Influence of Parasympathetic Dysfunction and Hyperinsulinemia on the Hemodynamic Response to an Isometric Exercise in Non–Insulin-Dependent Diabetic Patients

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The handgrip test has long been used as a test for investigating cardiac autonomic neuropathy in diabetic patients. However, the factors involved in the hemodynamic response to the handgrip test have not been thoroughly studied. The aim of this study was to investigate blood pressure (BP) and heart rate (HR) responses to an isometric test in non–insulin-dependent diabetics (NIDDs) and to correlate the results with vagal function evaluated by three standardized tests and with plasma insulin levels. Fifty-five NIDDs, 35 of whom had one to three abnormal parasympathetic tests (PS+), were compared with 10 healthy control subjects. Fasting and postprandial plasma insulin levels were significantly higher in the PS+ than in the PS− patients. Resting HR correlated significantly with log fasting and postprandial insulin. In PS+ NIDDs, resting HR was significantly higher than in PS− patients. Age-matched comparisons also showed that resting systolic BP was significantly higher in PS+ patients than in controls. In PS− patients, the mean acceleration of HR was significantly higher than in the control group from the second to the fifth minute, and the BP response was also higher than in controls. These data suggest that (1) sympathetic response to an isometric exercise is increased in PS− NIDDs; (2) cardiac parasympathetic dysfunction is associated with a more severe insulin resistance; and (3) the subsequent higher plasma insulin level may contribute to the increase in resting HR and BP through sympathetic activation while limiting the hemodynamic response to an isometric exercise through its vasodilative effect.

A REDUCTION IN heart rate (HR) variability assessed by cardiac autonomic function tests is a frequent complication of diabetes mellitus. It mainly accounts for an alteration in cardiac parasympathetic control. This complication is found in up to 60% to 75% of diabetic patients.[1,2] Its prevalence is higher in patients with peripheral neuropathy or microangiopathic complications.[3] The role of glycemic control is strongly suggested by cross-sectional studies and by the improvement in the cardiac autonomic function tests obtained by optimizing glycemic control.[3,4]

Sympathetic nervous system function is more difficult to investigate. Spectral analysis of HR and blood pressure (BP) variability has been proposed,[5,6] as well as analysis of the variability in cutaneous blood flow at rest and the vasoconstrictive responses to maneuvers involving sympathetic activation.[7-12] In diabetic patients, we have previously found a reduction in vasoconstrictive response to maneuvers that activate the sympathetic nervous system,[13] which suggests an alteration in sympathetic cardiovascular activity.

The normal cardiovascular reflex response to sustained handgrip is characterized by an increase in HR and BP.[14] The increase in HR occurs in two phases, with an initial rapid increase due to the withdrawal of cardiac parasympathetic activity followed by a slower increase that is probably mediated by cardiac sympathetic stimulation.[15,16] In diabetic patients with clinically overt autonomic neuropathy, the increase in HR during the first minute was found to be impaired, whereas the increase during the second and third minutes was unchanged.[17,18] Cardiovascular responses to exercise appeared also to be impaired in diabetic patients with subclinical autonomic neuropathy.[19-24]

Several investigators have shown that insulin resistance is associated with an increase in BP.[25-27] Hyperinsulinemia may be involved in the BP changes, as suggested by the studies using an intravenous insulin infusion and hyperinsulinemic euglycemic clamping.[28-31] However, insulin may also induce a peripheral vasodilative effect.[32,33] Insulin may therefore be involved in changes in hemodynamic parameters at rest and during exercise in hyperinsulinemic subjects. The aim of the present study was to investigate BP and HR responses to an isometric test in non–insulin-dependent diabetics (NIDDs) compared with a control group, and to correlate the results with the vagal function evaluated by standardized tests, and with plasma insulin levels.

MATERIALS AND METHODS

Subjects

Fifty-five NIDDs, 28 men and 27 women, were investigated. Mean (±SEM) age was 48.7 (±1.3) years (range, 30 to 68). The handgrip test was also performed by 10 healthy control subjects, three men and seven women, with a mean age of 44.5 ± 2.3 years.

All of the subjects were normotensive, free of cardiac or pulmonary disease, anemia, and overt peripheral vascular disease, and none of them was taking drugs known to modify BP or HR (eg, vasodilators, calcium-channel blockers, angiotensin-converting enzyme [ACE] inhibitors, adrenergic agents, nitrates, beta-blockers). None of these patients was insulin-treated. Clinical and biologic parameters are listed in Table 1.

Methods

Handgrip test. The test was performed with a dynamometer by a subject in a sitting position for 10 minutes. For each subject, the maximal voluntary contraction was first determined. The subject was then asked to maintain 30% of the maximal handgrip contraction for 5 minutes as previously described.[24] HR and BP were measured each minute by a Dinamap (Critikon, Tampa, FL) on the contralateral arm with a cuff adapted to the size of the arm. HR response was expressed as the percent change in HR compared with its resting value. The increase

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Table 1. Clinical and Biological Parameters in the NIDDs With (PS+) or Without (PS−) Cardiac Parasympathetic Dysfunction

Parameter	PS−	PS+	*P* Value
No.	20	35	
Sex (male/female)	15/5	13/22	.007
Age (yr)	48.6 ± 2.0	48.8 ± 1.7	NS
BMI (kg/m²)	27.7 ± 1.1	28.6 ± 0.9	NS
Duration of diabetes (mo)	87.6 ± 13.2	128.4 ± 15.6	NS
Treatment			
Diet alone	3	6	
Metformin	15	24	
Sulfonylurea	12	23	
HR at rest (bpm)	66.0 ± 1.9	75.7 ± 2.2	.002
Systolic BP at rest (mm Hg)	119.3 ± 3.7	123.2 ± 3.2	NS
Diastolic BP at rest (mm Hg)	72.1 ± 1.5	72.3 ± 1.6	NS
Deep-breathing*	1.32 ± 0.04	1.21 ± 0.02	.017
Valsalva*	1.53 ± 0.05	1.31 ± 0.05	.008
Lying-to-standing*	1.28 ± 0.06	1.17 ± 0.04	.126
Fasting glycemia (mmol/L)	9.2 ± 0.7	10.4 ± 0.8	NS
Postprandial glycemia (mmol/L)	11.6 ± 1.0	13.4 ± 1.0	NS
Hemoglobin A_{1c} (%)	8.3 ± 0.5	8.4 ± 0.4	NS
Fructosamine (μmol/L)	351 ± 23	347 ± 20	NS
Fasting insulin (pmol/L)	69 ± 9	149 ± 41	.031
Postprandial insulin (pmol/L)	163 ± 19	336 ± 69	.020
Total cholesterol (mmol/L)	5.15 ± 0.25	5.74 ± 0.19	.065
High-density lipoprotein cholesterol (mmol/L)	1.40 ± 0.09	1.46 ± 0.07	NS
Triglycerides (mmol/L)	1.60 ± 0.25	1.84 ± 0.17	NS

Abbreviation: NS, not significant.

*Results expressed as HR ratios: highest HR during breathing in/lowest HR during breathing out, highest HR during Valsalva/lowest HR after Valsalva release, highest HR around 15 seconds/lowest HR around 30 seconds after standing up.

in systolic and diastolic BP during the test was calculated and compared with resting BP.

Cardiac autonomic function tests. Three standardized tests analyzing changes in HR were performed as previously described.[34-36] The results, based on the assessment of HR variation during these three tests, were obtained by computerized analysis (Autocaft; BBC Master, Edinburgh, UK)[37] and provided information mainly on cardiac parasympathetic control. These tests were a Valsalva test, performed with the subject seated; a deep-breathing test, performed in a recumbent position; and a lying-to-standing test. Their good reproducibility has previously been demonstrated, with the intrasubject coefficients of variation being, respectively, 9.2%, 12.6%, and 6.4%.[38] Results of these tests were compared with those obtained in a previously published large series of healthy controls, in which age was taken into account.[39] When at least one of these tests was abnormal, the parasympathetic function was considered to be altered (patient PS+) and when the three tests were normal, it was considered to be normal (patient PS−).

Finally, postural hypotension, defined as a decrease in systolic BP of at least 20 mmHg, was looked for, but not found in any of the subjects in this series.

These tests, as well as the handgrip test, were performed in the morning, within 24 hours after admission to the hospital, with no coffee, tobacco, or alcohol consumption in the 4 hours preceding the tests.

Biological investigations. Biological assays consisted of fasting and postprandial blood glucose, and plasma insulin at fasting and after lunch in the NIDDs. Plasma insulin was measured by radioimmunoassay (RIA; Behring kit, Mahrburg, Germany). Hemoglobin A_{1c} and serum fructosamine were also determined by microcolumn chromatography (normal, <6.25%) and a colorimetric method with nitrotetrazolium blue (Roche Diagnostic System, Neuilly sur Seine, France), respectively. Lipid measurements included plasma total cholesterol, high-density lipoprotein cholesterol, and triglycerides. Serum and urinary creatinine were also measured, and the creatinine clearance calculated.

Statistical Analyses

Results are expressed as means ± SEM. Comparisons were made using one-way ANOVA and the χ^2 test. Fasting and postprandial insulin levels were analyzed after logarithmic transformation to improve skewness and kurtosis, but untransformed units are also presented. The associations between continuous variables were studied using the Pearson correlation. Multivariate analyses were performed by using models of logistic regression and multiple linear regression.

To study the hemodynamic response to the handgrip test, a repeated-measures ANOVA was performed, taking into account the variations in connection with the repeated measurements over time (ie, the within-subjects model), the differences between groups, and the interaction between these two factors. The dependent variables were reasonably close to a normal distribution. In checking assumptions, Mauchly's test and Box's M test were used. When the difference between subjects (average *F* test) was significant at one time period of the handgrip test, the Bonferroni test was used to identify which groups differed from each other. A one-way ANOVA was also performed to compare the mean value for the overall BP response and for the HR response from the second to the fifth minute between the three groups.

Statistical analyses were conducted with the SPSS general linear model procedure (SPSS, Chicago, IL).

RESULTS

Control Group

HR increased regularly from the first to the fifth minute and the percent change in HR was maximal at 5 minutes. Systolic and diastolic BP increased also from the first to the fifth minute, with a maximum increase at the fifth minute. Hemodynamic response did not differ significantly in men and women.

NIDDs

Clinical and biological parameters. At least one of the three standardized tests analyzing HR variability was abnormal in 35 of 55 NIDDs. In the PS+ group, HR variability was lower than in the PS− group, with the difference being significant for the deep-breathing and Valsalva tests (Table 1). Mean age, body-mass index (BMI), duration of diabetes, and glycemic control were similar in the 35 PS+ and 20 PS− patients. The percentage of women was higher in the PS+ group than in the PS− group ($P = .007$). Fasting and postprandial plasma insulin levels were significantly higher in PS+ than in PS− patients (Table 1). This comparison was also significant in men taken separately ($P = .026$ and $P = .036$, respectively). The number of patients treated by diet alone, metformin, or sulfonylurea did not differ significantly among PS+ and PS− patients. A model of logistic regression was used to explain PS status (PS+ or PS−), with gender, fasting plasma glucose, and insulin taken as independent variables. In the forward stepwise analysis, the independent predictors for parasympathetic neuropathy were gender and fasting plasma insulin ($P < .05$). Postprandial plasma insulin level was also an independent predictor ($P = .04$) when it was used instead of fasting plasma insulin.

Both log fasting and postprandial plasma insulin also correlated negatively with HR variability during the deep-breathing

test ($P = .054$ and $P = .041$, respectively) and the lying-to-standing test ($P = .021$ and $P = .055$, respectively).

Resting HR and BP. In the NIDDs, resting HR correlated significantly with log fasting and postprandial insulin levels ($r = .317$, $P = .03$ and $r = .378$, $P = .009$) and did not correlate significantly with gender, age, BMI, duration of diabetes, or glycemic control. It was significantly higher in PS+ than in PS− patients (Table 1). The multiple linear regression analysis, with resting HR as dependent variable, and PS status (PS+ or PS−) and log postprandial plasma insulin as independent variables, showed a significant and independent association between resting HR and PS status ($P = .022$) and log postprandial insulin ($P = .047$). Resting systolic and diastolic BP were similar in the two groups (Table 1).

Hemodynamic response to the handgrip test. The handgrip was released before the fifth minute by one PS− and 8 PS+ diabetic patients. In the series of 46 NIDDs taken as a whole who completed the handgrip test and in the PS+ and the PS− patients taken separately, there was no significant correlation between the mean percent acceleration in HR from the second to the fifth minute compared with resting HR and the mean value for the overall systolic and diastolic BP responses on the one hand, and fasting and postprandial plasma insulin on the other hand.

To compare hemodynamic response in NIDDs and controls, 17 PS+ and 15 age-matched PS− patients were compared together and with the 10 age-matched controls. Mean age did not differ significantly between the three groups, and mean BMI, duration of diabetes, and glycemic control were similar in PS+ and PS− patients. In PS+ patients, fasting and postprandial plasma insulin levels were significantly higher and plasma triglycerides slightly higher ($P = .132$) than in PS− patients (Table 2). Resting HR was significantly higher in the PS+ group than in the PS− group, and systolic BP was significantly higher in the PS+ group than in the control group (Table 2). The mean percent acceleration in HR from the second to the fifth minute compared with resting HR was significantly different among the three groups ($P = .04$) and was higher in the PS− than in the control group (20.7% ± 3.0% *v* 9.5% ± 2.5%) (Fig 1). When calculating the ratio of the mean HR from the second to the fifth minute over HR at 1 minute, a difference was also found among the three groups ($P = .054$), with a lower value in the PS+ group than in the PS− and control groups. The response of systolic BP was higher in the PS− group than in the controls, with the difference being significant at 4 minutes ($P = .047$). There was also a trend to a higher (nonsignificant) response of diastolic BP in the PS− group than in the controls (Fig 1).

Table 2. Clinical and Biological Parameters in 32 NIDDs With (PS+) or Without (PS−) Cardiac Parasympathetic Dysfunction Compared With 10 Age-Matched Controls

Parameter	PS−	PS+	Controls
No.	15	17	10
Sex (male/female)	13/2	6/11	3/7
Age (yr)	46.0 ± 1.7	44.7 ± 1.9	44.5 ± 2.3
BMI (kg/m²)	28.2 ± 1.3*	29.4 ± 1.4*	23.4 ± 0.7
Duration of diabetes (mo)	76.3 ± 13.5	129.5 ± 23.7	
HR at rest (bpm)	62.9 ± 1.6	75.3 ± 3.6‡	68.9 ± 2.9
Systolic BP at rest (mm Hg)	117.5 ± 3.3	123.6 ± 5.0†	108.0 ± 4.2
Diastolic BP at rest (mm Hg)	78.9 ± 2.5	74.2 ± 2.4	68.3 ± 3.5
Fasting glycemia (mmol/L)	9.2 ± 0.7	11.4 ± 1.0	
Postprandial glycemia (mmol/L)	11.6 ± 1.1	15.8 ± 1.5‡	
Hemoglobin A1c (%)	8.0 ± 0.6	8.9 ± 0.4	
Fructosamine (μmol/L)	336 ± 27	340 ± 25	
Fasting insulin (pmol/L)	71 ± 12	202 ± 83‡	
Postprandial insulin (pmol/L)	175 ± 25	431 ± 127‡	
Total cholesterol (mmol/L)	5.10 ± 0.30	6.06 ± 0.28‡	
High-density lipoprotein cholesterol (mmol/L)	1.36 ± 0.10	1.41 ± 0.11	
Triglycerides (mmol/L)	1.63 ± 0.32	2.15 ± 0.29	

*$P = .005$ and †$P = .016$, *v* controls.
‡$P < .05$, *v* PS−.

DISCUSSION

This study confirms the high prevalence of alterations in HR variability, suggesting cardiac parasympathetic dysfunction in diabetic patients. The handgrip test was used here in a large series of NIDDs. It was continued until the fifth minute in most of the subjects. It has been demonstrated that the acceleration in HR at the first minute results from parasympathetic withdrawal.[17] In the PS− NIDDs, an increase in the later HR acceleration and a higher increase in BP were found. This suggests an increased response to sympathetic activation. Recent works have shown an increased response to hypoglycemia (considered as an intense sympathetic stimulation) in NIDDs[40] and a normal response to another sympathetic stimulation (lower-body negative pressure) in patients with short-term NIDD.[41] On the contrary, reduced cardiovascular sympathetic activity[5] and a reduction in vasoconstrictor responses to sympathetic activation[13] have also been found in NIDDs.

Thus, the present data suggest that isometric exercise can disclose an increased response to sympathetic activation. It might act by increasing cardiac output and/or augmenting the increase in the peripheral and splanchnic vascular resistance response to exercise.[20]

In the PS+ NIDDs, HR and BP at rest were significantly higher than in the PS− NIDDs and the control subjects. This difference does not seem great enough to account for the difference in the cardiac autonomic function tests. Such an increase in BP at rest has been reported in PS+ diabetic patients by Bottini et al,[23] who also noted an increase in HR acceleration and systolic BP elevation in PS+ diabetic patients without postural hypotension at the first minute of a heterometric exercise, a finding previously shown in heart-transplanted subjects.[42] The isometric and heterometric exercises seem to induce different hemodynamic patterns in diabetic patients. In the PS+ NIDDs, the increase in HR and the BP response during the handgrip test were indeed similar to those in age-matched controls, which suggests a normal sympathetic response. The limited BP increase during the handgrip test compared with PS− NIDDs, which was unexpected because of the increase in BP at rest, may result from a myocardial dysfunction. Indeed, an impairment in left ventricular compliance has been reported

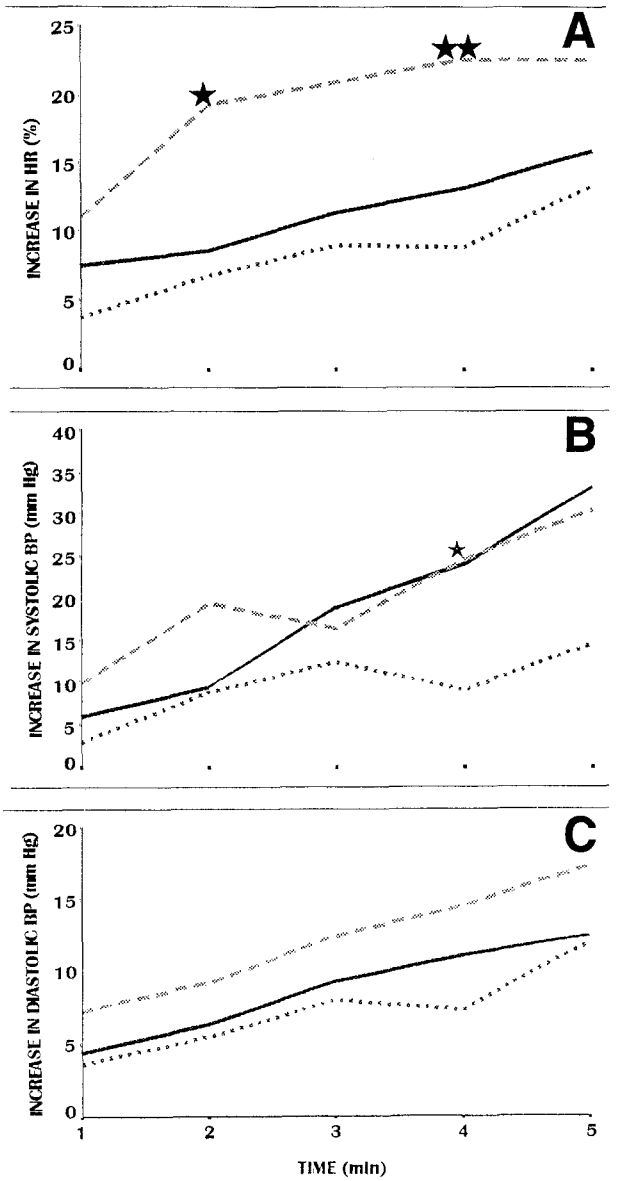

Fig 1. Mean pattern of hemodynamic response to the handgrip test in 17 NIDDs with (PS+, —) and 15 NIDDs without (PS− :- - - -) cardiac parasympathetic dysfunction, *v* 10 age-matched controls (. . . .). (A) Mean percent increase in HR *v* resting level. (B and C) Mean increase in systolic and diastolic BP. *$P < .05$ and **$P = .025$, respectively (repeated-measures ANOVA and Bonferroni test). Mean percent acceleration in HR from the second to the fifth minute was significantly different in the 3 groups ($P = .04$) and was higher in PS− patients than in controls ($P = .05$) (A).

several times[43,44] and may be linked to diabetic cardiomyopathy or left ventricle hypertrophy.[44,45] A reduction of left ventricle ejection fraction at rest and during exercise has also been found in diabetic patients with cardiac autonomic neuropathy.[46] However, the limited BP increase is likely to result mainly from a reduction in the increase in vascular resistances secondary to sympathetic activation. This hypothesis is supported by the reduced vasoconstrictive response to maneuvers activating the sympathetic nervous system, which we have found in NIDDs.[13]

Finally, plasma insulin levels were significantly higher in PS+ than in PS− diabetic patients. Several reports have demonstrated the peripheral vasodilative effect of systemic hyperinsulinemia.[32,33] In NIDDs, a decrease in insulin-induced vasodilation has been reported.[47] The influence of the duration of diabetes, glycemic control,[48] and obesity itself[32,49] has been suggested. Insulin-induced vasodilation seems to be maintained in patients with recent NIDD and without excessive overweight and poor glycemic control.[41,50] Such was the case in our patients. Therefore, high plasma insulin levels in PS+ NIDDs may have contributed to limiting the effect of sympathetic activation induced by the handgrip test.

The higher resting HR level in PS+ than in PS− NIDDs may result from a decrease in parasympathetic tone, but also from an increase in sympathetic activity. The positive correlations between plasma insulin levels and resting HR is consistent with the positive effect of insulin on HR. The latter is likely to result from sympathetic activation, as suggested by the studies using an intravenous insulin infusion and hyperinsulinemic euglycemic clamping.[29-31] The role of sympathetic activation in the cardiac effect of insulin is supported by plasma norepinephrine measurements, microneurographic readings,[33,49,51,52] and total-body norepinephrine spillover.[41] Moreover, the stimulating effect of insulin on sympathetic activity has recently been shown to be maintained in NIDDs.[41]

The role of chronic hyperglycemia in the onset of alterations in cardiac parasympathetic tests has been suggested by cross-sectional studies[3] and the improvement found in these tests after optimization of glycemic control in patients with newly diagnosed type 2 diabetes.[4] But, the impact of glycemic control does not appear as clear in other studies.[53] In the present series, PS+ NIDDs were characterized by slightly higher blood glucose levels than PS− NIDDs. However, they also had slightly higher triglyceride levels, and significantly higher plasma insulin, which could not be explained by any significant difference in oral hypoglycemic treatment. This suggests a more severe insulin resistance in PS+ NIDDs. The increase in resting BP found in these patients is also a feature of the insulin-resistance syndrome.[25-27] Our data suggest that the increase in BP might result from an increase in sympathetic tone induced by chronic hyperinsulinemia, and this effect might be amplified by the reduction in the parasympathetic tone. Recently, high plasma insulin has been shown to be a strong predictor of the occurrence of parasympathetic neuropathy irrespective of the hyperglycemia in patients with newly diagnosed NIDD.[54] The reason for the link between insulin resistance and parasympathetic dysfunction is not yet clearly established. Heart parasympathetic nerve endings may be damaged or parasympathetic nerve activity may be reduced in association with hyperinsulinemia. However, obesity may be implicated. Since cardiac parasympathetic dysfunction may be found in nondiabetic obese subjects,[36,55] obesity may be involved in the link between parasympathetic dysfunction and hyperinsulinemia in NIDDs.

In conclusion, NIDDs with normal cardiac parasympathetic function have an increased sympathetic response to an isometric exercise. Although it is generally accepted that poor glycemic control contributes to the deterioration of cardiac parasympa-

thetic control, parasympathetic dysfunction is shown here for the first time to be associated with a more severe insulin resistance. The secondary increase in the insulin level may contribute to the increase in resting HR and BP through sympathetic activation while limiting the hemodynamic response to an isometric exercise through its vasodilative effect. Increased sympathetic drive has been linked to an increase in cardiovascular disease[56] and might be relevant to the development of hypertension. The part played by parasympathetic dysfunction in the hemodynamic changes linked to the insulin resistance syndrome needs further investigation.

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