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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 \pm 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.

	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 \pm 10.4	60.2 \pm 9.5	59.1 \pm 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 \pm SD, or n (%).
 ACS = acute coronary syndrome; CAD = coronary artery disease; STEMI = ST-segment elevation myocardial infarction.

Figure 1 represents the results of sCD40L, sVCAM1-1, and MCP-1. Study patients had significantly higher sCD40L levels compared with the reference group (2.7 ± 0.9 ng/ml vs. 1.1 ± 0.4 ng/ml, $p < 0.001$). Moreover, sCD40L of the reference group was significantly increased compared with that of the healthy volunteers (1.1 ± 0.4 ng/ml vs. 0.9 ± 0.2 ng/ml, $p < 0.002$). The sVCAM-1 was also significantly increased in the study patients compared with the reference population (485 ± 98 ng/ml vs. 334 ± 78 ng/ml, $p < 0.001$), whereas no statistical difference was found between the latter and healthy volunteers (334 ± 78 ng/ml vs. 314 ± 57 ng/ml, $p = 0.85$). Likewise, MCP-1 was significantly increased in the study group compared with the reference group (508 ± 122 pg/ml vs. 305 ± 61 pg/ml, $p < 0.001$); a significant difference was also found between reference patients and the healthy population (305 ± 61 pg/ml vs. 229 ± 63 pg/ml, $p < 0.001$).

Figure 2 represents the results of TNF- α , hsCRP, and RANTES. TNF- α again was markedly raised in the World Cup group compared with reference subjects (10.6 ± 2.9 pg/ml vs. 7.2 ± 1.4 pg/ml, $p < 0.001$); the latter had significantly enhanced levels compared with healthy probands (7.2 ± 1.4 pg/ml vs. 5.5 ± 0.6 pg/ml, $p < 0.001$). Concentrations of hsCRP of both the study and reference group were almost the same (0.9 ± 0.3 mg/dl vs. 0.8 ± 0.3 mg/dl, $p = 0.47$), whereas reference patients had significantly higher levels when compared with healthy volunteers (0.8 ± 0.3 mg/dl vs. 0.4 ± 0.1 mg/dl, $p < 0.001$). In contrast, study patients had significantly lower RANTES levels compared with the references (36.1 ± 13.2 ng/ml vs. 63 ± 19 ng/ml, $p < 0.001$), the latter having significantly higher values compared with healthy controls (63 ± 19 ng/ml vs. 47 ± 15 ng/ml, $p < 0.001$).

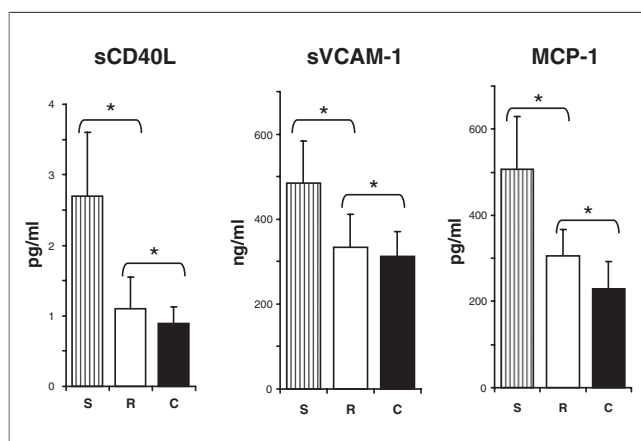


Figure 1 Circulating Inflammatory Mediators sCD40L, sVCAM-1, and MCP-1

Serum levels of soluble CD40L (sCD40L), soluble vascular cell adhesion molecule (sVCAM)-1, and monocyte chemoattractant protein (MCP)-1 in the study group (S [ruled bars]) compared with reference patients (R [open bars]) and healthy control group (C [solid bars]). Bars and vertical lines represent mean \pm SD values. *Significance between S, R, and C.

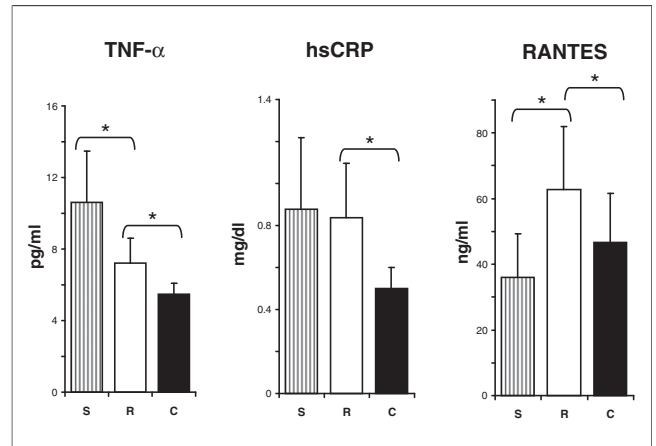


Figure 2 Circulating Inflammatory Mediators TNF- α , hsCRP, and RANTES

Serum levels of tumor necrosis factor α (TNF- α), high-sensitivity C-reactive protein (hsCRP), and regulated on activation, normal T-cell expressed and secreted (RANTES) in the study group (S [ruled bars]) compared with reference patients (R [open bars]) and healthy control group (C [solid bars]). Bars and vertical lines represent mean \pm SD values. *Significance between S, R, and C.

As Figure 3 illustrates, ET-1 levels were significantly higher in the study population as compared with reference patients (4.0 ± 0.5 pg/ml vs. 2.0 ± 0.5 pg/ml, $p < 0.001$), the latter having significantly higher levels compared with healthy volunteers (2.0 ± 0.5 pg/ml vs. 1.1 ± 0.2 pg/ml, $p < 0.001$). Significant differences in serum concentrations of both inflammatory mediators and ET-1 were not observed between specified clinical subgroups or between men and women (data not shown).

Table 2 yields the correlation between ET-1 and inflammatory mediators. In the study group, a strong positive correlation was found between ET-1 and the markers TNF- α ($r = 0.750$, $p < 0.001$) and sCD40L ($r = 0.709$, $p < 0.001$). MCP-1 and sVCAM-1 also showed a positive correlation with respect to ET-1 ($r = 0.611$, $p < 0.001$, and $r = 0.529$, $p < 0.001$, respectively). No correlation was found between ET-1 and hsCRP ($r = 0.161$, $p = 0.227$) or RANTES ($r = 0.048$, $p = 0.722$).

In the reference group, a positive correlation was detected between ET-1 and sCD40L or MCP-1 ($r = 0.556$, $p < 0.001$, and $r = 0.512$, $p < 0.001$, respectively). TNF- α ($r = 0.284$, $p = 0.031$), hsCRP ($r = 0.258$, $p = 0.050$), and RANTES ($r = 0.249$, $p = 0.059$) also showed a weak positive correlation with ET-1, whereas no correlation was analyzed between ET-1 and sVCAM-1 ($r = -0.099$, $p = 0.461$).

To investigate the diagnostic value of analyzed parameters, ROC curves were calculated; the results are summarized in Table 3. The ROC analysis for the study and the comparison group displays a high performance for both ET-1 and MCP-1, the area under the curve being 0.99 and 0.98, respectively. Estimation of the cutoff was based on the maximization of sensitivity and specificity,

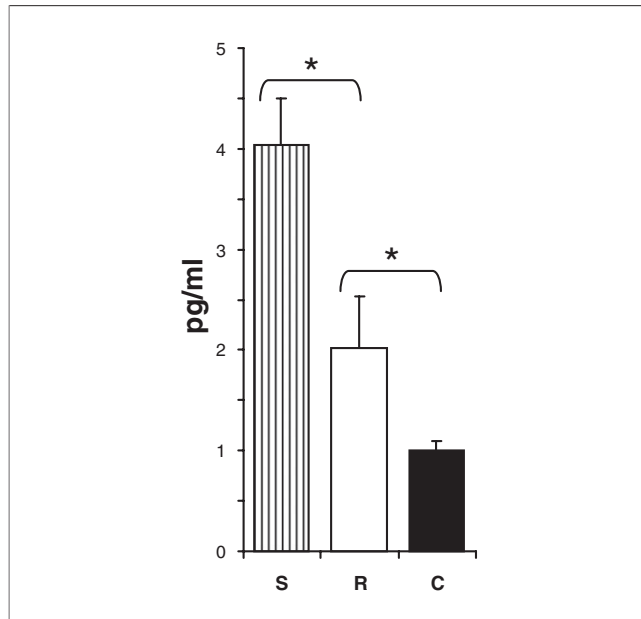


Figure 3 Circulating ET-1

Serum level of endothelin (ET)-1 in study patients (S [ruled bar]) compared with reference patients (R [open bar]) and healthy control group (C [solid bar]). Bars and vertical lines represent mean \pm SD values. *Significance between S, R, and C.

leading to a cutoff of 3.1 pg/ml for ET-1 with 100% sensitivity and 96.6% specificity, and 396 pg/ml for MCP-1, resulting in 93.1% sensitivity and 93.1% specificity (Fig. 4).

Table 2 Correlation Between ET-1 and Inflammatory Mediators

Correlation Between	ET-1	
	Study Group	Reference Group
sCD40L		
Correlation coefficient*	0.709	0.556
p value	<0.001	<0.001
sVCAM-1		
Correlation coefficient*	0.529	0.099
p value	<0.001	0.461
TNF-α		
Correlation coefficient†	0.777	0.284
p value	<0.001	0.031
MCP-1		
Correlation coefficient†	0.638	0.512
p value	<0.001	<0.001
RANTES		
Correlation coefficient*	0.048	0.249
p value	0.722	0.059
hsCRP		
Correlation coefficient*	0.161	0.258
p value	0.227	0.050

*Pearson correlation coefficient (r). †Spearman rank correlation coefficient.

ET = endothelin; hsCRP = high-sensitive C-reactive protein; MCP = monocyte chemoattractant protein; RANTES = regulated on activation, normal T-cell expressed and secreted; sCD40L = soluble CD40L; sVCAM = soluble vascular cell adhesion molecule; TNF = tumor necrosis factor.

Table 3 Receiver-Operating Characteristic Curve Analysis for Study and Reference Group of Inflammatory and Vasoconstrictive Mediators

Mediators	Sensitivity	Specificity	Cutoff
sCD40L (ng/ml)	82.8%	94.8%	1.9
sVCAM-1 (ng/ml)	91.4%	79.3%	375
TNF- α (pg/ml)	84.4%	82.8%	8.5
MCP-1 (ng/ml)	93.1%	93.1%	396
RANTES (ng/ml)	79.3%	86.2%	47.8
ET-1 (pg/ml)	100%	96.6%	3.1

Abbreviations as in Table 2.

Discussion

This is a unique report describing a modification of proinflammatory mediators and increased vasoconstrictor activity in patients with sustained ACS, occurring during the days of stressful soccer matches, versus a matched reference group. The ROC analysis displays a high performance for both ET-1 and MCP-1 as event-specific markers in such circumstances. Finally, our results show that serum levels of both vasoconstrictive and inflammatory mediators were higher in the reference population compared with healthy volunteers, confirming previous findings (3–7).

In the last decade, research has focused on identifying inflammatory signaling pathways specifically involved in ACS (8–11). Emotional stressors are now increasingly recognized as precipitants of cardiovascular events (12). One of the main stress responsive systems is the hypothalamic-pituitary-adrenal axis, as indicated by elevated stress hor-

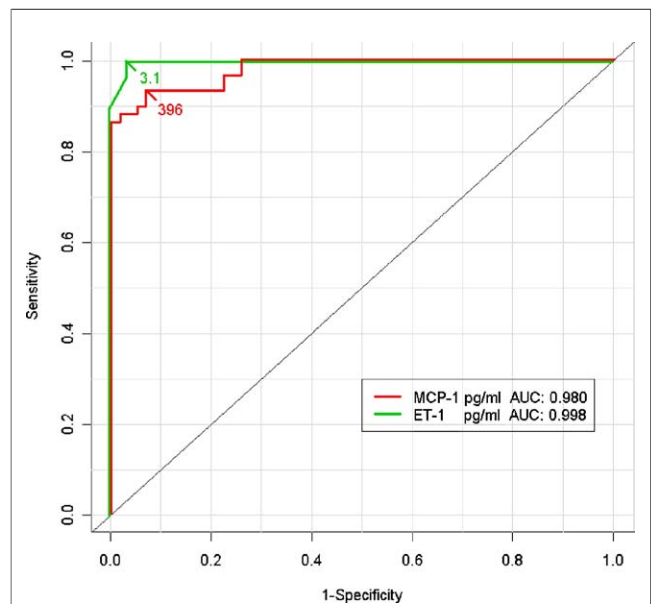


Figure 4 ROC Analysis of ET-1 and MCP-1

Receiver-operating characteristic (ROC) curves for the study group and reference group to assess both endothelin (ET)-1 (green line) and monocyte chemoattractant protein (MCP)-1 (red line) as specific markers of stress-associated acute coronary syndrome.

mones, the most important being corticotropin-releasing hormone. We have previously reported that corticotropin-releasing hormone may play a crucial role in endothelial dysfunction, including stimulation of ET-1, sCD40L, and sVCAM-1 expression (13,14). Thus, we hypothesize that these mediators are also involved in stress-related ACS.

As demonstrated in the present study, both sCD40L and sVCAM-1 are essentially increased in patients with sustained ACS on the day of stressful soccer matches as compared with ACS patients not undergoing stress.

Our results are supported by recent studies (15,16) that specify 3 different pathways that may be responsible for both our *in vitro* and *in vivo* findings, namely, stress-induced activation of platelets and endothelial cells. All of these are known to stimulate sCD40L and sVCAM-1 expression, most likely mediated by (stress-induced) adrenergic stimulation.

The inflammatory mediators TNF- α and MCP-1 play a pivotal role in plaque rupture and acute myocardial infarction (5). In the present study, both TNF- α and MCP-1 are significantly enhanced in study patients compared with patients whose event occurred in the absence of stress. Our findings are consistent with several previous studies (17–19) demonstrating an association between psychogenic stress, recruitment of monocytes, and an elevated MCP-1 response. Thus, stress may increase plasma TNF- α and MCP-1 in patients with ACS, most likely mediated by an enhanced activity of monocytes and macrophages.

Interestingly, hsCRP levels were roughly similar in both groups, arguing against the assumption that the increase of the mediators described in the preceding text merely reflects an acute phase reaction. In contrast to our results, Shah *et al.* (20) demonstrated that increased hsCRP was associated with a 20% higher risk of a mental stress-induced myocardial infarction. The conceptual study design, however, differed greatly. First, serum levels were measured 24 h after stress testing, whereas we analyzed blood samples collected 1 to 3 h after the onset of syndromes. Second, the study was performed in a laboratory environment as opposed to our “natural” stress experiment. Both aspects may explain the different results.

hsCRP has emerged as a strong independent risk factor, especially for future cardiovascular events (21). The strength of the association, however, has been modest in some studies or not conclusive (22). Thus, hsCRP did not help to characterize our stress-induced ACS patients.

Reports on RANTES have been contradictory in patients with coronary artery disease (23); serum levels have been shown to be elevated (24) or down-regulated (25). Data of the present study document a decrease of RANTES in patients who experienced an ACS during a stressful soccer match. The inverse association may reflect

increased deposition of RANTES on the activated vascular endothelium, leading to low serum concentrations and up-regulation of CCR5, a crucial RANTES receptor associated with atherosclerosis and adverse cardiovascular outcomes (26). To clarify the impact on stress-related ACS, the use of a modified ELISA is required (23) to simultaneously quantify soluble and adherent RANTES.

ET-1 is an established mediating factor in atherogenesis (27) and myocardial infarction (28). In analogy to our previously reported *in vitro* experiments (13,14), we find a pronounced increase of ET-1 in study patients suffering a stressful ACS. Results were confirmed by a former study demonstrating increased ET-1 levels after mental stress testing, associated with a prolonged endothelial dysfunction and reduced by a selective ET_A-receptor antagonist (29).

To emphasize the relevance of the markers used in the present study, and to identify whether there is a specific cutoff that is able to differentiate between the 2 entities (stress vs. nonstress-related ACS), we employed ROC analysis focused on these 2 groups. Compared with all analyzed mediators, a specific cutoff value for ET-1 was associated with a very high sensitivity and specificity, indicating that ET-1 may serve as a specific marker of such events.

While myocardial ischemia was comparable both in the study and the matched reference group, it was the additional emotional stress that uniquely defined the study group. The positive correlation between enhanced ET-1 and increased sCD40L, sVCAM-1, TNF- α , and MCP-1 provides evidence that only the combination of ischemia and emotional stress was a strong enough combined trigger mechanism to activate both the inflammation pathway and the ET-1 system.

Study limitations. Because of the design of the initial pre-clinical study (1), the database of the present study group was also anonymous; consequently, no information about troponin or stress-hormone levels, cardiovascular risk factors, infarct size, left ventricular function, clinical outcome, or Holter electrocardiography to assess the vagal-sympathetic balance was available. Only 27% of all screened patients (1) were included in the present study. However, this limitation is unlikely to affect our results as this group is a representative sample of all ACS patients.

Conclusions

We found an up-to-now unknown relationship between stress-induced ACS and increased inflammatory status, associated with enhanced ET-1 release. In view of this relationship, the evaluation of a targeted prophylactic and therapeutic drug delivery is warranted, including anti-inflammatory agents and, particularly with regard to analyzed ET-1 effects, ET receptor antagonists to reduce stress-mediated cardiovascular morbidity.

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Key Words: emotional stress ■ atherosclerosis ■ inflammation ■ endothelin-1.

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