Heart Rate in Relation to Insulin Sensitivity and Insulin Secretion in Nondiabetic Subjects

ANDREAS FESTA, MD
RALPH D'AGOSTINO JR., PHD
C. NICK HALES, MD, PHD
LEENA MYKKÄNEN, MD, PHD
STEVEN M. HAFFNER, MD

OBJECTIVE — Elevated heart rate has been predictive of cardiovascular disease and has been proposed as a global index of the autonomic nervous system influence on the heart. Hyperinsulinism has been shown to trigger sympathetic activity experimentally; however, the clinical and epidemiological data on the association of heart rate with hyperinsulinism and insulin resistance are conflicting.

RESEARCH DESIGN AND METHODS — Insulin sensitivity (S_I) and the acute insulin response (AIR) to glucose were assessed by a frequently sampled intravenous glucose tolerance test and related to resting heart rate in the tri-ethnic nondiabetic population (n = 1,000) of the Insulin Resistance Atherosclerosis Study.

RESULTS — Heart rate was related to fasting insulin (r = 0.20), intact proinsulin (r = 0.15), split proinsulin (r = 0.17), and AIR (r = 0.18), and an inverse relation was found between heart rate and S_I (r = −0.19) (all P values <0.0001, adjusted for age, sex, ethnicity, glucose tolerance status, and smoking). In a multiple linear regression analysis (adjusting for age, sex, ethnicity, clinical center, glucose tolerance status, and smoking), heart rate was significantly and independently associated with AIR, proinsulin, and S_I.

CONCLUSIONS — Proinsulin, acute insulin secretion, and S_I are associated with heart rate in nondiabetic subjects.

Diabetes Care 23:624–628, 2000

Elevated heart rate has been predictive of cardiovascular disease and total or cardiovascular mortality (1–3). Heart rate has been proposed as a global index of the autonomic nervous system influence on the heart (4), and elevated heart rate may reflect a shift in autonomic balance toward enhanced sympathetic and suppressed vagal tone. Hyperinsulinism has been shown to trigger sympathetic activity experimentally (5–7); however, the clinical and epidemiologic data on the association of heart rate with hyperinsulinism and insulin resistance are conflicting (8–12).

Herein, we sought to investigate the relation of heart rate to fasting insulin, its precursors (intact and split proinsulin), as well as insulin sensitivity (S_I) and the acute insulin response (AIR). This was measured by a frequently sampled intravenous glucose tolerance test (FSIGTT) and minimal model analysis, in a large tri-ethnic nondiabetic population (n = 1,000). The focus of this study is on nondiabetic individuals to simplify the analysis and because previous studies have shown *1*) a strong association of postload glucose levels with heart rate (9) and *2*) a limited range of S_I in patients with type 2 diabetes (13).

RESEARCH DESIGN AND METHODS

Patients and methods

A full description of the design and methods of the Insulin Resistance Atherosclerosis Study (IRAS) has been published (14).

A total of 1,088 nondiabetic individuals participated in the IRAS. Subjects taking drugs influencing heart rate (antiarrhythmics, β-blockers, tri- and tetracyclic antidepressants) were excluded from the analysis (n = 88). Thus, this article includes data on 1,000 nondiabetic subjects (Table 1). Height, weight, girths (minimum waist and hips), and blood pressure (BP) were measured following standardized procedures. Hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg or current use of antihypertensive medication. Cigarette smoking (none, past, or current smoking) and physical activity (frequency of vigorous activity using 5 predefined responses from "rarely-to-never" to "5 or more times per week") were assessed using a standard questionnaire.

Electrocardiograms (ECGs) were recorded after a strictly standardized protocol on the day the oral glucose tolerance test (OGTT) was performed. The ECG was recorded as soon as possible and no later than 45 min after the glucose ingestion to avoid confounding by glucose resorption. A bioelectrical impedance measurement procedure (supine position, lasting ~10 min) preceded the ECG recording. The heart rate was determined using the portable MAC/PC electrocardiograph (Marquette Electronics, Milwaukee, WI). The computer program uses successive R-R intervals between all

From the Department of Medicine (A.F., L.M., S.M.H.), Division of Clinical Epidemiology, University of Texas Health Science Center, San Antonio, Texas; the Department of Public Health Sciences (R.D.'A.), Wake Forest University School of Medicine, Winston-Salem, North Carolina; and the Department of Clinical Biochemistry (C.N.H.), University of Cambridge, Cambridge, U.K.

Address correspondence and reprint requests to Steven M. Haffner, MD, Department of Medicine, Division of Clinical Epidemiology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr., San Antonio, TX. E-mail: haffner@uthscsa.edu.

Received for publication 9 September 1999 and accepted in revised form 4 February 2000.

Abbreviations: AA, African-American; AIR, acute insulin response; BP, blood pressure; ECG, electrocardiogram; FSIGTT, frequently sampled intravenous glucose tolerance test; H, Hispanic; HT, hypertensive; IRAS, Insulin Resistance Atherosclerosis Study; NHW, non-Hispanic white; NT, normotensive; OGTT, oral glucose tolerance test; S_I, insulin sensitivity; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic and metabolic characteristics stratified by ethnicity*

	AA	H	NHW
n	262	343	395
% Impaired glucose tolerance	34	33	31
Sex (% male)	44	42	46
Age (years)	54.2 ± 0.5	53.7 ± 0.5	55.7 ± 0.4
BMI (kg/m^2)	29.1 ± 0.3	28.7 ± 0.3	27.5 ± 0.3
WHR	0.84 ± 0.005	0.87 ± 0.005	0.85 ± 0.004
Waist (cm)	90.4 ± 0.8	90.9 ± 0.7	89.5 ± 0.6
Fasting glucose (mmol/l)	5.63 ± 0.04	5.36 ± 0.03	5.45 ± 0.03
Fasting insulin (pmol/l)	98.7 ± 5.4	104.3 ± 4.8	82.1 ± 4.8
Proinsulin (pmol/l)	6.57 ± 0.3	6.25 ± 0.3	5.39 ± 0.3
Split proinsulin (pmol/l)	8.98 ± 0.5	8.89 ± 0.5	7.16 ± 0.4
PI/I ratio	0.078 ± 0.003	0.070 ± 0.003	0.079 ± 0.003
$S_I \times 10^{-4}$ (min^{-1} · μU^{-1} · ml^{-1})	1.96 ± 0.1	1.98 ± 0.1	2.57 ± 0.1
AIR (pmol/l)	445.5 ± 21.6	452.0 ± 18.6	313.2 ± 17.4
Heart rate (min^{-1})	66.4 ± 0.6	65.6 ± 0.5	65.1 ± 0.5

Data are *n* or means ± SEM, unless otherwise indicated.

ventricular muscle depolarizations (QRS complexes) in the standard 12-lead resting supine ECG to calculate the mean heart rate within the recording period of 10 s. These principles also applied for subjects with arrhythmias and extrasystoles.

The IRAS examination required 2 visits. Before each visit, patients were asked to fast for 12 h, to abstain from heavy exercise and alcohol for 24 h, and to refrain from smoking the morning of the examination. A standard 75-g OGTT was performed and glucose tolerance status was based on the World Health Organization criteria (15). Plasma glucose, insulin, proinsulin, and S_I were measured as described previously (14). AIR was calculated as the mean of 2- and 4-min insulin concentrations after glucose administration.

Statistical analysis

Statistical analyses were performed using the SAS statistical software system (SAS, Cary, NC). Spearman rank correlations were calculated. Potentially confounding covariates (age, sex, ethnicity, smoking, glucose tolerance status, blood pressure, and physical activity) were included in multivariate analyses. Partial Spearman correlation analyses were also stratified by sex, glucose tolerance status, ethnicity, and hypertension. We also tested for interactions between sex, ethnicity, and glucose tolerance status and fasting insulin, proinsulin (intact, split), the proinsulin-to-insulin ratio, AIR, and S_I, respectively, in association with heart rate by calculating interaction terms (sex × fasting insulin, ethnicity × fasting insulin, etc.). Because we found no significant interactions between sex, glucose tolerance status, and the variables of interest, pooled analyses are presented.

Multiple linear regression models were performed, including all variables of interest at the same time as independent variables to demonstrate the relative contribution of each of these variables to the outcome variable. After age, sex, ethnicity, clinic, glucose tolerance status, and smoking were forced into the model, the following independent variables were considered for the model: fasting insulin, proinsulin (intact, or in separate models split proinsulin), AIR, and S_I. Only variables with a P value of ≤0.05 were considered in the final fitted model (Table 3). Finally, linear regression models were fit including systolic BP, physical activity, or both as additional covariates.

P values <0.05 (2-sided) were considered statistically significant.

RESULTS

Spearman correlation analysis

Unadjusted correlation analysis showed a significant relationship among heart rate and BMI (r = 0.15), waist (r = 0.08), waist-to-hip ratio (WHR) (r = −0.08), fasting insulin (r = 0.22), intact proinsulin (r = 0.15), split proinsulin (r = 0.18), S_I (r = −0.21), and AIR (r = 0.14). Partial analyses (Table 2) showed correlation coefficients comparable to those of the unadjusted analyses, with the exception of WHR, which was positively associated with heart rate in the partial analysis.

Stratified analysis by ethnicity

Fasting insulin and AIR were related to heart rate in all 3 ethnic groups. The relationships between S_I and heart rate was more pronounced and significant only in Hispanics (Hs) and non-Hispanic whites (NHWs) as compared with African-Americans (AAs) (interaction term, P = NS). Heart rate was related to proinsulin (intact and split) only in H and NHW but not in AA (interaction term, P = 0.02 for intact proinsulin and P = 0.03 for split proinsulin) individuals. These ethnic differences were consistently seen after further adjustment for systolic BP and physical activity (data not shown).

Stratified analysis by hypertension

In both hypertensive (HT) (n = 291) and normotensive (NT) (n = 709) subjects

Table 2—*Partial Spearman correlation analysis of heart rate and variables of interest in the overall population (adjusted for age, sex, ethnic, clinic, glucose tolerance status, and smoking status) and stratified by ethnicity*

	Heart rate			
	Overall	AA	H	NHW
BMI	0.10*	0.12	0.13†	0.08
WHR	0.10*	0.08	0.09	0.11†
Waist	0.13‡	0.16†	0.12†	0.12†
Fasting glucose	0.06	−0.01	0.05	0.11†
Fasting insulin	0.20‡	0.21*	0.20*	0.20‡
Proinsulin (intact)	0.15‡	0.02	0.17*	0.21‡
Proinsulin (split)	0.17‡	0.12	0.22‡	0.16*
PI/I ratio	−0.01	−0.14†	0.02	0.04
Insulin sensitivity (S_I)	−0.19‡	−0.10	−0.20*	−0.24‡
AIR	0.18‡	0.19*	0.21*	0.11†

*P < 0.005; †P < 0.05; ‡P < 0.0001.

Table 3—*Multiple linear regression analysis with heart rate as the dependent variable, after adjustment for age, sex, ethnicity, clinic, glucose tolerance status, and smoking*

Independent variable	*B*	SE(*B*)	*P*	Partial r^2 (%)
AIR (pmol/l)	0.15	0.03	0.0001	3.7
Proinsulin (pmol/l)	0.20	0.06	0.0001	1.5
$S_I \times 10^{-4}$ ($min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$)	−0.39	0.16	0.019	0.5

r^2 for the model = 13.8%. *B*, regression coefficient; SE (*B*), standard error of regression coefficient. Independent variables entered into the model were as follows: S_I, fasting insulin, AIR, and proinsulin (intact). Only variables significantly contributing to heart rate are shown.

Table 4—*Multiple linear regression analysis with heart rate as the dependent variable, after adjustment for age, sex, ethnicity, clinic, glucose tolerance status, smoking, systolic BP, and physical activity*

Independent variable	*B*	SE(*B*)	*P*	Partial r^2 (%)
AIR (pmol/l)	0.16	0.03	0.0001	3.2
Proinsulin (pmol/l)	0.19	0.06	0.0014	1.0

r^2 for the model = 17.9%. *B*, regression coefficient; SE (*B*), standard error of regression coefficient. Independent variables entered into the model were as follows: S_I, fasting insulin, AIR, and proinsulin (intact). Only variables significantly contributing to heart rate are shown.

heart rate was significantly related to fasting insulin ($r = 0.15$, $P < 0.05$ in HT; $r = 0.22$, $P < 0.0001$ in NT), split proinsulin ($r = 0.18$, $P < 0.005$ in HT; $r = 0.16$, $P < 0.0001$ in NT), AIR ($r = 0.18$, $P < 0.005$ in HT; $r = 0.17$, $P < 0.0001$ in NT), and S_I ($r = -0.24$, $P < 0.0001$ in HT; $r = -0.16$, $P < 0.0001$ in NT). Intact proinsulin was significantly related to heart rate in NT ($r = 0.15$, $P < 0.0005$) and reached borderline significance in HT ($r = 0.11$, $P = 0.08$).

Multiple linear regression analysis

Significant independent determinants of heart rate were AIR, proinsulin (intact as well as split [data not shown]), and S_I (Table 3). After further adjustment for systolic BP or physical activity, AIR and proinsulin, but not S_I ($P < 0.15$), remained significant determinants of heart rate, as well as in the final model, including all potentially confounding covariates (Table 4).

CONCLUSIONS — The novel finding of the present study is the independent association of heart rate with first-phase insulin secretion, as assessed by an FSIGTT. Furthermore, heart rate was related to proinsulin in H and NHW, but not in AA individuals. Additionally, heart rate was inversely related to S_I, and this relation was attenuated after adjusting for blood pressure or physical activity.

A positive association of heart rate and the plasma insulin response to oral glucose has been reported previously in middle-aged NT nondiabetic individuals (10). However, time-points of insulin sampling were not reported; therefore, it cannot be determined whether this association reflects insulin resistance or insulin secretion (16). A positive association of heart rate with fasting insulin, as a potential marker of insulin resistance (17), has been reported repeatedly (8,9), but studies on the association of heart rate with S_I, as assessed by direct measures, are controversial. Moan et al. (18) report a negative association of heart rate with S_I, as measured by a clamp technique, in young healthy men ($n = 40$) only in univariate analysis. Facchini et al. (10), using an insulin suppression test, found a negative association of S_I with average heart rate during sleep in middle-aged NT nondiabetic individuals ($n = 45$) also in multivariate analysis. In contrast to these reports, in young NT nondiabetic individuals, no association of mean heart rate during 24 h with S_I, as measured by an FSIGTT, was found (12). In Japanese subjects, the sum of insulin during an OGTT, as a surrogate marker of insulin resistance, showed a weak association ($P < 0.09$) with resting heart rate (11). Results of these studies have to be interpreted with caution because of small sample size (8,9) or the use of surrogate markers of insulin resistance (10–12,18), rather than more specific direct measures of S_I.

Resting heart rate is a marker of hemodynamic and autonomic nervous system states (19) and has been suggested as an integrated index of autonomic nervous system influences on the heart (4). There are several lines of evidence linking sympathetic nerve activity with insulin resistance and hyperinsulinemia. The sequence of pathophysiological events over time, however, is unknown.

Assuming that the initial event is sympathetic overactivation, insulin resistance and/or impaired insulin secretion would fol-

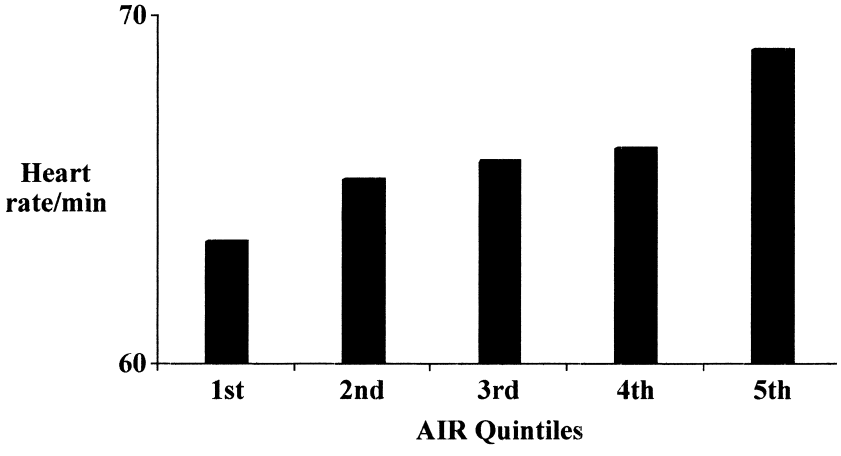

Figure 1—*Mean values of heart rate/min adjusted for age, sex, ethnicity, clinic, glucose tolerance status, and smoking stratified by quintiles of AIR (in pmol/l: first <141, second 144–252, third 255–378, fourth 381–570, fifth >573). Mean heart rate values per min were 63.7, 65.3, 65.8, 66.2, and 69.0, respectively.* P *values (group comparisons between quintiles by analysis of covariance): first vs. third <0.05, first vs. fourth <0.01, first vs. fifth <0.0001, second vs. fifth <0.0001, third vs. fifth <0.01, and fourth vs. fifth <0.01).*

low secondarily. Selective sympathetic activation in skeletal muscle/reduced insulin-induced stimulation of glucose uptake (20). The relationship of sympathetic nerve activity and insulin secretion is even more complex, partly due to differential sympathetic effects on pancreatic α- and β- adrenergic receptors. Acute adrenergic stimuli, such as insulin-induced hypoglycemia, markedly blunt insulin secretion, mainly via α_2-receptors, but catecholamines in low concentrations potentially stimulate insulin secretion by activating β_2-receptors (21).

Alternatively, one might also assume that sympathetic overactivation is not the cause but rather the consequence of hyperinsulinemia and/or insulin resistance. Although it is well established that acute short-term insulin infusion (5–7,22,23) stimulates sympathetic nerve activity, including an increase in heart rate (23), the impact of chronic hyperinsulinemia is conflicting in animals (24,25) and unknown in humans.

Finally, a common underlying process may exist, triggering both sympathetic nerve activity and insulin resistance, such as thinness at birth. Heart rate in middle-aged individuals was inversely related to birth weight, leading to the hypothesis that elevated sympathetic nerve activity established in utero may be one mechanism linking small size at birth with the insulin resistance syndrome in adult life (26).

The question of whether an improvement in S_I by pharmacological or nonpharmacological interventions leads to a decrease in heart rate has, to our knowledge, not been addressed in a prospective study. In hyperlipidemic rabbits, however, treatment with the insulin-sensitizing drug troglitazone reduced heart rate (27), and in 24 obese HT subjects, weight loss within 4 weeks resulted in increased S_I and decreased heart rate (28).

There are several possible explanations for the association of proinsulin with heart rate as shown in the present study. First, if proinsulin is a marker of insulin secretion (29), the view that insulin secretion contributes to heart rate, as discussed above, would be supported. Second, although the biological potency of proinsulin is only ~10% that of insulin, in terms of its glucose-lowering effect (30), its potency may be considerably higher in terms of other effects, and proinsulin split products may even be biologically more potent than intact proinsulin (31). The sympathetico-excitatory effects of insulin are conceivably mediated via a central neural action (32) and insulin receptors have been identified in several regions of the central nervous system (33). It is well known that proinsulin acts through insulin receptors (31); however, to our knowledge, no data on central nervous effects of proinsulin have been reported. It is interesting to note that the sympathetico-excitatory effect of insulin, including an increase in heart rate, is operative even at modestly elevated plasma levels (6,34), corresponding to insulin levels that can be observed in the postprandial state (25 μU/ml) (34). Also, it has been shown that, in both patients with type 2 diabetes and in nondiabetic healthy subjects, circulating proinsulin levels were associated with the sympathovagal balance of autonomic nervous function, as assessed by analysis of heart rate variability (35). Therefore, even small differences in circulating proinsulin levels may be of pathophysiological significance in terms of influencing sympathetic nerve activity. Finally, proinsulin may also be a proxy of S_I in nondiabetic subjects (29).

In summary, we have shown an association of heart rate with proinsulin, AIR, and S_I in nondiabetic subjects. Prospective studies are needed to determine the clinical significance of these findings.

Acknowledgments — This work was supported by the National Heart, Lung and Blood Institute (grants HL47887, HL47889, HL47890, HL47892, HL47902, and HL55208) and the General Clinic Research Centers Program (Grants NCRR GCRC, M01 RR431, and M01 RR01346), and the Medical Research Council, U.K.

References

1. Schroll M, Hagerup LM: Risk factors of myocardial infarction and death in men aged 50 at entry: a ten-year prospective study from the Glostrup population studies. *Dan Med Bull* 24:252–255, 1977
2. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA: Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 113:1489–1494, 1987
3. Gillum RF, Makuc DM, Feldman JJ: Pulse rate, coronary heart disease, and death: the NHANES I epidemiologic follow-up study. *Am Heart J* 121:172–177, 1991
4. Perski A, Olsson G, Landou C, de Faire U, Theorell T, Hamsten A: Minimum heart rate and coronary atherosclerosis: independent relations to global severity and rate of progression of angiographic lesions in men with myocardial infarction at a young age. *Am Heart J* 123:609–616, 1992
5. Rowe JW, Young JB, Minaker KL, Stevens AL, Pallotta J, Landsberg L: Effect of insulin and glucose infusions on sympathetic nervous system activity in normal men. *Diabetes* 30:219–225, 1981
6. Vollenweider P, Randin D, Tappy L, Jéquier E, Nicod P, Scherrer U: Impaired insulin-induced sympathetic neural activation and vasodilation in skeletal muscle in obese humans. *J Clin Invest* 93:2365–2371, 1994
7. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL: Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest* 87:2246–2252, 1991
8. Feskens EJM, Kromhout D: Hyperinsulinemia, risk factors, and coronary heart disease: the Zutphen Elderly Study. *Arterioscler Thromb* 14:1641–1647, 1994
9. Palatini P, Casiglia E, Pauletto P, Staessen J, Kaciroti N, Julius S: Relationship of tachycardia with high blood pressure and metabolic abnormalities. *Hypertension* 30:1267–1273, 1997
10. Facchini FS, Stoohs RA, Reaven GM: Enhanced sympathetic nervous system activity: the linchpin between insulin resistance, hyperinsulinemia, and heart rate. *Am J Hypertens* 9:1013–1017, 1996
11. Adachi H, Hashimoto R, Tsuruta M, Jacobs DR, Crow RS, Imaizumi T: Hyperinsulinemia and the development of ST-T electrocardiographic abnormalities. *Diabetes Care* 20:1688–1692, 1997
12. Osei K, Schuster DP: Effects of race and ethnicity on insulin sensitivity, blood pressure, and heart rate in three ethnic populations. *Am J Hypertens* 9:1157–1164, 1996
13. Haffner SM, Howard G, Mayer E, Bergman RN, Savage PJ, Rewers M, Mykkänen L, Karter AJ, Hamman R, Saad MF: Insulin sensitivity and acute insulin response in African-Americans, non-Hispanic whites, and Hispanics with NIDDM: the Insulin Resistance Atherosclerosis Study. *Diabetes* 46:63–69, 1997
14. Wagenknecht LE, Mayer EJ, Rewers M, Haffner SM, Selby J, Borok GM, Henkin L, Howard G, Savage PJ, Saad MF, Bergman RN, Hamman R: The Insulin Resistance Atherosclerosis Study (IRAS): objectives, design and recruitment results. *Ann Epidemiol* 5:464–471, 1995
15. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no. 727)
16. DeFronzo RA, Bonadonna RC, Ferrannini E: Pathogenesis of NIDDM: a balanced overview. *Diabetes Care* 15:318–368, 1992
17. Laakso M: How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 137:959–965, 1993
18. Moan A, Nordby G, Os I, Birkeland KI, Kjeldsen SE: Relationship between hemorrheologic factors and insulin sensitivity in

healthy young men. *Metabolism* 43:423–427, 1994
19. Grobbee DE: The rhythm and the risk: heart rate and cardiovascular disease. *Curr Opin Cardiol* 3 (Suppl. 3):S15–S21, 1988
20. Lembo G, Capaldo B, Rendina V, Iaccarino G, Napoli R, Guida R, Trimarco B, Saccá L: Acute noradrenergic activation induces insulin resistance in human skeletal muscle. *Am J Physiol* 266:E242–E247, 1994
21. Miller RE: Pancreatic neuroendocrinology: peripheral neural mechanisms in the regulation of the islets of Langerhans. *Endocrin Rev* 2:471–494, 1981
22. Scherrer U, Randin D, Tappy L, Randin D, Vollenweider P, Jéquier E, Nicod P: Body fat and sympathetic nerve activity in healthy subjects. *Circulation* 89:2634–2640, 1994
23. Hausberg M, Hoffman RP, Somers VK, Sinkey CA, Mark AL, Anderson EA: Contrasting autonomic and hemodynamic effects of insulin in healthy elderly versus young subjects. *Hypertension* 29:700–705, 1997
24. Koopmans SJ, Ohman L, Haywood JR, Mandarino LJ, DeFronzo RA: Seven days of euglycemic hyperinsulinemia induces insulin resistance for glucose metabolism but not hypertension, elevated catecholamine levels, or increased sodium retention in conscious normal rats. *Diabetes* 46:1572–1578, 1997
25. Tomiyama H, Kushiro T, Abata H, Kuruatani H, Taguchi H, Kuga N, Saito F, Kobayashi F, Otsuka Y, Kanmatsue K, Kajiwara N: Blood pressure response to hyperinsulinemia in salt-sensitive and salt-resistant rats. *Hypertension* 20:596–600, 1992
26. Phillips DI, Barker DJ: Association between low birth weight and high resting pulse in adult life: is the sympathetic nervous system involved in programming the insulin resistance syndrome? *Diabet Med* 14:673–677, 1997
27. Saku K, Zhang B, Ohta B, Arakawa K: Troglitazone lowers blood pressure and enhances insulin sensitivity in Watanabe heritable hyperlipidemic rabbits. *Am J Hypertens* 10:1027–1033, 1997
28. Ikeda T, Gomi T, Hirawa N, Sakurai J, Yoshikawa N: Improvement of insulin sensitivity contributes to blood pressure reduction after weight loss in hypertensive subjects with obesity. *Hypertension* 27: 1180–1186, 1996
29. Mykkänen L, Haffner SM, Hales CN, Rönnemaa T, Laakso M: The relation of proinsulin, insulin, and proinsulin-to-insulin ratio to insulin sensitivity and acute insulin response in normoglycemic subjects. *Diabetes* 46:1990–1995, 1997
30. Galloway JA, Hooper SA, Spradlin CT, Howey DC, Frank BH, Bowsher RR, Anderson JH: Biosynthetic human proinsulin: review of chemistry, in vitro and in vivo receptor binding, animal and human pharmacology studies, and clinical trial experience. *Diabetes Care* 15:666–692, 1992
31. Peavy DE, Brunner MR, Duckworth WC, Hooker CS, Frank BH: Receptor binding and biological potency of several split forms (conversion intermediates) of human proinsulin. *J Biol Chem* 260:13989–13994, 1985
32. Muntzel MS, Anderson EA, Johnson AK, Mark AL: Mechanisms of insulin action on sympathetic nerve activity. *Clin Exp Hypertens* 17:39–50, 1995
33. Sauter A, Goldstein M, Engel J, Ueta K: Effect of insulin on central catecholamines. *Brain Res* 260:330–333, 1983
34. Hausberg M, Mark AL, Hoffman RP, Sinkey CA, Anderson EA: Dissociation of sympathoexcitatory and vasodilator actions of modestly elevated plasma insulin levels. *J Hypertens* 13:1015–1021, 1995
35. Toyry JP, Niskanen LK, Mantysaari MJ, Lansimies EA, Haffner SM, Miettinen HJ, Uusiputa MI: Do high proinsulin and C-peptide levels play a role in autonomic nervous dysfunction? Power spectral analysis in patients with non-insulin-dependent diabetes and nondiabetic subjects. *Circulation* 96:1185–1191, 1997