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The Autonomic Control of Heart Rate and Insulin Resistance in Young Adults*

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ABSTRACT

The pathophysiology of insulin resistance is unclear. A link between increased heart rate (HR) and insulin resistance suggests an association with sympathetic nervous system activity. To further evaluate this, we examined autonomic activity using spectral analysis of HR variability (HRV), which provides a measure of cardiac sympathovagal modulation, and related this to insulin sensitivity (Si) in 137 men and women (20 yr old). The HRV spectrum displays 2 major peaks: a high-frequency peak, reflecting vagal activity, and a low-frequency peak caused by vagal and sympathetic activity. The high-to-low ratio (HLratio) reflects sympathovagal balance. Si was measured, using the iv glucose tolerance test with minimal modeling, and HR data was derived from a 15-min supine electrocardiogram. Women were more insulin resistant than men (Si, 3.94 *vs.* 5.09 10^4 min^{-1}/per pmol·L; $P = 0.002$), had higher HR (59 *vs.* 56 beats/min, $P = 0.019$), but had a higher HLratio (2.04 *vs.* 1.31, $P = 0.001$). In men (but not women), Si correlated with HR ($r = -0.410$, $P = 0.001$) and measures of HRV: HLratio ($r = 0.291$, $P = 0.002$) independently of body mass index. In conclusion, Si correlates with cardiac sympathovagal balance in men, but not women, suggesting gender differences in the autonomic modulation of insulin resistance. (*J Clin Endocrinol Metab* **84:** 1263–1267, 1999)

THE INSULIN resistance syndrome is characterized by glucose intolerance, raised blood pressure, dyslipidemia, and reduced Si (insulin sensitivity). Although it predisposes to cardiovascular disease and is an important cause of mortality and morbidity, its pathophysiology is poorly understood (1). Epidemiological studies have shown that the syndrome or its components are associated with a high resting HR (heart rate) (2–4). Furthermore, insulin resistance, measured by the euglycemic clamp, correlates strongly with the overnight HR (5). Because a high resting HR is an index of increased sympathetic nervous system (SNS) activity, these observations have suggested a link between increased SNS activity and insulin resistance. It is not clear whether this association is causal. Because catecholamines are powerful vasopressor agents and directly induce insulin resistance, increased SNS activity may be one of the processes initiating both insulin resistance and hypertension (and hence, the insulin resistance syndrome) (6–8). However, there is also experimental evidence that hyperinsulinemia may itself increase SNS activity (9).

Most studies relating HR to the insulin resistance syndrome have depended on the resting pulse rate, which is an imprecise and highly variable physiological measurement, influenced by many factors. Analysis of the small beat-to-beat variations of the HR has been shown to provide a more accurate assessment of the neural regulation of the heart than the HR itself. The recent development of computer techniques to quantify HR variability (HRV) provides quantitative indices of sympathetic and vagal activity by means of power spectral analysis (10). We have applied this technique to examine the relationship between autonomic activity, as indicated by HRV, and Si in a group of young men and women. Si was measured using the iv glucose tolerance test (IVGTT) with minimal model analysis.

Subjects and Methods

This study sample was drawn from an existing cohort of young adults, the Adelaide Children's Hospital Family Heart Study (11). The subjects represent a subset of an ongoing epidemiological study to determine the relationship between fetal growth and glucose tolerance. The obstetric records of singleton births between 1975–1976 at the Queen Victoria Hospital, Adelaide, were used to trace 764 individuals currently living in Adelaide. Computer-generated random samples were drawn for each sex, to obtain a subset of approximately 150 subjects, which *a priori* power calculation indicated would be sufficient for the present analyses. IVGTTs were performed on 163 subjects; further electrocar-

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diogram (ECG) analysis was performed on 137 of this group. The study was approved by the Human Ethics Committee of the Women's and Children's Hospital. Informed written consent was obtained from each of the subjects. Subjects were requested to consume more than 200 g/day carbohydrate for 3 days. They were asked to fast overnight and to refrain from smoking and alcohol overnight before attending the department between 0800 and 0900 h. Exclusion factors included current diabetes or other current illness. Medical history, smoking habits, alcohol consumption, and stage of the menstrual cycle were recorded. Alcohol consumption was converted into the total number of units each week (1 U = 8 g ethanol). Subjects were categorized as either not doing exercise, doing less than 3 sessions of aerobic exercise, or 3 or more sessions per week. Measurements of the subjects' weight, using an electronic scale (A.N.D. weighing equipment Ltd., Adelaide, Australia), and height, using a stadiometer (Holtain Ltd., Crymych, Dyfed, Wales, UK), were used to calculate the body mass index [BMI; defined as weight divided by the height squared (kg/m^2)]. Waist and hip circumferences were measured using a steel tape measure. Waist circumference was measured at the level of the umbilicus, and hip circumference at the level of the greater trochanters. The ratio of the waist and hip measurements was used as an index of central obesity. Skinfold thicknesses were measured, by a single observer with Harpenden skinfold calipers, at the biceps and triceps sites.

An ECG was performed on each subject using a portable analogue tape recorder (Oxford Instruments Co. Ltd., Osney Mead, Oxford) via bipolar skin electrodes applied to the chest wall. Subjects lay supine on a couch in a quiet room; and before the start of each recording, a 30-min rest period was allowed, to enable HR, blood pressure, and ventilation to stabilize. A 15-min undisturbed ECG recording was then obtained.

Subjects then underwent a fifteen-point frequently-sampled IVGTT. Each subject received a glucose dose of 0.5 g/kg BW, as 50% wt/vol dextrose via an antecubital vein, over a 3-min period. Blood was sampled from the opposite arm at the following time points: −30, −5, 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 120, and 180 min. Plasma samples were analyzed for glucose using the hexokinase method and insulin using two-site immunometric assays with alkaline phosphatase as the label (12). The within-assay coefficient of variation of the insulin measurements was less than 10%.

Data analysis

Si was determined, from the IVGTT glucose and insulin profiles, using the minimal model of glucose disappearance (13), with programs written in Fortran 77 run on a PDP-11/83 microcomputer. The IVGTT protocol employed in the present study differs, in two respects, from that traditionally used with mathematical modeling analysis. First, after glucose injection, a reduced sample schedule of 15 (rather than 26) samples is followed, the reduced schedule being more useful for relatively large studies. Second, a glucose load of 0.5 g/kg (rather than 0.3 g/kg) is employed, which provides for a sufficient endogenous insulin response in nondiabetic volunteers, without recourse to additional augmentation of pancreatic insulin secretion. The validity and effectiveness of the IVGTT protocol employed in the present study, with regard to the measurement of Si, is apparent in the high rate of model identification and good correlation with measures of Si derived from the euglycemic clamp (r = 0.92) that it provides (14, 15).

The ECG tape cassettes were replayed on a separate playback deck (Oxford Instruments Co. Ltd.). The ECG signal was sampled at 125 Hz, digitized into 12 bits, and analyzed by an Apple Macintosh IIci microcomputer, running Lab-View software (National Instruments Corp., Austin, TX). R waves were detected by individually adjusted thresholds for each recording. Of the initial 15-min recordings, 256-beat segments were selected for analysis, based on the absence of ectopic beats and stationarity of the time series, by an observer who was blinded to the insulin resistance results. HRV was analyzed off-line using the Lab-View 3.1 software.

Frequency domain analysis was performed to determine the power of the underlying component oscillations. Power spectral analysis was performed using the Burg Algorithm (16) with a model order between 8 and 12 (17). The power of each underlying frequency was quantified by decomposing the total variability signal with the method of Zetterberg (18). This enabled the determination of power at the two major peaks in the HRV spectrum: low-frequency (LF) power (arising between 0.05–0.15 Hz) and high-frequency (HF) power (0.15–0.40 Hz). Because total power varies greatly between individual subjects, power was expressed as normalized units, calculated by dividing the [absolute power of a given component (area under the component curve)] by the [total variance minus the DC component] (10). Evidence suggests that the power of the LF peak is determined by sympathetic activity with vagal modulation (19), whereas the HF peak corresponds to respiratory sinus arrhythmia and provides an index of cardiac vagal activity (10). Thus, the high-to-low ratio (HLratio) is taken as a measure of sympathovagal balance (10, 20).

Statistical methods

Where necessary, the data was transformed to normality using logarithms or square-root transformation (Si), and the means are therefore presented as back-transformed values. Independent samples (*t* tests) were used to compare means in Table 1. We analyzed the data using multiple linear regression; all analyses were undertaken using continuous variables. *P* values in Tables 2–4 are derived from the relevant correlation or regression equations.

Results

Table 1 compares the mean age, BMI, measurements of body fat distribution, fasting insulin, Si, HR, and the determinants of HRV for men and women in the study. Although the men and the women had similar age and BMI, the women had significantly greater bicep and tricep skinfold thicknesses. They also had higher fasting insulin levels and lower Si. Women also had higher resting HRs, higher HF power (representing vagal tone) but lower LF power (representing sympathetic with vagal tone), giving a higher ratio of HF to LF power, suggesting less sympathetic and more vagal drive. Because of these gender differences, the data for men and women are presented separately.

Figure 1 shows the relationship between Si and HR for men and women. Men, with a lower HR, were more insulin sensitive ($r = -0.410$, $P = 0.004$). However, in women, there was no association between Si and the resting HR ($P = 0.67$). Although Si correlated strongly with all indices of obesity in both genders ($P < 0.001$), HR was not associated with indices of obesity in either men or women. HR was higher in subjects reporting a lower level of physical activity (none, 69; moderate exercise or more, 64; $P = 0.04$) but was not associated with either smoking habit or alcohol consumption. In a multiple regression analysis in men (with Si as the dependent variable and HR, BMI, and the usual level of physical activity as independent variables), the effects of HR ($P < 0.001$) and BMI ($P = 0.001$), but not physical activity, were statistically

TABLE 1. Mean age, level of obesity, fasting insulin, Si, HR, and spectral analysis according to sex

	Men (n = 73)	Women (n = 64)	*P* value
Age (yr)	20.9 (0.28)	20.9 (0.29)	0.649
BMI (kg/m^2)	23.9 (3.7)	23.8 (6.9)	0.906
Waist-to-hip ratio	0.82 (0.06)	0.71 (0.06)	<0.001
Bicep skinfold (mm)	5.0 (2.9)	8.6 (4.4)	<0.001
Tricep skinfold (mm)	9.4 (4.7)	17.6 (6.9)	<0.001
Fasting insulin (pmol/L)	36.8 (23.5)	46.9 (34.2)	0.003
Si (10^4 min^{-1}/pmol·L)	5.09 (2.87)	3.94 (2.57)	0.002
HR (beats/min)	56 (8)	59 (8)	0.019
HF (normalized units)	41.4 (12.7)	49.6 (14.6)	0.001
LF (normalized units)	33.6 (14.4)	26.7 (13.1)	0.004
HLratio	1.31 (1.15)	2.04 (2.07)	0.001

Parentheses, SD.

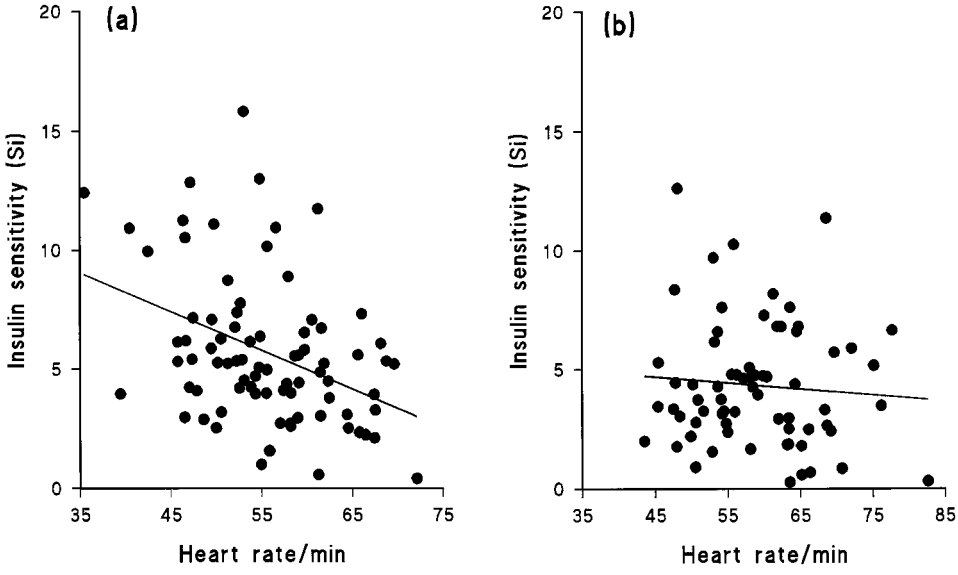

FIG. 1. Relationship between Si and HR in men (a) and women (b).

TABLE 2. Mean Si by adult BMI and HR in men and women

Men BMI (kg/m^2)	HR (beats/min)				
	−51	−56	−61	>61	All
−23	7.67 (10)	6.50 (9)	5.71 (7)	3.95 (10)	6.07 (36)
>23	5.26 (10)	4.66 (11)	4.19 (7)	3.86 (11)	4.28 (39)
All	6.47 (19)	5.42 (20)	4.98 (14)	3.90 (20)	5.09 (73)

Women BMI (kg/m^2)	HR (beats/min)				
	−53	−58	−64	>64	All
−23	5.42 (7)	5.59 (12)	4.81 (10)	4.42 (8)	5.11 (37)
>23	2.39 (7)	3.17 (4)	3.03 (9)	2.68 (8)	2.48 (38)
All	3.56 (14)	4.53 (16)	3.96 (18)	3.40 (16)	3.94 (64)

Parentheses, number of subjects.

TABLE 3. HF and LF spectral power and HLratio, according to HR for men and women

Men HR (beats/min)	No. of subjects	HF (normalized units)	LF (normalized units)	HL ratio
−51	19	45.2	29.5	2.08
−56	20	43.0	34.1	1.75
−61	14	43.6	33.2	1.57
>61	20	34.9	38.4	1.11
All	73	41.4	33.6	1.31
P value		0.002	0.045	0.005

Women HR (beats/min)	No. of subjects	HF (normalized units)	LF (normalized units)	HL ratio
−53	14	53.2	20.9	3.42
−58	16	51.2	24.2	3.09
−64	18	53.4	30.1	2.39
>64	16	41.8	29.3	2.02
All	64	49.6	26.7	2.04
P value		0.025	0.043	0.011

significant. In a similar regression analysis in women, Si was associated with BMI ($P < 0.001$) but not HR or physical activity. The interaction between gender and HR was tested in a least-squares regression model with Si as the dependent variable and BMI, HR, gender, and the interaction term (gender × HR). The interaction term was significant at $P = 0.002$.

Table 2 shows how the level of Si depends on both BMI and HR in each gender. In men, Si fell with increasing HR at any level of BMI; whereas, at any HR, Si fell with increasing BMI. The most insulin-resistant individuals (and therefore, the lowest Si values) were associated with the highest HR and the highest BMI. The most insulin-sensitive individuals were those who had the lowest HR and the lowest BMI. In women, Si fell with increasing BMI, but there was no separate association with HR.

Table 3 shows the relationship between resting HR and HF and LF power obtained for men and women. In both genders, a higher HR was associated with a lower HF power, an increase in the LF power, and a lower ratio of HF to LF power (HLratio), suggesting a shift in the balance (away from vagal, towards sympathetic influence) as HR increases. Table 4 shows the relationship between Si and the HLratio for men and women. As was observed in Fig. 1, the trends differ in men and women. In men, greater Si was associated with a fall in the LF component of HR ($P = 0.008$), an increase in HF component ($P = 0.001$), and (as shown in Table 4) a rise in HLratio ($r = 0.291$, $P = 0.002$). These relationships were not seen in women. Neither the HF nor the LF peaks were associated with indices of obesity or exercise in either gender. In multiple regression analyses, the relationship between Si and the HLratio in men was independent of BMI, fat distribution, or the current level of physical exercise.

Because Si did not relate to either the HR or HRV in women, we investigated the hypothesis that exposure to hormonal contraception or endogenous steroids, as indicated by the menstrual cycle, might confound the association between Si and HR. A total of 32 women were taking oral contraceptives; but neither their Si, HR, nor their HRV differed significantly from that of the other women. Furthermore, in the subset of women not on hormonal contraception, there was no evidence of a relationship between Si and

TABLE 4. Mean Si according to HLratio for men and women

Men			Women		
HLratio	No. of subjects	Si (10^{-4} min^{-1}/pmol·L)	HLratio	No. of subjects	Si (10^{-4} min^{-1}/pmol·L)
−0.6	18	4.52	−1.2	15	3.58
−1.3	18	4.47	−2.0	17	4.44
−2.3	19	4.99	−3.8	17	3.46
>2.3	18	6.61	>3.8	15	4.41
All	73	5.09	All	64	3.94
P value		0.013			0.516
P adjusted for BMI		0.002			0.593

TABLE 5. Mean HR, Si, and measures of HR variability by stage of menstrual cycle for 64 women

Menstrual cycle (days)	No. of subjects	HR (beats/min)	Si (10^{-4} min^{-1}/pmol · L)	HF (normalized units)	LF (normalized units)	HL ratio
0–14	29	56	4.04	50.8	27.0	2.05
15–28	35	60	3.22	49.5	26.9	2.12
All (SD)	64	59 (8)	3.94 (2.57)	49.6 (14.6)	26.7 (13.1)	2.04 (2.07)
P value		0.006	0.036	0.500	0.800	0.650

HR or HRV. In Table 5, we have analyzed the relationship between the phase of the menstrual cycle and the measurements of HR, HRV, and Si in women. During the follicular phase (days 0–14), the HR was significantly lower and Si significantly higher than during the luteal phase (days 15–28). However, the higher luteal HR does not seem to be caused by altered sympathovagal influence, because neither the measurements of HF and LF power nor their ratio were related to the phase of the menstrual cycle.

Discussion

We have shown that Si is inversely associated with the resting HR in men, but not women, during young adult life. Si is also associated with altered beat-to-beat HRV. Power spectral analysis of this variability suggests that reduced Si is associated with a higher ratio of sympathetic-to-vagal cardiac tone. These associations are independent of current BMI, fat distribution, and other possible confounding factors, including the pattern of physical activity.

The resting HR is a highly variable physiological measurement and is affected by many influences, including stress, activity, and stimulant drugs (including caffeine or nicotine). Although we carried out this study under standardized conditions, and we controlled for these factors as much as possible (by dietary restriction before the study and by performing a relatively long resting ECG), the measurements we obtained are likely to be imprecise. Despite this imprecision, which will tend to lead to underestimation of the strength of the associations, we have found strong and statistically significant relationships between Si and HR in male subjects.

The power spectral analysis of HRV provides further evidence that the relationships between HR and Si are attributable to alterations in autonomic function. Power spectral analysis of HR fluctuations enables quantitative evaluation of beat-to-beat cardiovascular control. Although cardiac automaticity is intrinsic, the resting HR is largely under the control of the autonomic nervous system. The parasympathetic influence on HR is mediated via cholinergic vagal nerve fibers. In contrast, the sympathetic influence is mediated by catecholamines. Under resting conditions, beat-to-beat variations in HR are dependent on the interaction of vagal and sympathetic activity. HF power is recognized as a marker of the influence of vagal tone on HR, whereas LF power is thought to represent a combination of sympathetic and vagal mechanisms (10, 20). Hence, the HLratio is considered to represent the balance between vagal and sympathetic contributions to HRV (10, 20). Our data showing that insulin-resistant individuals have a lower HF component (together with an increased LF component and a lower HL-ratio) suggest that reduced Si in men is associated with a reduced vagal contribution and an increased sympathetic contribution to cardiac autonomic control.

A striking feature of our study is the finding of gender differences in the association between Si and HR. Although the women in our study had a similar BMI to that of the men, they had a greater degree of upper or truncal adiposity, as shown by their increased bicep and tricep skinfold thicknesses, and were less insulin sensitive (Table 1). Compared with the men, women also had a higher resting HR, but evidence of reduced sympathetic cardiac autonomic activity, as indicated by an increased HLratio. These findings suggest that the interrelationships between Si, HR, and HRV differ in women. Together with our finding of marked gender differences in the correlation between Si and HR (Fig. 1), they suggest that Si is less dependent on autonomic tone in women. It is possible that this reflects an underlying gender difference in the response to stressful stimuli, which has been reported in both human and animal studies (21). Another possible explanation, which is supported by our data, is that the influence of gonadal steroids on HR obscures the influence of autonomic effects. We showed that women had a higher HR and lower Si during the luteal (than during the follicular) phase of the menstrual cycle (Table 5). Similar relationships have been reported in some, but not all, previous studies (22, 23). Because HRV was not related to stage of the menstrual cycle, it seems that these menstrual variations in HR are not mediated by alterations in autonomic tone.

In conclusion, we have shown, in young men but not

young women, that a raised resting HR and increased HRV are associated with greater insulin resistance. Though our data provide support for the hypothesis that SNS activity and insulin resistance are linked, they also show that the interrelationships are complex and differ substantially between the sexes.

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