Clinical features associated with pre-hospital time delay in acute myocardial infarction

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Background. **The pre-hospital time delay in acute myocardial infarction (AMI) is still a challenging problem since for many patients there are long intervals between the onset of symptoms and the initiation of therapy. The aim of this study was to verify which, among several clinical variables, are associated with a prolonged pre-hospital time delay.**

Methods. **Five hundred and twenty-six unselected patients with AMI and consecutively admitted to three coronary care units were enrolled. The pre-hospital time delay was defined as the time interval from the onset of symptoms to admission to the coronary care unit. Clinical variables included: age, gender, body mass index, level of education, alcohol consumption, smoking habits, regular physical activity, history of hypertension, diabetes mellitus, history of coronary artery disease (documented history of angina and/or previous myocardial infarction), chronic atrial fibrillation, Q-wave AMI and off hours onset of symptoms. After univariate analysis, multivariable regression analysis was used.**

Results. **The mean age of the patients was 66.6 ± 12.1 years and 28.7% were female. The median pre-hospital time interval was 200 min (95% confidence interval 60-1140). For 342 patients the pre-hospital time interval was ≤ 6 hours and for 184 patients it was > 6 hours. Those variables which, at univariate analysis, were found to significantly influence the pre-hospital delay were analyzed using a multivariable regression model where the dependent variable was the pre-hospital time interval. Chronic atrial fibrillation (p = 0.010), a history of coronary artery disease (p = 0.017), diabetes (p = 0.016) and age ≥ 70 years (p = 0.009) were found to be independently associated with a prolonged pre-hospital time interval. Similar results were obtained when considering only Q-wave AMI. As expected, the thrombolytic therapy rate was much lower in patients with a longer pre-hospital time delay.**

Conclusions. **The present study shows that, in case of AMI, the time interval between the onset of symptoms and a patient's arrival to hospital is still far from being optimal. This is especially true for older patients with diabetes, a history of coronary artery disease or chronic atrial fibrillation. Cardiologists should be aware of this problem and should implement adequate educational strategies addressed to those patients at highest risk.**

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Introduction

The delay between the onset of symptoms and admission to a coronary care unit is crucial for the outcome of patients with acute myocardial infarction (AMI)[1-4] and the prompt initiation of therapy is a central goal in the management of these patients[5-9]. However, for many patients the time interval between the onset of symptoms and the initiation of therapy is too long. Although this delay may partly occur inside the hospital, most of it takes place before hospital admission[5,10-12].

Several studies investigated the delay between the onset of symptoms of AMI and coronary care unit admission and have mainly highlighted logistical[11-15], individual[4,12,16,17], and socio-economic[9,13,18] factors. Among patients' clinical characteristics, few were usually taken into account[4,8]. Moreover, most studies reported data from selected samples of patients such as elderly patients or subjects enrolled for trials on thrombolytic agents[5,13,18-20].

The aim of the present study was to evaluate, in case of AMI, the influence of many patients' clinical characteristics on the pre-hospital time delay.

Methods

Study sample. For the present investigation the sample included 526 unselected patients consecutively admitted to three intensive coronary care units (Adria-RO, Bassano del Grappa-VI and Conegliano-

TV, Italy) with symptoms suggestive of AMI and who had AMI confirmed by standardized criteria, based on the fulfillment of at least two of the following: central chest pain lasting > 30 min, typical changes in the levels of serum enzymes (total creatine kinase, creatine kinase-MB, aspartate transaminase and lactic dehydrogenase) and typical electrocardiogram changes including the occurrence of pathological Q waves and/or localized ST-T changes in at least two contiguous leads[21]. Patients with symptoms of acute coronary occlusion and who were found not to have AMI were excluded from this investigation. Other details on patients' data collection were reported elsewhere[22]. The three Cardiology Departments involved in the study serve three Social-Health Care Districts in the Veneto Region each with population ranging from 80 000 to 200 000. Their territory includes an urban area surrounded by wide rural areas and is served by an efficient 24-hour full-working public emergency service. The network of health care services in Veneto is considered to be among the best in Italy and the level of education is good (percentage of illiterate subjects 0.8%) compared to that of the rest of the country (1.9%).

Study variables. During the hospital stay the patients were interviewed by a physician who completed a standard record form covering details of their past medical history. The time of onset of AMI symptoms was recorded as accurately as possible. For some patients (i.e., patients with cardiogenic shock, signs of dementia, etc.) this information was obtained from family members. The time of admission to the coronary care unit was recorded and the pre-hospital time delay was defined as the time interval from the beginning of the most recent onset of chest pain or the latest episode of intensified or prolonged pain to admission to the coronary care unit.

Study variables included: age, gender, body mass index, level of education, alcohol consumption, cigarette smoking, regular physical activity, history of hypertension, diabetes mellitus, history of coronary artery disease (documented history of angina and/or myocardial infarction), atrial fibrillation, Q-wave AMI and off hours onset of symptoms (from 8.00 p.m. to 8.00 a.m.).

Statistical analysis. Statistical analysis was performed using Systat 7.0 for Windows package (SPSS Inc. 1997, Evanston, IL, USA) and JMP 3.1.4 for Windows (SAS Institute Inc. 1995, Cary, NC, USA).

The pre-hospital time delay was expressed in minutes and used either as a continuous variable or as a second-class categorical variable (cut off 360 min). Due to its skewed distribution (Shapiro-Wilk, W test, $p < 0.0001$), the pre-hospital time delay was presented as the median value and as the 5th and 95th percentiles and also as the mean ± SD. In the univariate and the multivariable analyses, the pre-hospital time delay was used after log-transformation which resulted in a much more symmetric distribution (Shapiro-Wilk, W test, $p = 0.03$). Proportions were compared using the Pearson χ^2 test while for continuous variables the Student's t test was used. Candidate predictor variables were first analyzed by linear regression analysis (continuous predictors) or ANOVA (categorical predictors). Variables, which were found to be significantly associated with the log pre-hospital time delay at these univariate analyses and those known to be of clinical relevance were evaluated as independent variables in a multiple regression analysis (using the general linear model) with the logged pre-hospital time delay as the dependent variable (minimum tolerance for entry into the model 0.01)[23].

Since the pre-hospital time delay strongly affects the decision regarding the administration of thrombolytic therapy, we performed the same multivariable analysis on the subset of patients with a Q-wave myocardial infarction in whom thrombolysis is indicated.

Statistical significance was established at $p < 0.05$. All p values are two-tailed.

Results

The median (5th and 95th percentiles) pre-hospital time delay was 200 min (60-1140 min) (mean 484 ± 687 min). Patients were divided into two groups according to whether their pre-hospital time delay was ≤ 6 hours or > 6 hours, and their baseline characteristics are reported in table I. Patients with a prolonged pre-hospital time delay were older and had a lower body mass index. Moreover, in this group there was a higher proportion of diabetics and of subjects with chronic atrial fibrillation and a lower proportion of cigarette smokers. The proportion of patients with "off hours onset of symptoms" was higher in the group with a shorter pre-hospital time delay. The proportion of Q-wave and non-Q-wave AMI was similar in the two groups. No difference in the time delay-related creatine kinase peak was observed while the presence of heart failure upon admission was higher among the subjects with a longer pre-hospital time delay.

In figure 1 the distribution of the patients by the pre-hospital time delay and by thrombolytic therapy rate is shown. As expected, the thrombolytic therapy rate strongly decreased as the pre-hospital time delay increased ($p < 0.0001$). The exclusion of non-Q-wave patients did not affect the results.

Variables associated with the pre-hospital time delay. At univariate analysis, age, body mass index, current smoking, diabetes mellitus, chronic atrial fibrillation and off hours onset of symptoms were found to be associated with a longer pre-hospital time delay. Hypertension and alcohol consumption were only marginally significant. Gender, level of education, regular physical activity, a history of coronary artery disease,

Table I. Characteristics of the patients by pre-hospital time delay.

Characteristics	Delay		p
	≤ 6 hours (n=342)	> 6 hours (n=184)	
Age (years)	65.1 ± 12.2	69.6 ± 11.4	< 0.0001
Gender (% female)	26	33	NS
Level of education (% above elementary)	27	22	NS
Body mass index (kg/m^2)	26.4 ± 4.0	25.5 ± 3.5	0.006
Alcohol consumption (% yes)	71	79	0.05
Current smoking (% yes)	42	29	0.005
Regular physical activity (% yes)	6	6	NS
Hypertensives (%)	44	53	0.05
Diabetics (%)	20	31	0.005
Prior coronary artery disease (%)	28	35	NS
Chronic atrial fibrillation (%)	2	7	0.004
Off hours onset of symptoms (% yes)	62	47	0.001
Q-wave AMI (%)	75	74	NS
CK peak (IU/l)	1644 ± 1425	1270 ± 1166	0.001
Heart failure upon admission (%)	30	40	0.019

AMI = acute myocardial infarction; CK = creatine kinase.

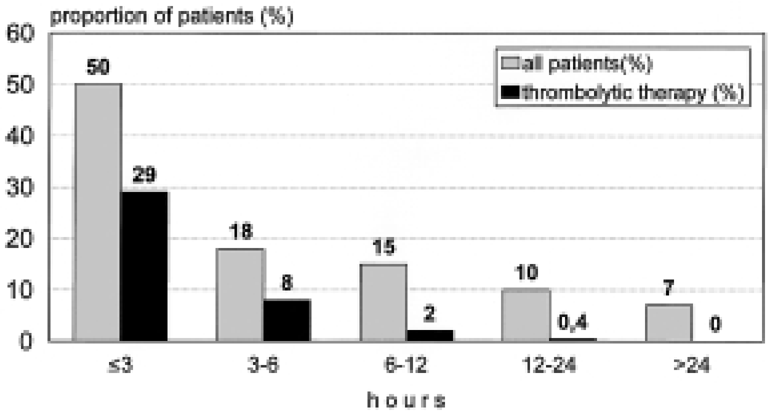

Figure 1. *Distribution of the patients and thrombolytic therapy rate according to the pre-hospital time delay in 526 patients with acute myocardial infarction.*

and a Q-wave AMI were also included because of their clinical relevance. Results of the multivariable regression analysis are reported in table II. Diabetes, coronary artery disease, chronic atrial fibrillation and age ≥ 70 years were found to be independently associated with a prolonged pre-hospital delay. When considering the subset of patients with a Q-wave AMI (n = 392), similar results were obtained (Table II). The pre-hospital time delay according to the patients' clinical characteristics is reported in table III. The pre-hospital time delay was longer in subjects with chronic atrial fibrillation, in diabetics and in older patients. Similar results were obtained for the patients with a Q-wave infarction (n = 392). In figure 2, the thrombolytic therapy rate in the patients with characteristics associated with a longer pre-hospital time delay and in the rest of the subjects is shown. Elderly patients ($p < 0.0001$) and patients with history of coronary artery disease (p

Table II. Independent predictors of the pre-hospital time delay at multivariable regression analysis.

Independent variable	All patients (n=526) (model 1)		Q-wave AMI (n=392) (model 2)	
	T	p	T	p
Chronic atrial fibrillation	2.58	0.010	2.13	0.034
Previous CAD	2.40	0.017	2.56	0.011
Diabetes	2.42	0.016	3.50	0.001
Age ≥ 70 years	2.64	0.009	3.07	0.002

The models included age, gender, body mass index, level of education, alcohol consumption, cigarette smoking, regular physical activity, a history of hypertension, diabetes mellitus, a history of coronary artery disease (CAD), atrial fibrillation, Q-wave acute myocardial infarction (AMI) (only for model 1), off hours onset of symptoms as independent variables and the pre-hospital time delay (in minutes) as the dependent one.

Table III. Differences in the time delay in the patients with acute myocardial infarction grouped according to the clinical characteristics independently associated with a prolonged pre-hospital time delay.

Variable	Pre-hospital time delay (min)	Difference	p
Atrial fibrillation (no/yes)	466 ± 667/940 ± 1003	474	0.001
Median	180/750		
History of CAD (no/ yes)	428 ± 598/611 ± 845	183	0.005
Median	180/240		
Diabetes (no/yes)	440 ± 638/622 ± 809	182	0.002
Median	180/300		
Elderly (no/yes)	420 ± 622/565 ± 754	145	0.016
Median	180/240		

CAD = coronary artery disease.

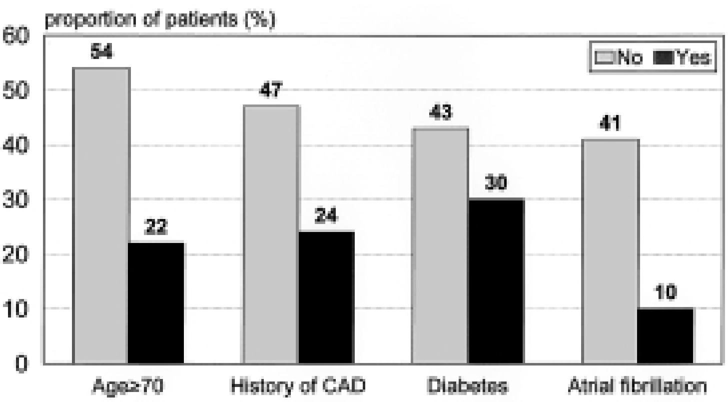

Figure 2. *Thrombolytic therapy rate according to patient's age ≥ 70 years, a history of coronary artery disease (CAD), diabetes mellitus and atrial fibrillation.*

< 0.0001), diabetics (p = 0.012) and patients with chronic atrial fibrillation (p = 0.005) received thrombolytic therapy much less frequently than the others.

Among the patients with a history of coronary artery disease, the pre-hospital time delay did not differ between subjects with history of angina (626 ± 901 min) and those with a previous AMI (610 ± 828 min).

Discussion

Distribution of the pre-hospital time delay. The importance of early thrombolytic treatment in improving the survival of AMI patients has been clearly demonstrated and recent trials have shown that mortality can be reduced if the time interval to treatment is shortened[2,24,25]. All the same, the pre-hospital time delay in AMI patients still constitutes a challenging problem. In prior analyses, 20 to 37% of AMI patients arrived at the hospital ≥ 6 hours after the onset of symptoms and some 20% more than 12 hours later[12,26-30]. In the GISSI study, the median pre-hospital time delay was reported to be 3.50 hours (mean time 8.15 hours)[12].

The present results, obtained from a non-selected cohort of AMI patients studied in the second half of the '90s, show that the pre-hospital time delay is still too long, with 32% of the patients arriving at the coronary care units after 6 hours and 17% arriving after 12 hours. This finding emphasizes the need for increased public awareness of the appropriate responses to AMI symptoms.

Clinical factors associated with the pre-hospital time delay. The present study shows that among several clinical features, old age, diabetes mellitus, a history of coronary artery disease and chronic atrial fibrillation are independently associated with a prolonged pre-hospital time delay. The time span from the onset of symptoms to hospital admission can be roughly divided into three phases. A "patient time" lasting from the onset of symptoms to the request for help. This phase chiefly depends on the patients themselves. The second and third phases are mainly associated with logistical and organizational issues before admission to the coronary care unit. In the GISSI study, most of the time elapsed from the onset of symptoms to admission to the coronary care unit was attributable to "patient time"[12] and, thus, our analysis focused on this phase of the pre-hospital time delay.

In past studies, patients with diabetes mellitus were shown to be at an increased risk of delay[12,18,29]. This association may relate to diabetic neuropathy which may alter the perception of myocardial ischemia and lead to a delayed arrival at hospital. Patients with a history of angina may initially interpret AMI symptoms as a typical anginal episode and thus delay presentation[18]. In contrast with previous studies[12,13,29] in which a previous AMI was inconsistently associated with the pre-hospital time delay, in our analysis it was significantly associated with a delayed arrival to hospital. This suggests that, at least in some areas, information about the urgency of seeking medical advice when symptoms occur is still inadequate.

Patients with chronic atrial fibrillation showed the longest pre-hospital time delay and it was found to be 474 min longer than in patients with sinus rhythm. To our knowledge this variable has never been taken into account in previous studies. Although the reason for this association is unclear, patients with this arrhythmia should be well informed about the importance of AMI symptoms.

In agreement with previous studies[12,18], our elderly subjects showed a prolonged pre-hospital time delay probably due to more difficulties in getting help[12]. Female gender was found to be associated with a longer pre-hospital time delay in some studies[18] but not in others[12]. In our population, neither the level of education nor gender significantly influenced the pre-hospital time delay.

It has recently been shown that the patients' interpretation of symptoms is an important source of delay in reaching hospital following the onset of symptoms[16,31]. A mismatch between expected symptoms and those actually experienced may occur in over 50% of patients with AMI and is associated with the pre-hospital time delay[16]. This aspect was not taken into account in our protocol and constitutes a possible limitation of our study. Another possible limitation is that the results obtained in our three Social-Health Care Districts cannot be extrapolated to the rest of the country as they depend on the efficiency of the local public emergency service.

Conclusions. The present study shows that, in case of AMI, the time interval between the onset of symptoms and the patient's arrival in hospital is still far from being optimal. This is especially true in older subjects with diabetes, a history of coronary artery disease or chronic atrial fibrillation. Cardiologists should be aware of this problem and should implement adequate educational strategies including discussions of this issue with those patients at highest risk.

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