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Effect of Thrombolysis on Heart Rate Variability and Life-Threatening Ventricular Arrhythmias in Survivors of Acute Myocardial Infarction

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Objectives. The aim of the present study was to determine the influence of early thrombolysis on ventricular tachyarrhythmias (clinical and inducible) and heart rate variability in survivors of myocardial infarction at high risk for life-threatening ventricular arrhythmias.

Background. A greater electrical heart stability may be important in improving survival in patients treated with thrombolysis. Few data are available about the influence of fibrinolysis on postinfarction arrhythmic events and other prognostic variables, such as inducible ventricular tachycardia and heart rate variability.

Methods. The study group comprised 51 consecutive patients who underwent electrophysiologic study within 30 days of infarction, owing to the presence of two or more of the following criteria: left ventricular ejection fraction <40%, late potentials and repetitive ventricular ectopic beats. Thirty patients underwent thrombolysis within 6 h of the onset of symptoms (Group A), and 21 received conventional treatment (Group B). Inducibility of sustained monomorphic ventricular tachycardia was tested in both groups, and the standard deviation of all normal RR intervals during 24-h Holter monitoring was calculated. All patients were prospectively evaluated for occurrence of arrhythmic events.

Results. The two groups were similar with regard to left ventricular ejection fraction (mean ± 1 SD 38 ± 6% [Group A] vs. 36 ± 8% [Group B]). Ventricular tachycardia was induced in 6 (20%) of 30 Group A patients versus 14 (67%) of 21 Group B patients ($p = 0.002$). The standard deviation of normal RR intervals was higher in Group A than in Group B (113 ± 36 vs. 90 ± 39 ms, $p = 0.05$). In patients with anterior infarction, the standard deviation of normal RR intervals was higher in 19 patients with thrombolysis than in 16 patients with conventional treatment (118 ± 41 vs. 74 ± 24 ms, $p = 0.0002$). During a mean follow-up period of 23 ± 11 months, 4 (13%) of 30 Group A patients had an arrhythmic event versus 9 (43%) of 21 Group B patients ($p = 0.04$).

Conclusions. After myocardial infarction, in high risk patients, thrombolysis significantly reduced the occurrence of arrhythmic events independently of left ventricular function. This effect may be related to both an improvement in electrical heart stability, as elucidated by electrophysiologic study, and a favorable action on the cardiac sympathovagal balance.

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It is well known that early fibrinolytic treatment during acute myocardial infarction reduces subsequent mortality, but it is unclear whether only improved left ventricular function or other factors contribute to this favorable effect (1). An increased electrical heart stability could have an important role (1), but the effect of fibrinolytic treatment on postinfarction arrhythmic events has not yet been defined. Reduced heart rate variability and inducibility of sustained monomorphic ventricular tachycardia at electrophysiologic study have been found to predict postinfarction arrhythmic events independently of left ventricular ejection fraction (2–8). If, after reperfusion, a change in arrhythmic propensity occurs, an influence of thrombolytic therapy on both the aforementioned risk markers may be expected. At present, the relation between intravenous thrombolysis and heart rate variability has not yet been investigated, and controversial data are available about the influence of fibrinolytic treatment on induced ventricular arrhythmias (9–13). We performed a prospective study of survivors of a recent myocardial infarction at high risk for late arrhythmic events to assess 1) the influence of thrombolysis on inducibility of sustained monomorphic ventricular tachycardia at programmed stimulation, 2) the influence of fibrinolysis on heart rate variability, 3) the influence of thrombolysis on postinfarction arrhythmic events, and 4) the hypothesis of an independent relation between limitation of infarct size and improvement of electrical heart stability after thrombolytic therapy.

Methods

Patient selection and study design. In the period from September 1989 to January 1992, 319 consecutive patients aged <70 years who survived an acute myocardial infarction were admitted to our institute within 30 days of the infarction

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for cardiac rehabilitation and underwent a standard risk stratification protocol to evaluate electrical heart instability. It included measurement of left ventricular ejection fraction by two-dimensional echocardiography, detection of ventricular late potentials by a signal-averaged electrocardiogram (ECG) and 48-h Holter monitor analysis for ventricular ectopic beats and heart rate variability. Signal-averaged ECG and Holter monitoring were performed in all patients in the drug-free state. The period of washout from digitalis, beta-adrenergic blocking agents, calcium antagonists and antiarrhythmic drugs was five or more times the plasma half-life of the drug. No patient had bundle branch block, atrial flutter or atrial fibrillation, ventricular paced rhythm, heart failure, unstable angina, poor echocardiogram, balloon angioplasty or coronary artery grafting before being admitted to our institute. Lown class 4a or b ventricular ectopic beats, late potentials and left ventricular ejection fraction <40% were defined noninvasive markers of arrhythmic risk. Those patients who had two or more of these risk factors were considered at high risk for arrhythmic events and were eligible for programmed ventricular stimulation after consent of both patient and attending physician. Of 319 patients, 71 (22%) were eligible for electrophysiologic testing, but programmed stimulation was performed only in 51 of these (72%). The 20 other patients, or their attending physicians, were unwilling to give informed consent. Thus, 51 patients comprise the study group. Clinical and demographic characteristics of both the study group and the 20 patients who refused to participate in the investigation are listed in Table 1. The study protocol was approved by the committee on human investigation at our institution.

All patients had follow-up contact by phone. A *late arrhythmic event* was defined as sudden death or the occurrence of symptomatic or sustained ventricular arrhythmia >5 days after infarction. *Sudden death* was defined as a witnessed, unexpected death occurring within 1 h of the onset of symptoms or during sleep. *Sustained ventricular arrhythmia* was defined as spontaneous ventricular fibrillation or tachycardia lasting >30 s or necessitating cardioversion because of hemodynamic collapse.

On hospital discharge, neither beta-blockers nor other antiarrhythmic drugs were prescribed routinely to patients with or without inducible ventricular tachycardia or high grade ventricular ectopic activity.

Thrombolytic therapy. The decision to treat a patient with a thrombolytic agent was made by the attending physician in the coronary care unit. Of 51 patients included in the study, 30 (59%) received intravenous thrombolysis (streptokinase [1.5 million U for 60 min] or recombinant tissue-type plasminogen activator [100 mg for 180 min]), and 21 (41%) were treated conventionally because of late hospital admission or contraindications to fibrinolytic treatment. Thrombolytic therapy was initiated within 6 h of the onset of symptoms. The mean time from symptom onset to initiation of thrombolysis was 110 ± 67 min.

Table 1. Clinical and Demographic Characteristics of Tested and Excluded Patients

	Tested (n = 51)	Excluded (n = 20)	p Value
Age (yr)	58 ± 7	55 ± 10	0.08
Male/female	47/4	16/4	0.20
Previous AMI	10 (20)	6 (30)	1.00
VF 0–5 days after AMI	8 (16)	4 (20)	1.00
Anterior AMI	35 (69)	10 (50)	0.23
Q wave AMI	49 (96)	16 (80)	0.05
Thrombolysis	30 (59)	11 (55)	0.97
LVEF (%)	37 ± 7	42 ± 5	0.008
Late potentials	32 (63)	17 (85)	0.12
QRS (ms)	110 ± 13	108 ± 12	0.53
RMS 40 (μV)*	13, 8, 31	13, 8, 17	0.88
LAS 40 (ms)	40 ± 12	43 ± 22	0.50
VPCs/h*	2.5, 0.45, 20.8	1.0, 0.35, 5.75	0.37
Paired VPCs	33 (65)	14 (70)	0.88
Unsustained VT	26 (51)	8 (40)	0.56
Mean RR interval (ms)	801 ± 110	828 ± 75	0.32
SDNN (ms)	103 ± 39	118 ± 27	0.19

*Median and lower and upper quartiles. Other values presented are mean value ± 1 SD or number (%) of patients. AMI = acute myocardial infarction; LAS 40 = duration of low-amplitude signals <40 μV; LVEF = left ventricular ejection fraction; QRS = duration of filtered QRS complex; RMS 40 = root-mean-square voltage of last 40 ms of filtered QRS complex; SDNN = standard deviation of normal RR intervals; VF = ventricular fibrillation; VPCs = ventricular premature complexes; VT = ventricular tachycardia.

Electrophysiologic study. Programmed ventricular stimulation was performed in the drug-free state 25 ± 8 days after infarction using a protocol we (8) have previously described. Up to three extrastimuli were introduced after 8 ventricular paced beats at three drive cycle lengths (600, 500 and 400 ms) in the right ventricular apex. Only the induction of sustained monomorphic ventricular tachycardia at a rate <270 beats/min was regarded as a positive result. Polymorphic ventricular tachycardia, ventricular fibrillation or unsustained arrhythmias were each regarded as nonspecific responses.

Heart rate variability assessment. Heart rate variability was computed over the 1st 24-h interval of Holter monitoring (recorded 21 ± 6 days after infarction). Each beat was characterized as normal or aberrant according to its recognition by the algorithm for tape analysis and after human overreading. Cycles in which beats had normal morphologic characteristics and cycle lengths within 20% duration of the preceding cycle length were measured. Periods with the highest and the lowest average RR intervals were always reviewed. To measure heart rate variability we used a Marquette Electronics software program, and the mean heart period and standard deviation of all normal RR intervals for 24 h were computed.

Echocardiographic studies. A two-dimensional echocardiogram was obtained using a Ving Med CFM 750 unit 16 ± 6 days after infarction, and evaluation of left ventric-

ular ejection fraction by the Simpson formula was performed.

Other diagnostic procedures. A signal-averaged ECG was recorded 20 ± 7 days after infarction using a commercially available system (Fidelity Medical LP 3000) whose principles and operation we (14) have previously described. The high pass filter was set at 40 Hz. Signals from 203 ± 55 beats were averaged to achieve a final noise level <0.5 μV. The normal values of a signal-averaged ECG were defined as follows: filtered QRS complex duration ≤114 ms, root-mean-square voltage of the last 40 ms of the filtered QRS complex ≥20 μV and duration of terminal low amplitude (<40 μV) signals ≤38 ms. Late potentials were considered present if two or more determinants of the signal-averaged ECG were abnormal. A 48-h Holter monitor recording 21 ± 6 days after infarction was analyzed with a Marquette Electronics Holter 8000 T. The following ventricular arrhythmia data were quantified for each tape: ventricular ectopic beats/h and the presence of both ventricular couplets and runs of unsustained ventricular tachycardia (run of ≥3 consecutive ventricular ectopic beats lasting <30 s).

Statistical analysis. Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov goodness-of-fit test for normality. When a normal distribution was observed, continuous variables were expressed as mean value ± 1 SD and compared by using the Student unpaired *t* test. When observed frequencies were significantly different from the expected normal distribution, continuous variables were expressed as median and lower and upper quartiles and were compared by using the nonparametric Mann-Whitney test. Discrete variables were compared by chi-square analysis with the Yates correction for continuity or the Fisher exact test. To assess the relation between heart rate variability and continuous variables, simple linear regression analysis was fitted. In all statistical tests, a two-tailed p value < 0.05 was required for statistical significance. A multifactor analysis of variance was used to assess the influence of age, left ventricular ejection fraction and previous infarction on the relation between heart rate variability and thrombolysis in patients with anterior wall myocardial infarction. All of these analyses were performed by the Statgraphics statistical package, version 4.0. Using the BMDP LR program (BMDP Statistical Software, 1990), logistic regression analysis was performed to determine which of five variables (see Appendix) contributed independent information to the prediction of both inducibility of sustained monomorphic ventricular tachycardia and occurrence of late arrhythmic events during follow-up. The BMDP LR program enters independent variables in a stepwise manner. The step selections are based on the maximal likelihood ratio. The p values used for entry and removal of variables were set at 0.05 and 0.1, respectively. At each step in the stepping process, log-likelihood, the change in the log-likelihood since the previous step and evaluations of the model using goodness of fit chi-square statistics were provided.

Results

Study group characteristics. We compared clinical and demographic characteristics of patients who were or were not studied in the present investigation. As shown in Table 1, only left ventricular ejection fraction was significantly different (p = 0.008) between the two groups of patients: It was lower in the study group.

Follow-up data. Follow-up data for all 51 patients were analyzed. At 23 ± 11 months after infarction, 13 patients (25%) developed a late arrhythmic event. Sustained ventricular tachycardia occurred in eight patients, sudden death in two and aborted sudden death with evidence of ventricular fibrillation at the time of cardioversion in three. Of 13 events, 10 (77%) occurred in the 1st 2 months after infarction (mean 29 ± 17 days, range 9 to 55); 3 (33%) were observed 6 to 18 months after infarction; and 9 (69%) occurred during the hospital period. Follow-up data for 20 excluded patients were also available. At 29 ± 9 months after infarction, four (20%) of these patients had an arrhythmic event. Sustained ventricular tachycardia occurred in two patients, sudden death in one, and aborted sudden death in one. When arrhythmic event rate was compared between tested and nontested patients, no significant difference was found in the total number of arrhythmic events (13 [25%] of 51 vs. 4 [20%] of 20, p = 1.00) or the occurrence of arrhythmic events before study selection (4 [31%] of 13 vs. 2 [50%] of 4, p = 1.00).

Prescription of beta-blocker and antiarrhythmic drug therapy. Most arrhythmic events (9 of 13) occurred during the hospital period. During this period, patients with and without events were undergoing pharmacologic washout from antiarrhythmic drugs and beta-blockers. At hospital discharge, empiric antiarrhythmic therapy was administered by the attending physician to 11 (26%) of 42 asymptomatic patients (mexiletine in 5, amiodarone in 6) because of inducible, sustained ventricular arrhythmias. Two (18%) of 11 patients receiving antiarrhythmic drugs had arrhythmic events compared with 2 (6%) of 31 without (p = 1.00). At hospital discharge, beta-blockers were prescribed in 5 (12%) of 42 asymptomatic patients owing to residual ischemic symptoms or hypertension. None of 5 patients with beta-blockers developed arrhythmic events compared with 4 (11%) of 37 without (p = 1.00).

Comparison of patients with and without inducibility of sustained monomorphic ventricular tachycardia at programmed ventricular stimulation. Of 51 patients tested by programmed ventricular stimulation, 20 (39%) had positive findings on electrophysiologic study because sustained monomorphic ventricular tachycardia at a rate <270 beats/min was inducible. Of the variables listed in Table 2, the following had a significant relation to the inducibility of sustained monomorphic ventricular tachycardia: thrombolysis (p = 0.002), left ventricular ejection fraction (p = 0.001) and filtered QRS complex duration (p = 0.03).

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Table 2. Characteristics of Patients With and Without Inducible Sustained Monomorphic Ventricular Tachycardia at Programmed Ventricular Stimulation

	Sustained Monomorphic VT at Programmed Stimulation		
	Present (n = 20)	Absent (n = 31)	p Value
Age (yr)	61 ± 7	58 ± 6	0.13
Male/female	19/1	28/3	1.00
Previous AMI	5 (25)	5 (16)	1.00
VF 0–5 days after AMI	3 (15)	5 (16)	1.00
Anterior AMI	16 (80)	19 (61)	0.18
Q wave AMI	19 (95)	30 (97)	1.00
Thrombolysis	6 (30)	24 (77)	0.002
LVEF (%)	33 ± 7	39 ± 6	0.001
Late potentials	13 (65)	19 (61)	1.00
QRS (ms)	115 ± 13	107 ± 11	0.03
RMS 40 (μV)*	15, 6, 30	13, 8, 33	0.85
LAS 40 (ms)	40 ± 14	40 ± 11	0.92
VPCs/h*	2.14, 0.43, 11.55	6.67, 1.04, 72.08	0.18
Paired VPCs	10 (50)	23 (74)	0.14
Unsustained VT	11 (55)	15 (48)	0.86
Mean RR interval (ms)	782 ± 109	819 ± 117	0.26
SDNN (ms)	90 ± 36	112 ± 38	0.06

*Median and lower and upper quartiles. Other values presented are mean value ± 1 SD or number (%) of patients. Abbreviations as in Table 1.

Comparison of patients with and without late arrhythmic events. Of the variables listed in Table 3, the following had a significant relation to late arrhythmic events: thrombolysis (p = 0.04), left ventricular ejection fraction (p = 0.0005) and the standard deviation of normal RR intervals (p = 0.03). Inducibility of sustained monomorphic ventricular tachycardia at a rate <270 beats/min was strongly related to postinfarction arrhythmic events. Late arrhythmic events occurred in 12 (60%) of 20 patients with positive, compared with 1 (3%) of 31 with negative findings on electrophysiologic study (p = 0.0002). In the group with thrombolysis, time from symptom onset to initiation of fibrinolysis was significantly longer in 4 patients with arrhythmic events than in 26 patients without arrhythmic events (184 ± 94 vs. 97 ± 63 min, p = 0.02).

Table 3. Characteristics of Patients With and Without Arrhythmic Events

	Events (n = 13)	No Events (n = 38)	p Value
Age (yr)	60 ± 7	58 ± 6	0.56
Male/female	12/1	35/3	1.00
Previous AMI	4 (31)	6 (16)	1.00
VF 0–5 days after AMI	1 (8)	7 (18)	1.00
Anterior AMI	11 (85)	24 (63)	1.00
Q wave AMI	12 (92)	37 (97)	1.00
Thrombolysis	4 (31)	26 (68)	0.04
LVEF (%)	32 ± 7	39 ± 6	0.0005
Late potentials	8 (61)	24 (63)	1.00
QRS (ms)	113 ± 12	109 ± 13	0.28
RMS 40 (μV)*	17, 7, 41	13, 8, 30	0.60
LAS 40 (ms)	37 ± 15	41 ± 11	0.36
VPCs/h*	1.79, 0.45, 14.1	4.66, 0.8, 64.77	0.41
Paired VPCs	9 (69)	24 (63)	1.00
Unsustained VT	7 (54)	19 (50)	1.00
Mean RR interval (ms)	760 ± 83	820 ± 121	0.09
SDNN (ms)	84 ± 33	111 ± 38	0.03

*Median and lower and upper quartiles. Other values presented are mean value ± 1 SD or number (%) of patients. Abbreviations as in Table 1.

Multivariate analysis. The results of stepwise logistic regression analysis are shown in Table 4. Of the five variables listed in the Appendix, only left ventricular ejection fraction and thrombolysis were found to be independent predictors of both inducibility of sustained monomorphic ventricular tachycardia and occurrence of postinfarction arrhythmic events.

Comparison of patients with and without thrombolytic therapy. We compared the characteristics of patients who received thrombolysis with those of patients treated conventionally. Of the variables listed in Table 5, only filtered QRS complex duration on the signal-averaged ECG was different between the two groups of patients. It was significantly (p = 0.02) lower after thrombolysis.

Relations among heart rate variability, thrombolytic therapy and other variables. The standard deviation of all normal RR intervals for 24 h was higher in patients with thrombolysis than in conventionally treated patients (113 ± 36 vs. 90 ± 39 ms); the statistical analysis showed a borderline p value (p = 0.05) (Fig. 1). No significant difference was observed between the two groups of patients with regard to the mean heart period (818 ± 115 vs. 785 ± 113 ms, p = 0.30). We evaluated the relation between heart rate variability and other variables that are known to influence the sympathovagal interaction after acute myocardial infarction (15–18). The standard deviation of all normal RR intervals for 24 h had a significant linear relation with both age (r = −0.42, p = 0.003) and left ventricular ejection fraction (r = 0.46, p = 0.001). Heart rate variability was significantly lower in 10 patients with a previous infarction than in 41 patients without a previous infarction (80 ± 29 vs. 109 ± 38 ms, p = 0.03). Heart rate variability was not related to infarct site. No significant difference was found between 35 patients with anterior wall infarction and 16 patients with inferior wall infarction (100 ± 40 vs. 111 ± 32 ms, p = 0.50). Because only two patients had a non-Q wave infarction, the relation between Q wave development and heart rate variability was not assessed.

Relation between heart rate variability and thrombolytic therapy in patients with anterior wall myocardial infarction. Because patients with anterior wall myocardial infarction and low ejection fraction are known to be at high risk for arrhythmic events, especially when a left ventricular aneurysm is present (12), we analyzed the influence of thrombolysis on heart rate variability in 35 patients with anterior infarction. Of these, 18 (51%) had a left ventricular aneurysm, and mean left ventricular ejection fraction was 34 ± 5%. Both standard deviation of all normal RR intervals

Table 4. Summary of Stepwise Logistic Regression Analysis

Step No.	Term Entered	Term Removed	Degrees of Freedom	Log of Likelihood	Improvement Chi-Square	Improvement p Value	Goodness of Fit Chi-Square	Goodness of Fit p Value
Dependent Variable: Inducibility of Sustained Monomorphic VT at Programmed Stimulation								
0				−30.301			60.603	0.060
1	LVEF		1	−25.655	9.292	0.002	51.310	0.209
2	Thrombolysis		1	−22.590	6.131	0.013	45.179	0.381
Dependent Variable: Occurrence of Late Arrhythmic Events								
0				−27.388			54.777	0.151
1	LVEF		1	−20.067	14.643	0.000	40.134	0.638
2	Thrombolysis		1	−17.714	4.705	0.030	35.429	0.787

Abbreviations as in Table 1.

(118 ± 41 vs. 74 ± 24 ms, p = 0.0002) (Fig. 2) and mean heart period (807 ± 83 vs. 739 ± 85 ms, p = 0.04) were significantly higher in 19 patients treated with thrombolysis than in 16 patients who received conventional therapy. Left ventricular ejection fraction was higher after thrombolysis (36 ± 5% vs. 32 ± 4%); statistical analysis showed a borderline p value (p = 0.05). A multifactor analysis of variance was performed in patients with anterior infarction to assess the effects of three covariates (age, left ventricular ejection fraction and previous infarction) on the relation between thrombolysis and heart rate variability. After allowing for these possible influences, heart rate variability was still significantly (p = 0.03) related to thrombolytic therapy (Table 6).

Discussion

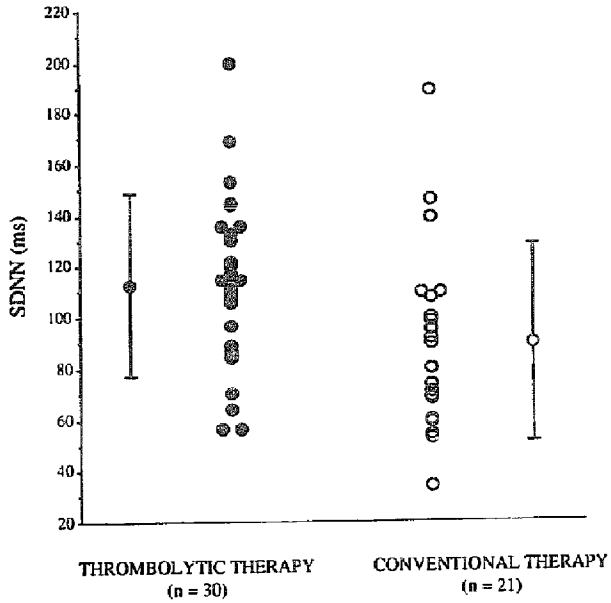
Thrombolytic therapy and arrhythmogenic propensity after acute myocardial infarction. An extremely low mortality rate was observed in patients with reperfusion compared with the rate in those without (1). This finding contrasts strikingly with the relatively modest changes in left ventricular function observed between the two groups of patients. The mechanism responsible for reduced mortality after fibrinolysis has not yet been examined (19), and previous studies suggest that improvement in electrical heart stability could be important in increasing survival in patients after reperfusion (9,12,13). The crucial determinant of predisposition to ventricular tachycardia or fibrillation (and sudden death) is the capacity to sustain ventricular tachycardia or fibrillation in the presence of an arrhythmogenic substrate and spontaneous ventricular ectopic beats. Inducibility of sustained monomorphic ventricular tachycardia during electrophysiologic study seems to be marker for that determinant (4–8). If a change in electrophysiologic milieu after thrombolytic therapy occurs, a favorable action of reperfusional therapy on inducibility of sustained ventricular tachy-

Table 5. Characteristics of Patients With and Without Thrombolytic Therapy

	Thrombolysis (n = 30)	No Thrombolysis (n = 21)	p Value
Age (yr)	58 ± 6	60 ± 7	0.45
Male/female	28/2	19/2	1.00
Previous AMI	4 (13)	6 (28)	0.28
VF 0–5 days after AMI	5 (17)	3 (14)	1.00
Anterior AMI	19 (63)	16 (76)	0.36
Q wave AMI	29 (97)	20 (95)	1.00
LVEF (%)	38 ± 6	36 ± 8	0.31
Late potentials	16 (53)	16 (76)	0.17
QRS (ms)	107 ± 12	115 ± 11	0.02
RMS 40 (μV)*	14, 10, 40	13, 7, 17	0.09
LAS 40 (ms)	37 ± 12	43 ± 11	0.07
VPCs/h*	7.1, 0.6, 47.7	2.5, 0.4, 14.1	0.37
Paired VPCs	21 (70)	12 (57)	0.51
Unsustained VT	17 (57)	9 (43)	0.49

*Median and lower and upper quartiles. Other values presented are mean value ± 1 SD or number (%) of patients. Abbreviations as in Table 1.

Figure 1. Effect of thrombolytic therapy on standard deviation of all normal RR intervals (SDNN) for 24 h. The group mean value ± 1 SD is displayed adjacent to scatter plot data. Standard deviation of normal RR intervals was higher (p = 0.05) after thrombolysis.



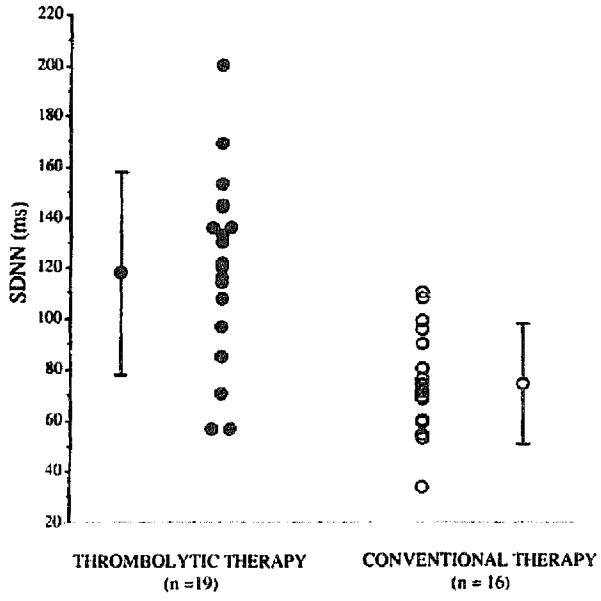


Figure 2. Effect of thrombolytic therapy on standard deviation of all normal RR intervals (SDNN) for 24 h in patients with anterior wall myocardial infarction. The group mean value ± 1 SD is displayed adjacent to scatter plot data. A strong ($p = 0.0002$) improvement in standard deviation of normal RR intervals was found in patients treated with thrombolysis.

arrhythmias may be hypothesized. Controversial data are available concerning this point. Kersschot et al. (9), Sager et al. (12) and Bourke et al. (13) found a lower rate of inducibility after thrombolytic therapy, whereas Treese et al. (10) did not. Moreover, in the study of McComb et al. (11), successful reperfusion by thrombolytic agents did not influence inducibility of sustained ventricular tachycardia. In patients preselected by noninvasive techniques, with a high event rate during follow-up, the present investigation showed that a significantly lower proportion of patients had inducible, sustained monomorphic ventricular tachycardia after thrombolysis. Because inducibility of sustained monomorphic ventricular tachycardia during electrophysiologic study strongly predicts the occurrence of arrhythmic events after myocardial infarction (4–8), the evidence of a lower inducibility rate in patients treated with thrombolysis could have clinical relevance.

The signal-averaged ECG allows the noninvasive detection of late potentials at the end or after the QRS complex (20). Late potentials represent low amplitude fractionated electrical activity and are markers for an arrhythmogenic substrate that may become the site for reentry (21) and provide important prognostic information in identifying patients at risk for arrhythmic events after acute myocardial infarction (4,8,22–25). Several studies found a significantly lower prevalence of late potentials after thrombolysis (14,26–29). Moreover, a significant correlation between patency of the infarct-related coronary artery and reduced prevalence of late potentials was found (14,26–29), and the status (patency or occlusion) of the infarct-related artery appeared to be the strongest independent predictor of late potentials on the signal-averaged ECG (14,26,28). In the present investigation, in a high risk group of patients, thrombolysis significantly reduced filtered QRS duration, the most important of the signal-averaged ECG determinants (8,23,25). This finding could have particular relevance. In fact, in other reports the relation between signal-averaged ECG abnormalities and thrombolysis was analyzed in unselected groups of patients (14,26–29). Our finding may reflect a lower mass of myocardium with inhomogeneous propagation of conduction in patients treated with thrombolysis and is in agreement with the lower prevalence of inducible, sustained monomorphic ventricular tachycardia. Both of these results were obtained despite the failure of thrombolytic therapy to significantly improve global left ventricular function and could be related to the status of the infarct-related artery.

Thrombolytic therapy and heart rate variability after acute myocardial infarction. Calculating the standard deviation of all normal RR intervals, Kleiger et al. (2) found that heart rate variability was a significant independent predictor of mortality in the 1st year after acute myocardial infarction. Some frequency domain measures of heart period variability were significantly associated with both all-cause mortality and arrhythmic death (3). At present, the influence of thrombolytic therapy on autonomic function has not been widely examined. Casolo et al. (18) have evaluated heart rate variability during the early phase of myocardial infarction to study its changes over time and its relation with clinical and

Table 6. Results of Multifactor Analysis of Variance

Source of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F Ratio	p Value
Covariates	14,276.245	3	4,758.7482	4.141	0.01
LVEF	6,795.483	1	6,795.4828	5.913	0.02
Age (yr)	1,851.887	1	1,851.8869	1.611	0.21
Previous AMI	958.261	1	958.261	0.834	0.37
Main effects	6,062.6799	1	6,062.6799	5.275	0.03
Thrombolysis	6,062.6799	1	6,062.6799	5.275	0.03
Residual	29,880.043	26	1,149.2324		
Total	50,218.968	30			

Abbreviations as in Table 1.

instrumental data available in the coronary care unit. These investigators pointed out a greater 24-h standard deviation in patients receiving thrombolytic therapy related to a higher left ventricular ejection fraction (18). However, multivariate analysis was not performed. The present investigation showed a favorable effect of thrombolysis on heart rate variability, especially in patients with anterior wall infarction and low left ventricular ejection fraction, who represent a group with a very high risk for late arrhythmic events (12). Moreover, when adjusted for age, ejection fraction and previous infarction, the standard deviation of all normal RR intervals was still significantly influenced by thrombolysis. This previously unreported finding suggests that in patients with a low left ventricular ejection fraction who are at high risk for arrhythmic events, thrombolytic therapy could induce an improvement in autonomic function that is independent of infarct size limitation. Because the autonomic dysfunction is of primary importance in determining life-threatening ventricular tachyarrhythmias after myocardial infarction, our finding may have clinical relevance.

Thrombolytic therapy and late arrhythmic events after acute myocardial infarction. Previous studies (9,12–14,26–29) and the present investigation showed a significant reduction in invasive and noninvasive risk markers in patients receiving thrombolytic therapy, suggesting reduced ventricular electrical instability. After thrombolysis we found a significantly lower prevalence of arrhythmic events at a mean follow-up interval of 23 months. This finding is in agreement with data of Sager et al. (12), who found that early thrombolytic therapy resulted in improved arrhythmic outcome in patients with a transmural anterior myocardial infarction and subsequent left ventricular aneurysm formation. Moreover, in our high risk patients multivariate analysis showed that thrombolytic therapy was a significant predictor of arrhythmic events, independent of left ventricular ejection fraction. Nevertheless, ejection fraction was more significant than thrombolysis as a predictor of late arrhythmic events, probably because the reopening of the infarct-related coronary artery, not thrombolytic therapy itself, may exert a protective effect on postinfarction ventricular electrical instability. A recent study strongly supports this hypothesis (30). Horvitz et al. (30) analyzed the influence of infarct-related artery patency on appropriate shock-free survival in 54 patients with a left ventricular aneurysm and lethal arrhythmias who received an impiantable defibrillator. These investigators found a trend toward improved shock-free survival in the patients with an aneurysm and an open infarct-related artery and suggested a potential therapeutic role for a patent infarct-related vessel in subsequent malignant ventricular arrhythmias. We found that the timing of the administration of thrombolytic agents influenced the arrhythmic event rate. Therefore, the time from symptom onset to initiation of thrombolytic therapy could influence heterogeneity of myocardial injury and the subsequent development of an arrhythmogenic substrate (31). Benefit occurred in patients who received therapy earlier, probably because higher rates of reperfusion can be achieved by early administration of thrombolytic agents (32).

Mechanisms of reduction of electrical heart instability by thrombolytic therapy. Because the structure of the border zone is a critical determinant of arrhythmogenesis after myocardial infarction (13), one can hypothesize that reperfusion of the infarct-related coronary artery may cause some favorable changes in the border zone. Thrombolytic therapy may reduce ischemia, facilitate focal hemorrhage (33) and induce alterations in the electrophysiologic characteristics of the border zone myocardial cells. All of these effects may suppress slow and inhomogeneous conduction that supports reentrant ventricular tachyarrhythmias. Moreover, reperfusion may influence the remodeling process (34), making the establishment of a functional arrhythmic circuit unlikely. The effect on the remodeling process may be important in explaining the improvement induced by thrombolysis in heart rate variability because the remodeling of the left ventricle may increase the firing of sympathetic afferent fibers by mechanical distortion of the sensory endings (35).

Study limitations. We examined a well defined cohort of patients, and it is possible that our results are not applicable to other groups of patients, especially those with uncomplicated myocardial infarction. This was not a randomized investigation. Because thrombolysis clearly improves survival in patients with acute myocardial infarction, particularly those with a larger infarct size, withholding such therapy for research purposes would be unethical. Coronary angiography was not available, and this represents an important limitation of the study. Results would be strengthened by the addition of angiographic data concerning patency of the infarct-related artery.

This was an uncontrolled study. Thus, it is possible that the use of antiarrhythmic drugs influenced the arrhythmic event rate. A greater proportion of patients with than without an arrhythmic event were receiving antiarrhythmic drug therapy, but this difference did not reach statistical significance. In the present investigation, beta-blockers were infrequently used, probably because most patients had a low left ventricular ejection fraction. It is impossible at present to exclude the effects of infrequent use of beta-blockers on the arrhythmic event rate. However, statistical analysis did not find a significant difference in event occurrence between patients with and without beta-blockade.

Of patients suitable for electrophysiologic study, only a proportion (72%) underwent programmed ventricular stimulation. Statistical analysis found that the patients tested were similar to those excluded for all arrhythmic risk markers except ejection fraction, which was significantly lower in patients who consented to undergo the study. The proportion of patients with an arrhythmic event before study selection was similar between the two groups. Although arrhythmic event frequency and other prognostic variables did not influence patient selection, referring physicians or patients were more likely to accept performance of the study if a large infarct had occurred. Therefore, doubt must exist

as to the applicability of these results to our patients, who were preselected by noninvasive tests, as a whole.

Appendix

Variables Used in Stepwise Logistic Regression Analysis

Variables used in stepwise logistic regression analysis were those that reached a p value < 0.10 at univariate statistical analysis: thrombolytic therapy, left ventricular ejection fraction, filtered QRS complex duration, standard deviation of all normal RR intervals for 24 h and mean heart period.

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