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Free wall rupture (FWR) in patients with acute ST-elevation myocardial infarction (STEMI) receiving fibrinolytic therapy (FT): A 7-year prospective study

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ABSTRACT

Previous studies have shown a paradoxical increase in early mortality in older patients (>70 years) with acute STEMI treated with fibrinolytic therapy (FT), which has been attributed to the development of free wall rupture (FWR). Our aim was to assess occurrence of FWR in STEMI patients receiving FT. In this 7-year prospective study, data from 1701 consecutive patients were obtained. We analyzed predictors of the in-hospital mortality in patients > 70 years old. The independent contribution of several variables to overall mortality and FWR development was assessed using multiple logistic regression analyses. The mortality of entire cohort was 18% (306/1701). Diabetes mellitus, anterior infarction, smoking, female gender and hypercholesterolemia were independent predictors of in-hospital mortality. FT was given to 18% of all patients (304/1701) of which 13% died (39/304). FWR was 18.4-times more often in patients who received FT. Among patients younger than 70 years who received FT there was no FWR, while in patients ≥70 years of age FWR was found in almost half of the deceased (30/68; 44%). Application of FT in STEMI patients is not associated with higher mortality, but significantly increases number of FWR, especially in patients over 70 years of age.

1. Introduction

Prompt reperfusion of ischemic myocardium is the major focus of acute treatment of patients with STEMI (Van de Werf et al., 2003; Huynh et al., 2009). The benefit obtained by an effective and prompt restoration of the coronary flow either with FT or with primary percutaneous coronary intervention (PPCI) limits infarct size, reduces the degree of ventricular dysfunction, and improves survival (The GUSTO investigators, 1993; Channer, 2004). PPCI is considered the gold standard of myocardial reperfusion when promptly performed by skilled teams (The GUSTO investigators, 1993; Channer, 2004).

Inter-hospital transfer for PPCI improves the short- and long-term composite outcome of death, clinical re-infarction, or disabling stroke when compared with on-site fibrinolysis (Khalil and Abba, 2003; Terkelsen et al., 2005). Therefore PPCI should be the preferred reperfusion strategy when inter-hospital transfer can be completed within 2 h. However, early administration of FT is at least as effective as PPCI, and can abort infarction and dramatically reduce mortality when given during the first 3 h of STEMI onset (The GUSTO investigators, 1993; Van de Werf et al., 2003). Thus, in the absence of contraindications, FT should be administered to STEMI patients admitted to a hospital without PPCI facilities during the first 3 h after onset of symptoms, if the inter-hospital transfer to invasive-treatment hospitals is anticipated to be >2 h (Van de Werf et al., 2003; Townend and Doshi, 2005).

Early studies of STEMI patients randomized to FT or placebo showed a paradoxical increase in early mortality in those treated with FT, which was primarily attributed to the development of free wall rupture (FWR) (Slater et al., 2000; Ikeda et al., 2004). Both patient age and timing of FT have been implicated in FWR development (Polic et al., 2000; Tanaka et al., 2002; Birnbaum et al., 2003). Bueno et al. (2005, 2006) and Polic et al. (2006) observed that in patients > 75 years, treatment of first STEMI with FT markedly increases the risk of FWR, particularly when treatment is started after the first 6 h from symptom onset. Importantly, this risk is not observed in patients treated with PPCI. Moreover, data from studies comparing PPCI with FT showed a significantly lower risk of FWR in patients of all age groups treated with PPCI; therefore, FWR was accepted as a direct complication of the FT (Slater et al., 2000; Channer, 2004).

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Previous results of our group indicated high mortality and incidence of FWR of patients with AMI in our hospital, especially those receiving FT (Polic et al., 2000; Fabijanic et al., 2006). Therefore, the aim of this study was to assess overall mortality, mechanism of death and risk factors for development of FWR in patients with STEMI, with a particular emphasis on FT.

2. Subjects and methods

2.1. Study design

We prospectively studied clinical records of patients treated because of STEMI in coronary care units (CCU) at the University Hospital Split, Croatia, between January 1, 1999 and December 31, 2005.

2.2. Participants and procedures

For inclusion into the study patients were required to meet two of the following three criteria diagnostic for STEMI according to the World Health Organization: (1) typical chest pain that lasted for more than 30 min; (2) characteristic ECG changes demonstrating significant evolution such as a new pathologic Q-waves or 1 mm ST-segment elevation in any of two or more limb leads; (3) activities of creatine kinase (CK) and/or its isoenzyme CK-MB more than two times the upper limit of normal range.

Trained research assistants abstracted information from the hospital medical record and entered the data into an electronic database. The data included demographic variables, prior cardiac history, clinical course during hospitalization, laboratory data and ECG. The clinical variables analyzed were age, gender, hypertension, hypercholesterolemia, diabetes, cigarette smoking and FT.

Arterial hypertension was defined as a systolic blood pressure > 140 mmHg or a diastolic blood pressure > 90 mmHg or the use of antihypertensive medication. Hypercholesterolemia was defined as a total serum cholesterol level > 5 mmol/l or the use of lipid-lowering therapy. Diabetes was defined as a fasting plasma glucose level > 6.9 mmol/l or a non-fasting plasma glucose level > 11 mmol/l and/or use of antidiabetic medication. Smoking was categorized as no smoking or smoking (current or stopped < 1 year ago). If undertaken, FT consisted always of streptokinase (SK) infusion (1.5 MU/1 h). During the study in our hospital PPCI was not available.

Criteria for treatment with FT were: chest pain that lasted more than 30 min, changes in ECG (ST-segment elevation or new left branch block), and <6 h from the onset of pain to the beginning of fibrinolytic therapy. All three criteria had to be fulfilled for patients to be included in the study. Patients that were not included in the study were those for whom more than 6 h elapsed from the onset of chest pain and all those with contraindications for FT. Patients who were not given SK were treated with routine therapy for acute myocardial infarction that consisted of acetylsalicylic acid, beta-blocker and ACE inhibitor, if there were no contraindications for such therapy.

Patients were divided in four groups according to their age and treatment: (1) patients below 70 years with FT; (2) patients over 70 years with FT; (3) patients below 70 years without FT, and (4) patients over 70 years without FT. Each group was additionally split in two subgroups, based upon survival or death during their hospital stay.

According to the clinical, ECG and echocardiographic presentation cardiac deaths were grouped into the following categories: (1) arrhythmic death. Death from rapid ventricular tachycardia (VT), ventricular fibrillation (VF) or asystole; the loss of cardiac output and pulse was sudden and preceded collapse of the circulation (defined as a state of very low cardiac output, poor peripheral perfusion, systolic blood pressure < 80 mmHg, or dependence on intravenous inotropic support) or severe pulmonary edema, characterized by severe respiratory distress of a sudden onset without evidence of non-cardiac cause. The patient was not in shock or pulmonary edema at the time of onset of arrhythmia. (2) Cardiogenic shock was defined as clinical state of severely compromised organ perfusion (diaphoresis, oliguria, mental confusion, and cold extremities), with systolic blood pressure < 90 mmHg and pulmonary capillary wedge pressure > 20 mmHg, or a cardiac index < 1.8 l/min/m^2, for at least 30 min before inotropes/vasopressors or intraaortic balloon pump were prescribed to maintain a systolic blood pressure > 90 mmHg and a cardiac index >1.8 l/min/m^2. The diagnosis of cardiogenic shock was made when other causes of hypotension have been excluded, such as hypovolemia, vasovagal reactions, electrolyte disturbance, pharmacological side effects, or arrhythmias. (3) Pulseless electrical activity (PEA): monitored patients who had a rhythm generally compatible with the normal cardiac output immediately before an abrupt circulatory collapse. PEA is the most common manifestation of the FWR. Clinical and ECG suspicion of FWR had to be verified by echocardiography (pericardial effusion/tamponade) or at autopsy (recent infarction with external rupture and hemopericardium).

2.3. Analysis

Statistical analyses were performed with the SPSS statistical software package (version 12.0 Statistical Package for the Social Sciences Inc., Chicago, USA). Continuous variables were presented as mean $\pm$ S.D. Dichotomous variables were presented as the percentage of presence in a particular subgroup. Differences between two groups were tested by t-test and Mann–Whitney U test for continuous variables and by the χ^2-test with Yates' continuity correction for dichotomous variables. In our analysis we used also univarate and multivariate logistic regression analyses. Statistical significance was defined as $p < 0.05$.

3. Results

During the 7-year study period, 1701 patients were admitted to CCU because of STEMI: 1083 (63.7%) men (64.0 $\pm$ 2.5 years), and 618 (36.3%) women (71.2 $\pm$ 11.4 years, $p < 0.001$). There were 306 (18%) patients who died during the hospitalization; 201 patients died with clinical presentation of cardiogenic shock, 94 as a consequence of FWR and 11 due to arrhythmic death. Death rate was higher among

Table 1
Demographic and clinical characteristics of the study patients, n, n (%), mean $\pm$ S.D.

Parameters	Survivors	Deceased	p^*
Number	1395	306	
Sex			
Male	933 (67)	150 (49)	
Female	462 (33)	156 (51)	<0.001
Age			
<70 years (1032)	929 (67)	103 (34)	
≥70 years (669)	466 (33%)	203 (66%)	<0.001
STEMI location			
Anterior	590 (42.3)	187 (61.1)	
Inferior	685 (49.1)	78 (25.5)	
Lateral	120 (8.6)	41 (13.4)	<0.001
FT	265 (19)	39 (13)	<0.01
Diabetes mellitus	152 (11)	156 (51)	<0.001
Arterial hypertension	611 (44)	205 (67)	<0.001
Smoking	415 (30)	196 (64)	<0.001
Hypercholesterolemia	405 (29)	167 (55)	<0.001
Previous MI	44 (3.2)	14 (4.6)	0.215
Pain-to-coronary care unit, h	3.8 $\pm$ 3.2	3.9 $\pm$ 3.7	0.196

* χ^2-test.