Original articles

Effect of primary percutaneous coronary intervention versus thrombolysis on ventricular arrhythmias and heart rate variability in acute myocardial infarction

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Key words:
Arrhythmias, ventricular; Heart rate variability; Myocardial infarction; Primary coronary intervention; Thrombolysis.

Background. **Several studies showed that thrombolysis reduces ventricular arrhythmias and improves heart rate variability (HRV) in patients with acute myocardial infarction (AMI). Primary percutaneous coronary intervention (PCI) has recently become the treatment of choice for AMI, but it is still unknown whether it has favorable effects on these prognostic variables.**

Methods. **We studied a group of 44 consecutive AMI patients (39 males, 5 females, mean age 59 ± 9 years) submitted to primary PCI and 93 consecutive AMI patients (80 males, 13 females, mean age 61.0 ± 11 years) treated with thrombolytic therapy within 6 hours of symptom onset. All patients underwent 24-hour Holter recording before discharge.**

Results. **The number of premature ventricular beats and the prevalence of non-sustained ventricular tachycardia in the 24 hours were lower in the PCI group (162 ± 474 and 9%, respectively) than in the thrombolysed group (334 ± 1730 and 14%, respectively), but the difference did not achieve statistical significance (p = 0.62 and p = 0.58, respectively). There were also no significant differences in HRV variables between the two groups, although a lower proportion of PCI patients tended to have bottom quartile values of HRV variables. The favorable trend for arrhythmias and HRV in PCI patients, however, seemed to be related to a worse basal clinical profile of thrombolysed patients, including a higher prevalence of previous AMI (14 vs 2%, p = 0.065), diabetes (27 vs 18%, p = 0.14) and, in particular, a lower use of beta-blockers (35 vs 93%, p < 0.001).**

Conclusions. **In this study, we failed to show any significant benefit of primary PCI compared to thrombolysis on ventricular arrhythmias and HRV in patients with ST-segment elevation AMI. The clinical implications of these findings deserve investigation in future studies.**

(Ital Heart J 2005; 6 (8): 629-633)

Received February 1, 2005; revision received March 23, 2005; accepted March 24, 2005.

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Ventricular arrhythmias and impaired cardiac autonomic function, as assessed by heart rate variability (HRV) analysis, have been shown to be predictors of death in patients with a recent acute myocardial infarction (AMI), both in the pre-thrombolytic and thrombolytic era[1-8]. Previous studies also showed that successful reperfusion in AMI patients treated with thrombolytic drugs was associated with a lower prevalence of ventricular arrhythmias and with better HRV indices[9-11], which may contribute to the prognostic benefits of thrombolysis.

Primary percutaneous coronary intervention (PCI) has recently become, wherever possible, the treatment of choice for AMI, being associated with a significant higher rate of coronary recanalization and a lower incidence of global cardiac events at follow-up, when compared with optimal medical therapy[12-17]. However, the favorable effect on mortality remains debated when compared with timely performed thrombolysis[15-17]. In fact, it is poorly known whether PCI improves the clinical risk profile of AMI patients, according to variables demonstrated to be predictive of survival in the pre-PCI era.

In this study we investigated whether PCI reduced ventricular arrhythmias and improved HRV in patients with ST-segment elevation AMI, compared to a control group of patients treated with thrombolytic drugs. Since thrombolysis is no longer used to treat AMI at our Institute, this latter group was represented by historical patients included in a previous study assessing the prognostic value of HRV in AMI patients[7].

Methods

Study groups. The PCI group included 44 consecutive patients (39 males, 5 females,

mean age 59 ± 9 years) admitted to hospital with an AMI who were submitted to primary PCI within 6 hours of symptom onset and were alive at discharge. AMI was diagnosed according to prolonged (> 30 min) chest pain and persistent ST-segment elevation in two or more ECG leads and was confirmed by typical variations in serum cardiac enzymes.

Patients who underwent rescue PCI or primary PCI after more than 6 hours from symptom onset were excluded from this study. Patients with cardiac rhythm abnormalities (e.g., atrial fibrillation, pacemaker rhythm, frequent premature supraventricular beats) which made unreliable HRV analysis were also excluded.

The group of thrombolysis included 93 consecutive patients surviving an AMI (80 males, 13 females, mean age 61.0 ± 11 years), who had undergone intravenous thrombolytic therapy (either recombinant tissue-type plasminogen activator or streptokinase) within 6 hours of symptom onset and had been studied before discharge by Holter monitoring using the same method and software of analysis as PCI patients[7]. These patients constituted the whole subgroup of AMI patients who had received thrombolysis enrolled in a previous study on the prognostic role of HRV[7].

The following variables were recorded for each patient of either group: age, gender, ECG site of AMI, history of diabetes, history of previous AMI, peak of creatine kinase and beta-blocker therapy at the time of Holter recording. Left ventricular ejection fraction was assessed before discharge at two-dimensional echocardiography (Simpson method) in 87 (93.5%) and 39 (92.8%) patients of the thrombolysis and PCI groups, respectively.

Holter monitoring. All patients underwent 24-hour ECG Holter recording before discharge. Holter monitoring was performed 3 to 7 days (median 5 days) after AMI in PCI patients and 4 to 10 days (median 6 days) after AMI in thrombolysed patients. A 3-channel digital Holter recorder (Oxford Medilog FD5) was used to monitor the bipolar chest leads CM5, CM3 and modified aVF in PCI patients whereas a 2-channel tape recorder (Oxford Medilog MR-45) had been used to monitor two bipolar chest leads (CM5 + CM3 or modified aVF) in thrombolysed patients.

Holter recordings were analyzed by experienced cardiologists using the Oxford Excel 3.0 device (Oxford Medilog, Abingdon, UK). For each patient we recorded the average 24-hour RR interval, and the number of premature ventricular beats (PVBs), couplets of PVBs and episodes of non-sustained ventricular tachycardia (defined as ≥ 3 PVBs with a rate ≥ 100 b/min).

HRV was analyzed both in the time domain and in the frequency domain by the version 7.0 Oxford HRV analysis package. Frequency-domain HRV was assessed in the range of frequencies 0 to 0.5 Hz by a fast Fourier transform spectral analysis algorithm, with a spectral resolution of 0.0005 Hz. As long-term and short-term time domain variables we obtained the standard deviation of all RR intervals (SDNN) and the mean of the standard deviations of all RR intervals for all 5-min segments (SDNNi), respectively. As a measure of long-term frequency-domain HRV we obtained the very-low frequency (VLF, 0.0033-0.04 Hz) amplitude, whereas the amplitudes of the low frequency (LF, 0.04-0.15 Hz) and of the high frequency (HF, 0.15-0.40 Hz) components of the spectrum were obtained as short-term frequency-domain variables. The LF/HF ratio was also calculated for each patient.

Statistical analysis. Continuous variables were compared by the unpaired Student's t-test or, in case of a distribution significantly different from normal, as assessed by the Kolmogorov-Smirnov test, by the Mann Whitney U-test. Proportions were compared by the Fisher exact test.

Data are reported as average ± SD. A p value of < 0.05 was required for statistical significance. Statistical analyses were performed using the SPSS 12.02 statistical package.

Results

Clinical findings. The main clinical characteristics of PCI and thrombolysed patients are summarized in table I. The two groups were similar in age, gender and site of AMI. Primary PCI patients had a higher peak of creatine kinase ($p = 0.02$), likely related to the more rapid restoration of coronary blood flow. Thrombolysed patients, on the other hand, tended to have a higher prevalence of diabetes and of previous AMI, and were less frequently being treated with beta-blocker therapy ($p < 0.001$).

Ventricular arrhythmias and heart rate variability. Although there was a tendency to a reduction of ventricular arrhythmias in PCI patients, there were no significant differences in the number of PVBs as well as in the occurrence of repetitive forms of PVBs between the two groups (Table II).

Similarly, no significant differences were found in average values of HRV parameters between the two groups at univariate analysis (Table II), although SDNNi tended to be lower in PCI patients compared to thrombolysed patients (48 ± 19 vs 57 ± 31 ms, $p = 0.06$).

When considering the proportion of patients with bottom quartile values of HRV parameters, no statistically significant differences were also found between the two groups, although a lower proportion of PCI patients tended to present bottom quartile values of HRV parameters (Fig. 1).

Table I. Main clinical characteristics of the two groups of patients.

	PCI	Thrombolysis	p
No. patients	44	93	
Age (years)	59 ± 9	61 ± 11	0.18
Gender			0.88
Male	39 (89%)	80 (86%)	
Female	5 (11%)	13 (14%)	
Site of AMI			0.40
Anterior/lateral	20 (45%)	51 (55%)	
Inferior/lateral	24 (55%)	42 (45%)	
CK peak (IU/l)	3003 ± 3620	1880 ± 1385	0.02
Diabetes	8 (18%)	25 (27%)	0.14
Previous AMI	1 (2%)	12 (14%)	0.065
LVEF < 40%	6 (15%)	13 (15%)	0.99
Beta-blockers	41 (93%)	24 (35%)	< 0.001

AMI = acute myocardial infarction; CK = creatine kinase; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Table II. Ventricular arrhythmias and heart rate variability results in the two groups of patients.

	PCI (n=44)	Thrombolysis (n=93)	p
Ventricular arrhythmias			
PVB/24 hours	162 ± 474	334 ± 1730	0.62
PVB > 10/hour (%)	5 (11%)	15 (16%)	0.61
NSVT	4 (9%)	13 (14%)	0.58
Repetitive ventricular arrhythmias*	11 (27%)	30 (32%)	0.43
HRV variables			
Time domain			
RR (ms)	882 ± 108	866 ± 133	0.49
SDNN (ms)	102 ± 31	109 ± 42	0.36
SDNNi (ms)	47 ± 19	57 ± 31	0.06
Frequency domain			
VLF (ms)	46 ± 55	38 ± 16	0.18
LF (ms)	20 ± 9	20 ± 11	0.86
HF (ms)	14 ± 10	14 ± 11	0.99
LF/HF ratio	1.62 ± 0.4	1.53 ± 0.5	0.28

HF = high frequency; HRV = heart rate variability; LF = low frequency; PCI = percutaneous coronary intervention; PVB = premature ventricular beats; NSVT = non-sustained ventricular tachycardia; SDNN = standard deviation of all RR intervals; SDNNi = mean of the standard deviations of all RR intervals for all 5-min segments; VLF = very low frequency. * PVB couplets and/or NSVT.

Discussion

In this study we failed to find a significant improvement of ventricular arrhythmias and cardiac autonomic function by primary PCI, as compared with thrombolysis, in patients with ST-segment elevation AMI treated within 6 hours of symptom onset.

Percutaneous coronary intervention versus thrombolysis. Several studies have demonstrated the significant role of ventricular arrhythmias and of low HRV in predicting prognosis in patients with a recent AMI[1-8], but they were carried out before the coming of primary PCI. In fact, primary PCI is now considered, whenever possible, the treatment of choice for AMI, being able to achieve a quick and effective restoration of coronary blood flow in more than 95% of patients. Thrombolytic therapy, on the other hand, has been shown to be effective in restoring coronary blood flow in no more than 75% of cases[18].

In spite of the great diffusion of primary PCI and of data showing a better clinical outcome of this form of treatment compared to thrombolysis, there have been no studies evaluating whether primary PCI improves variables known to be of prognostic value in AMI patients in the pre-PCI era.

In our study, primary PCI, as compared with a historical group of patients treated with thrombolysis, did not show any significant benefit on the prevalence and characteristics of ventricular arrhythmias. Similarly, we could not show any significant improvement of HRV variables by primary PCI.

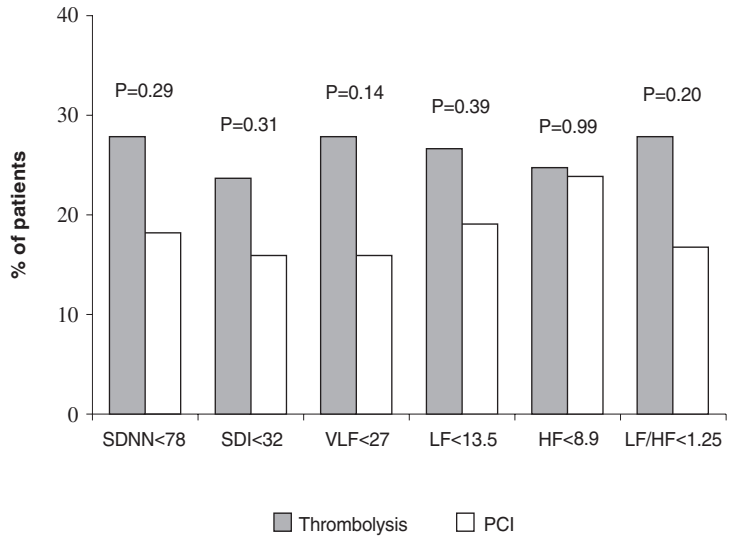

Figure 1. *Proportion of patients treated with thrombolysis or submitted to percutaneous coronary intervention (PCI) with values of heart rate variability parameters in the bottom quartile, as derived in the whole study population. HF = high frequency; LF = low frequency; SDNN = standard deviation of all RR intervals; SDI = mean of the standard deviations of all RR intervals for all 5-min segments; VLF = very low frequency.*

Our data, however, should be interpreted with caution, as they were obtained in a limited number of patients, which may have precluded the achievement of statistical significance for differences. In fact, it can be noticed that the number of PVBs and the prevalence of repetitive forms of ventricular arrhythmias tended to be lower in the group of patients submitted to primary PCI. In fact, statistical assessment indicated that, with regard to the proportion of patients with frequent premature ventricular complexes, we would have needed 750 patients per group to have a power of 80% to detect as significant a difference between the two groups equal to or higher than that observed in our study (16 vs 11% in thrombolysed and PCI patients, respectively).

Moreover, despite the tendency to lower average values of some HRV parameters (Table II), a non-significant lower proportion of patients with bottom quartile values was consistently found among PCI patients, compared to thrombolysed patients, for all HRV parameters, suggesting a more favorable risk profile. Also in this case, however, our study was underpowered. Indeed, taking into account the VLF, which showed the highest difference between the two groups among patients with bottom quartile values, we calculated that 185 patients per group would have needed to have a power of 80% to detect as significant a difference between the two groups equal to or higher than that observed in our study (28 vs 16% in thrombolysed and PCI patients, respectively).

However, it should also be observed that the tendency to improvement of ventricular arrhythmias and HRV variables in our PCI group might have been influenced by some basal clinical differences suggesting worse clinical conditions of thrombolysed patients. Thrombolysed patients, indeed, tended to be older and more frequently diabetic, and also had a higher prevalence of anterior AMI and a history of previous AMI. Even more, almost all PCI patients were treated with beta-blocking agents, whereas only 35% of patients received beta-blockers in the thrombolysed group, a difference which might have favored better HRV values in PCI patients, due to the well-known positive effects of beta-blockers on HRV parameters[19,20]. PCI patients actually showed a higher peak of creatine kinase, but this latter was likely related to the more frequent complete and quick recanalization, rather than to larger AMIs, as suggested by the similar proportion of patients with reduced left ventricular ejection fraction in the two groups.

Study limitations. As previously stated, our study presents some obvious limitations, including the limited number of patients, the use of historical thrombolysed controls and the presence of some differences between PCI and thrombolysed patients in basal clinical characteristics and, even more, in beta-blocker drug therapy.

However, the failure to demonstrate a significant improvement in ventricular arrhythmias and HRV in PCI patients, despite a better global clinical profile, may suggest that PCI may not actually offer any considerable advantage, compared to timely performed thrombolysis, on these prognostic variables, although further studies are needed to definitely address this issue.

In conclusion, in this study, in patients with ST-segment elevation AMI, we failed to show any significant effects of PCI on ventricular arrhythmias and HRV parameters, as compared to thrombolysis. The prognostic implications of these findings need to be carefully investigated in appropriately designed future studies.

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