predictable by chance alone (kappa values).

Statistical methods. Data are expressed as mean value ± 1 SD. Differences in mean values between patients with and without reperfusion in the acute phase were assessed by t statistics for unpaired data. Contingency table analysis was performed for categoric variables. The relation between number of premature ventricular contractions per hour and ejection fraction in both groups of patients was evaluated by linear regression analysis according to the least squares method. Differences in this relation or between the slopes and the intercepts of the regression lines for the two groups of patients were assessed by analysis of covariance and by t statistics for unpaired data. A multiple regression model was also used to account for the potential contribution of between-group differences to the final results. A two-sided p value < 0.05 was considered statistically significant.

Results

Data on predischarge number of premature ventricular contractions per hour at Holter monitoring and an echocardiographic examination were available for 5,508 patients discharged alive from the hospital who had entered the trial with a first infarction and who could be classified as either with or without reperfusion in the acute phase of infarction as assessed by ECG criteria. Of this group only 1,944 patients had an ejection fraction computed according to the methods reported previously. The clinical characteristics of this subgroup did not differ in any respect from those of the rest of the original population considered (Table 1) other than a slight prevalence of male patients (83.4% vs. 81.0%, p < 0.05) and an earlier randomization (72.7% vs. 70.2% enrolled between 0 and 3 h, p < 0.05) for selected patients.

Reperfusion was considered to have been achieved in the acute phase of infarction in 1,309 (67.3%) of 1,944 patients. Lack of reperfusion in the acute phase, defined as a percent decrease ≤50% in the sum of ST segment elevation, was detected in 635 patients (32.7%). Clinical characteristics were similar in patients with and without reperfusion (Table 2), except for the site of myocardial infarction. This site (defined by the GISSI committee according to previously described criteria [13]) was more frequently anterior in the cohort without acute reperfusion (49.0% vs. 33.1%, p < 0.02). The thrombolytic drug used also differed significantly between the two groups. Streptokinase was more frequently associated with a decrease in the sum of ST segment

Table 1. Clinical Characteristics of the Selected Patient Population Relative to the Original Population Considered

	Selected (n = 1,944)	Excluded (n = 3,564)	p Value
Gender (%)			
Female	16.6	19.0	< 0.05
Male	83.4	81.0	
Age (%)			
≤70 yr	82.7	81.9	NS
>70 yr	17.3	18.1	
Time interval (h) from onset of symptoms to randomization (%)			
0-3	72.7	70.2	< 0.05
>3-6	27.3	29.8	
Infarct site (%)			
Anterior	38.3	38.6	NS
Other	61.7	61.4	
Killip scale at randomization (%)			
I	83.4	83.8	
II	14.7	14.5	NS
III + IV	1.9	1.7	

p values compare selected versus excluded patients.

elevations ≥50% than was recombinant tissue-type plasminogen activator (rt-PA) (52.4% vs. 47.6%, p < 0.001). This finding, which is surprising in view of the reported higher

Table 2. Clinical Characteristics and Thrombolytic Regimen of the Selected Patient Population According to Noninvasive Detection of Acute Reperfusion

	Sum ST ≥50% (n = 1,309)	Sum ST <50% (n = 635)	p Value
Gender (%)			
Female	17.3	15.0	NS
Male	82.7	85.0	
Age (%)			
≤70 yr	83.0	82.1	NS
>70 yr	17.0	17.9	
Time interval (h) from onset of symptoms to randomization (%)			
0-3	72.4	73.5	NS
3-6	27.6	26.5	
Infarct site (%)			
Anterior	33.1	49.0	< 0.02
Other	66.9	51.0	
Killip class at randomization (%)			
I	84.4	81.4	
II	13.9	16.2	NS
III + IV	1.7	2.4	
Thrombolytic drug (%)			
SK	52.4	40.0	< 0.001
rt-PA	47.6	60.0	
Heparin (%)	51.4	46.9	NS

p values compare patients with sum of ST segment elevations (Sum ST) ≥50% versus patients with sum ST <50%. rt-PA = recombinant tissue-type plasminogen activator; SK = streptokinase.
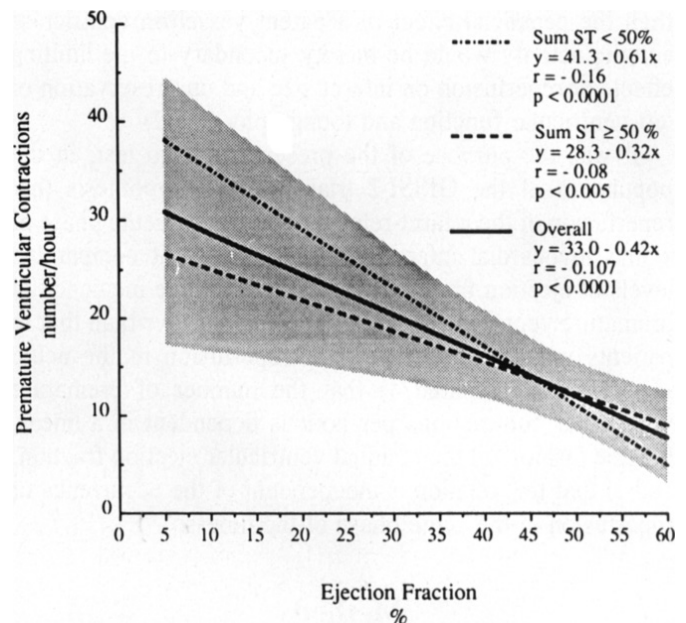
Figure 1. Regression of number of premature ventricular contractions per hour and ejection fraction in patients with reperfusion (sum of ST segment elevations [sum ST] ≥ 50%) and in patients without reperfusion (Sum ST < 50%) in the acute phase of the illness. There is a significant linear, inverse relation between the two variables in both groups. However, there is no statistical difference between the slopes of the two regression lines by the parallelism test (p = NS, both by analysis of covariance and t test), and the analysis of intercepts showed no statistical difference between the two regression lines. Thus, the relation between number of premature ventricular contractions per hour and ejection fraction can be adequately described by a single equation independently of the occurrence of reperfusion in the acute phase (95% confidence limits [shaded area]).

recanalization rate of rt-PA at 90 min (15), should be viewed simply as a snapshot at 4 h of the complex and time-variable process of postthrombolytic recanalization, in which differences between the two drugs at 90 min may no longer be evident at a later assessment (16). There was no difference between the two groups with regard to the use of heparin (51.4% vs. 46.9%, p = NS).

Ejection fraction, premature ventricular contractions and reperfusion. An ejection fraction ≤35% was present in 10.6% versus 15.3% of patients with and without reperfusion, respectively, in the acute phase (p < 0.01). However, the incidence of premature ventricular contractions was comparable between the two groups (≥10 premature ventricular contractions/h in 20.2% versus 20.8% of patients with and without reperfusion, respectively, in the acute phase [p = NS]). Because different degrees of impairment of ventricular pump performance could have a bearing on the number of premature ventricular contractions per hour, we tested the relation between premature ventricular contractions and ejection fraction in both groups (Fig. 1). There was a significant linear inverse relation between number of premature ventricular contractions per hour and ejection fraction both in patients with reperfusion (r = −0.08, p <

Table 3. Multiple Linear Regression Analysis of Number of Premature Ventricular Contractions per Hour With Group Characteristics*

	Coefficient	SE	t Value	p Value
EF	-0.39	0.09	-4.20	< 0.00001
Age†	0.53	0.10	5.50	< 0.00001
Gender	-4.56	2.89	-1.58	0.12
Infarct site	3.21	2.23	1.44	0.15
Time interval from onset of symptoms to randomization	0.67	2.32	0.29	0.77
Sum ST ≥50%	0.14	2.23	0.06	0.95
Killip scale	0.04	2.87	0.02	0.99
Constant	-2.33	8.50	-0.27	0.78

*Overall regression (r) was 0.17, with F = 8.10, p < 0.00001; the individual regression coefficients and their respective standard errors and t and p values are shown. EF = ejection fraction; MI = myocardial infarction; Sum ST = sum of ST segment elevations. †Expressed as a continuous variable. p values compare dependent versus independent variables.

0.005, y [premature ventricular contractions/h] = 28.3 − 0.32x [ejection fraction]) and those without reperfusion (r = −0.16, p < 0.0001, y [premature ventricular contractions/h] = 41.3 − 0.61x [ejection fraction]). There was no statistical difference, however, between the slopes of the two regression lines by the parallelism test (p = NS, both by analysis of covariance and t test), and subsequent analysis of the intercepts revealed no statistical difference between the two regression lines (p = NS, by both analysis of covariance and t test). Hence the relation between premature ventricular contractions and ejection fraction could be adequately described by a single equation (y [premature ventricular contractions/h] = 33.0 − 0.42x [ejection fraction], r = −0.107, p < 0.0001) (Fig. 1) independently of the occurrence of reperfusion in the acute phase.

A multivariate analysis was also performed to test the role of several independent variables (ejection fraction, age, gender, killip class, site of myocardial infarction, noninvasive detection of reperfusion and time interval from symptom onset to thrombolysis in determining the number of premature ventricular contractions per hour at predischarge Holter monitoring (Table 3). Of these variables only ejection fraction, together with age when considered as a continuous variable, was significantly correlated with the incidence of premature ventricular contractions (p < 0.00001 for both). No significant relation could be detected for the noninvasive detection of reperfusion (p = 0.95) or for the other variables (Table 3).

In conclusion, of the patients with an ejection fraction ≤35%, 30.2% with and 30.9% without reperfusion in the acute phase experienced ≥10 premature ventricular contractions/h at predischarge Holter monitoring. Of patients with an ejection fraction >35%, 19.0% in both groups experienced ≥10 premature ventricular contractions/h (p = NS).

Quality control. The kappa statistic showed satisfactory agreement between local and central evaluations. For ejec-

tion fraction, the overall proportion of agreement was 0.95, and the coefficient of agreement was 0.75. For number of premature ventricular contractions per hour, the overall proportion of agreement was 0.98, and the coefficient of agreement was 0.94.

Discussion

Although several studies have indeed shown that thrombolysis may decrease the incidence of ventricular arrhythmias and the prevalence of other markers of electrical instability of the infarcted heart (17,18), whether patency of the infarct-related vessel is in itself responsible for a reduced arrhythmogenic substrate in the infarcted ventricle is open to question. Previous studies (2-4,19-21), although largely supportive of a link between vessel patency and electrical stability of the heart, have not clearly defined the exact role of residual topography and pump performance on such stability and do not clearly distinguish between the impact of reperfusion on left ventricular function and on the electrophysiologic substrate alone. Our study, derived from the GISSI-2 data base, represents a further attempt to address this major topic in a large, randomized trial devoted to thrombolysis. Although the mean incidence of premature ventricular contractions, detected at predischarge Holter monitoring after an acute myocardial infarction, was not dissimilar in patients with or without early signs of reperfusion (12.4 ± 46.2 vs. 12.0 ± 45.8 premature ventricular contractions/h, respectively, p = NS), the frequency of ectopic beats depended in a linear, inverse fashion on the residual left ventricular pump performance in both groups, with slightly fewer premature ventricular contractions in the cohort with than without reperfusion when ejection fraction was <45% (Fig. 1). However, there was no significant difference between the slopes of the two regression lines, suggesting that such a relation would hardly be affected by the occurrence of acute reperfusion itself. Thus, patency of the infarct-related vessel would contribute to the improved electrical stability of the reperfused heart mainly through the beneficial impact of reperfusion on infarct size, which would minimize pump damage, rather than by a direct effect on the electrical stabilization of the infarcted heart.

Postmyocardial infarction arrhythmias and ventricular performance. Alternative explanations for the improved electrical stability of the reperfused heart must thus be found in the preservation of ventricular topography and pump performance. A study by Calkins et al. (10), in the dog model of healed myocardial infarction, suggested a link between ventricular remodeling with chamber dilation and electrical instability. That study showed a differential volume load-dependent shortening of refractoriness between normal and infarct zones of chronically infarcted canine hearts that increased the inducibility of sustained tachyarrhythmias at high volume (10). Although the exact mechanism could not be elucidated, these investigators suggested that the abnormal increase in wall stresses at the border zones of normal

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