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Modified Serum Profiles of Inflammatory and Vasoconstrictive Factors in Patients With Emotional Stress-Induced Acute Coronary Syndrome During World Cup Soccer 2006

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Objectives We sought to assess whether emotional stress-induced acute coronary syndrome (ACS) is mediated by increased inflammatory and vasoconstrictive mediators.

Background The World Cup soccer 2006 has been shown to provoke levels of stress sufficient to increase the incidence of ACS. However, the mechanisms by which stress translates into vascular injury up to plaque rupture still remain elusive.

Methods Serum levels of soluble CD40L (sCD40L), soluble vascular cell adhesion molecule (sVCAM)-1, monocyte chemoattractant protein (MCP)-1, tumor necrosis factor (TNF)-α, high-sensitivity C-reactive protein (hsCRP), regulated on activation, normal T-cell expressed and secreted (RANTES), and endothelin (ET)-1 were determined in patients who experienced an ACS during World Cup matches, in ACS reference patients (not associated with emotional stress), and in healthy volunteers. Correlations and receiver-operating characteristic curves were calculated to develop multivariable analysis and to investigate the diagnostic value of each parameter.

Results The sCD40L, sVCAM-1, MCP-1, TNF-α, and ET-1 were significantly higher in study patients compared with the reference group. The hsCRP was similar in both groups, whereas RANTES was decreased in study patients. A positive correlation was found between ET-1 and soccer-induced enhanced levels of sCD40L, sVCAM-1, MCP-1, and TNF-α. Receiver-operating characteristic analysis displayed high performance of both MCP-1 and ET-1 as a measure to discriminate between stress-induced ACS and ACS controls.

Conclusions Stress-induced ACS is associated with a profound increase of inflammatory and vasoconstrictive mediators. The evaluation of a targeted drug delivery, such as anti-inflammatory agents, ET-1 receptor antagonists, or inhibition of endothelin-converting enzyme is warranted to reduce stress-mediated cardiovascular morbidity. (J Am Coll Cardiol 2010;55:637–42) © 2010 by the American College of Cardiology Foundation

We have recently demonstrated a 2.7-fold increase in the incidence of acute cardiovascular events in association with World Cup soccer matches. Because of the close time relationship, it seems likely that these additional cardiac emergencies were triggered by emotional stress (1). The pathophysiologic processes underlying emotional stress are still unknown. The triggering hypothesis suggests that the emotional impact of challenging events results in plaque ruptures with subsequent thrombosis (2).

See page 643

The aim of the present study was to evaluate proinflammatory mediators such as soluble CD40L (sCD40L), soluble vascular cell adhesion molecule (sVCAM)-1, monocyte chemoattractant protein (MCP)-1, regulated on activation, normal T cell expressed and secreted (RANTES), tumor necrosis factor (TNF)-α, and high-sensitivity C-reactive protein (hsCRP), and vasoconstrictive endothelin (ET)-1 in victims of stress-associated acute coronary syndrome (ACS) in the context of World Cup soccer. For comparison, we used an age-, sex-, and type of ACS-matched reference

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Abbreviations and Acronyms

ACS = acute coronary syndrome
ELISA = enzyme-linked immunosorbent assay
ET = endothelin
hsCRP = high-sensitivity C-reactive protein
MCP = monocyte chemoattractant protein
RANTES = regulated on activation, normal T-cell expressed and secreted
ROC = receiver-operating characteristic
sCD40L = soluble CD40L
sVCAM = soluble vascular cell adhesion molecule
TNF = tumor necrosis factor

group with cardiac events that occurred in the absence of emotional stress. Furthermore, a healthy control group was used.

Atherosclerosis is clearly an inflammatory disease, but emotional stress-related conditions are also associated with a proinflammatory status. Thus, we hypothesize that increased inflammatory mediators, associated with an enhanced ET-1 release, may be an important signaling pathway specifically involved in stress-induced ACS.

Methods

Data collection. STUDY GROUP. The study group (n = 58) and patient selection is described in detail in our previous publication (1). Of all patients screened (n = 214), a representative sample of 58 patients (27%) were included in the present study whose blood sample collection matched the requirements of the laboratory procedures; 156 patients were excluded because no blood sample was taken by the emergency doctors or blood sample collection did not meet the quality control. However, the study group did not differ significantly in age or sex distribution from the total ACS population. The sampling frequency was not significantly different at any time period of the soccer matches and did not differ at any of the participating centers.

The time delay between the onset of symptoms and blood sampling, obtained before any medical treatment, varied from 1 to 3 h. The database includes only anonymous data of the study patients, being reported as age, sex, and type of ACS. Information on the infarct size, left ventricular function, or specific biomarkers was not available.

ACS REFERENCE GROUP. Inpatients of the Department of Cardiology, Ludwig-Maximilians-Universität München (LMU), Munich, Germany (frequency matched for age, sex, and type of ACS) were screened prospectively for accompanying emotional circumstances after the World Cup. Of all patients screened (n = 175), 58 patients reported no relevant emotional circumstances that may have provoked a considerable contribution to the ACS. The time delay between the onset of symptoms and blood sampling was comparable to that of the study group.

HEALTHY VOLUNTEERS. A group of healthy volunteers (n = 58) with no cardiovascular risk factors and no history of coronary artery disease was recruited prospectively after the World Cup from among inpatients and personnel of the Department of Cardiology, LMU, Munich, Germany.

The study protocol was approved by the ethics committee of the Medical Faculty of the LMU, Munich.

BIOCHEMICAL ASSAYS. Sample collection, storage, and analysis were performed according to manufacturers' recommendations by investigators blinded to categorization into the 3 patient groups. Concentrations of sCD40L, sVCAM-1, MCP-1, and RANTES were measured by a DuoSet enzyme-linked immunosorbent assay (ELISA) (R&D Systems GmbH, Wiesbaden, Germany), TNF-α by a chemiluminescent assay (Siemens Medical Solutions Diagnostics, Bad Nauheim, Germany), hsCRP by a sensitive immunoturbidimetry (Olympus, Center Valley, Pennsylvania), and ET-1 by an ELISA (R&D Systems).

STATISTICAL ANALYSIS. Statistical analysis was performed using the computer software SPSS version 15 (SPSS Inc., Chicago, Illinois). Categorical variables are expressed as the number and the percentage of patients; data are reported as mean ± SD. Normal distribution was approved by the Kolmogorov-Smirnov test. All parametric values were compared by Student *t* test. In case of deviation from normality, the Mann-Whitney *U* test was applied. Because the matching was not paired, we used methods for independent samples. Pearson correlations were calculated between ET-1 and the inflammatory mediators. For non-normality, Spearman's rank correlation was used. All statistical tests were 2-tailed. Statistical significance was considered to be indicated by a value of $p < 0.05$. No adjustment for multiple testing has been done. Receiver-operating characteristic (ROC) analysis was carried out using the ROC function in the R software package (Version 2.4.0, R Foundation for Statistical Computing, Vienna). Estimation of cutoff values was based on maximization of the sum of sensitivity and specificity. The present study was designed to have 80% power to detect a group difference of 10% in a 2-sided alpha of 0.05, and an SD with a difference of 5%.

Results

The present study is based on comparative analysis in 3 different groups, and their characteristics are summarized in Table 1.

Table 1 Characteristics of the Study Group, ACS Reference Group, and Healthy Volunteers

	Study Group (n = 58)	ACS Reference Group (n = 58)	Healthy Volunteers (n = 58)
Men	52	52	52
Women	6	6	6
Age, yrs	61.3 ± 10.4	60.2 ± 9.5	59.1 ± 4.4
Known CAD	24 (41)	25 (43)	
STEMI	17 (29)	17 (29)	
Non-STEMI or unstable angina	41 (71)	41 (71)	

Values are n, mean ± SD, or n (%).
ACS = acute coronary syndrome; CAD = coronary artery disease; STEMI = ST-segment elevation myocardial infarction.