Original Article

Effects of Obesity and Smoking on Mental Stress–Induced Blood Pressure and Augmentation Index Responses in Normotensive Young Males: The J-SHIPP Study

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Exaggerated blood pressure (BP) response to mental stress has been known to be a prognostic factor for cardiovascular disease. It has been argued that such unusual vascular reactivity to mental stress may arise from insulin resistance. To examine the vascular responses to mental stress, we evaluated the stress-related changes in BP and the augmentation index (AI), an index of arterial stiffness, in normotensive young males. Changes in late systolic BP (SBP2) representing central aortic pressure were also examined. Subjects were 86 males (21±2 years), 13 of whom were classified as obese (≥25 kg/m^2). AI was obtained from the radial arterial waveform as a ratio of the height of the late systolic peak to that of the first peak. Blood pressure and AI measurements were taken before, during and after a simple mental arithmetic test (MAT) lasting 3 min. Systolic BP (baseline 125±13, during MAT 133±13, post-MAT 124±11 mmHg; $p<0.001$) and heart rate (74±12, 81±13, 74±11 beats/min; $p<0.001$) were significantly increased during the MAT, whereas AI showed a slight reduction. In a separate analysis, the opposite response was observed between obese subjects showing increased AI (54±11, 56±13, 52±11%) and non-obese subjects who showed reduced AI (54±12, 51±12, 53±12%; $p=0.032$). The responses in SBP and SBP2 (obese 103±14, 117±12, 104±12; non-obese 98±13, 104±12, 97±12 mmHg; $p=0.007$) were also larger in the obese subjects. Stress-related transient increases in arterial stiffness may be involved in the exaggerated responses in aortic pressure in obese subjects. (*Hypertens Res* 2008; 31: 1219–1224)

***Key Words*: mental stress, arterial stiffness, obesity, blood pressure response**

Introduction

Enhanced blood pressure responses to the laboratory mental stress test have been shown to have prognostic significance in hypertension (*1*, *2*) and carotid atherosclerosis (*3*, *4*). A significant association with future silent cerebrovascular disease has also been demonstrated (*5*).

Unlike the handgrip and cold-pressor tests, tests inducing mental stress are associated with increased forearm blood flow and decreased systemic vascular resistance to counteract an increase in cardiac output (*6*). In obese subjects, however, unusual increases in systemic vascular resistance with exaggerated blood pressure (BP) responses during mental stress

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tests have been observed (*7*, *8*), although their basal hemodynamic parameters did not differ from those of non-obese subjects. It has been suggested that insulin resistance is a possible underlying mechanism for the unusual vascular reactivity (*8*).

The augmentation index (AI) obtained from the arterial pressure waveform is an index for vascular stiffness and wave reflection (*9*, *10*). AI is defined as the ratio of the reflected wave to the pulse pressure in the central artery. Higher AI values indicate increased wave reflection or earlier return of the reflected wave from the periphery as a result of increased arterial stiffness or peripheral arterial remodeling. AI can also be obtained from the radial artery as a ratio of the height of the late systolic peak (SBP2) to that of the first peak (SBP), and radial AI closely relates to aortic AI determined by either direct measurement (*11*) or indirect estimation using a transfer function (*9*).

Aortic pressure reflects cardiac load. However, brachial BP does not always represent aortic pressure due to the peripheral amplification of pulse pressure. Pauca *et al*. (*12*) reported the coincidence of radial SBP2 with aortic SBP by direct measurements. Takazawa *et al*. (*11*, *13*) also showed that while nitroglycerin-induced reduction of aortic SBP was not reflected in radial SBP, it was closely associated with radial SBP2. These findings indicate that radial SBP2 could be used for the assessment of the aortic SBP level as well as its variation. Radial SBP2 can be obtained from radial AI by calibrating with brachial BP.

From these lines of evidence, it was hypothesized that the cardiac load induced by mental stress is higher in obese subjects due to the unusual increase in systemic vascular resistance, which increase AI and consequently SBP2. Cigar smoking has also been known to cause an acute and transient increase in arterial stiffness in addition to chronic vascular inflammation and atherosclerotic vascular change, and the latter effects also increase AI and SBP2 (*14*).

In the present study, we investigated the changes in radial AI during a mental arithmetic test (MAT) in order to examine these hypotheses in normotensive young subjects.

Methods

Study Subjects

Subjects were 86 healthy young males (mean age 21±2 years; range 18 to 28 years) randomly recruited from among students at Ehime University School of Medicine. All subjects were free from any history or symptoms of cardiovascular disease and were taking no medication. Among them, 13 subjects were classified as obese (body mass index [BMI] ≥25 kg/m^2) according to the guidelines of the Japanese Society for the Study of Obesity (*15*). The frequency of current smokers and former smokers was 14.0% (n=12) and 15.1% (n=13), respectively. The objectives and protocols of the study were fully explained before the recruitment. All participants agreed to participate of their own free will.

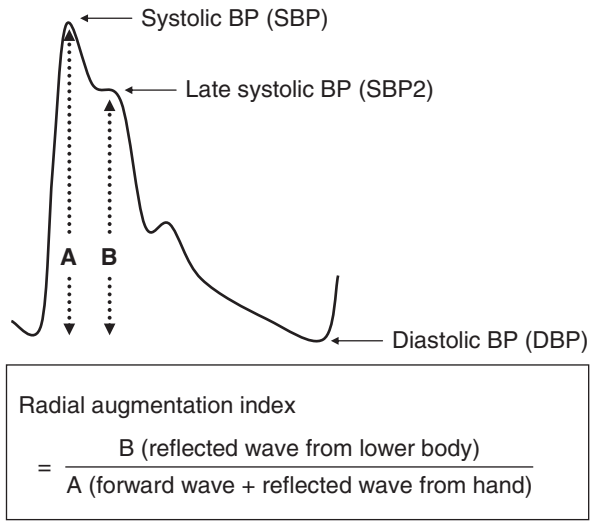

Fig. 1. *Definition of radial augmentation index. The trace line indicates the radial arterial waveform. The radial augmentation index was defined as the ratio of the height of the late systolic peak to that of the first systolic peak. The first peak is composed of two waveforms, the incident pressure wave by cardiac ejection and the reflected wave from the hand. The late peak is generated by the reflection wave from the lower body. The first and late systolic peaks were defined by using the fourth derivative wave as the second and third zero crossing points, respectively. The absolute pressure of the late systolic peak was defined as SBP2.*

MAT and Measurement of BP and AI

After more than 5 min of rest in a sitting position, a simple mental arithmetic exercise involving sequential subtractions of 17 from 10,000 was performed for 3 min. Subjects were instructed to perform the calculation as accurately and quickly as possible. Radial AI and brachial BP (HEM9000-AI; OMRON HEALTHCARE Co., Ltd., Kyoto, Japan) (*8*, *9*) were measured 3 times during this procedure: just before the MAT, 2 min after starting the MAT, and 1 min after finishing the MAT. Brachial BP was measured at the right upper arm by the cuff-oscillometric method. The radial arterial waveform was simultaneously obtained from the left wrist using a multi-element tonometric sensor. The tonometric sensor unit consists of a pressure sensor with an array of multiple 40-microtransducer elements, and one of these 40 sensor elements was selected automatically to obtain the optimal radial pressure waveforms. The signals were digitized at 500 Hz. The hold-down pressure of the sensor units was also adjusted for each subject automatically. Radial AI was obtained from the waveform as a ratio of the height of the late systolic peak to that of the first peak (Fig. 1) (*16*). The first and late systolic peaks were identified by using the fourth derivative wave as the second and third zero crossing points, respectively. The

Table 1. Basal Hemodynamic Characteristics of the Study Subjects

	Total (n=86)	Obesity			Smoking		
		Non-obese (n=73)	Obese (n=13)	p	Non-smoker (n=61)	Smoker (n=25)	p
SBP (mmHg)	125±13	124±12	130±19	0.107	124±13	126±14	0.466
SBP2 (mmHg)	98±13	98±13	103±15	0.172	97±13	103±13	0.074
DBP (mmHg)	69±11	68±11	73±13	0.154	68±11	71±11	0.203
HR (beats/min)	74±12	74±12	77±13	0.468	75±12	73±11	0.618
AI (%)	54±12	54±12	54±11	0.946	52±12	58±11	0.057

Values are means±SD. SBP, systolic blood pressure; SBP2, radial artery late systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; AI, augmentation index. Statistical significance was assessed by analysis of variance.

Table 2. Hemodynamic Responses to the Mental Arithmetic Test

	Mental arithmetic test			p values for repeated ANOVA
	Immediately before (−1 min)	During MAT (2 min)	Post MAT (4 min)	
SBP (mmHg)	125±13	133±13	124±11	<0.001
SBP2 (mmHg)	98±13	106±13	98±12	<0.001
DBP (mmHg)	69±11	78±11	71±11	<0.001
HR (beats/min)	74±12	81±13	74±11	<0.001
AI (%)	54±12	52±12	53±12	0.143

Values are means±SD. MAT, mental arithmetic test; SBP, systolic blood pressure; SBP2, radial artery late systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; AI, augmentation index. Statistical significance was assessed by repeated measure of analysis of variance.

absolute pressure of the late systolic peak (SBP2) was obtained by calibrating the radial waveform with brachial SBP.

Statistical Analysis

All values are expressed as means±SD unless otherwise specified. To assess the differences in hemodynamic parameters according to obesity and smoking status, one-way analysis of variance (ANOVA) was used (Table 1). Hemodynamic response to the MAT was assessed by repeated measures of ANOVA (Table 2), and the interactions of obesity and smoking with MAT were evaluated by two-way layout ANOVA (Figs. 2, 3). Multi-factorial analysis for the hemodynamic responses was assessed by a general linear model. All analyses were performed with a commercially available statistical package (SPSS Ver 14.0; SPSS Inc., Chicago, USA). p values less than 0.05 were defined as statistically significant.

Results

Baseline hemodynamic characteristics of the study subjects are summarized in Table 1. The mean BMI values of obese (n=13) and non-obese (n=73) subjects were 27.9±2.7 kg/m^2 and 21.1±2.0 kg/m^2, respectively. Smokers showed marginally higher basal AI and SBP2 than non-smokers. However, no significant differences were observed in the other parameters. The frequency of smokers among obese subjects (30.8%) was not different from that among non-obese subjects (28.8%; p=0.999). The mean BMI of smokers (22.1±3.1 kg/m^2) was also not different from that of non-smokers (22.2±3.3 kg/m^2; p=0.970). There were no significant differences in age between non-obese (21.3±2.1 years) and obese subjects (21.7±2.6 years; p=0.556), or between smokers (21.4±2.4 years) and non-smokers (21.4±2.1 years; p=0.999).

Hemodynamic responses to the MAT are shown in Table 2. All three BP and HR values measured were significantly higher during the MAT. The increased values were immediately returned to the basal levels after finishing the arithmetic test. AI showed no significant changes throughout the procedure. However, in a separate analysis (Fig. 2), obese subjects showed opposite AI responses compared with non-obese subjects. The responses in both SBP and SBP2 were also larger in the obese subjects. In contrast, smokers showed significantly higher AI and SBP2 throughout the procedure (Fig. 3). However, the stress responses of these parameters in smokers were not different from those of non-smokers. Although the responses in HR were significantly larger in smokers, the absolute differences in HR between smokers and non-smokers at each measured time point were not significant.

To eliminate a possible confounding association between

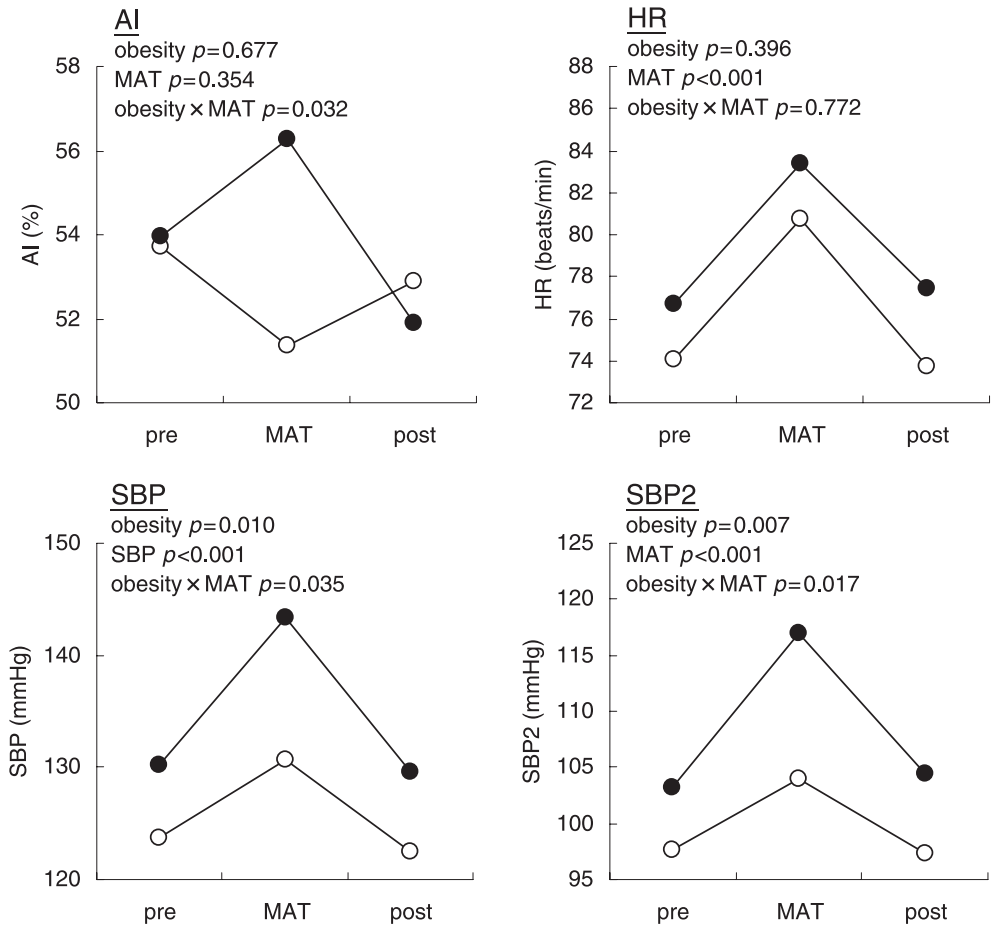

Fig. 2. *Hemodynamic responses to the mental arithmetic test (MAT) by obesity status. Statistical significance was assessed by two-way analysis of variance. The p values for obesity, MAT and the obesity×MAT interaction are indicated in each graph. Values are shown as means. Closed circles, obese subjects; open circles, non-obese subjects. MAT, mental arithmetic test; AI, augmentation index; HR, heart rate; SBP, systolic blood pressure; SBP2, late systolic blood pressure.*

obesity and smoking, multi-factorial analyses for the hemodynamic responses were performed with the following parameters: obesity, smoking, the obesity×MAT interaction and the smoking×MAT interaction. The obesity×MAT interaction ($p=0.033$) and smoking ($p=0.028$), but not obesity ($p=0.696$) and the smoking×MAT interaction ($p=0.953$), were significant determinants for AI in agreement with the single factorial analysis by obesity (Fig. 2) and smoking (Fig. 3). Analysis for the SBP (obesity, $p=0.011$; obesity×MAT, $p=0.037$; smoking, $p=0.187$; smoking×MAT, $p=0.228$) and SBP2 (obesity, $p=0.015$; obesity×MAT, $p=0.008$; smoking, $p=0.022$; smoking×MAT, $p=0.820$) also showed similar results, indicating that association of obesity and obesity×MAT interaction with the stress-induced hemodynamic responses were independent of the smoking status.

Discussion

In the present study, we revealed that the mental stress responses in AI, SBP and SBP2, but not their basal levels, were significantly larger in obese subjects. In contrast, smokers showed higher basal AI and SBP2, though the differences did not reach the level of statistical significance.

The obese subjects showed higher AI during MAT. Altered arterial impedance by increased systemic vascular resistance is a possible explanation for this finding, since it has been demonstrated that the enhanced arterial impedance increases AI by altering pulse wave velocity and wave reflection points (*16*).

HR significantly influences AI. Wilkinson *et al*. (*17*) demonstrated that AI decreases approximately 4% with every 10 beats/min increment in HR in patients with permanent pacemaker implantation. In the present study, however, the observed stress response in AI in obese subjects was thought to be independent from the changes in HR, because the changes in HR did not differ significantly from those of non-obese subjects. These observations further suggest that the unusual vascular reactivity is the principal pathogenetic

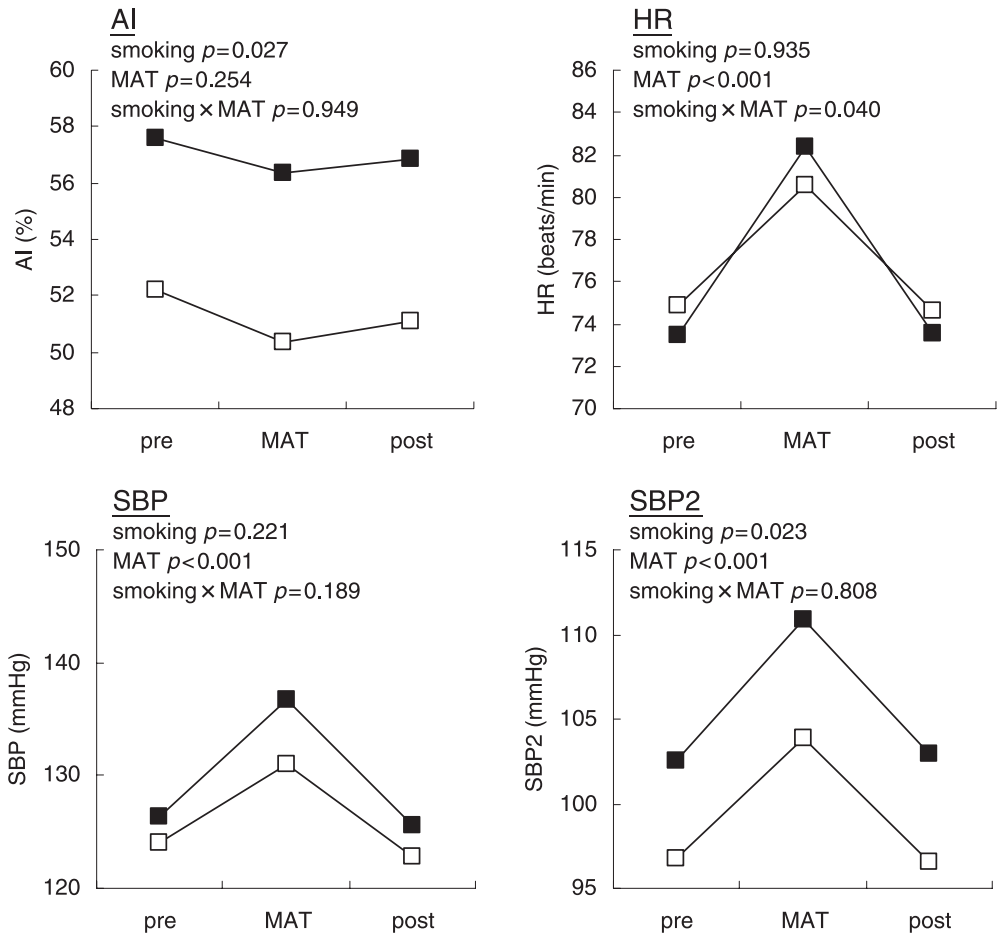

Fig. 3. *Hemodynamic responses to the MAT by smoking status. Statistical significance was assessed by two-way analysis of variance. p values for smoking status, MAT and the smoking×MAT interaction are indicated. Values are shown as means. Closed squares, smokers; open squares, non-smokers. MAT, mental arithmetic test; AI, augmentation index; HR, heart rate; SBP, systolic blood pressure; SBP2, late systolic blood pressure.*

mechanism responsible for the opposite response in AI in obese subjects.

Arterial stiffness could be involved in the mental stress–related pressure responses (*18*). However, our obese subjects did not show significant differences in basal AI compared to the non-obese subjects, despite the fact that the AI is partially dependent on the arterial properties. Additionally, the changes in BP and AI did not differ between smokers and non-smokers, although the smokers showed significantly higher AI throughout the procedure. Thus basal arterial stiffness itself might not have played a role in the stress responses in AI and BP in our young subjects.

Smokers showed significantly higher AI throughout the procedure, a finding in agreement with Mahmud and Feely (*19*), who reported higher AI in young habitual smokers. Since no significant differences were observed in the basal brachial BP and HR by smoking status, the deleterious effects of chronic smoking on arterial stiffness and cardiac load could be overlooked by the usual BP measurements.

Aortic systolic pressure is a direct burden to the left ventricle and myocardial oxygen demands (*20*). It has been indicated that SBP2 could represent aortic systolic pressure as well as its variation (*12–13*). In the present study, both SBP and SPB2 were significantly increased by the mental stress test in obese subjects. Although obesity itself could be a major risk factor for future cardiac events, exaggerated changes in SBP2 induced by mental stress may further enhance the risks by adding extra cardiac load. Smokers also showed significantly higher AI and SBP2 values during the procedure, but their SBP did not differ from that of nonsmokers. These observations further indicate the clinical usefulness of measuring the two components of systolic pressure for accurate evaluation of cardiac load.

We recognize some limitations of this study. First, we did not assess the synergistic associations between obesity and smoking due to the limited number of subjects. Secondly, we did not measure the smoking intensity. Accordingly, the possible dose-dependency in the hemodynamic responses was

not clarified. Finally, we did not examine female subjects so as to avoid the effects of estrogen and menstrual cycle on vascular properties (*21*).

In summary, we demonstrated an unusual stress–related transient increase in AI as well as in both peripheral and central BP in obese subjects. Changes in vascular reactivity may have been involved in these exaggerated responses. Countermeasures to obesity need to be taken to prevent future cardiovascular events, not only in view of preventing metabolic diseases but also in order to reduce stress-induced extra cardiac load. Smoking also increased arterial stiffness and cardiac load even in apparently healthy young subjects with normal BP.

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