Acute Mental Stress Has a Prolonged Unfavorable Effect on Arterial Stiffness and Wave Reflections

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Objective: Large-artery stiffness and arterial wave reflections have been identified as independent markers and prognosticators of cardiovascular risk. Mental stress is a novel risk factor for coronary artery disease and has been associated with left ventricular dysfunction, myocardial ischemia and infarction, and sudden cardiac death. The purpose of this study was to assess the effect of acute mental stress on aortic stiffness and wave reflections. **Methods:** The effect of a mental arithmetic test was assessed in 19 healthy individuals using a randomized, sham-procedure-controlled, crossover design. Carotid-femoral pulse wave velocity and augmentation index were measured as indices of aortic stiffness and wave reflections, respectively. **Results:** Mental stress induced a sustained increase in central systolic and pulse pressure throughout the whole study (systolic: by 7.5 mm Hg, $p < .05$; pulse: by 5.7 mm Hg, $p < .01$). The increase in peripheral systolic and pulse pressure was not significant throughout the study, but only when their peak values were compared with baseline (systolic: by 6.2 mm Hg, peak at 0 minutes; pulse: by 6.6 mm Hg, peak at 5 minutes, $p < .05$ for both). There was a sustained increase in pulse wave velocity (by 0.57 m/s, $p < .005$) throughout the study denoting a sustained increase in aortic stiffness. Similarly, augmentation index showed a sustained increase with mental stress (by 6.16%, $p < .05$) denoting increased wave reflections from the periphery. **Conclusion:** Acute mental stress results in a prolonged increase in aortic stiffness and wave reflections. Given the important pathophysiologic and prognostic role of these parameters, our results provide important mechanistic links between acute mental stress and increased cardiovascular risk. **Key words:** mental stress, aortic stiffness, wave reflections, pulse wave velocity.

Tr = timing of the reflected wave; **ANOVA** = analysis of variance.

INTRODUCTION

Large artery stiffness and arterial wave reflections are important determinants of left ventricular function, coronary blood flow and mechanical integrity of arteries (1–3). As a result, they are involved in the pathogenesis of systolic hypertension and they have been identified as independent markers and prognosticators of cardiovascular risk (1,4–7). Arterial elastic properties and wave reflections are impaired in the presence of cardiovascular risk factors, such as smoking, diabetes mellitus, hypertension, obesity, hypercholesterolemia, family history of premature coronary artery disease, and they are modified by several pharmacologic and nonpharmacologic means such as nutritional products and lifestyle habits, including smoking status and caffeine intake (8–14).

Mental stress is an inherent element of everyday life. Chronic mental stress is associated with atherosclerosis and coronary artery disease (15). Acute mental stress may induce myocardial ischemia (16–18) and left ventricular dysfunction (19) and may even lead to myocardial infarction or sudden cardiac death (20–22). Although catecholamine release is a major pathophysiologic mechanism that is activated (16,19,23), endothelial dysfunction is also a key event that accompanies acute mental stress (24–26). Both catecholamine levels and endothelial function are regulators of arterial stiffness and wave reflections (27–28).

Given the mechanistic background for the effects of mental stress on the cardiovascular system and the importance of arterial stiffness and wave reflections in regulating cardiac function and determining cardiovascular risk, we have hypothesized that mental stress exerts part of its harmful effects through impairment of arterial function. Accordingly, the purpose of this study was to assess the effect of acute mental stress on aortic stiffness and wave reflections in healthy subjects.

METHODS

Study Population

The study population consisted of 19 apparently healthy individuals (nine men, age 28.5 ± 0.6 years, range 23–32) studied on two separate occasions each. All participants were nonobese (body mass index <27 kg/m^2) and they did not have hypertension, diabetes, hyperlipidemia, or a family history of premature vascular disease. Seven subjects were current smokers (8.8 ± 1.8 pack-years; range 4.5–17.5) and 14 (7 smokers and 7 nonsmokers) were coffee consumers (32.5 ± 4.9 cup-years; range 1.5–67.5). They were clinically well and taking no regular cardiovascular medications or antioxidant vitamin supplementation. Subjects abstained from smoking and from caffeine and ethanol intake for at least 12 hours before each session. Female participants were examined during the follicular phase of the menstrual cycle, and none was on oral contraceptives. The study protocol was approved by our institutional research ethics committee, and all participants gave written informed consent.

Study Design

The study was carried out using a randomized, sham-procedure-controlled, crossover design. Participants were studied on two separate days on which they took (i) a standard mental arithmetic stress test and (ii) a control procedure (see below). Measurements were obtained in a quiet, temperature-controlled room at 23°C, while the participants had fasted for at least 8 hours. After a 20-minute rest period in the supine position, during which participants were encouraged to relax with lights lowered and ambient noise reduced, baseline measurements for evaluation of arterial elastic properties were taken. Measurements were repeated at the end of the mental stress or the control procedure (time 0) and at 5, 15, 30, 45, and 60 minutes thereafter.

Mental Stress Test

The mental arithmetic test is a validated and widely used test able to induce a considerable degree of perceived stress (17,29–31). In detail, in the mental stress occasion, participants were instructed to subtract the number 7 from a 4-digit number, continuously and as quickly and as accurately as possible, for 3 minutes. During the test, participants were intentionally frustrated by being asked to perform faster and by being immediately corrected in case of wrong answers. A metronome was played loudly as an additional

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Received for publication May 30, 2005; revision received August 30, 2005.
DOI: 10.1097/01.psy.0000203171.33348.72

0033-3174/06/6802-0231

distracter. In the control procedure occasion, participants were asked in a nonstressful manner to count upward slowly from 1 for 3 minutes.

After the end of the mental stress test, participants were asked to rate negative emotions on 7-point Likert scales (anger, frustration, irritation, and anxiety, total score range from 4 to 28), before and during the task. After the control procedure, they were asked to rate 2 control items (interest and tiredness, total score range from 2 to 14).

Evaluation of Aortic Elastic Properties

The pulse travels at a higher velocity in a stiff aorta and vice versa. Carotid-femoral pulse wave velocity (PWV), an established index of aortic stiffness (1,5,32), was calculated from measurements of pulse transit time and the distance traveled between two recording sites (pulse wave velocity = distance [meters]/transit time [seconds]) using a validated noninvasive device (Complior; Artech Medical, Pantin, France), which allows online pulse wave recording and automatic calculation of pulse wave velocity (33). Two different pulse waves were obtained simultaneously at two sites (at the base of the neck for the common carotid and over the right femoral artery) with two transducers. The distance was defined as: (distance from the suprasternic notch to femoral artery) − (distance from carotid artery to the suprasternic notch).

Measurement of Wave Reflection Indices

Augmentation index (AIx) and augmented pressure of the central (aortic) pressure waveform were measured as indices of wave reflections (1,2,32,33). Augmented pressure is the pressure added to the incident wave by the returning reflected one and represents the pressure boost that is caused by wave reflection and with which the left ventricle must cope. Augmentation index (defined as augmented pressure divided by pulse pressure and expressed as a percentage) is a composite measure of the magnitude of wave reflection and arterial stiffness, which affects timing of wave reflection. Larger values of augmentation index indicate increased wave reflection from the periphery and/or earlier return of the reflected wave as a result of increased pulse wave velocity (due to increased arterial stiffness), and vice versa. Because augmentation index depends on heart rate, augmentation index was also corrected according to changes in heart rate (34). Timing of the reflected wave (Tr), i.e., the time the pulse wave needs to travel to the periphery and return to meet the incident wave is an index of pulse wave velocity and was also calculated. All these indices were measured by using a validated, commercially available system (SphygmoCor; AtCor Medical, Sydney, Australia), which employs the principle of applanation tonometry and appropriate acquisition and analysis software for noninvasive recording and analysis of the arterial pulse. The technique has been described in detail previously (1,2). In brief, from radial artery recordings, the central (aortic) arterial pressure was derived with the use of a generalized transfer function, which has been shown to give an accurate estimate of the central arterial pressure waveform and its characteristics (1,35,36). Waveforms of radial pressure were calibrated according to sphygmomanometric systolic and diastolic pressure measured in the brachial artery because there is practically negligible pressure pulse amplification between the brachial and the radial artery (1).

Statistical Analysis

Numeric data are expressed as the mean ± SEM. All variables were tested for homogeneity of variance and normal distribution before any statistical analysis was applied. Baseline parameters between the two sessions were compared using the Student *t* test for paired measures. In order to evaluate the composite effect of mental stress versus control procedure over time on the variables of interest, an overall 7 × 2 analysis of variance (ANOVA) for repeated measures was performed (7 periods [baseline, 0, 5, 15, 30, 45, and 60 minutes] × 2 interventions [mental stress versus control]). To assess changes at time 0 (or at 5 minutes for pulse pressure) both between mental stress and control procedure, as well as within each session separately, ANOVA for repeated measures was performed (two periods: baseline and 0 or 5 minutes). To take into account the potential effect of mean pressure on pulse wave velocity changes, a cross-sectional time-series random-effect regression model was applied. To examine whether the effect of mental stress on arterial function was related to the level of perceived stress, to smoking status, and to caffeine intake, we adjusted for these covariates using a repeated-measures ANOVA-covariance.

A p value < 0.05 was considered statistically significant. Data analysis was performed using the SPSS statistical package for Windows (version 10.0, SPSS Inc., Chicago, IL) and STATA 8.0 software (Stata Corporation, TX).

RESULTS

Baseline Characteristics

There were no differences in all baseline characteristics between mental stress and control sessions in each study (Table 1).

TABLE 1. Characteristics of the Study Sessions at Baseline and at the End of Mental Stress (0 min)

	Mental Stress (n = 19)			Control Procedure (n = 19)		
	Baseline	0 min	p	Baseline	0 min	p
HR (beats/min)	67.3 ± 2.3	66.4 ± 2.5	NS	65.9 ± 2.3	64.9 ± 2.2	NS
Peripheral SP (mm Hg)	107.7 ± 2.1	114.0 ± 2.9	<.01	107.5 ± 2.0	107.6 ± 3.1	NS
Peripheral DP (mm Hg)	70.3 ± 2.4	73.8 ± 2.7	NS	68.3 ± 1.8	69.7 ± 1.7	NS
Peripheral PP (mm Hg)	37.4 ± 1.9	40.2 ± 2.1	NS	39.2 ± 1.9	37.9 ± 2.9	NS
Peripheral Mean P (mm Hg)	82.2 ± 2.3	87.4 ± 2.6	<.05	81.9 ± 1.6	81.4 ± 1.9	NS
Aortic SP (mm Hg)	96.1 ± 2.2	102.2 ± 2.7	<.01	96.0 ± 1.7	94.5 ± 2.2	NS
Aortic DP (mm Hg)	71.4 ± 2.3	74.6 ± 2.7	NS	69.2 ± 1.8	70.4 ± 1.7	NS
Aortic PP (mm Hg)	24.7 ± 1.4	27.5 ± 1.6	<.05	26.8 ± 1.4	24.1 ± 1.2	<.05
Aortic Mean P (mm Hg)	82.2 ± 2.3	87.4 ± 2.6	<.05	81.9 ± 1.6	81.4 ± 1.9	NS
AIx (%)	11.0 ± 2.6	14.7 ± 2.2	<.05	13.1 ± 2.6	10.7 ± 2.4	<.05
AIx corrected for HR (%)	11.0 ± 2.6	14.3 ± 2.2	<.05	13.1 ± 2.6	10.3 ± 2.5	<.05
AP (mm Hg)	3.0 ± 0.7	4.3 ± 0.8	<.01	3.6 ± 0.7	2.8 ± 0.6	<.05
Tr (ms)	129.6 ± 8.1	113.2 ± 5.1	<.05	127.1 ± 7.9	126.9 ± 7.9	NS
PWV (m/s)	5.4 ± 0.2	5.6 ± 0.3	<.05	5.5 ± 0.2	5.2 ± 0.2	<.01

Values are mean ± SEM. p Values refer to comparisons between baseline and 0 min within each study session separately. For all comparisons regarding baseline characteristics between study sessions: p = NS.

AIx = augmentation index; AP = augmented pressure; DP = diastolic pressure; HR = heart rate; Mean P = mean pressure; PP = pulse pressure; PWV = pulse wave velocity; SP = systolic pressure; Tr = timing of reflected waves.

The Level of Perceived Stress

Compared with baseline, subjects perceived a greater feeling of negative emotions during the mental arithmetic stress test (from 5.7 ± 0.4 to 12.5 ± 0.9, $p < .001$). Control items did not change significantly after the control procedure (from 3.5 ± 0.3 to 3.2 ± 0.3, p = NS).

Changes After Mental Stress

The effect of mental stress on each variable is better described as changes in the *response* of each variable, where response is defined as net mental stress minus sham-procedure values at each time point. Accordingly, p values refer to repeated-measures ANOVA significance between the mental stress and the control session throughout the study, unless otherwise noted. Additionally, in Table 1, p values refer to changes at time 0 within each study session separately.

Effect on Heart Rate and Blood Pressure

Heart rate remained unchanged up to 30 minutes and increased by 1.8 and by 1.6 beats per minute at 45 and 60 minutes, respectively (p for specific time points and overall p = NS).

Mental stress induced a sustained increase in central systolic and pulse pressure throughout the whole study (systolic: by 7.5 mm Hg, peak at 0 minutes, $p < .05$; pulse: by 5.7 mm Hg, peak at 5 minutes, $p < .01$). In contrast, the increase in peripheral systolic and pulse pressure was not significant throughout the study (systolic: by 6.2 mm Hg, peak at 0 minutes, $p = .3$; pulse: by 6.6 mm Hg, peak at 5 minutes, $p = .2$). However, both peripheral systolic and pulse pressure were significantly increased when their peak values (at 0 minutes for peripheral systolic pressure and at 5 minutes for pulse pressure) were compared with baseline values ($p < .05$ for both). The responses in systolic and pulse pressures are shown in Figure 1. Mean pressure did not change throughout the whole study (increase by 5.7 mm Hg, peak at 0 minutes, $p = .3$). However, it was significantly increased when its peak value (at 0 minutes) was compared with its baseline value ($p < .05$). Peripheral and central diastolic pressure did not change with mental stress either during the whole study or when their peak values were compared with baseline (p = NS for all).

Effect on Aortic Pulse Wave Velocity and Wave Reflection Indices

Mental stress produced a sustained increase in pulse wave velocity ($p < .005$) throughout the study, denoting an increase in aortic stiffness. Pulse wave velocity increased promptly at 0 minutes, reached a peak at 15 minutes (increase by 0.57 m/s) and remained significantly increased thereafter (Figure 2). Pulse wave velocity adjusted for changes in mean pressure remained significantly increased ($p < .01$), denoting that a pressure-independent mechanism contributed to the changes observed. Augmentation index and augmented pressure showed a sustained increase with mental stress (augmentation index by 6.16%, peak at 0 minutes, $p < .05$; augmented pressure by 2.2 mm Hg, peak at 0 minutes, $p < .05$), denoting an increase in wave reflections (Figure 2). Augmentation index corrected for changes in heart rate also showed a sustained increase (by 6.18% at 0 minutes, $p < .05$). Tr showed a trend to decrease at 0 minutes (nadir by 16.2 ms, $p = .07$); however, the decrease during the whole study did not reach statistical significance.

Pulse wave velocity and augmentation index changes within the mental stress session were no more statistically

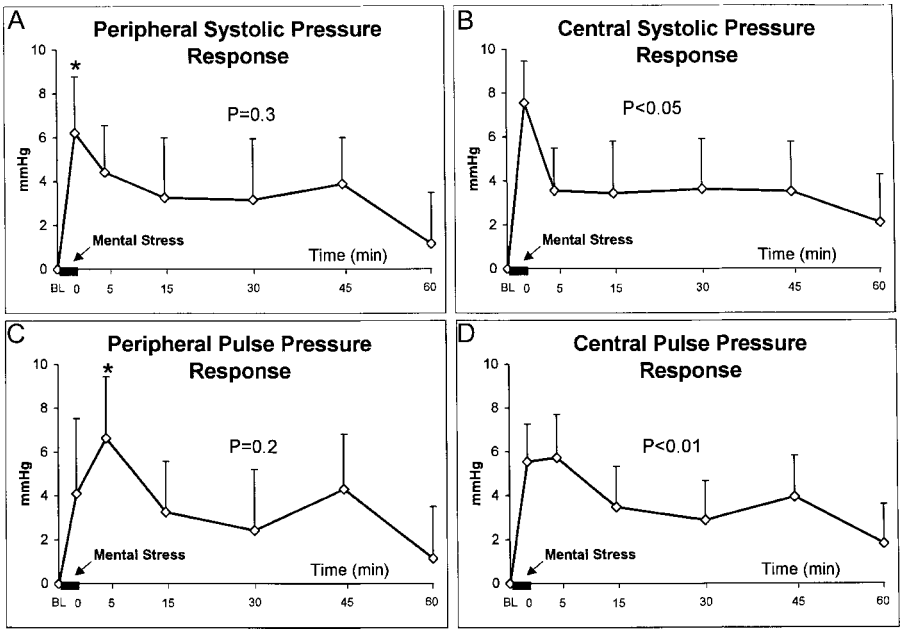

Figure 1. Peripheral (radial) and central (aortic) systolic and pulse pressure response during the mental stress study. Each line represents response defined as net mental stress effect minus sham procedure effect at each time point. p Values refer to the response of mental stress compared with sham procedure during the whole study duration. * $p < .05$ When only the peak effect is compared with baseline. Error bars: SEM.

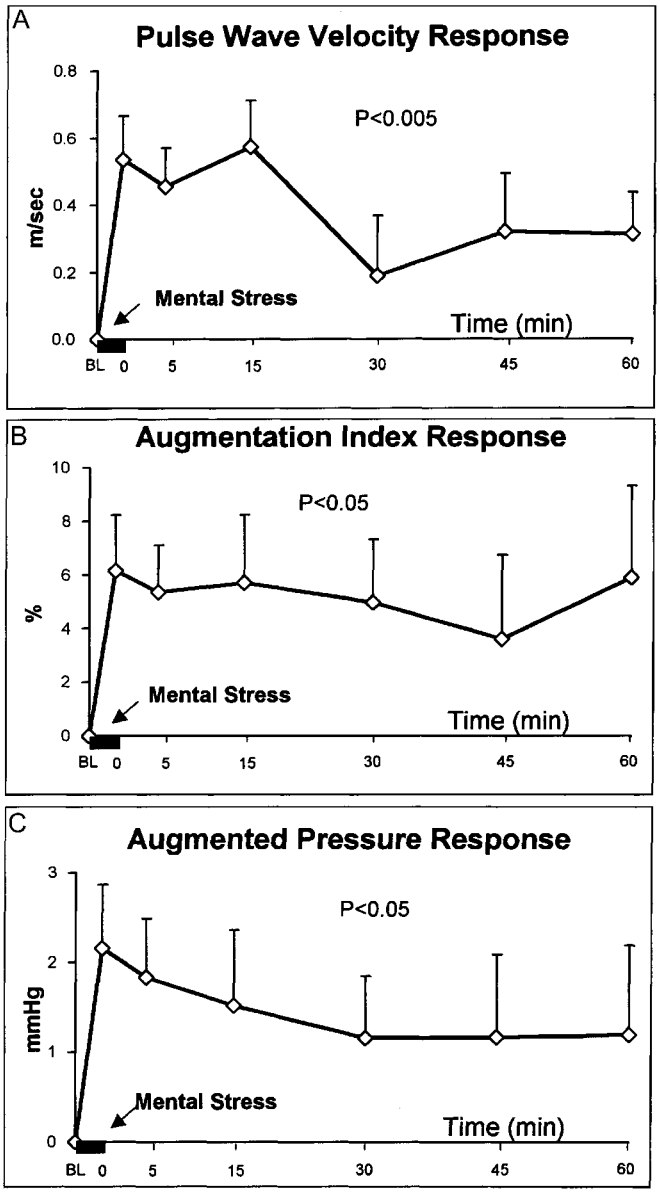

Figure 2. Pulse wave velocity and augmentation index response during the mental stress study. Each line represents response-defined net mental stress effect minus sham procedure effect at each time point. *p* Values refer to the response of mental stress compared to sham procedure during the whole study duration. Error bars: SEM.

significant when adjusted for the level of perceived stress, indicating that this covariate was largely responsible for the changes observed.

Pulse wave velocity, augmentation index, and the augmented pressure remained significant when adjusted for smoking status or caffeine intake.

A representative example of a subject regarding changes in pressure waveforms and wave reflections is shown in Figure 3.

DISCUSSION

This is the first study, to the best of our knowledge, to investigate the effect of acute mental stress on both aortic stiffness and wave reflections. According to our results, mental stress of a brief period results in a prolonged (for at least 1 hour) deterioration in aortic stiffness and wave reflections. Furthermore, a significant pressor effect of mental stress is evident regarding central pressures, which is not accompanied by a similar increase in peripheral pressures.

Mechanisms

A possible underlying mechanism for the unfavorable effect of mental stress on arterial stiffness could be catecholamine release. It has been consistently shown that acute mental stress results in a substantial increase in the circulating levels of catecholamines, i.e., epinephrine, norepinephrine, and dopamine (19,31,37). On the other hand, norepinephrine infusion results in a great increase in peripheral and central pulse pressure and an increase in augmentation index and aortic stiffness (28).

Acute mental stress induces prolonged endothelial dysfunction, which, among other things, can explain why myocardial ischemia caused by mental stress occurs with a lower double product (heart rate × blood pressure) than exercise (16). A brief period of mental stress results in prolonged endothelial dysfunction (24), and, interestingly, this effect is mediated via endothelin rather than catecholamines (25). Endothelial function regulates arterial stiffness (27), thus indicating that endothelial dysfunction may contribute to the mental-stress-induced deterioration of arterial elastic properties and the increase in wave reflections.

It has also been demonstrated that acute mental stress leads to immune activation and inflammation, as evidenced by an elevation in circulating lymphocytes immediately after the end of a mental stress (38) and by an elevation in the levels of interleukin-6 immediately after (39) and in interleukin-6 and interleukin-1Ra two hours after mental stress (40). On the other hand, acute inflammation leads to endothelial dysfunction (41), and the same effect is also true for arterial stiffness (42), indicating that it may also play a role in the detrimental effect of mental stress on arterial function found in our study.

Although specially designed methodology (43) is needed in order to distinguish whether the effect of an intervention on aortic stiffness is due to changes in the intrinsic properties of the aortic wall or due to changes in blood pressure, insights on the mechanism of action of mental stress can be inferred from our study. Indeed, the facts that (i) pressures did not change during the whole study period, whereas pulse wave velocity did, and (ii) pulse wave velocity changes remained significant after adjusting for changes in mean pressure indicate that, apart from a blood pressure effect, an active effect of mental stress on aortic wall may contribute to aortic stiffness changes. Nevertheless, the importance and the clinical implications of our findings are valid irrespective of the mechanism involved.

Effect of Mental Stress on Arterial Properties in Different Vascular Beds

There is no consistency regarding the effects of mental stress on the elastic properties of arteries in different vascular beds. Tanaka et al. (44) found that finger arterial

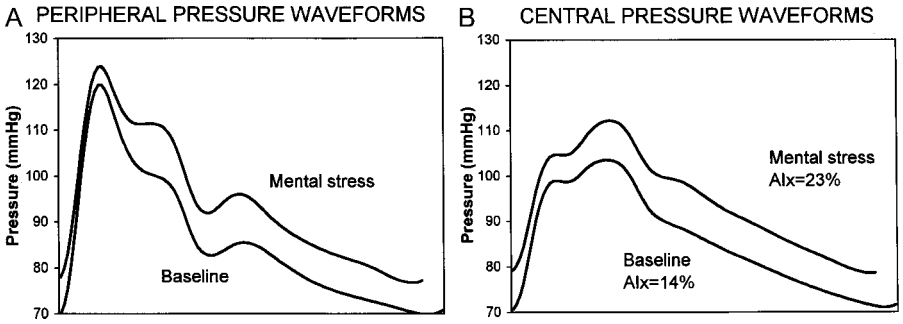

Figure 3. Peripheral (radial) tonometric and derived central (aortic) pressure recordings from a subject during the mental stress study at baseline and immediately after the end of mental stress test. After the mental stress test, peripheral and central pressures increased significantly, and so did the augmentation index (from 14% to 23%), indicating increased wave reflections from the periphery. AIx = augmentation index.

compliance is decreased after mental arithmetic stress test. Interestingly, Goor et al. (45) demonstrated that mental-stress-induced peripheral arterial vasoconstriction (assessed by peripheral arterial tonometry) predicts mental-stress-induced myocardial ischemia. On the other hand, compliance of the muscular radial artery was decreased by mental stress in healthy subjects (46) but not affected in normotensive offspring of hypertensive patients (47). Also, Tsai and al. (48) reported that, although mental stress resulted in a reduction in arterial compliance both in normotensive and mildly hypertensive individuals, wave reflections were not increased in either of these two groups.

Clinical Implications

Our findings may have important clinical implications. Mental stress is linked to increased cardiovascular morbidity and mortality. Acute mental stress may lead to left ventricular dysfunction, myocardial ischemia, infarction, and sudden cardiac death (16–22). Furthermore, mental-stress-induced ischemia in patients with coronary artery disease is a predictor of subsequent all-cause mortality (49). By determining left ventricular function, as well as coronary blood flow and arterial integrity, large-artery stiffness and arterial wave reflections are implicated in the pathogenesis of systolic hypertension, and they are independent markers and prognosticators of cardiovascular risk (1–7). When reflected waves return to the ascending aorta late, as in normal young subjects, they merge with the incident wave in diastole, thus augmenting the diastolic part of the final waveform and facilitating coronary perfusion, which occurs during diastole. When reflected waves return earlier (due to increased aortic stiffness and, hence, increased pulse wave velocity) and they are enhanced, as was the case after the mental stress in our study, they merge with the incident wave in early systole and augment the systolic part of the final waveform. In such a way, not only the diastolic part of the waveform is not increased and coronary perfusion is not favored but left ventricular afterload is elevated, leading to elevated oxygen demand and unfavorable myocardial supply/demand balance. This may contribute, at least in part, to the observed myocardial ischemia induced with acute mental stress. Moreover, the increased pulsatile load when frequently repeated may accumulate over time and lead to mechanical fatigue of the structural elements of the arterial wall, thus endangering arterial wall integrity (1,2).

The effect of mental stress on central pressures was more prominent compared with the effect on peripheral pressures. This has important implications because central pressures are the ones physiologically significant. The systolic pressure in the ascending aorta is the pressure that the left ventricle has to confront. Furthermore, the distending pressure in the central arteries is very important because these elastic arteries (aorta, carotid) are those that are predominantly affected and degenerate with aging and in hypertension, in contrast to the less-affected muscular peripheral arteries, such as the brachial and the radial (1,50). Importantly, central and not brachial pulse pressure is a predictor of mortality in patients with end-stage renal disease (7), as well as a determinant of intima media thickness in the carotid arteries (3) and of ascending aorta diameter in patients with Marfan syndrome (51).

An interesting aspect our study is that mental stress is able to induce an increase in vascular stiffening even in young apparently healthy subjects with no traditional cardiovascular risk factors except from smoking. Smoking and caffeine consumption status, which are known to affect arterial elastic properties (10–13), do not seem to affect the response, although this may be due to the small sample size of our study. It would be very interesting to assess in further studies the response to mental stress in populations with impaired arterial elastic properties such as the elderly or the hypertensives.

Specific Comments: Study Limitations

Our population consisted of young, healthy subjects, and, therefore, our results may not be applicable to other populations, such as in patients with coronary artery disease.

Although the arithmetic test is a validated and widely used test, it is not the most powerful mental stress test (16). More powerful stress events in real life may induce greater impairment in arterial function. This is reinforced by our finding that the changes in arterial stiffness indices were largely dependent on the level of perceived stress.

CONCLUSIONS

Acute mental stress of a brief period results in a prolonged increase in aortic stiffness and wave reflections. Given the

important role that arterial dysfunction plays in the development of left ventricular dysfunction, myocardial ischemia, and disturbance of arterial integrity, these results provide important mechanistic links between acute mental stress and increased cardiovascular risk.

The authors would like to express their acknowledgment to Theodoros Gialernios, MD, for expert statistical advice.

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