Diabetologia (1983) 24: 422–427

Diabetologia

Relationship Between Impaired Parasympathetic and Sympathetic Cardiovascular Control in Diabetes Mellitus

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Summary. We have investigated the relationship between vagal and sympathetic lesions in 62 diabetic patients and compared the results with those from 37 healthy subjects. Vagal function was assessed by heart rate changes with forced breathing. Sympathetic control was measured by the heart rate and blood pressure changes after standing and the concomitant plasma catecholamine response. The integrity of the postganglionic sympathetic neuron was evaluated separately by testing sudomotor function. Impaired sympathetic control was found only in 15 diabetic patients with severely impaired or absent vagal heart rate control. In 12 patients the chief abnormalities consisted of a delayed and diminished heart rate increase, an excessive fall in systolic blood pressure (> 20 mmHg) in combination with an abnormally small noradrenaline increment (< 120 ng/l) and a lesion of the postganglionic sympathetic neuron. Three patients with severely impaired parasympathetic heart rate control in combination with an intact postganglionic sympathetic neuron demonstrated a large noradrenaline increase on standing (> 700 ng/l). Measurement of vagal heart rate control and testing of sudomotor function makes it possible to classify a spectrum of abnormal cardiovascular responses to standing in diabetic patients.

Key words: Diabetic autonomic neuropathy, posture, vagal heart rate control, blood pressure, orthostatic reflexes, catecholamines.

Measurement of the instantaneous heart rate (HR) changes with forced breathing is a simple and reliable method of establishing a diagnosis of impaired vagal HR control in diabetic patients [1–2]. The initial HR response after standing is also used to assess vagal HR control [1–5]. Orthostatic hypotension and an abnormal plasma catecholamine response after standing in diabetic patients has been reported as a sign of impaired sympathetic control [6–11]. However, the interrelationship between abnormal parasympathetic and sympathetic cardiovascular control is not well described. We have therefore studied the interrelationship between impaired parasympathetic and sympathetic cardiovascular control in 62 diabetic and 37 healthy subjects. The instantaneous HR response to forced breathing was used as an index of vagal HR control. Sympathetic control was measured by the heart rate, blood pressure and catecholamine response after 5 min standing. The integrity of the postganglionic sympathetic neuron in the legs was evaluated separately by testing sudomotor activity [12–13].

Patients and Methods

Sixty-two diabetic outpatients participated in the study after giving informed consent. They were divided in three groups according to their HR variation during forced breathing, expressed as the inspiration-expiration (I–E) difference [2].

Group 1 ($n = 15$): Patients with severe impairment of vagal HR control documented by an I–E difference of < 5 beats/min [14]. Clinical data are listed in Table 1. Eight patients were almost blind. Four patients were in the haemodialysis or peritoneal dialysis program. Of the remaining 11, six had proteinuria. Ten patients had symptomatic autonomic neuropathy [1].

Group 2 ($n = 11$): Patients with an I–E difference of ≥ 5 beats/min but less than the lower 2.5th percentile in healthy subjects, taking age into account [2].

Group 3 ($n = 36$): Patients with a normal I–E difference (≥ 2.5th percentile) [2].

Three patients in group 1 were under diuretic treatment. No other drugs influencing the cardiovascular system were used. Group 1 diabetic patients were older and had a longer duration of diabetes than those in group 3. Group 2 patients were in between groups 1 and 3 for age, duration of diabetes and long-term complications (Table 1). The

Table 1. Clinical data of diabetic and healthy subjects

	Group 1 ($n=15$) Severe vagal impairment	Group 2 ($n=11$) Mild vagal impairment	Group 3 ($n=36$) No apparent vagal impairment	Control subjects ($n=37$)
I–E difference[a] (beats/min)	1[b] (0–4)	7[c] (5–11)	24 (10–46)	24 (10–37)
Age (years)	49[d,e] (29–65)	42 (29–56)	32 (20–62)	37 (20–57)
Sex	5 M 10 F	5 M 6 F	18 M 18 F	19 M 18 F
Percentage ideal body weight	94[f] (72–125)	99 (88–128)	99 (67–131)	95 (64–123)
Duration of diabetes (years)	20[g] (3–33)	11 (1–30)	10 (0–39)	–
Therapy	14 insulin 1 oral agents	11 insulin	30 insulin 3 oral agents 1 diet	–
Glucose (mmol/l)	14 (8–26)	11 (4–20)	13 (3–20)	–
Glycosylated haemoglobin (%)	12 (10–16)	13 (9–17)	12 (10–16)	–
Retinopathy	14/15	6/11	13/36	–
Proteinuria	6/11	0/11	1/36	–
Symptomatic autonomic neuropathy	10/15	1/11	0/36	–

Results are expressed as median with range in parentheses.
[a] I–E difference = heart rate variation during forced breathing expressed as inspiration-expiration difference; [b] Group 1 versus 2, 3, Control, $p < 0.001$; [c] Group 2 versus 3, Control, $p < 0.001$; [d] Group 1 versus 3, $p < 0.005$; [e] Group 1 versus Control, $p < 0.02$; [f] Not significant; [g] Group 1 versus 3, $p < 0.02$

Table 2. Heart rate changes on standing in diabetic and control subjects

	Resting heart rate (beats/min)	ΔHR_{max} (beats/min)	T_{max} (s)	ΔHR_{1min} (beats/min)	ΔHR_{5min} (beats/min)
Group 1 ($n=15$) Severe vagal impairment	80 (61–111)	6 (2–17)	[13][a]	9 (1–19)	5 (–1–21)
Group 2 ($n=11$) Mild vagal impairment	69 (60–93)	23 (14–36)	15 (11–20)	10 (4–25)	11 (1–22)
Group 3 ($n=36$) No apparent vagal impairment	74 (51–88)	33 (14–56)	15 (6–20)	12 (3–30)	14 (5–31)
Control subjects ($n=37$)	60 (46–86)	34 (17–52)	13 (7–17)	9 (2–30)	11 (–2–31)
Significance (p)	1 vs 3 < 0.05 1 vs control < 0.001 2 vs control < 0.001 3 vs control < 0.001	1 vs 2 < 0.001 1 vs 3 < 0.001 1 vs control < 0.001 2 vs 3 < 0.01 2 vs control < 0.005	NS	1 vs 3 < 0.02	1 vs 3 < 0.001 1 vs control < 0.05 3 vs control < 0.02

Results expressed as median with range in parentheses. ΔHR_{max} = peak HR increase in the first 30 s after standing; T_{max} = time of peak HR increase. [a] = T_{max} was absent in group 1. ΔHR_{max} in group 1 was therefore measured at the median T_{max} of the control subjects; ΔHR_{1min} and ΔHR_{5min} = HR increase after 1 and 5 min standing, respectively. NS = not significant

diabetic patients were compared with 37 healthy community and hospital volunteers (Table 1).

Examinations were performed in the morning between 10.00 and 11.00 h, at least 1 h after the last meal and insulin injection. All subjects were requested to abstain from coffee and cigarettes on the day of the experiment. After a thorough explanation of the procedures, subjects were asked to lie supine. An indwelling i. v. catheter was inserted in the antecubital vein. The instantaneous HR (beats/min) was determined by a cardiotachometer and monitored on a pen recorder (Servogor RE511, Brown Boveri, Heidelberg, FRG). The subjects rested supine for 20 min and subsequently stood up. A marker connected to the pen recorder was used to identify the moment the subject began to stand up (time $t = 0$).

The following measurements were made:

Table 3. Changes in blood pressure after 1 and 5 min standing compared to resting values in diabetic and control subjects

	Blood pressure (mmHg)		Changes in blood pressure (mmHg)			
	Systolic resting	Diastolic resting	Systolic 1 min standing	Diastolic 1 min standing	Systolic 5 min standing	Diastolic 5 min standing
Group 1 ($n=15$) Severe vagal impairment	150 (105–215)	80 (55–100)	−30 (−50–0)	−10 (−20–5)	−30 (−50–0)	−10 (−20–5)
Group 2 ($n=11$) Mild vagal impairment	120 (95–165)	65 (60–95)	0 (−20–15)	5 (−5–20)	0 (−20–15)	5 (−5–20)
Group 3 ($n=36$) No apparent vagal impairment	120 (95–140)	70 (50–95)	5 (−25–15)	10 (−5–25)	5 (−25–15)	10 (−5–25)
Control subjects ($n=37$)	115 (95–145)	70 (60–85)	0 (−15–15)	10 (−5–20)	0 (−15–15)	20 (−5–20)
Significance (p)	1 vs 2 < 0.005 1 vs 3 < 0.001 1 vs < 0.001 control	1 vs 2 < 0.05 1 vs 3 < 0.001 1 vs < 0.005 control	1 vs 2 < 0.001 1 vs 3 < 0.001 1 vs < 0.001 control	1 vs 2 < 0.001 1 vs 3 < 0.001 1 vs < 0.001 control	1 vs 2 < 0.001 1 vs 3 < 0.001 1 vs < 0.001 control	1 vs 2 < 0.001 1 vs 3 < 0.001 1 vs < 0.001 control

Results expressed as median with range in parentheses

Heart rate changes: The resting HR was taken as the mean value over a 10 s period before standing up. Instantaneous HR was measured after 1 and 5 min standing and expressed as deviation from the resting HR. The peak HR increase in the first 30 s after standing (ΔHR_{max}) and its time of occurrence, T_{max} [2], were also measured.

Blood pressure: Blood pressure was measured by the cuff method at rest and after 1 and 5 min in the erect posture. Phase V was used to define diastolic blood pressure. Orthostatic hypotension was defined as a fall of systolic blood pressure of > 20 mmHg. A fall of diastolic blood pressure of > 5 mmHg was considered abnormal. These values were obtained by calculating the lower limit of the 95% confidence interval (P 0.025) for changes in systolic and diastolic blood pressures after the change of position from supine to standing in 133 healthy subjects [2].

Plasma catecholamines: Blood was sampled from the intravenous catheter 1 min before and 5 min after standing up. Plasma concentrations of adrenaline and noradrenaline were determined by radio-enzymatic assay using high performance liquid chromatography [15]. The intra-assay and interassay coefficients of variation were 6.2% and 10% for noradrenaline and 5.3% and 8.8% respectively for adrenaline. The sensitivity of the assay was 32 ng/l for noradrenaline and 16 ng/l for adrenaline. To facilitate comparison with other studies [6–11], catecholamines are expressed in ng/l. Conversion factors are: for adrenaline, 1 ng/l = 5.46 pmol/l, and for noradrenaline, 1 ng/l = 5.92 pmol/l.

Testing of the Postganglionic Sympathetic Axon (Axon Reflex)

The integrity of the postganglionic sympathetic neurons in the legs was evaluated by injecting 10 mg of acetylcholine intradermally on the medial site of the calf muscle half way between the knee and ankle [12, 13]. The largest diameter of the area of piloerection was measured. The average value of the scores in both legs rounded off to the nearest 0.5 cm was used as the result of the test.

Blood was sampled for glucose [16] and glycosylated haemoglobin (HbA_1) [17] determination at $t = -1$ min.

Statistical Analyses

Statistical comparison of the results was performed initially with a non-parametric analysis of variance technique (Kruskal and Wallis) [18, 19] to detect significant differences between the three groups of diabetic patients and the control subjects. If it was established that there were different responses, the two-tailed Wilcoxon rank sum test was used to detect pairwise differences between groups [18, 19]. Results are expressed as median and range. A p value of < 0.05 was considered to indicate a significant difference.

Results

Resting HR was lower in healthy subjects than in groups 1, 2 and 3 and lower in group 3 than in group 1 (Table 2). Standing up evoked an abrupt HR rise in groups 2 and 3 and control subjects, whereas the initial HR rise was delayed by > 1 s in 10/15 of group 1 patients. In these 10 patients the delay in cardioacceleration was a reproducible phenomenon.

ΔHR_{max} was higher in control subjects and group 3 than in groups 1 and 2 and higher in group 2 than in group 1. The HR increase after 1 min of standing hardly differed between diabetic patients and control subjects. After 5 min of standing, the HR increase was lower in group 1 than in group 3 and control subjects and higher in group 3 patients than in control subjects (Table 2).

Blood Pressure

Supine systolic and diastolic blood pressures were higher in group 1 than in groups 2 and 3 diabetic patients and control subjects (Table 3). After 1 and 5 min of standing, systolic pressure had hardly changed and diastolic pressure had increased 5–10 mmHg in groups 2 and 3 and the control subjects. In contrast, group 1 had a marked decrease in blood pressure on standing.

Plasma Catecholamines

No significant correlation was found in healthy subjects between plasma adrenaline, noradrenaline and age.

Table 4. Plasma adrenaline and noradrenaline in the supine position and increments after 5 min standing in diabetic and control subjects

	Adrenaline resting (ng/l)	Noradrenaline resting (ng/l)	Δ Adrenaline (ng/l)	Δ Noradrenaline (ng/l)	Acetylcholine test[a] (cm)
Group 1 ($n=15$) Severe vagal impairment	67 (10–129)	352 (99–702)	16 (–59–58)	113 (–2–906)	0 (0–8)
Group 2 ($n=11$) Mild vagal impairment	58 (15–97)	361 (127–542)	35 (8–148)	241 (116–1270)	7.0 (4–7.5)
Group 3 ($n=36$) No apparent vagal impairment	40 (14–102)	303 (107–658)	27 (–7–115)	289 (47–828)	6.5 (3.5–10)
Control subjects ($n=37$)	46 (10–162)	308 (152–533)	12 (–34–70)	278 (122–757)	7.0 (4–9)
Significance (p)	NS	NS	1 vs 2 < 0.02 1 vs 3 < 0.05 2 vs control < 0.02 3 vs control < 0.02	NS	1 vs 2 < 0.005 1 vs 3 < 0.001 1 vs control < 0.001

Results expressed as median with range in parentheses.
Δ Adrenaline and Δ Noradrenaline = increment in adrenaline and noradrenaline after 5 min standing; [a] Acetylcholine test = area of piloerection after injecting 10 mg of acetylcholine intradermally on the medial site of the calf muscle; NS = not significant. Conversion factors: adrenaline 1 ng/l = 5.46 pmol/l; noradrenaline 1 ng/l = 5.92 pmol/l

Table 5. Changes in circulatory parameters after 5 min standing compared to supine values in group 1: 12 patients with an abnormal and three patients with a normal axon reflex

Group 1 diabetic patients ($n=15$) Severe vagal impairment Changes after 5 min standing	Abnormal axon reflex group 1 A ($n=12$)	p (group 1 A versus control)	Normal axon reflex group 1 B ($n=3$)	p (group 1 B versus control	p (group 1 A versus group 1 B)
HR (beats/min)	5 (–1–16)	< 0.002	17 (12–21)	NS	< 0.02
Systolic blood pressure (mmHg)	–35 (–50–15)	< 0.001	–5 (–30–0)	NS	NS
Diastolic blood pressure (mmHg)	–10 (–20–5)	< 0.001	5 (–15–5)	NS	NS
Plasma adrenaline (ng/l)	9 (–59–56)	NS	45 (18–58)	NS	NS
Plasma noradrenaline (ng/l)	65 (–2–503)	< 0.001	673 (632–906)	< 0.01	< 0.01

Results expressed as median with range in parentheses; NS = not significant. Conversion factors: adrenaline 1 ng/l = 5.46 pmol/l; noradrenaline ng/l = 5.92 pmol/l

Plasma noradrenaline and adrenaline in the supine position and after standing showed a wide range of values and were not significantly different in diabetic and control subjects (Table 4). The 95% confidence interval for the difference between standing and supine noradrenaline levels in control subjects was calculated after log-transformation because distributions were skewed to the right. The noradrenaline increment after standing was lowest in group 1, but both abnormally high (> 700 ng/l) and abnormally low (< 120 ng/l) values were present and the difference was not significant in comparison with groups 2 and 3 and control subjects. The adrenaline increment after standing was lower in group 1 and control subjects than in groups 2 and 3. Group 1 and control subjects and groups 2 and 3 did not differ.

Testing of the Postganglionic Sympathetic Axon

Significantly smaller responses were obtained in group 1 compared with groups 2 and 3 and control subjects. Patients in groups 2 and 3 had normal scores (Table 4). An axon reflex of 4.5 cm was calculated as the lower one sided 97.5% confidence limit in controls. An abnormally small axon reflex was found in 12/15 patients in group 1, compared with 1/11 in group 2, 1/36 in group 3 and 1/37 of the control subjects. Ten of the 15 patients in group 1 had no axon reflex at all.

Relationship Between Impaired Sympathetic Cardiovascular Control and a Diminished Axon Reflex

Consistent abnormalities in sympathetic cardiovascular control were exclusively found in group 1. Group 1 pat-

ients were further analysed according to the function of the postganglionic sympathetic neuron (Table 5). In patients with an abnormally small axon reflex (group 1 A) sympathetic circulatory control was more markedly abnormal than in patients with an intact axon reflex (group 1 B) (Table 5). The initial fast HR increase after standing was delayed in 9/12 of group 1 A and one out of three of group 1 B diabetics. Ten out of twelve patients in group 1 A had an abnormal fall in systolic and 7/12 an abnormal fall in diastolic blood pressure compared with 1/3 abnormal systolic and 1/3 abnormal diastolic blood pressure reactions in group 1 B.

Abnormally low scores on the acetylcholine test were associated with a decreased noradrenaline response after standing, 9/12 patients in group 1 A had an abnormal low response. Group 1 B patients had a large increase in noradrenaline after standing. In group 1 B the HR and adrenaline increase after standing was comparable to groups 2 and 3, in group 1 A a low HR and adrenaline increment was found.

Discussion

A spectrum of abnormalities in adrenergic physiology and circulatory control after standing has been described in diabetic patients [5–11]. Measurement of parasympathetic HR control and testing of the postganglionic neuron in the legs made it possible to classify the different abnormal responses in this study.

Sympathetic lesions were almost exclusively found in diabetic patients with severely impaired or absent parasympathetic HR control. The main abnormalities consisted of a delayed and diminished HR response, an excessive fall in systolic and diastolic blood pressure in combination with an abnormally small adrenaline and noradrenaline increment and a lesion of the postganglionic sympathetic fibres in the legs. A minority of the patients with severely impaired parasympathetic function had a normal function of the postganglionic sympathetic neuron. These patients had a normal or exaggerated noradrenaline response after standing and less severe abnormalities in circulatory control. A high HR and adrenaline increment on standing was found in diabetic patients with little or no long-term complications.

A dual mechanism is responsible for the normal increase in heart rate elicited by the upright posture [20]. HR initially increases predominantly by means of parasympathetic withdrawal [3, 5, 20], whereas sustained tachycardia of later phases depends almost exclusively on sympathetic stimulation [20]. Severe impairment of vagal HR control in group 1 was established by the virtual absence (< 5 beats/min) of HR variation with forced breathing [2, 14]. A delay of more than 1 s in cardioacceleration after standing in 9/12 of group 1 A patients implies that vagal HR control was completely lost [21, 22]. A sluggish sympathetic HR response remained [5, 21, 22]. In group 1 A the HR increase after 5 min standing was abnormally small demonstrating impaired sympathetic HR control as well [20]. Some patients had almost no HR increase at all after 5 min standing. These patients are almost totally denervated. Group 1 B had a normal HR increase after 5 min standing. There was one patient in this group with an I–E difference of only 2 beats/min and a delayed onset to cardioacceleration, but with a HR increase of more than 20 beats after 5 min standing, demonstrating absent parasympathetic HR control in combination with intact sympathetic HR control.

An abnormally small increment of noradrenaline on standing in combination with a lesion of the sympathetic postganglionic fibres in the legs is a consistent finding in diabetic patients with orthostatic hypotension [6, 8, 10, 13, 23]. On the other hand, a markedly high noradrenaline increment on standing may, in our opinion, be viewed as a compensatory response to a variety of conditions, that are not specific for diabetes mellitus [7–9, 24, 25]. Since group 1 A experienced pronounced orthostatic hypotension, an exaggerated adrenaline response was to be expected [26]. The fact that group 1 A had a low adrenaline increment on standing, is an indication of impaired sympathetic outflow to the adrenal medulla, as has been reported during insulin-induced hypoglycaemia in diabetic patients with severe autonomic neuropathy [27].

A high HR and adrenaline increment after standing in combination with a normal blood pressure and noradrenaline response seems to be a feature of diabetic patients with few or no long-term complications [11]. The physiological background for this abnormality needs further study. A decreased plasma volume could be involved [28].

In conclusion, sympathetic lesions were found only in patients with longstanding complicated diabetes and extensive cardiac vagal damage. A combination of tests is required to assess both sympathetic and parasympathetic cardiovascular control in diabetic patients suspected of autonomic neuropathy.

Acknowledgements. We would like to express our appreciation to J. M. Karemaker and R. de Boer, Department of Physiology, for critical suggestions, and to N. J. D. Nagelkerke and W. L. Posthumus, Department of Medical Physics and Medical Informatics for statistical advice and computer assistance. We are indebted to J. A. Schouten and G. H. Krull for the referral of their patients. This study was supported by the Dutch Heart Foundation.

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Received: 12 August 1982
and in revised form: 23 March 1983

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