Mental stress induces prolonged endothelial dysfunction via endothelin-A receptors

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Background—Mental stress is a risk factor for atherosclerosis and may precipitate myocardial ischemia and infarction. Because endothelial dysfunction is an early manifestation of atherosclerosis, we investigated the impact of mental stress on endothelial function.

Methods and Results—The effects of a 3-minute mental stress task on endothelium-dependent vasodilation were studied in healthy subjects without cardiovascular risk factors. Flow-mediated (FMD) and nitroglycerin (0.4 mg sublingual)-induced vasodilation were studied before and after mental stress by high-resolution ultrasound of the radial artery. Additionally, FMD was assessed before and 10 to 45 minutes after mental stress during intraarterial infusion of a selective endothelin A receptor antagonist (BQ-123, 1 nmol/min) or saline, respectively. Endothelium-dependent vasodilation was reduced by half for about 45 minutes (8.0±1.1% versus 4.1±1.0%; P<0.002), whereas endothelium-independent vasodilation to nitroglycerin remained unaffected (15.6±1.6 versus 14.3±1.3%; NS). Intraarterial infusion of BQ-123, a selective endothelin-A receptor antagonist, but not saline prevented the impairment of endothelium-dependent vasodilation (8.6±1.2 versus 9.4±1.3%; NS). In contrast, intraarterial infusion of norepinephrine of similar duration as mental stress did not inhibit FMD.

Conclusions—Mental stress induces prolonged endothelial dysfunction, which is prevented by selective endothelin-A receptor antagonism. This represents a novel and important link between mental stress and atherosclerotic vascular disease. (Circulation. 2002;105:2817-2820.)

Key Words: atherosclerosis • endothelin • nitric oxide • reactive hyperemia

Mental stress triggers myocardial ischemia in patients with coronary artery disease. In fact, sudden life stressors, such as anger, bereavement, earthquakes, or war can even precipitate cardiac events such as acute myocardial infarction or sudden cardiac death. However, the mechanisms by which stress translates into vascular injury still remain elusive.

Cardiovascular risk factors, eg, hypercholesterolemia and hypertension, impair endothelial function as they blunt bioavailability of NO and enhance ET-1 formation in the vascular wall. Hence, the aim of this study was to investigate the effects of mental stress on endothelial function in humans and to delineate the mechanisms involved.

Methods

Subjects
Twenty-three healthy subjects (aged 20 to 31 years; body mass index, 21.6±1.7 kg/m²; arterial blood pressure, 113±8/67±7 mm Hg; total cholesterol 4.5±0.3 mmol/L) without any cardiovascular risk factor participated in the study. All subjects gave written informed consent and the study protocol was approved by the local research ethics committee of the University Hospital Zürich, Switzerland.

Study Protocol

Flow-mediated dilation (FMD) and nitroglycerin (0.4 mg, Nitrolingual Spray, Pohl-Boskamp, Germany)-induced vasodilation of the radial artery were assessed before and 10 minutes after a 3-minute mental stress test with a high-resolution A-mode ultrasonic echotracking device (Nius, Asulab, Switzerland) as described previously. Intraarterial infusion of BQ-123, a selective endothelin-A receptor antagonist, but not saline prevented the impairment of endothelium-dependent vasodilation (8.6±1.2 versus 9.4±1.3%; NS). In contrast, intraarterial infusion of norepinephrine of similar duration as mental stress did not inhibit FMD.
before and after stress testing; in 5 subjects, FMD was repeatedly measured before and 10, 30, and 45 minutes after mental stress; and in 6 subjects, FMD was measured before and 10 minutes after completing the mental stress task during continuous intraarterial infusion of BQ-123 (1 nmol/min; Clinalfa, Switzerland), a selective endothelin-A receptor (ETA) receptor antagonist, started 15 minutes before the mental stress test. The 10-minute measuring point was selected because the acute hemodynamic effects of mental stress had disappeared at that time. In control experiments (n/H11005 3), saline (NaCl 0.9%) was infused intraarterially. Drugs were infused with a constant rate infusion pump (1 mL/min; Perfusor, Braun, Germany) through an indwelling catheter (20G; Ohmeda, Swindon, UK) inserted under local anesthesia into the brachial artery of the nondominant arm. In contrast to pilot experiments and previous studies with higher dosages (10 and 100 nmol/min), in the present study a 10-times lower dosage of BQ-123 was chosen to exclude any hemodynamic effect. In further experiments (n/H11005 6), radial artery blood flow was measured before and after mental stress (PW-Doppler; angle of insonation, 60°; range gate in the center of the artery). Venous blood samples were drawn before and immediately after the mental stress test in additional experiments (n/H11005 8). Circulating ET-1 and norepinephrine levels were measured by radioimmunoassay. In separate experiments, FMD was measured before and 10 minutes after terminating a brief (3 minutes) intraarterial infusion of norepinephrine (30 ng/min) to simulate an activation of the sympathetic nervous system (n/H11005 5).

Statistical Analysis
Results are presented as mean±SEM unless stated otherwise. Measurements of FMD and nitroglycerin-induced vasodilation represent the maximal increase in radial diastolic artery diameter and are expressed as percent change from baseline.6,9 Differences in parameters before and after mental stress were examined by 2-tailed paired Student’s t test and between-group analysis was performed by unpaired t test. Changes in vital signs during mental stress were examined by ANOVA for repeated measures (StatView 4.5, Abacus Concepts). Statistical significance was accepted at P<0.05.

Results
FMD of the radial artery before mental stress averaged 8.0±1.1%, and nitroglycerin-induced vasodilation averaged 15.6±1.6%. The mental stress test transiently increased mean arterial blood pressure (from 83±1 before the mental stress task to 96±3 mm Hg during the last minute of the stress task; P<0.0001 by ANOVA) and heart rate (from 63±5 before mental stress to 81±7 bpm during the last minute of the stress test; P<0.0001 by ANOVA). Circulating ET-1 (2.1±0.1 pmol/mL before mental stress versus 2.1±0.1 pg/mL at the end of the stress task; NS) and norepinephrine levels (1827±417 versus 1788±333 pmol/L, NS) remained stable. Baseline hemodynamic conditions were reestablished 10 minutes after completing the mental stress task (mean arterial blood pressure, 82±2 mm Hg; heart rate, 64±6 beats per minute; radial artery blood flow, 66±11 versus 75±10 mL/min; radial artery diameter, 2.82±0.13 versus 2.86±0.13 mm; all NS). However, FMD was reduced by half to 4.1±1.0% (P<0.002 versus baseline; Figure 1A), whereas nitroglycerin-induced vasodilation remained unaltered (14.3±1.3%, NS; Figure 1A). FMD progressively returned to baseline levels over a period of approximately 45 minutes (Figure 2; P=0.0002 for trend). The impairment in FMD of the radial artery after...
Flow-dependent vasodilation of large conduit arteries is a physiologically important adaptive response of the cardiovascular system during stress mediated by NO. Impaired flow-dependent vasodilation after mental stress reflects an acute imbalance of endothelium-derived NO and ET-1. Indeed, ET-1 reduces the vasodilator effects of NO. In line with this, the impairment of endothelial function induced by mental stress was prevented by ET<sub>A</sub> receptor blockade.

We have previously described a small increase of plasma ET-1 levels after mental arithmetic in offspring of hypertensive but not normotensive parents. As most of ET-1 produced by endothelial cells is secreted abuminally where it exerts its actions in a paracrine rather than endocrine fashion, circulating ET-1 levels thus do not reflect the local activity of ET-1 in vascular tissue. This is particularly interesting because vascular tissue and circulating levels of ET-1 are elevated in patients with atherosclerosis. In patients with coronary artery disease, vascular tissue levels increase as the process becomes unstable and particularly after infarction.

A contribution of the sympathetic nervous system to the derangement of vascular function after mental stress could be excluded. An intraarterial infusion of norepinephrine of similar duration as mental stress resulting in a 4-fold increase of plasma norepinephrine only caused a short transient vasoconstriction for about 5 minutes but did not affect endothelial function 10 minutes later when baseline conditions were reached.

The findings of the present study are in line with the concept of an atherogenic effect of mental stress. Endothelial dysfunction induced by mental stress offers a novel and unique link between psychological factors and the pathogenesis of atherosclerosis similarly to other risk factors that impair endothelial function, eg, hypercholesterolemia and hypertension. Because the underlying mechanism is ET<sub>A</sub> receptor activation, ET<sub>A</sub> receptor antagonism may represent a new therapeutic strategy in the prevention of atherosclerotic vascular disease and its complications.

**Acknowledgments**

This study was supported by the Swiss National Research Foundation (grants 32-51069.97/1 and 32-52690.97), the Swiss Heart Foundation, and the Stanley Thomas Johnson Foundation. The authors thank Manuela Zahno and Rosy Hug for expert technical assistance.

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_Circulation_. 2002;105:2817-2820; originally published online May 20, 2002;
doi: 10.1161/01.CIR.0000021598.15895.34

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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