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Physiological responses to emotional excitement in healthy subjects and patients with coronary artery disease☆

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ABSTRACT

Emotional excitement may trigger cardiovascular (CV) events, particularly in patients with coronary artery disease (CAD). Our aim was to compare changes in various biomarkers in CAD patients and age-matched healthy male subjects during "real-life" emotional excitement. Enthusiastic male ice hockey spectators (CAD n = 18, healthy subjects n = 16) attended Finnish national ice hockey play-off matches. Heart rate variability, plasma catecholamines, endothelin-1 (ET-1) and interleukin-6 (IL-6) were determined at the baseline and during the match. A significantly more marked increase in both ET-1 and IL-6 was observed in CAD patients compared with healthy subjects during the match (time × group interaction $p = 0.009$ and $p = 0.018$ for ET-1 and IL-6, respectively). The high-frequency power of R–R intervals decreased in CAD patients ($p < 0.001$) but did not change in healthy subjects (p = ns, time × group interaction $p < 0.001$). Changes in adrenaline and noradrenaline did not differ between the groups. Emotional excitement causes more marked increases of markers of vasoconstriction and acute inflammation and withdrawal of cardiac vagal regulation in patients with CAD.

1. Introduction

Emotional excitement has been shown to be an important trigger of cardiovascular events, so that earthquakes, wars, and sporting events, for example, are associated with peaks in the incidence of sudden cardiac death, myocardial infarction, and acute coronary syndrome (Meisel et al., 1991; Leor et al., 1996; Serra et al., 2005). A recent study showed that an exciting soccer game more than doubled the risk of acute cardiovascular events, including acute coronary syndrome and symptomatic cardiac arrhythmias, during the World Cup soccer tournament held in Germany from June 9 to July 9, 2006, while another study pointed to an increase in the incidence of acute myocardial infarction after the English national team lost a World Cup penalty shoot-out (Carroll et al., 2002; Wilbert-Lampen et al., 2008). It has also been proposed that such triggering is more common in patients with coronary artery disease (CAD) than in those without it (Leor et al., 1996).

We have recently shown endothelin-1 (ET-1) and interleukin-6 (IL-6) increase in CAD patients during emotional excitement caused by watching an exciting ice hockey match (Piira et al., 2012). Secondly, the autonomic nervous system is activated during emotional excitement, which may partly explain the vulnerability to cardiovascular events. Our previous results showed that cardiac vagal outflow is attenuated and vasomotor sympathetic activity is elevated in CAD patients during exciting sports events (Piira et al., 2011). Elevations in both systolic and diastolic blood pressure and in markers of vasoconstriction and acute inflammatory response also occurred rapidly in CAD patients during exciting periods of a match and despite beta-blocking medication.

It has been shown that both the inflammation pathway and ET-1 system are more markedly activated in acute coronary syndrome triggered by emotional excitement than acute coronary syndrome without emotional trigger (Wilbert-Lampen et al., 2010). Furthermore, in our recent study vagally mediated short-term heart variability was associated with the ET-1 levels during emotional excitement in CAD patients (Piira et al., 2012). Thirdly, inflammation has been proposed to be associated with reduced heart rate variability and named as "inflammatory reflex" (Tracey, 2002). Therefore we tested the hypothesis that particularly plasma ET-1 and IL-6 responses and heart rate variability may differ between patients with CAD and control subjects without clinical evidence of CAD. We compared changes in heart rate variability, plasma endothelin-1 and interleukin-6 levels, catecholamine levels, and hemostatic parameters, i.e. blood coagulation and platelet activation, caused by leisure-time emotional excitement in patients with stable CAD and age-matched healthy subjects.

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2. Methods

2.1. Subject selection

The patients were selected from the ARTEMIS (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection, registered at ClinicalTrials.gov, Record 1539/31/06) study database, which comprised of 665 patients with CAD who underwent a thorough evaluation of their cardiovascular status, including a baseline examination performed by a cardiologist, echocardiography, an exercise stress test, and 24-hour Holter recordings. CAD and its severity were assessed by coronary angiography at the Oulu University Hospital within six months of inclusion. All the subjects gave informed consent before participating. This sub-study of the ARTEMIS project was approved by the Ethics Committee of Oulu University Hospital and was deemed to comply with the Declaration of Helsinki. To maximize the likelihood of emotional arousal, 162 candidates were interviewed by telephone about their devotion to spectator sports and the most enthusiastic ice hockey fans were chosen for the present investigation (55 males). Control subjects were recruited with flyers and via the internet (n = 16, all males). Subjective experience of excitement was assessed with a questionnaire during the match (0 = none, 1 = very low, 2 = low, 3 = medium, 4 = high, 5 = very high excitement).

2.2. Protocol

The subjects were spectators at the Finnish National Ice Hockey League play-off matches held in the city of Oulu, Finland, in 2008, 2009, and 2011. The Oulu team "Kärpät" won the league championship in 2008 and came in second in 2009 and seventh in 2011. The number of play-off matches when measurements were performed at each year was 6 in 2008, 3 in 2009, and 1 in 2011. Fifty five CAD patients and 16 healthy subjects were measured. All healthy subjects (age range from 41 to 60 years) and all the CAD patients less than 61 years were included in the final analysis (age range from 45 to 60 years). Patients older than 60 years were excluded since it's well known that age has significant effects on heart rate variability values. The characteristics and clinical data of the patients and healthy subjects are shown in Table 1.

The subjects watched the matches in a private balcony of the ice hockey stadium with an excellent view of the ice rink at a constant temperature of 20 °C. A baseline blood sample was collected before the match with the patient in a sitting position and a second sample, 1.5 h after the beginning of the match, in between the second and third periods, in the private balcony of the ice hockey stadium.

2.3. Maximal exercise test

All the subjects performed a maximal bicycle exercise stress test which started at 30 W, followed by an incremental protocol with the work rate increasing at a rate of 15 W every min. The CAD patients were encouraged to reach a symptom-limited maximal workload and the healthy controls were encouraged until voluntary exhaustion. The control subjects were tested to exclude subjects with asymptomatic CAD; those with more than 0.1 mV ST segment depression were excluded (n = 0).

2.4. Heart rate and heart rate variability

A 24-hour ECG recording was taken of all the attending subjects on the match day and during a reference day within one week after the match. Heart rate variability was analyzed during the match hours (three hours from the beginning of the match) and at the corresponding time of day during the reference measurement. Average heart rate, standard deviation of normal-to-normal R–R intervals (SDNN), high-frequency power (HF power 0.15–0.4 Hz), low-frequency power (LF power 0.04–0.15 Hz), and very-low-frequency power (VLF 0.0033–0.04 Hz) were analyzed from the R–R interval data using standard methods (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Table 1
Characteristics and clinical data of the CAD patients and healthy subjects.

	CAD	Healthy
Males	18 (100%)	16 (100%)
Age, years	51 ± 6	48 ± 6
BMI	29 ± 4	26 ± 2‡
Type 2 diabetes	9 (50%)	–
Current smoker	1 (5%)	–
Sleep apnea	3 (6%)	–
Hypertension	9 (50%)	–
Clinical features of CAD		
History of AMI	11 (61%)	–
Prior CABG	6 (33%)	–
Prior PCI	10 (56%)	–
1-vessel CAD	11 (61%)	–
2-vessel CAD	1 (5%)	–
3-vessel CAD	6 (33%)	–
Angina pectoris CCS class 1	18 (100%)	–
Echo-Doppler EF (%)	65 ± 6	
Bicycle stress test		
Max load, W	183 ± 33	242 ± 39‡
METs	7.2 ± 1.5	9.9 ± 1.7‡
Heart rate max, bpm	143 ± 21	176 ± 10‡
ST depression >0.1 mm	7 (39%)	0
Medication		
Aspirin	17 (94%)	–
Clopidogrel	6 (33%)	–
Beta blocker	17 (94%)	–
Calcium antagonist	6 (33%)	–
ACEI/ARB	14 (77%)	–
Diuretic	4 (22%)	–
Statin	18 (100%)	–
Nitro, daily	2 (11%)	–
Oral antidiabetic	6 (33%)	–
Insulin	2 (11%)	–

Values are means ± SD; BMI, body mass index; diabetes (all type 2 diabetes); AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneus coronary intervention; EF, ejection fraction measured by 2-dimensional echo-Doppler according to ASE guidelines; CCS, Canadian cardiology society functional class; CAD, coronary artery disease; 1-, 2-, and 3-CAD, angiographically evaluated proximal coronary arteries with more than 50% stenosis; ACEI, angiotensin conversion enzyme inhibitor; ARB, angiotensin receptor blocker.
*$p < 0.001$.

2.5. Blood collection, sample preparation, and laboratory analysis

Blood samples for determining plasma catecholamines, markers of blood coagulation, and platelet activation were collected by venipuncture from the cubital vein via a 20 G needle (Venoject, Terumo Medical Corporation, NJ, USA) connected to vacutainer tubes. The first 5 mL of blood were discarded. The samples were collected in a sitting position. Baseline samples were collected after a quiet steady period of 3–5 min. To avoid any confounding effects, considerable attention was paid to proper blood collection, handling, and storage. All the laboratory analyses were performed in high-quality national reference laboratories.

2.6. Analysis of endothelin-1 and interleukin-6

The concentrations of endothelin-1 (ET-1) and interleukin-6 (IL-6) were determined from serum samples. Serum was prepared by allowing the blood to clot for 30 min followed by centrifugation at 2000 ×g for 10 min. The serum was stored at −20 °C until analyzed. ET-1 levels were analyzed using a sandwich, enzyme-linked immunosorbent assay (ELISA) (QuantiGlo Chemiluminescent Immunoassay,