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Plasma High-Mobility Group Box 1 Levels Predict Mortality After ST-Segment Elevation Myocardial Infarction

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Objectives We evaluated the potential association between plasma high-mobility group box 1 (HMGB1) levels and outcome in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention.

Background The positive effect of reperfusion after STEMI may be compromised by ischemic/reperfusion injury. HMGB1 is released by necrotic cells and, in pre-clinical studies, has been implicated to play a role in myocardial ischemic/reperfusion injury.

Methods The study included 141 STEMI patients, with acute occlusion of the left anterior descending coronary artery successfully treated with percutaneous coronary intervention. Plasma HMGB1 levels were measured by enzyme-linked immunoadsorbent assay at admission. Forty-two healthy individuals served as control subjects.

Results After a median of 10 months of follow-up, 13 STEMI patients died. There were no significant differences with regard to baseline variables between the group of patients who survived and those who died. Baseline HMGB1 levels were increased in STEMI patients when compared with control subjects. Furthermore, the STEMI patients who died had higher HMGB1 levels than those who survived. After adjusting for age, sex, troponin I, and creatine kinase-myocardial band, we found that a doubling of HMGB1 concentrations increased the risk of mortality by 75% (hazard ratio: 1.75; 95% confidence interval: 1.1 to 2.8).

Conclusions Plasma HMGB1 levels are elevated in STEMI patients compared with healthy control subjects. Furthermore, after a follow-up period of 10 months, plasma HMGB1 levels are shown to be independently associated with increased mortality in STEMI patients treated with PCI. These data suggest that plasma HMGB1 may be used as a new prognostic biomarker in STEMI patients. (J Am Coll Cardiol Intv 2011;4:281–6) © 2011 by the American College of Cardiology Foundation

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The prevalence of acute and chronic ischemic heart disease, ischemic-reperfusion (I/R) injury and heart failure, reaches up to 8% in the Western countries and accounts for more than 30% of all deaths (1). It is now well established that the most effective treatment strategy for acute myocardial infarction is immediate reperfusion by primary percutaneous coronary intervention (PCI) or thrombolytic agents (2,3). Nevertheless, patients surviving an acute myocardial infarction have a 10% risk of dying and a 25% risk of heart failure within 1 year (4). Patients with ST-segment elevation myocardial infarction (STEMI) treated with primary PCI or thrombolytic agents experience ischemia followed by reperfusion and are consequently at risk of I/R injury (5–10). Paradoxically, I/R injury can limit the effect of reperfusion because of several mechanisms, for example, oxidative stress and an intense inflammatory response (5–10).

High-mobility group box 1 (HMGB1), a potent factor for the innate host defense and/or tissue repair, has recently been suggested to be a key player in I/R injury, as evaluated in pre-clinical studies (11). In addition to being a ligand for toll-like receptors 4 (TLR4) and 9 (TLR9) (12,13), HMGB1 is also a potent ligand for the receptor for advanced glycation end products (14,15). Data from some recently published pre-clinical experiments (15–19) and cross-sectional clinical observations (15,19,20) have indicated a pivotal role of HMGB1 in ischemic heart disease. However, the precise role of HMGB1 in I/R injury in the heart is uncertain and HMGB1 has been suggested to be a risk factor for heart injury, and accordingly involved in the pathogenesis, but by contrast also to hold cardioprotective properties (15–20). Accordingly, the aim of this study was to examine the prognostic value of plasma HMGB1 levels, collected at admission, in STEMI patients treated with primary PCI, in terms of subsequent mortality after a median follow-up period of 10 months.

Abbreviations and Acronyms

CK-MB = creatine kinase-myocardial band
HMGB1 = high-mobility group box 1
I/R = ischemic/reperfusion
LAD = left anterior descending branch
MI = myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
TLR = toll-like receptor

Methods

Patients. The Gentofte University Hospital serves a catchment population of 1.2 million citizens (with respect to PCI, this is more than 20% of the total Danish population) referred directly or via noninvasive centers. More than 650 primary PCIs are performed annually. Inclusion criteria in the present study were: significant (minimum 2-mm) ST-segment elevation in at least 2 contiguous precordial leads (V_1 to V_6) of the electrocardiogram; significant increase in cardiac markers (troponin I >0.5 μg/l and creatine kinase-myocardial band [CK-MB] >5 μg/l); <12 h from onset of symptoms to primary PCI; acute occlusion of the anterior descending branch (left anterior descending branch [LAD]) of the left coronary artery (pre-procedure Thrombolysis In Myocardial Infarction [TIMI] flow grade ≤1); and successful primary PCI (post-procedure TIMI flow grade 3). Exclusion criteria were: previous myocardial infarction (MI), history of heart failure, and current infectious or inflammatory disease. From October 2006 to July 2008, 141 patients fulfilled the inclusion criteria. Forty-two healthy individuals without ischemic heart disease, randomly selected from a large community-based database (21), served as control subjects. All patients gave informed consent.

Primary PCI. The primary PCI was performed according to international guidelines using pre-treatment with 10,000 IU of unfractionated heparin, 300 to 500 mg acetyl salicylic acid, and 300 to 600 mg clopidogrel. The transfemoral approach was used with 6- or 8-F sheath, conventional devices, and Iomeron contrast fluid (Bracco, Minneapolis, Minnesota). The occluded LAD was stented in all cases by 1 or more drug-eluting or bare-metal stents. Glycoprotein IIb/IIIa inhibitors were used at the discretion of the operator. Distal protection or thrombectomy devices were not used (22,23). Subsequent medical treatment included anti-ischemic, lipid-lowering, and antithrombotic drugs according to guidelines.

Measurement of plasma HMGB1. Peripheral arterial blood was drawn from the femoral sheath at the beginning of the procedure, thus avoiding contamination with contrast fluid. Blood was allocated to different containers including 4-ml ethylenediamine tetraacetic acid containers and within 0.5 h centrifuged at 10,000 revolutions/min for 10 min. Plasma was stored in Nunc Cryo-tubes (Nunc, Roskilde, Denmark) at −80°C. Plasma HMGB1 levels were measured by an enzyme-linked immunoadsorbent assay (Shino-Test Corporation, Kanagawa, Japan). The intraassay and interassay coefficients of variance were <5% and <10%, respectively.

Follow-up and study end points. Information regarding death was collected from the National Person Identification Registry. The median follow-up time was 10 months and the study end point was all-cause mortality. Follow-up was 100% complete.

Statistics. Baseline characteristics were compared between the group of STEMI patients who died and those who survived by the Fisher exact test for dichotomous variables and by Student unpaired *t* test and Mann-Whitney *U* test for continuous Gaussian and non-Gaussian distributed variables, respectively. Comparisons among all 3 groups (STEMI groups and controls) were done by chi-square test and parametric 1-way analysis of variance. Linear and logistic regression analyses were used to evaluate any potential associations between baseline variables and level of

HMGB1. Associations between prognostic variables and end points were examined by univariate and multivariate Cox proportional hazards regression models. Before performing adjusted Cox regression, the assumptions of linearity and proportional hazards were ensured. To avoid functional form misspecification, HMGB1 concentrations were transformed logarithmically (using the binary logarithm). The reported means of HMGB1 represent geometric means. The p values <0.05 were considered of statistical significance. SPSS for Windows (version 17.0, IBM Corp., Somers, New York) was used.

Results

Patient characteristics and outcome. This study included 141 STEMI patients with culprit lesion in the LAD artery (all mid- or proximal LAD). All patients had pre-procedure TIMI flow grade ≤1 and a successful primary PCI with a post-procedure TIMI flow grade 3. After a median follow-up of 10 months, 13 STEMI patients died from cardiovascular deaths. The clinical characteristics of the STEMI patients who survived, the STEMI patients who died, and the 42 healthy control subjects are given in Table 1. Although the healthy control subjects were significantly younger than the STEMI patients, there were no significant differences according to baseline variables between the 2 STEMI groups.

HMGB1 levels and predictive value. HMGB1 was collected initially during the PCI procedure. As shown in Figure 1A, STEMI patients had significantly higher levels than healthy control subjects did (2.9 μg/l [range: 2.6 to 3.2 μg/l] vs. 1.3 μg/l [1.1 to 1.5 μg/l]). Moreover, as illustrated in Figure 1B, STEMI patients who died during follow-up had significantly higher HMGB1 levels than surviving STEMI patients did (4.8 μg/l [range: 3.1 to 7.5 μg/l] vs. 2.9 μg/l [range: 2.6 to 3.2 μg/l]). We evaluated potential associations between baseline variables and level of HMGB1 using linear and logistic regression, and no significant associations were found. Univariate Cox regression analyses revealed that for each doubling of the HMGB1 level, the risk of mortality increased by 101% (HR: 2.01, 95% CI: 1.3 to 3.1; p = 0.002). After adjustment for age and sex, high HMGB1 levels significantly predicted mortality (HR: 1.85, 95% CI: 1.2 to 2.9; p = 0.003) (Fig. 2) (Table 2). Even after adjustment for age, sex, troponin I, and CK-MB, high HMGB1 levels significantly predicted mortality (HR: 1.75, 95% CI: 1.1 to 2.8; p = 0.022).

Discussion

The major new finding of the present study is that high HMGB1 levels significantly predict mortality in STEMI patients treated with primary PCI. We found that a doubling of plasma HMGB1 levels was associated with a 75% increased risk of mortality, even after adjustment for age, sex, troponin I, and CK-MB. This finding may be a clinically important and relevant finding because of the potential role of HMGB1 as a biomarker of outcome in STEMI patients, as well as a factor potentially involved in myocardial I/R injury and ischemic pre-conditioning. Furthermore, our data

Table 1. Baseline Variables for 141 STEMI Patients (Dead or Alive at Follow-Up) and 42 Healthy Control Subjects

	STEMI Patients				
	Dead at Follow-Up (n = 13)	Alive at Follow-Up (n = 128)	p Value	Healthy Control Subjects (n = 42)	p Value
Age, yrs	68.8 ± 13.4	68.6 ± 15.5	0.15	52.0 ± 12.9	<0.001*
Male, %	53.4	75.6	0.09	76.2	0.22†
Current smoker, %	30.8	48.4	0.22	33.3	0.13†
Hypertension, %	23.1	28.1	0.70		
Diabetes, %	0	7.8	0.30		
Hereditary IHD, %	30.8	27.3	0.79		
Hypercholesterolemia, %	84.6	83.6	0.92		
Symptom-to-balloon, min	150 (110–380)	170 (115–258)	0.88		
Door-to-balloon, min	30 (20–35)	25 (17–33)	0.64		
Glycoprotein IIb/IIIa, %	22.7	15.4	0.55		
Multivessel disease,‡ %	27.2	25.0	0.87		
Complex lesions,§ %	51.6	53.8	0.86		
Drug-eluting stents, %	76.9	85.8	0.39		
Peak TnI	242 (39–427)	160 (51–302)	0.40		
Peak CK-MB	430 (175–909)	252 (96–467)	0.09		

Values are mean ± SD, %, or median (interquartile range). The data, being normally distributed are given as mean with 95% confidence interval, whereas data not being normally distributed (i.e., symptom-to-balloon and door-to-balloon) are given as median with IQR. *Analysis of variance for all 3 groups (comparison of means); †Fisher exact test for all 3 groups (comparison of proportions rates); ‡Multivessel disease: 2- or 3-vessel disease; §Complex lesion: Type B lesion.

CK-MB = creatine kinase-myocardial band; IHD = ischemic heart disease; STEMI = ST-segment elevation myocardial infarction; TnI = troponin I.

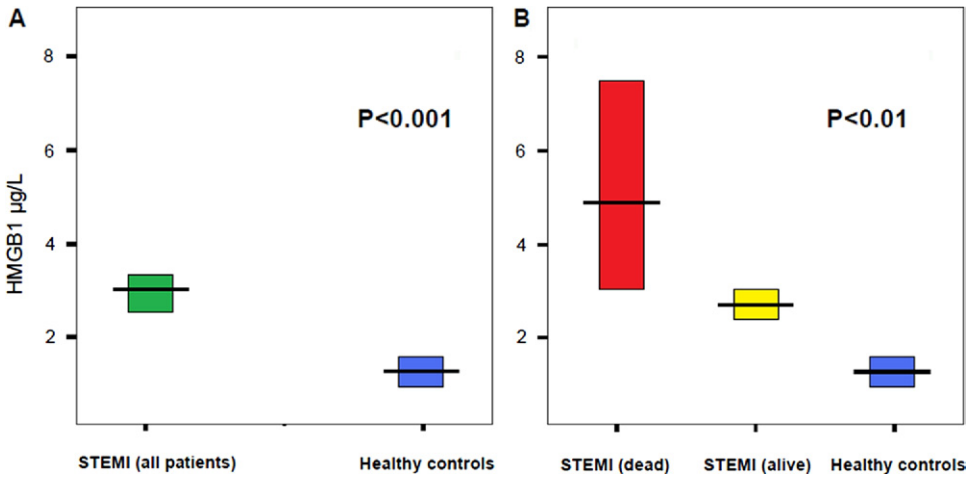

Figure 1. Plasma HMGB1 Levels

(A) Plasma high-mobility group box 1 (HMGB1) levels in ST-segment elevation myocardial infarction (STEMI) patients (all, n = 141) versus healthy control subjects (n = 42); Student *t* test <0.001. **(B)** Plasma HMGB1 levels in STEMI patients who were dead at follow-up (n = 13) versus STEMI patients who were alive at follow-up (n = 128) versus healthy control subjects (n = 42); analysis of variance <0.01. **Bars** are geometric means and **boxes** are 95% confidence intervals.

confirm the results of 2 previously published cross-sectional studies of elevated plasma HMGB1 levels in STEMI patients compared with that in healthy control subjects.

HMGB1 is a DNA binding protein that plays several roles in intra- and extracellular processes. HMGB1 has been found to play an important role in inflammatory responses and tissue repair. Furthermore, HMGB1 has been suggested to play a pivotal role in the response to ischemia or I/R in various organs. Accordingly, this role is subject to intensive research in various diseases such as sepsis, acute hepatic injury, cerebral infarcts, acute lung injury, and myocardial ischemia (11,14–20,24–26). HMBG1 is passively released from necrotic cells or by activated inflammatory cells and leads to increased production of proinflammatory mediators. Interestingly, HMBG1 has been shown to be an important ligand for receptor for advanced glycation end products and TLR4 and TLR9 (12,13).

The potential role of HMGB1 in myocardial I/R injury has been suggested in some recent pre-clinical studies (15–19). In studies in mice and rats, increased heart and/or circulating HMGB1 levels have been reported after exper-

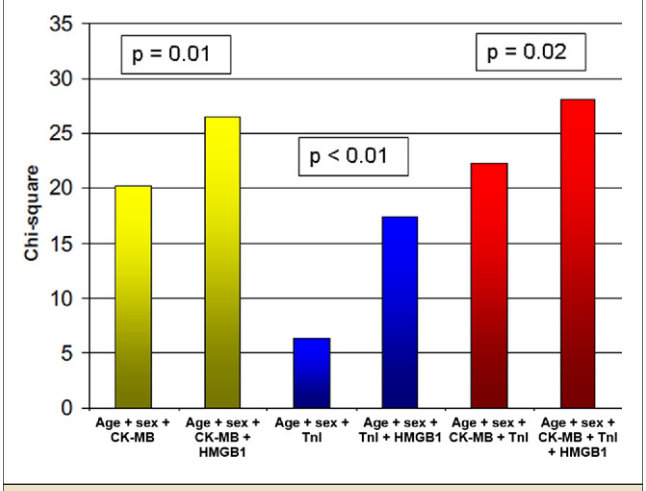

Figure 2. Chi-Square Evaluation of the Predictive Value of HMGB1

Chi-square evaluation of the predictive value of HMGB1: adjusted for age, sex, and CK-MB **(yellow)**; adjusted for age, sex, and troponin I **(blue)**; and adjusted for age, sex, CK-MB, and troponin I **(red)**. CK-MB = creatine kinase-myocardial band; HMGB1 = high-mobility group box 1.

Table 2. Multivariable Cox's Regression Analyses Estimating Hazard Ratio for Mortality

	HMGB1 (per Each Doubling of HMGB1)	
End Point: Mortality	**HR (95% CI)**	**p Value**
Model 1		
Univariate	2.01 (1.3–3.1)	0.002
Model 2		
Adjusted for age and sex	1.87 (1.2–2.9)	0.003
Model 3		
Adjusted for age, sex, and CK-MB	1.68 (1.1–2.7)	0.028
Model 4		
Adjusted for age, sex, and TnI	1.82 (1.2–3.0)	0.002
Model 5		
Adjusted for age, sex, CK-MB, and TnI	1.75 (1.1–2.8)	0.022

Hazard ratios (HRs) were estimated using HMGB1 as a continuous variable, with steps at each doubling of HMGB1 concentration.

CI = confidence interval; HMBG1 = high-mobility group box 1; other abbreviations as in Table 1.

imental MI (15–19). However, when it comes to the association between HMGB1 levels and the outcome, as measured by cardiac function and mortality, the published pre-clinical data are contradictory. In the study by Oozawa et al. (16), administration of a neutralizing monoclonal antibody against HMGB1 in rats exposed to cardiac I/R injury resulted in a further increase in troponin I, norepinephrine, and infarct size, which indicate a positive effect of HMGB1 in myocardial scarring. Additional support of a beneficial effect of HMGB1 comes from a study in transgenic mice with a cardiac-specific HMGB1 expression (17). In this study, cardiac overexpression of HMGB1 was associated with improved cardiac function and survival and cardiac function after experimental MI. In another study in mice with MI, local administration of HMGB1 to the injured myocardium induced myocardial regeneration (18). In contrast, 2 studies support a deleterious effect of HMGB1 in myocardial I/R injury. In one study (15) in mice, administration of HMGB1 in mice exposed to I/R injury of the heart worsened the tissue damage, whereas administration of a functional HMGB1 antagonist significantly reduced markers of tissue damage and infarct size. In a recent study, administration of a neutralizing anti-HMGB1 antibody to rats exposed to experimental MI reduced the infarct size, a thinning and expansion of the infarct scar, and a marked hypertrophy of the noninfarcted area (19). These contradictory pre-clinical results indicate diverse effects of HMGB1 in ischemia and may be an indicator that HMGB1 is capable of exerting both beneficial and deleterious effects to the heart during the complex process of tissue remodeling after I/R injury. Along these lines, a recent study suggested that the heterogeneity in the reported effects of HMGB1 might be due to different mechanisms during conditions characterized either of permanent ischemia or by ischemia reperfusion (27). Accordingly, during permanent ischemia, the infracted, necrotic myocardium might benefit from local increased HMGB1 levels via proliferation of cardiac c-kit stem cells. In addition, total blockade of HMGB1 results in impaired healing (16). Reperfusion by contrast is accompanied by an extensive release of free radicals and an enhanced inflammatory response, including neutrophils and macrophages infiltrations, causing further cardiac damage and significantly higher HMGB1 levels. Therefore, HMGB1 might act as a double edge in post-infarction inflammatory response.

Few clinical studies have been published on the potential association between myocardial ischemia and HMGB1 (15,19,20). Interestingly, all of these studies indicated that high HMGB1 levels were associated with impaired outcome, which supports the findings in our study. In a study by Goldstein et al. (20), serum HMGB1 levels were measured in 9 patients with acute coronary syndrome and these levels were elevated compared with that of healthy volunteers. In the pre-clinical study by Andrassy et al. (15), the investigators reveal that they have unpublished data showing elevated plasma HMGB1 levels in STEMI patients at admission. In the recent study by Kohno et al. (19), including 35 STEMI patients, serum HMGB1 levels were increased transiently within the first 7 days after admission with a peak value of 12 h. In the same study, there was an indication of an association between elevated HMGB1 levels and the risk of cardiac rupture and in-hospital death. However, these data were only based on data from 3 and 2 patients, respectively, and the data were not adjusted for potential confounders, for example, age and sex (19). Finally, in the study by Giallauria et al. (27), which included 67 STEMI patients, the investigators reported a significant association between increased circulating HMGB1 levels and autonomic dysfunction, by the demonstration of a low post-exercise heart rate in post-infarction patients performed 3 to 4 weeks after STEMI.

In the present study, we report elevated circulating levels of HMGB1 in STEMI patients when compared with relevant control subjects, and thereby confirm data from some recent cross-sectional studies (15,19,20). In addition, we report for the first time—in a larger clinical study—an association between high HMGB1 levels and mortality rate in STEMI patients. To exclude as many confounders as possible, we deliberately included a homogeneous group of well-characterized STEMI patients without previous MI, history of heart failure, or current infectious/inflammatory disease and with a successful primary PCI. Future studies are warranted to examine the usability of plasma HMGB1 as a predictor of mortality, in more heterogeneous groups of myocardial ischemic patients, including both patients with STEMI/non-STEMI and with varying degrees of successful reperfusion. To adjust for potential confounders, we performed multivariable analysis. Because we wanted to maintain a solid Cox model, we decided only to adjust for age, sex, troponin I, and CK-MB. We have tested for potential associations between HMGB1 and other baseline variables, and no such were found. Furthermore, no significant differences in baseline variables were found between the 2 groups.

Conclusions

Emerging pre-clinical and clinical data support the notion that HMBG1 may play a role in I/R-myocardial injury. In the present study, we confirmed previous reports that patients with STEMI have elevated levels of HMGB1 when compared with healthy subjects. Furthermore, we show for the first time that high HMGB1 levels in STEMI patients sampled at admission predict an increased mortality risk. These data suggest that plasma HMGB1 may be used as a new biomarker of mortality in STEMI patients.

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Key Words: high-mobility group box 1 ■ ischemia ■ ischemic/reperfusion injury ■ myocardial infarction ■ receptor for advanced glycation end products.