VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2007, Vol. 14, No. 2, pp. 180–185

ISSN 1507–4145

Mental stress, heart rate and endothelial function in patients with syndrome X

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Abstract

Background: *The aim of the study was to determine whether the baseline heart rate (HR) and changes in HR after mental stress (MS) can influence endothelial function in syndrome X.*

Methods: *Forty four patients with syndrome X (F/M: 21/23, mean age: 55.4 ± 10.7 years) were examined. The endothelium-dependent flow-mediated dilation (FMD) was defined as the percentage change in the brachial artery diameter during reactive hyperaemia related to baseline (%FMD). The %FMD was assessed before and after (at 10, 30, and 45 min) standardised three-minute MS. HR and blood pressure were monitored simultaneously. The %FMD values were compared between subgroups characterised by baseline HR, maximum HR and ΔHR, and HR after MS below and over the median values.*

Results: *The values of %FMD measured at 10, 30 and 45 min after MS (4.39 ± 5.4%, 4.99 ± 3.9%, 4.03 ± 3.5%, respectively; $p < 0.001$) were significantly lower than baseline values (7.73 ± 4.9%). Impaired vasodilatation after MS was observed in the following subgroups of patients: those with baseline HR below the median (< 71.5 bpm; baseline: 8.35 ± ± 5.8%; 10 min: 2.87 ± 3.6%, 45 min: 4.56 ± 3.9%; $p < 0.001$); those with HR after MS below the median (< 76.5 bpm; baseline: 8.19 ± 5.5; 10 min: 3.88 ± 4.3%, 45 min: 4.59 ± ± 3.7%; $p < 0.01$); and those with maximum HR after MS below the median (< 84 bpm; baseline: 8.88 ± 5.6%; 10 min: 3.88 ± 3.8%, 30 min: 5.88 ± 3.9%, 45 min: 4.51 ± 3.8; $p < 0.01$).*

Conclusion: *The stress-induced endothelial dysfunction syndrome X is related to the baseline HR and the changes in HR after MS, suggesting that the autonomic nervous system plays a part in its pathogenesis.* (Cardiol J 2007; 14: 180–185)

Key words: mental stress, heart rate, flow mediated dilatation, syndrome X

Introduction

The term "cardiac syndrome X" was first used in 1973, when Kemp et al. [1] reported on normal coronarography results (normal arteriograms) in patients with symptoms of angina pectoris. Endothelial dysfunction has been mentioned as a potential cause, resulting in the compromise of the coronary microcirculation and disturbance in sympathetic-parasympathetic control [2–5].

Mental stress (MS) is a well-recognised factor in the increase of sympathetic activation, which in turn affects the systemic circulation, increasing the heart rate (HR) and elevating arterial pressure, which potentially leads to myocardial ischaemia. Data in the literature suggest that stress may

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Received: 9.11.2006 Accepted: 27.01.2006

produce angina-like pain in syndrome X patients; thus, apart from haemodynamic changes, endothelial dysfunction should also be considered in its pathogenesis [4, 6, 7]. It is still unknown whether stress-induced haemodynamic changes may be associated with endothelial function.

The purpose of our study was to investigate whether baseline HR and HR increase induced by standardised MS affects endothelial function as reflected in the vasodilatory response in patients with cardiac syndrome X.

Methods

Study population

A total of 44 patients (23 men and 21 women with a mean age of 55.4 ± 10.7 years and ranging in age from 38 to 76 years) with cardiac syndrome X were included in the study. The inclusion criteria were typical symptoms of ischaemic heart disease, an exercise ECG showing a positive result and absence of any lesions within the coronary vessels on coronary arteriography.

Subgroups were defined on the basis of median values calculated for the following parameters: baseline HR (subgroups: A1 and A2), post-MS HR (subgroups: B1 and B2) and maximum HR (subgroups: C1 and C2). The parameter values in particular subgroups were lower or higher than the median value (Table 1).

Patients with concomitant inflammatory conditions, neoplastic disease, uncompensated metabolic disturbances, renal or liver failure, a history of acute coronary events, those who had undergone surgery within the 6 months preceding the study and those with difficult baseline ECG interpretation were excluded. Investigations were performed in the morning with the patients fasting and after at least twelve hours' abstinence from smoking. The study protocol was approved by the Bioethics Committee of the Medical University of Silesia.

Table 1. Division of study group into subgroups.

Division criteria	Study subgroups
Baseline heart rate (median 71.5)	A1 — below median value (N = 22)
	A2 — above median value (N = 22)
Post-mental stress heart rate	B1 — below median value (N = 22)
(median 76.5)	B2 — above median value (N = 22)
Maximum heart rate (median 84)	C1 — below median value (N = 24)
	C2 — above median value (N = 20)

Evaluation of clinical parameters

The clinical parameters were evaluated together with the results of the patients' lipid profiles (total serum cholesterol, serum HDL cholesterol, LDL cholesterol, and triglycerides), ECG, exercise test, echocardiography and coronarography. Patient histories of smoking, concomitant disease and pharmacotherapy used were also taken.

Mental stress

Prior to MS testing the patients were allowed to rest in a quiet room for 15 minutes. After baseline arterial blood pressure and HR had been recorded an arithmetic stress test was applied. The subjects were required to listen to a recorded message instructing patients how to perform the mental stress task. They were asked to subtract 7 repeatedly from 777 and the consecutive results of subtraction for 3 min. Arterial pressure and HR were measured during and following the MS. None of the investigators had any communication with the subjects during this time. The subjects were asked to fill in a psychological questionnaire grading emotional tension before and after the MS on scale of 1 to 4.

Flow-mediated dilation

Flow-mediated dilation (FMD) was measured before MS, and at 10, 30, and 45 min afterwards. Each time a dedicated and specifically trained investigator took measurements using a high-frequency ultrasound system in B-mode presentation. During image acquisition anatomical landmarks, including veins and facial planes, and a stereotactic clamp were useful for maintaining the same image of the artery throughout the study.

The baseline brachial artery diameter was determined. Subsequently a three-minute vessel occlusion was produced by inflating a manometer cuff up to over 200 mm Hg or a value equal to systolic pressure of + 50 mm Hg. Within 60 s of cuff deflation several measurements of the vessel diameter were taken. The percentage change in the diameter was calculated (%FMD). After 15 minutes vascular response to sublingual nitroglycerine (0.4 mg) was assessed on the basis of %NTG-MD (%NTG — mediated dilatation) [8].

Statistical analysis

The results were analysed statistically. Median values were calculated for the following parameters: baseline HR, post-MS HR and maximum HR. See above under "study population" for the subgroup division. Means and standard deviations were calculated for all the subjects and the subgroups examined. Clinical parameters and the results of accessory investigations were compared using the χ^2 test for proportions and the two-sample t-tests for normally distributed continuous variables; in the case of abnormal distribution the Mann-Whitney U test was used. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

The characteristics of the study group are presented in Table 2. The subgroups (delineated in Table 1) were similar regarding sex, age and incidence of arterial hypertension. Comparison of clinical data between subgroups revealed the following differences: subgroups A1 vs. A2 — difference in serum triglyceride concentrations (114.4 ± 43.6 *vs.* 178.9 ± 81.1; p = 0.005); subgroups B1 *vs.* B2 — differences in left ventricular mass index (150.3 ± ± 29.9 *vs.* 127.1 ± 24.5; p = 0.02) and in Ca-blocker use (40.1% *vs*. 9.1%; p = 0.005). No significant differences were found between the clinical parameters assessed in the subgroups C1 and C2.

The assessment of emotional tension questionnaires on a scale of 1 to 4 showed a significant increase in the parameter from baseline: 1.77 ± 1.12, to 2.34 ± 1.1; $p < 0.05$ after the MS. The increase was comparable in the subgroups studied. The results of arterial pressure and HR recordings during MS are presented in Table 3.

As shown in Figure 1, a reduction in %FMD was observed in all study subjects at 10, 30, and 45 min following MS (4.39 ± 5.4%, 4.99 ± 3.9%, 4.03 ± 3.5%, respectively; $p < 0.001$) as compared to the baseline (7.73 ± 4.9%).

Comparison of the results between subgroups revealed a significant %FMD decrease at 10, and 45 min in subgroups A1, and B1. The mean %FMD values were as follows: subgroup A1 (Fig. 2): 2.87 ± 3.6% at 10 min, 4.56 ± 3.9% at 45 min,

Table 2. Characteristics of study group.

N	44
Age (years)	55.4 ± 10.7
Body mass index [kg/m^2]	29.5 ± 3.9
Total cholesterol [mg/dl]	220.0 ± 46.1
HDL cholesterol [mg/dl]	49.5 ± 15.4
LDL cholesterol [mg/dl]	140.7 ± 40.6
Triglycerides [mg/dl]	146.7 ± 72.1
Left ventricular mass [g]	266.9 ± 66.4
Left ventricular mass index [g/m^2]	138.9 ± 29.5
Ejection fraction (%)	58.0 ± 7.6
Smoking status:	
active smoker	5 (11.4%)
ex-smoker	3 (29.5%)
never smoked	25 (56.8%)
Pharmacotherapy:	
ACE inhibitors	25 (56.8%)
Ca-blockers	11 (25%)
Statins	21 (47.7%)

ACE inhibitors: peridopril, quinalapril, enalapril; Ca-blockers: amlodipine, diltiazem; statins: atorwastatin, simvastatin, lovastatin

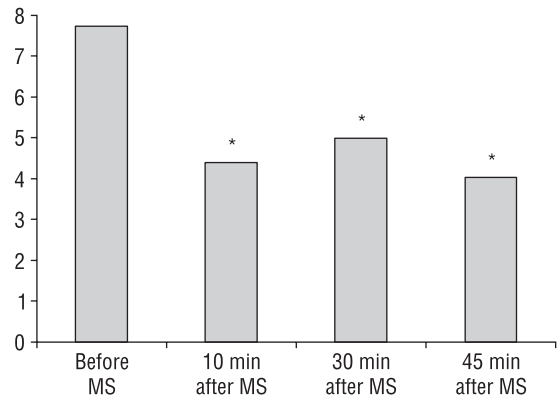

Figure 1. Flow mediated dilatation (%) measured at 10, 30 and 45 minutes after mental stress (MS) in study group; *p < 0.001 (*vs.* baseline values).

Table 3. Arterial blood pressure, heart rate before and after mental stress (MS).

	Before MS	After MS	Maximum values	Δ (increase)
Systolic blood pressure [mm Hg]	127.4 ± 14.6	144.1 ± 20.1	—	21.5 ± 15
Diastolic blood pressure [mm Hg])	77.7 ± 9.9	87.2 ± 13.2	—	13.3 ± 8.3
Heart rate [bpm]	71.2 ± 12.7	78.3 ± 16.9	86.5 ± 20.4	8 ± 7.3

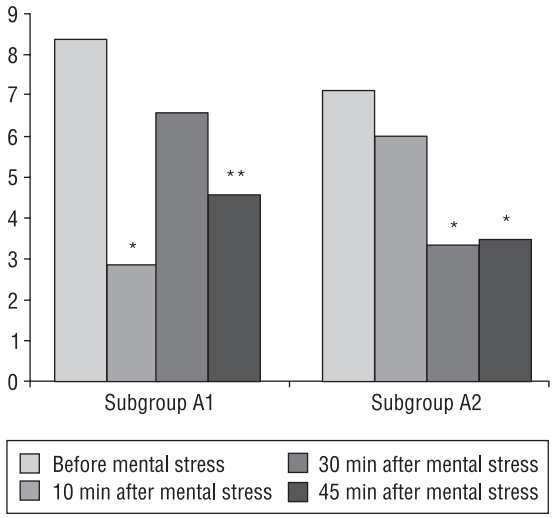

Figure 2. Flow mediated dilatation (%) in subgroups A1 and A2 (baseline heart rate below and above median values); *p < 0.001 (*vs.* baseline values); **p < 0.02 (*vs.* baseline values).

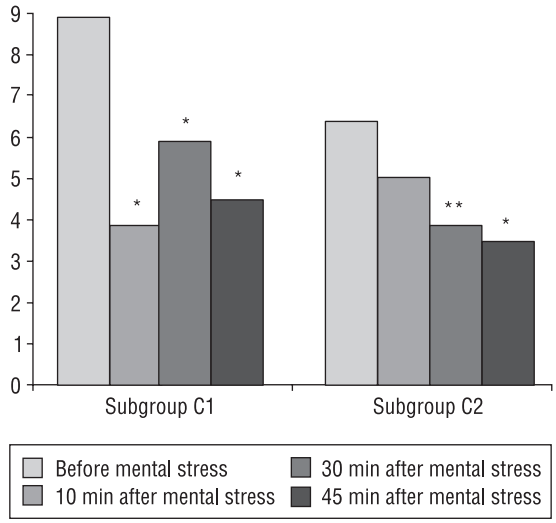

Figure 4. Flow mediated dilatation (%) in subgroups C1 and C2 (maximum heart rate below and above median values); *p < 0.02 (*vs.* baseline values); **p < 0.05 (*vs.* baseline values).

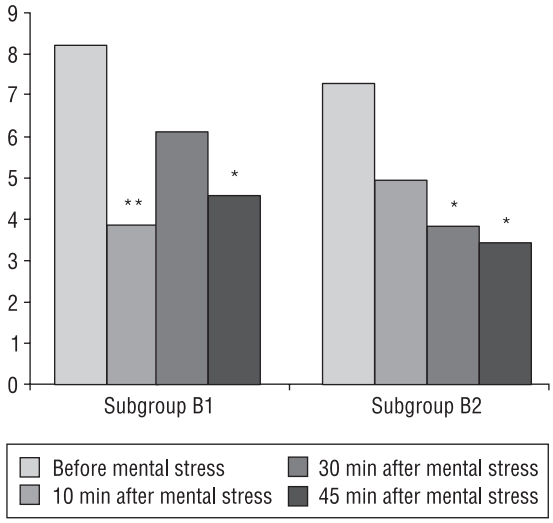

Figure 3. Flow mediated dilatation (%) in subgroups B1 and B2 (post-mental stress heart rate below and above median values); *p < 0.01 (*vs.* baseline values); **p < 0.001 (*vs.* baseline values).

8.35 ± 5.8% at baseline (p < 0.001); subgroup B1 (Fig. 3): 3.88 ± 4.3% at 10 min, 4.59 ± 3.7% at 45 min, 8.19 ± 5.5% at baseline (p < 0.01). In subgroup C1 (Fig. 4) %FMD was reduced at 10, 30, and 45 min after MS to 3.88 ± 3.8%, 5.88 ± 3.9%, and 4.51 ± ± 3.8% respectively; baseline: 8.88 ± 5.6%. In subgroups A2, B2 and C2 significant %FMD reduction was noted only at 30 and 45 min after MS: subgroup A2: 3.33 ± 3.8%, and 3.48 ± 3% at 30 and 45 min, respectively (p < 0.001); baseline: 7.11 ± 3.9% (Fig. 2); subgroup B2: 3.82 ± ± 4.1%, and 3.46 ± 3.3% at 30 and 45 min, respectively (p < 0.01); baseline: 7.27 ± 4.4% (Fig. 3); subgroup C2: 3.88 ± 3.6%, and 3.43 ± 3.0% at 30 and 45 min respectively (p < 0.01); baseline: 6.35 ± ± 3.6% (Fig. 4).

Discussion

The purpose of our study was to investigate whether HR increase induced by standardised MS affected endothelial function in patients with cardiac syndrome X. Endogenous vasodilatory response was indicated by FMD, a marker of endothelium-mediated dilation.

Reduction of %FMD was observed in all study subjects at 10, 30, and 45 min following MS. Thus endothelial dysfunction was noted, lasting for at least 45 min following three-minute standardised MS.

Subgroup analysis revealed a relationship between HR and early and late endothelial dysfunction after MS. Early dysfunction, at 10 min following MS, was observed in patients with a lower baseline HR. In those with a high baseline HR the mental stressor elicited compromised vasodilatory responses only at 30 and 45 min. It is important that the above-mentioned changes were observed despite a comparable increase in emotional tension after MS.

Literature data on the effect of MS on endothelial function are somewhat scarce. Those available are mostly related to animal studies and there are

few reports on the phenomenon in healthy volunteers and patients with coronary artery disease [9–13]. In animals prolonged stress caused endothelial dysfunction by increasing the number of damaged cells and compromising nitric oxide availability in the vascular wall [14].

In a healthy population MS induced an elevation of arterial pressure, an increase in HR and a decrease in brachial artery diameter. The values of %FMD were significantly attenuated at 30 and 90 min after MS and only normalised after four hours of observation [15]. In our group endothelial dysfunction was still seen at 45 min after MS; a study of longer duration would allow us to establish the time point at which %FMD normalises.

It is also significant that stress reduces both peripheral and coronary flow. Kop et al. [16] used a similar arithmetic stress test in patients with coronary artery disease and demonstrated coronary vasospasm in as many as 19% of the population. The elevation of arterial pressure observed correlated with a reduced diameter of atherosclerotic segments, while the diameter of the normal artery remained unchanged.

There is an even greater scarcity of reports on the relationship between endothelial and autonomic functions. Some indirect conclusions may, however, be drawn from reports on the relationship between sympathetic activation and ambulatory ischaemic events [17]. It has been shown that ischaemic events associated with high emotional stress have been preceded by a lowered HF-HRV component, still observed 20 min after ECG normalisation. This might suggest that stress causes prolonged disturbances of the autonomic balance. However, the results were obtained for patients with coronary artery disease; similar data on cardiac X syndrome are lacking.

Spieker et al. [18] confirmed that MS induces endothelial dysfunction but did not demonstrate any correlation between %FMD, arterial pressure and HR changes during MS. The authors suggest that endothelial dysfunction may be associated with endothelin activation. Administration of an endothelin type A receptor-selective antagonist prevented the development of endothelial dysfunction and %FMD approximated to baseline values as early as 10 min following MS. Intravascular norepinephrine with a similar duration to the MS caused only transient vasoconstriction.

The Framingham Heart Study on a sub-population of 3500 [19] demonstrated a positive correlation between %FMD, female subjects, physical exercise (the "walk test") and, significantly from our point of view, HR. Subsequent investigation [20] showed that patients with an impaired chronotropic response to the graded exercise test had endothelial dysfunction and enhanced systemic inflammation.

Animal studies [14] as well as our previous results [21] suggest that a higher-frequency pulsate flow is associated with increased nitric oxide release. In subjects with physical exercise applied before %FMD evaluation the mechanism undoubtedly affected the ultimate results. However, an analysis carried out for a subgroup not involved in the "walk test" demonstrated that HR-FMD was unrelated to physical effort.

Absence of a defence mechanism in the form of a higher HR increases the risk of early endothelial dysfunction after MS. HR elevation, possibly resulting from enhanced stimulation of nitric oxide synthesis, prevents the development of early dysfunction.

Studies on patients with metabolic syndrome yielded different results. A negative correlation was found between %FMD and HR [22]. The relationship between endothelial function and autonomic activation thus requires further investigation.

In summary, MS induces endothelial dysfunction in patients with cardiac X syndrome. Lower baseline and post-MS HR seem to promote early dysfunction. Although controversial, support is lent to the observation by the results of laboratory and clinical studies.

Since HR elevation increases oxygen demand, it can be concluded that bradycardia and tachycardia resulting from stress may induce heart ischaemia through two completely different mechanisms.

None of our patients had symptomatic ischaemia as a result of the mental stressor applied. Thus it would be difficult to speculate on the practical aspect of our observations. It should be emphasised, however, that %FMD remains one of the best markers of the risk for cardiovascular events, accurately reflecting the function of the endothelium. Attenuation of %FMD increases the risk of cardiovascular events. Prolonged post-MS %FMD depression constitutes an immediate threat to the patient's condition.

In conclusion, in patients with cardiac X syndrome mental stress induces endothelial dysfunction that is related to baseline and post-mental stress heart rates. This emphasises the role of the autonomic nervous system in the pathogenesis of the dysfunction. Lower baseline and post-mental stress heart rates seem to promote early endothelial dysfunction.

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