Insulin Resistance Syndrome and Autonomically Mediated Physiological Responses to Experimentally Induced Mental Stress in Adolescent Boys

Liisa Keltikangas-Järvinen, Niklas Ravaja, Katri Räikkönen, and Heikki Lyytinen

We investigated the relationship between hemodynamic and other autonomically mediated responses to experimentally induced mental stress and the parameters of the insulin resistance syndrome (IRS) in 48 healthy adolescent boys. Mental stress was induced with mental arithmetic and the Stroop Color-Word Test. Heart rate (HR), finger blood volume (FBV), and skin conductance level (SCL) were recorded continuously during task performance. IRS parameters measured were serum insulin, high-density lipoprotein (HDL) cholesterol, serum triglyceride (TG), systolic blood pressure (SBP), subscapular skinfold (SSF), and subscapular to triceps skinfold ratio (STR). The results indicated that a high level and an increasing linear trend of HR and FBV during task performance were related, independently of each other and of body mass index (BMI), to a high insulin concentration. An increasing linear trend of HR during mental stress was also related to high SSFs independently of BMI. In addition, a high SCL during task performance was associated with high TG levels, SSFs, and STRs. It is discussed whether stress-induced sympathetic overactivity might contribute to the development of the IRS.

INSULIN RESISTANCE syndrome (IRS) is the association of a cluster of clinical conditions—glucose intolerance, arterial hypertension, elevated levels of triglycerides (TG), and a low concentration of high-density lipoprotein (HDL) cholesterol—with hyperinsulinemia and insulin resistance.[1] There is also considerable evidence establishing that obesity, particularly android fat distribution, is highly associated with insulin resistance and hyperinsulinemia.[2] Resistance to insulin-stimulated glucose uptake has been postulated to be the primary metabolic defect in this syndrome.[3-5] Recent prospective studies have convincingly demonstrated that IRS is a risk factor for coronary heart disease (CHD) and type II diabetes.[1,5-7]

Even though insulin resistance is presumably genetically determined in most instances,[8] there is compelling evidence that environmental stress contributes to the development of IRS via neuroendocrine reactions in the corticotropin-releasing factor (CRF)-adrenocorticotropin hormone (ACTH)-adrenal cortex axis.[9,10] For example, experimental studies by Kaplan et al[11] and others[12] have indicated that monkeys with a submissive type of reaction, ie, defeat reaction characterized by helplessness and loss of control, to standardized stress respond with increased adrenal cortex activity paralleled by an apparent centralization of body fat. Likewise, Rebuffé-Scrive et al[13] reported comparable findings from a study where male Sprague-Dawley rats were exposed to chronic uncontrollable stress.[13] In line with animal studies, when stimulated with mental stress tests, obese women with an elevated waist to hip ratio (WHR) or large abdominal sagittal diameter have been shown to express elevated responses of serum cortisol, which is known to exert marked insulin resistance.[10,14]

From the Department of Psychology, University of Helsinki, Helsinki; and the Department of Psychology, University of Jyväskylä, Jyväskylä, Finland.
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Address reprint requests to Niklas Ravaja, MA, Department of Psychology, PO Box 4, FIN-00014 University of Helsinki, Finland.

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Moreover, we have previously found that stress-related personality dimensions, ie, type A behavior and aggressiveness, predict an increase in serum insulin concentration, as was shown in a 3-year follow-up period with adolescents and young adults.[15] The essential parameters of IRS appear also to cluster more strongly in type A males than in non–type As.[16]

Although the research done thus far has predominantly emphasized the role of the pituitary-adrenal system when searching for the mechanism mediating the relationship between stress and IRS, enhanced sympathetic activity may well be of importance as well. Individuals with a hyperdynamic circulation, as defined in terms of increased heart rate (HR) and pulse pressure, have been shown to exhibit many of the traits of IRS.[17] Several researchers have recently hypothesized that chronic sympathetic overactivity with a consequent defense reaction–like hemodynamic pattern, ie, elevated cardiac output mainly caused by an increased HR, may have pathogenetic importance in the development of IRS.[18-20] It has been suggested that this hemodynamic pattern may lead to structural changes, ie, vascular hypertrophy and rarefaction of vascularization, that will decrease the blood flow in peripheral tissues and thereby induce insulin resistance.

To our knowledge, the potential effects of stress-induced cardiovascular reactivity on IRS have not been previously investigated. It has been shown that the essential parameters of IRS express strong clustering even in healthy children and adolescents.[21-23] In addition, fasting insulin levels in young people have been shown to predict type II diabetes over an 11-year follow-up period.[24] Consequently, it is important to study the mechanisms through which stress might influence the parameters of IRS even in adolescence.

There is evidence that prior life stress is related to human cardiovascular reactivity to acute stress, ie, chronically stressed individuals show greater reactivity to and prolonged recovery from challenging tasks.[25,26] Therefore, we postulated that individuals expressing more pronounced sympathetically mediated physiological responses when faced with mentally challenging tasks might also express higher levels of parameters constituting IRS. Thus, the

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objective of the present study was to examine whether hemodynamic and other autonomically mediated responses (ie, HR, HR variability [HRV], finger blood volume [FBV], and SCL) to task-induced stress are related to the metabolic and anthropometric parameters of IRS in healthy adolescent boys. The question was asked as to whether temporal characteristics of physiological responses as defined as the trend of response during the performance might be even more strongly associated with these metabolic and anthropometric parameters than the magnitude of response.

MATERIALS AND METHODS

Subjects

The subjects were 48 healthy 16-year-old Finnish boys. They were taken from the prospective epidemiological Cardiovascular Risk in Young Finns Study (CRYF),[27] in which the development of risk factors for CHD has been monitored at intervals of 3 years beginning in 1980. The subjects of the CRYF study, a total of 3,596 healthy Finnish children, adolescents, and young adults, were a randomly selected sample of 360 rural and 360 urban girls and boys in the age cohorts of 3, 6, 9, 12, 15, and 18 in 1980. The design of the CRYF study and the selection of the sample are described in detail in Åkerblom et al.[27]

The present sample (N = 48) was the cohort of boys aged 9 years in 1980 who were residing in the urban and rural districts of Kuopio (ie, one of five university cities in which the CRYF study was performed). Of this entire cohort (N = 323), 262 participated in the CRYF 6-year follow-up study, when they were 15 years of age. Those residing in the Kuopio area (N = 80) were invited to take part in the psychophysiological study, which was performed 6 months after the CRYF 6-year follow-up study, when most of the boys were 16 years of age. A total of 57 boys participated in the study. Complete data with respect to metabolic, anthropometric, and physiologic parameters were available for 48 of them.

The present subjects did not differ significantly in metabolic and anthropometric parameters from the whole age cohort of 9-year-old boys.

Metabolic and Anthropometric Parameters

The following measurements relevant for IRS[3,8] were obtained in the 6-year medical follow-up examination of the CRYF study[27]: serum insulin, serum HDL cholesterol, serum TG, systolic blood pressure (SBP), weight, height, subscapular skinfold thickness (SSF), and triceps skinfold thickness (TSF).

Blood pressure was measured with a standard mercury gravity sphygmomanometer on the right arm after a rest of at least 3 minutes.[28] SSF and TSF were measured by Harpenden calipers (Holtain and Bull-British Indicators instruments) to 0.2-mm readings. SSF and the centrality index (the ratio of subscapular to triceps skinfold [STR]) were used as indices of upper-body subcutaneous fat distribution. SSF has also been shown to be a good indicator of intraabdominal fat deposition in children.[29] Height was measured by a Seca (Hamburg, Germany) anthropometer and weight by a Seca weighing scale. Body mass index ([BMI] an index of the total amount of body fat) was calculated as weight in kilograms divided by height in meters squared. The procedures for anthropometric measurements have been described in detail in Dahlström et al.[30]

Blood samples were taken after an overnight fast. Serum insulin level was measured using a modification of the immunoassay method of Herbert et al.[31] Serum HDL cholesterol concentrations were measured from the serum supernatant after precipitation of very–low-density and low-density lipoproteins with dextran sulfate 500,000.[32,33] Serum TG concentrations were determined enzymatically.[34] A more detailed description of the assessment protocol we used has been previously published.[35]

The Psychophysiological Experiment

The psychophysiological experiment was performed 6 months after the 6-year medical follow-up examination of the CRYF study. The entire study protocol of the CRYF study was approved by the ethics committees of the participating universities of the main study.

Experimental Procedure

Mental stress was induced by exposing subjects to a standardized computer-controlled experimental stimulation of about 50 minutes during which continuous physiological data were recorded. Participants were asked to complete two mental tasks—mental arithmetic (MA) and the Stroop Color-Word Test—presented on the computer screen with the sequence of the tasks randomized.

MA. The MA included four task items consisting of a problem such as "first add 11 to 67, then 9, then 7, etc., so that the last number to be added is 1."

Stroop Color-Word Test. The subject had to count the number of names of colors written in incongruent colors. The subject had to ignore the word itself and react to the color, eg, "count the number of times the word 'orange' is written in red." The Stroop test included four task items consisting of a visual display presented in 18 (rows) × 8 (columns) of different color-words.

The subject was asked to work as quickly as possible. The computer presented the next task item when the subject pushed a button indicating he had reached an answer. The oral answer was manually recorded by the experimenter.

Each set of mental tasks was preceded and followed by a 2-minute presentation of repeated neutral auditory stimuli (eight 1,000-Hz tones followed by four 500-Hz tones of 76-dB intensity). The first 2-minute period of neutral auditory stimuli was used as a baseline for physiological measurements.

Feedback was given visually after each of the task items, when the subject indicated he was ready. The subject was always informed he had used more time than "the best performer of the day." Each subject received exactly the same feedback.

The stressor protocol of the psychophysiological experiment was, in fact, two task items longer than described here, but in the present study, only task items followed by homogenous feedback, ie, the first four successive items of the MA and the Stroop test (a total of eight items), were used. This was done to construct more meaningful trends of physiological responses (see below). The whole psychophysiological experiment has been previously described.[36]

Physiological Variables

HR, FBV, and SCL were recorded continuously during the experiment. They were digitized and stored in 10-second intervals. HR (beats per minute) was measured using a cardiotachometric recording from the chest configuration using Ag/AgCl disposable electrodes. FBV (units) was measured from the middle finger using a photoplethysmographic Gilson transducer (Gilson Medical Electronics, Middleton, WI). FBV is used to index slow changes in the overall engorgement of the finger and is controlled to a large extent by the sympathetic (α-adrenergic) nervous system.[37] SCL (microsiemens [μS]) was recorded by constant-voltage (0.5 V) bridge. Beckman (Schiller Park, IL) Biopotential Electrodes (8 mm diameter) were fixed onto the palmar surface of the nonpreferred hand. SCL is controlled entirely by the sympathetic nervous system and may unambiguously reflect primary arousal.[38] HR, FBV, and SCL were quantified by computing the mean of the interval. An index of HRV in the time domain was calculated as the standard deviation of HR within the 10-second interval.

An Amiga (Bensheim, Germany) 1000 and special software (Event Organizer) were used to time and produce the stimulus displays, trigger pulses, and identification codes specific to each epoch and interval. All data were stored on the hard disk of a PC microcomputer after digitizing with a Lab Master 12-bit 16-channel AD converter (Tecmar, Cleveland, OH).

It has been previously shown that hemodynamic responses to the MA and Stroop tests are reproducible.[39,40]

Statistical Analyses

Magnitude of physiological response and metabolic and anthropometric parameters. Mean baseline values were computed for each subject across the first 2-minute period of neutral auditory stimuli for each physiological measure (ie, the mean of 12 10-second intervals). Task values for each measure were averaged separately for the MA and Stroop tests (ie, the mean of the 10-second intervals during which the subject performed the task). Change scores (representing the magnitude of the physiological response to stress) were computed by subtracting appropriate baseline values from each of the mean measurements.

The relation of the magnitude of physiological responses (HR, HRV, SCL, and FBV) with metabolic and anthropometric parameters (serum insulin, TG, HDL cholesterol, SSF, STR, and SBP) was evaluated with multiple regression analyses. A series of hierarchical regressions were performed in which predictors of the metabolic/anthropometric parameters were (1) BMI, (2) the mean baseline physiological value, and (3) the change score for the physiological variable. BMI was used as a covariate because individual differences in BMI may affect cardiovascular responses to stress.[41] Baseline physiological values were also statistically controlled because they can influence the degree of change during stress (ie, law of initial values).[42] Serum insulin and TG values were log-transformed before computing to obtain more nearly Gaussian distributions.

Trend of physiological response and metabolic and anthropometric parameters. When examining whether temporal changes in the task-level physiological responses during the MA and Stroop tests are related to the metabolic and anthropometric parameters, the first step was construction of the linear trends of the task levels of HR, HRV, FBV, and SCL. The task physiological values were averaged across the first two 10-second intervals within each task item. A curve estimation regression analysis[43] was used to estimate the linear trends separately for each subject. The trends were estimated on the basis of physiological scores specific to eight consecutive task items, ie, the first four MA and the first four Stroop task items. The regression line through the eight consecutive physiological scores indicated the linear trend of the task-level physiological response. A positive value of the slope (b_1) indicates an increasing linear trend, and a negative one, a decreasing trend of the response. The constant term (b_0) represents the initial task level of the physiological response. These trends were also constructed separately for the MA and Stroop tests.

Relationships between the linear trends of physiological responses (HR, HRV, SCL, and FBV) during the mental tasks and the metabolic and anthropometric parameters were evaluated by multiple regression analyses. Separate hierarchical regression analyses were performed with the metabolic/anthropometric parameters as the dependent variables and with (1) BMI, (2) the initial task level of the physiological response (ie, the constant term b_0), and (3) the linear trend of the task-level physiological response (ie, the slope b_1) as the independent variables.

RESULTS

Manipulation Check

Table 1 shows the mean baseline and task-induced changes in HR, HRV, SCL, and FBV, as well as the percentage of subjects showing an increase in these physiological variables. Overall, the tasks elicited physiological arousal. Both the MA and Stroop tests produced a significant increase in HR ($F(1, 47) = 55$ and 16, respectively, $P < .001$). In addition, there was a significant mean decrease in SCL, HRV, and FBV during both tasks when adjusting for the baseline ($9 < F < 51, P < .004$).

Examination of correlations between the baseline physiological values (HR, HRV, FBV, and SCL) and the metabolic and anthropometric parameters revealed that baseline HR correlated positively and significantly with serum insulin concentration (Pearson's $r = .32$, $P = .028$). Insulin concentration was positively and significantly correlated with TG concentration ($r = .30$, $P = .041$). Correlation of serum insulin with other metabolic and anthropometric parameters did not reach statistical significance, apparently because of the small sample size. [In the entire cohort of boys aged 15 years during the CRYF 6-year follow-up study, insulin was positively and significantly correlated with SBP, BMI, SSF, and STR: $r = .24$, .35, .35, and .14, and $P < .001$, .001, .001, and = .030, respectively. In this entire cohort, 3-year test-retest correlations (Pearson's r) of these parameters were .52, .66, .42, .30, .86, .81, and .65, respectively, for SBP, HDL cholesterol, TG, insulin, BMI, SSF, and STR ($P < .001$; measurements were made during the 3- and 6-year follow-up examinations).]

Magnitude of Physiological Response and Metabolic and Anthropometric Parameters

Table 2 shows the results of regression analyses in which the physiological responses (change scores) to the mental tasks were predictors of the metabolic and anthropometric

Table 1. Mean Baseline, Mean and Median of Task-Induced Changes, and Percentage of Subjects Showing an Increase in Physiological Parameters

Variable	HR (bpm)	HRV (bpm)	SCL (μS)	FBV (U)
Mean baseline	78.7 (1.5)	4.5 (0.2)	4.2 (0.4)	10.0 (0.02)
MA test				
Mean change	7.3 (0.9)	−0.5 (0.2)	−0.2 (0.3)	−0.1 (0.04)
Median	6.6	−0.4	0.2	−0.1
% subjects showing an increase*	81	6	48	2
Stroop test				
Mean change	5.4 (1.3)	−0.7 (0.2)	−0.6 (0.3)	−0.1 (0.04)
Median	5.0	−0.4	−0.3	−0.1
% subjects showing an increase*	77	2	33	2

NOTE. The standard error of the mean is shown in parentheses.

*Change score (delta) $> 0 + 1.65SE_{meas}$; SE_{meas} (standard error of measurement) $= SD_{delta}\sqrt{1 - r_{dd}}$; SD_{delta} = standard deviation of delta. The formula for the reliability of delta (r_{dd}) can be found in Llabre et al,[44] among other sources.

Table 2. Multiple Regression Model: Physiological Responses to the Mental Tasks in Predicting Metabolic and Anthropometric Parameters

Variable	β	t	P	R^2	Change in R^2
MA test					
STR					
Baseline SCL	.61	2.96	.005	.075	.075
Change in SCL	.45	2.17	.035	.163	.088
SSF					
BMI	.80	9.28	<.001	.637	.637
Baseline SCL	.23	1.71	.095	.637	.000
Change in SCL	.28	2.09	.042	.670	.033
Stroop test					
STR					
Baseline HRV	.76	3.33	.002	.087	.087
Change in HRV	.58	2.55	.015	.209	.122
SSF					
BMI	.76	7.94	<.001	.585	.585
Baseline HRV	.32	2.02	.050	.587	.002
Change in HRV	.34	2.17	.036	.630	.043

NOTE. β coefficients and t and P values are those computed at the final step of each analysis. Only statistically significant findings are reported. Change scores (task minus baseline) were used in these analyses.

parameters. Regression analysis indicated that both baseline SCL and SCL response to the MA were significant predictors of STRs ($P = .005$ and .035, respectively); that is, both high baseline SCL and an increase in SCL were related to high STRs. In addition, SCL response to the MA was positively and significantly related to SSFs after adjustment for BMI ($P = .042$). Furthermore, a Stroop-related increase (or lack of decrease) in HRV was significantly associated with high STRs and BMI-adjusted SSFs ($P = .015$ and .036, respectively). High baseline HRV was also related to high STRs and SSFs ($P = .002$ and .050, respectively).

There was a marginally significant positive association between the HR response to the MA and SSFs ($\beta = .16$, $P = .072$; not shown). Similarly, the positive association of SCL response to the MA with serum TG and insulin concentration was of borderline significance ($\beta = .40$ and .40, $P = .063$ and .073, respectively; not shown).

Trend of Physiological Response and Metabolic and Anthropometric Parameters

Table 3 shows the results of regression analyses in which the linear trends of task-level physiological responses during the MA and Stroop tests were predictors of the metabolic and anthropometric parameters. It was found that an increasing trend of HR during the mental tasks (the trend being estimated on the basis of eight task items, ie, four MA items and four Stroop items) was related to a high serum insulin concentration independently of BMI and the initial task level of HR ($P = .012$). However, a high initial task level of HR was also associated with a high insulin concentration ($P = .005$). These associations also remained significant when adjusted for SSF or STR (not shown). In addition, an increasing linear trend of HR during the task performance predicted high BMI-adjusted SSFs ($P = .001$). The positive association between the trend of HR and TG concentration was of borderline significance ($\beta = .39$, $P = .062$; not shown). Furthermore, a high initial task level of HRV was related both to high STRs and to BMI-adjusted SSFs ($P = .007$ and .046, respectively). There was also a marginally significant negative association between the trend of FBV during the tasks and serum HDL cholesterol concentration ($\beta = -.47, P = .082$; not shown). Likewise, the positive association of the initial task level of SCL with serum insulin and TG levels showed borderline

Table 3. Multiple Regression Model: Initial Task Level and Trend of Task-Level Physiological Responses During Mental Task Performance in Predicting Metabolic and Anthropoemtric Parameters

Variable	β	t	P	R^2	Change in R^2
MA and Stroop tests*					
Insulin					
BMI	.25	1.82	.076	.030	.030
Initial task level of HR	.59	2.97	.005	.075	.045
Trend of HR	.51	2.63	.012	.200	.125
SSF					
BMI	.78	9.67	<.001	.637	.637
Initial task level of HR	.14	1.20	.236	.656	.019
Trend of HR	.39	3.48	.001	.730	.074
SSF					
BMI	.72	7.82	<.001	.637	.637
Initial task level of HRV	.29	2.05	.046	.665	.028
Trend of HRV	.14	1.05	.300	.673	.008
STR					
Initial task level of HRV	.57	2.82	.007	.208	.208
Trend of HRV	.15	0.73	.467	.217	.009
MA test*					
Insulin					
BMI	.29	2.05	.046	.030	.030
Initial task level of HR	.46	3.10	.003	.198	.168
Trend of HR	.09	0.65	.519	.205	.007
TG					
BMI	.11	0.81	.424	.011	.011
Initial task SCL	.34	2.24	.030	.115	.104
Trend of SCL	.04	0.26	.794	.117	.002
SSF					
BMI	.80	9.29	<.001	.637	.637
Initial task SCL	.19	2.02	.050	.671	.034
Trend of SCL	.00	0.02	.987	.671	.000
STR					
Initial task SCL	.37	2.49	.016	.127	.127
Trend of SCL	.04	0.25	.803	.128	.001
Stroop test*					
Insulin					
BMI	.31	2.18	.036	.101	.101
Initial task level of FBV	.77	2.56	.015	.106	.005
Trend of FBV	.95	3.14	.003	.298	.192
SSF					
BMI	.73	7.92	<.001	.637	.637
Initial task level of HRV	.25	2.24	.030	.647	.010
Trend of HRV	.23	2.21	.032	.682	.035
STR					
Initial task level of HRV	.62	4.06	<.001	.231	.231
Trend of HRV	.25	1.65	.105	.275	.044

NOTE. β coefficients and t and P values are those computed at the final step of each analysis. Only statistically significant findings are reported.

*Mental task(s) used when estimating the trend of task-level physiological responses.

significance (β = .28 and .29, P = .061 and .056, respectively; not shown).

An increasing trend of HRV during the Stroop test (the trend being estimated on the basis of four Stroop items) was also found to predict high SSFs independently of BMI and the initial task level of HRV (P = .032). In line with the above-mentioned findings, a high initial task level of HRV during the Stroop test predicted high STRs and SSFs (P < .001 and = .030, respectively). In addition, the initial task level and linear trend of FBV during the Stroop test were both significant predictors of serum insulin concentration after adjustment for BMI (P = .015 and .003, respectively), with a high initial task level and an increasing trend of FBV being related to a high insulin level. This association remained significant when adjusted for SSF or STR (not shown).

It was also found that a high initial task level of HR during the MA was associated with a high insulin concentration after adjustment for BMI (P = .003). This was not changed when adjustment was made for SSF or STR (not shown). In addition, the initial task SCL during the MA was positively and significantly related to serum TG concentration, SSFs, and STRs (P = .030, .050, and .016, respectively).

DISCUSSION

The present study shows that autonomically mediated physiological responses (HR, HRV, FBV, and SCL) to experimentally induced mental stress are related to serum insulin level and other parameters of IRS in healthy adolescent boys. We found that the trend of the physiological responses during mentally challenging tasks contributed in many cases even more significantly than the magnitude of the response (ie, mean task level minus baseline) to the variance in IRS parameters.

The principal finding was that an increasing linear trend of HR during performance of mentally challenging tasks, ie, an increase in HR with increasing exposure to the MA and Stroop tests, was related to a higher serum insulin concentration and to larger SSFs independently of BMI or the initial task level of HR. Likewise, it was found that an increasing trend of FBV with increasing exposure to the Stroop test predicted a higher insulin concentration. However, high initial task levels of HR and FBV were also significantly related to high insulin levels. Although the cross-sectional nature of this study precludes causal inferences, we think the data presented herein are in line with the suggestion that stress-induced sympathetic overactivity may influence IRS parameters. The relationship found between hemodynamic responses to stress in terms of an increasing trend of HR and FBV and the parameters of IRS is compatible with the hypothesis that a defense reaction–like hemodynamic pattern resulting from chronic sympathetic overactivity may contribute to the pathogenesis of the IRS.[18] That is, stress-induced repeated episodes of elevated cardiac output (CO), mainly determined by increased HR, with consequent elevation of muscle blood flow have been suggested to contribute to the initiation of vascular hypertrophy. Structural alterations in blood vessels have been suggested, in turn, to lead to an unfavorable delivery of insulin and glucose to the tissues and thereby, in part, to cause insulin resistance.[18,19] Of course, even though vascular adaptations have been observed even in adolescence,[45] the possible structural changes are likely to have been relatively slight in the present healthy subjects.

However, the finding that a Stroop test–induced increasing trend of FBV was related to a high insulin concentration deserves further attention. Normally under physiological conditions, the regional hemodynamic pattern during acute mental stress is characterized by sympathetically mediated peripheral muscular vasodilation through β-adrenergic activity and digital vasoconstriction through α_1-adrenergic receptors.[46] Digital blood flow tended, on average, to decrease in the present subjects, as well. However, besides α-adrenergic activity, the other primary determinant of digital blood flow is CO.[47] If vasomotor tonus is held constant, an increase in CO can increase the radius of the arteriolar resistance vessels, thus increasing FBV.[47] That being the case, the vasoconstrictive effect of α-adrenergic activity may have been overridden by stress-induced exaggerated CO, resulting in an increasing trend of FBV in high-cardiac reactors. In the absence of more detailed information about the hemodynamic responses to stress (eg, CO, forearm blood flow, and forearm vascular resistance) in the present subjects, these suggestions must remain speculative. A recent observation that the Stroop test induces a pronounced increase in forearm blood flow may nevertheless bear on this point.[48] In this context, it is also of interest that individuals characterized by a type A behavior pattern, an established risk factor for CHD,[49] have been shown to express less digital vasoconstriction during stress as compared with type B subjects, whereas during rest type Bs are less vasoconstricted.[47] Moreover, digitial arterial pulse amplitude has been shown to decrease more markedly in normotensive as compared with hypertensive humans during MA stress.[50]

However, we recognize that in addition to the hypothesized role of a stress-induced hemodynamic pattern in the development of IRS, there are other possible pathways via which sympathetic overactivity might contribute to insulin resistance. The present results demonstrated that both a high task level of skin conductance and a large SCL response to the MA were related, independently of BMI, to a high TG concentration and increased STRs and SSFs. Thus, besides sympathetically mediated cardiovascular responses, overall differences in sympathetic activity reflected here by SCL may also be of importance. It has been shown, for example, that an infusion of epinephrine, the classic stress hormone, can produce β-receptor–mediated acute insulin resistance in the skeletal muscle.[51] Likewise, Lembo et al[52] have recently reported that an acute increase in skeletal muscle noradrenergic activity, as measured by noradrenaline outflow, is able to antagonize insulin-stimulated muscle glucose disposal. Insulin has been suggested as a stimulator of the sympathetic nervous system.[8] However, it appears unlikely that the relationship found between autonomic responses to stress and insulin concentration would be explained by insulin-induced heightened sympathetic tone, since only large insulin infusions have been shown to increase circulating noradrenaline concentrations, muscle sympathetic outflow, and HR in humans.[53-56] Moreover, we found that a stress-induced change in FBV predicted serum insulin level, whereas cutaneous blood flow has recently been reported to be unaffected by the elevated insulin concentrations during a euglycemic clamp.[57] Furthermore, abnormalities of autonomic function related to obesity would not seem to account for the present findings, since the association between autonomic responses and serum insulin remained significant when adjusting for BMI, SSF, or STR.

We also found that a high initial task level and an increasing linear trend of HRV and a change score–defined increase (or lack of decrease) in HRV during stress were related to increased STRs and SSFs. Since there is substantial evidence establishing that decreased indices of HRV, a crude index of sympathetic/parasympathetic balance, are associated with obesity, diabetes, and increased susceptibility to ventricular arrhythmias,[58,59] the present finding may well be an artifact. However, in general, HRV is decreased during mental effort, sustained attention, and organized behavioral responses to stress.[60] Likewise, the suppression of HRV has been associated with enhanced task performance.[60] Thus, an increase (or lack of decrease) in HRV during a stressful mental task might be an unadaptive response, although the mechanism that could explain the observed association is unknown. Interestingly, type A persons have been reported to exhibit greater HRV than type Bs—particularly just before and after the performance, and to a lesser extent during the task.[61] In addition, it has been recently suggested that HRV as measured by the standard deviation of HR is increased by both sympathetic and parasympathetic arousal.[62]

Although the present associations were statistically not very strong, they appeared to be highly stable in view of the 6-month interval between the metabolic and anthropometric measurements and the psychophysiological study. This is important, because although cardiovascular responsivity has been found to evidence high temporal stability,[63] there are rapid changes in insulin sensitivity during adolescence.[64]

The present study indicated that the trend of physiological response during exposure to a mentally challenging task is an important interindividual difference independently of the task level of the physiological response. Traditionally, cardiovascular reactivity research has focused on the magnitude of the physiological response to stress (change score). However, when the analyses were performed using change scores in lieu of trends, the association of HR and FBV response with insulin concentration and SSFs did not reach statistical significance (but the association of SCL response with STRs and SSFs was significant only when change scores were used). It might be suggested that the trend of response during task-induced stress might be at least as relevant as the magnitude of response in predicting significant response patterns during sustained real-life stress. Studies on determinants of this kind of response-trends during experimental stress are relatively few. However, Matthews and Jennings[65] have shown that type A boys had an increase in HR reactivity with increasing exposure to tasks relevant to type A characteristics, whereas in other boys reactivity remained the same or decreased. Variables associated with temperament and characteristic ways of coping also seem likely candidates to modulate the pattern and intensity of response to task-induced stress.[66] Nevertheless, acquiring an understanding of factors affecting physiological response-trends clearly requires further study.

To summarize, it was suggested that trends of physiological responses to task-induced stress implicate important individual differences in stress modulation. In addition, the present results suggest a relationship between stress-induced sympathetically mediated physiological responses and the metabolic and anthropometric parameters constituting IRS in healthy adolescent boys. These findings would argue that we should not ignore the potential role of a defense reaction–like hemodynamic pattern in the pathogenesis of insulin resistance.

REFERENCES

1. Ferrannini E: Syndrome X. Horm Res 39:107-111, 1993 (suppl 3)

2. Karam JH: Type II diabetes and syndrome X. Pathogenesis and glycemic management. Endocrinol Metab Clin North Am 21:329-350, 1992

3. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

4. Reaven GM: Role of insulin resistance in human disease (syndrome X): An expanded definition. Annu Rev Med 44:121-131, 1993

5. Haffner SM, Valdez RA, Hazuda HP, et al: Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 41:715-722, 1992

6. Vague P, Raccah D: The syndrome of insulin resistance. Horm Res 38:28-32, 1992

7. Fontbonne AM, Eschwège EM: Insulin and cardiovascular disease. Paris prospective study. Diabetes Care 14:461-469, 1991

8. DeFronzo RA, Ferrannini E: Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic vascular disease. Diabetes Care 14:173-194, 1991

9. Björntorp P: Metabolic implications of body fat distribution. Diabetes Care 14:1132-1143, 1991

10. Björntorp P: Regional fat distribution—implications for type II diabetes. Int J Obes 16:S19-S27, 1992 (suppl 4)

11. Kaplan JR, Adams MR, Clarkson TB, et al: Psychosocial influences on female protection among cynomolgus macaques. Atherosclerosis 53:283-295, 1984

12. Shively CA, Clarkson TB: Regional obesity and coronary artery atherosclerosis in females: A non-human primate model. Acta Med Scand [Suppl] 723:71-78, 1988

13. Rebuffé-Scrive M, Walsh UA, McEwen B, et al: Effect of chronic stress and exogenous glucocorticoids on regional fat distribution and metabolism. Physiol Behav 52:583-590, 1992

14. Mårin P, Darin N, Amemiya T, et al: Cortisol secretion in relation to body fat distribution in obese premenopausal women. Metabolism 41:882-886, 1992

15. Ravaja N, Keltikangas-Järvinen L, Keskivaara P: Type A factors as predictors of changes in the metabolic syndrome precursors in adolescents and young adults—A three-year follow-up study. Health Psychol 15:18-29, 1996

16. Ravaja N, Keltikangas-Järvinen L, Viikari J: Type A behavior and metabolic syndrome precursors in young adults. J Clin Epidemiol (in press)

17. Stern MP, Morales PA, Haffner SM, et al: Hyperdynamic circulation and the insulin resistance syndrome ("syndrome X"). Hypertension 20:802-808, 1992

18. Julius S, Gudbrandsson T: Early association of sympathetic overactivity, hypertension, insulin resistance, and coronary risk. J Cardiovasc Pharmacol 20:S40-S48, 1992 (suppl 8)

19. Lind L, Lithell H: Decreased peripheral blood flow in the pathogenesis of the metabolic syndrome comprising hypertension, hyperlipidemia, and hyperinsulinemia. Am Heart J 125:1494-1497, 1993

20. Ganrot PO: Insulin resistance syndrome: Possible key role of blood flow in resting muscle. Diabetologia 36:876-879, 1993

21. Smoak CG, Burke GL, Webber LS, et al: Relation of obesity to clustering of cardiovascular disease risk factors in children and young adults. The Bogalusa Heart Study. Am J Epidemiol 125:364-372, 1987

22. Freedman DS, Srinivasan SR, Burke GL, et al: Relation of body fat distribution to hyperinsulinemia in children and adolescents: The Bogalusa Heart Study. Am J Clin Nutr 46:403-410, 1987

23. Burke GL, Webber LS, Srinivasan SR, et al: Fasting plasma glucose and insulin levels and their relationship to cardiovascular risk factors in children: The Bogalusa Heart Study. Metabolism 35:441-446, 1986

24. Zimmet PZ, Collins VR, Dowse GK, et al: Hyperinsulinaemia in youth is a predictor of type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 35:534-541, 1992

25. Pardine P, Napoli A: Physiological reactivity and recent life stress experience. J Consult Clin Psychol 51:467-469, 1983

26. Fleming I, Baum A, Davidson LM: Chronic stress as a factor in physiological reactivity to challenge. Health Psychol 6:221-237, 1987

27. Åkerblom HK, Uhari M, Pesonen E, et al: Cardiovascular risk in young Finns. Ann Med 23:35-40, 1991

28. Uhari M, Nuutinen M, Turtinen J, et al: Blood pressure in children, adolescents and young adults. Ann Med 23:47-51, 1991

29. Fox K, Peters D, Armstrong N, et al: Abdominal fat deposition in 11-year-old children. Int J Obes 17:11-16, 1993

30. Dahlström S, Viikari J, Åkerblom HK, et al: Atherosclerosis precursors in Finnish children and adolescents. II. Height, weight, body-mass index, and skinfolds and their correlation to metabolic variables. Acta Paediatr Scand [Suppl] 318:65-78, 1985

31. Herbert V, Lau KS, Gottlieb CW, et al: Coated charcoal immunoassay of insulin. J Clin Endocrinol Metab 25:1375-1384, 1965

32. Kostner GM: Enzymatic determination of cholesterol in high density lipoprotein fractions prepared by polyanion precipitation. Clin Chem 22:695, 1976

33. Siegel J, Schlumberger H, Klose S, et al: Improved reagent for the enzymatic determination of serum cholesterol. J Clin Chem Clin Biochem 19:838-839, 1981

34. Wahlefeld AW: Triglycerides—Determination after enzymatic hydrolysis, in Bergmeyer HV (ed): Methods of Enzymatic Analysis (ed 2). New York, NY, Verlag Chemie/Academic, 1974, pp 1831-1835

35. Viikari J, Rönnemaa T, Seppänen A, et al: Serum lipids and lipoproteins in children, adolescents, and young adults in 1980-1986. Ann Med 23:53-59, 1991

36. Räikkönen K, Keskivaara P, Keltikangas-Järvinen L, et al: Psychophysiological arousal related to type A components in adolescent boys. Scand J Psychol 36:142-152, 1995

37. Papillo JF, Shapiro D: The cardiovascular system, in Cacioppo JT, Tassinary LG (eds): Principles of Psychophysiology. Physical, Social, and Inferential Elements. Cambridge, UK, Cambridge University Press, 1990, pp 456-512

38. Zuckerman M: Psychobiology of Personality. Cambridge, UK, Cambridge University Press, 1991

39. Jern S, Pilhall M, Jern C: Short-term reproducibility of a mental arithmetic stress test. Clin Sci 81:593-601, 1991

40. Freyschuss U, Hjemdahl P, Juhlin-Dannfelt A, et al: Cardiovascular and sympathoadrenal responses to mental stress: Influence of β-blockade. Am J Physiol 255:H1443-H1451, 1988

41. Alpert BS, Wilson DK: Stress reactivity in childhood and adolescence, in Turner JR, Sherwood A, Light KC (eds): Individual Differences in Cardiovascular Response to Stress. New York, NY, Plenum, 1992, pp 187-201

42. Wilder JF: Stimulus and Response: The Law of Initial Values. Baltimore, MD, Williams & Wilkins, 1968

43. Norušis MJ/SPSS: SPSS for Windows: Base System User's Guide, release 6.0. Chicago, IL, SPSS, 1993

44. Llabre MM, Spitzer SB, Saab PG, et al: The reliability and specificity of delta versus residualized change as measures of cardiovascular reactivity to behavioral challenges. Psychophysiology 28:701-711, 1991

45. Lovallo WR, Wilson MF: A biobehavioral model of hypertension development, in Turner JR, Sherwood A, Light KC (eds): Individual Differences in Cardiovascular Response to Stress. New York, NY, Plenum, 1992, pp 265-280

46. Folkow B: Physiological aspects of primary hypertension. Physiol Rev 62:347-504, 1982

47. Lovallo WR, Pishkin V: A psychophysiological comparison of type A and B men exposed to failure and uncontrollable noise. Psychophysiology 17:29-36, 1980

48. Lindqvist M, Kahan T, Melcher A, et al: Cardiovascular and sympatho-adrenal responses to mental stress in primary hypertension. Clin Sci 85:401-409, 1993

49. Matthews KA: Coronary heart disease and type A behavior: Update on and alternative to the Booth-Kewley and Friedman (1987) quantitative review. Psychol Bull 104:373-380, 1988

50. Östergren J, Kahan T, Hjemdahl P, et al: Effects of sympathoadrenal activation on the finger microcirculation in mild hypertension. J Hum Hypertens 6:169-173, 1992

51. Deibert DC, DeFronzo RA: Epinephrine-induced insulin resistance in man. J Clin Invest 65:717-721, 1980

52. Lembo G, Capaldo B, Rendina V, et al: Acute noradrenergic activation induces insulin resistance in human skeletal muscle. Am J Physiol 266:E242-E247, 1994

53. Christensen NJ, Gundersen HJG, Hegedus L, et al: Acute effects of insulin on plasma noradrenalin and the cardiovascular system. Metabolism 29:1138-1145, 1980

54. Scott AR, Bennett T, MacDonald IA: Effects of hyperinsulinaemia on the cardiovascular responses to graded hypovolaemia in normal and diabetic subjects. Clin Sci 75:85-92, 1988

55. Berne C, Fagius J, Niklasson F: Sympathetic response to oral carbohydrate administration: Evidence from microelectrode nerve recordings. J Clin Invest 84:1403-1409, 1989

56. Anderson EA, Hoffman RP, Balon TW, et al: Hyperinsulinemia in humans increases muscle sympathetic nerve activity but reduces forearm vascular resistance. Hypertension 16:319, 1990 (abstr)

57. Åman J, Berne C, Ewald U, et al: Cutaneous blood flow

during a hypoglycaemic clamp in insulin dependent diabetic patients and healthy subjects. Clin Sci 82:615-618, 1992

58. Stein PK, Bosner MS, Kleiger RE, et al: Heart rate variability: A measure of cardiac autonomic tone. Am Heart J 127:1376-1381, 1994

59. Zahorska-Markiewicz B, Kuagowska E, Kucio C, et al: Heart rate variability in obesity. Int J Obes 17:21-23, 1993

60. Porges SW, Byrne EA: Research methods for measurement of heart rate and respiration. Biol Psychol 34:93-130, 1992

61. Jennings JR: Attention and coronary heart disease, in Krantz DS, Baum A, Singer JE (eds): Handbook of Psychology and Health, vol 3: Cardiovascular Disorders and Behavior. Hillsdale, NJ, Erlbaum, 1983, pp 85-124

62. Moser M, Lehofer M, Sedminek A, et al: Heart rate variability as a prognostic tool in cardiology. A contribution to the problem from a theoretical point of view. Circulation 90:1078-1082, 1994

63. Sherwood A, Turner JR: A conceptual and methodological overview of cardiovascular reactivity research, in Turner JR, Sherwood A, Light KC (eds): Individual Differences in Cardiovascular Response to Stress. New York, NY, Plenum, 1992, pp 3-32

64. Caprio S, Amiel SA, Merkel P, et al: Insulin-resistant syndromes in children. Horm Res 39:112-114, 1993 (suppl 3)

65. Matthews KA, Jennings JR: Cardiovascular responses of boys exhibiting the type A behavior pattern. Psychosom Med 46:484-497, 1984

66. Houston BK: Personality characteristics, reactivity, and cardiovascular disease, in Turner JR, Sherwood A, Light KC (eds): Individual Differences in Cardiovascular Response to Stress. New York, NY, Plenum, 1992, pp 103-123