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Effect of glycaemic control on myocardial sympathetic innervation assessed by [^{123}I]metaiodobenzylguanidine scintigraphy: a 4-year prospective study in IDDM patients

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Summary Diabetic cardiovascular autonomic neuropathy (CAN) has been directly characterized by reduced or absent myocardial [^{123}I]metaiodobenzylguanidine (MIBG) uptake, but there is no information available on the relationship between the myocardial adrenergic innervation defects and long-term glycaemic control. In a prospective study over a mean of 4 years we examined myocardial sympathetic innervation in 12 Type 1 (insulin-dependent) diabetic patients using MIBG scintigraphy (absolute and relative global MIBG uptake at 2 h p.i.) in conjunction with cardiovascular autonomic function tests, QTc interval, and QT dispersion. Six healthy non-diabetic subjects served as controls for the MIBG scintigraphy at baseline. HbA_{1c} was measured twice a year. One patient, in whom MIBG accumulation was reduced maximally, died during follow up. Among the remaining patients 5 had good or borderline glycaemic control (mean $HbA_{1c} < 7.6\%$; Group 1), whereas 6 patients were poorly controlled (mean $HbA_{1c} \geq 7.6\%$; Group 2). Absolute global MIBG uptake increased from baseline to follow-up by 260 (–190–540) [median (range)] cpm/g in Group 1 and decreased by –150 (–450–224) cpm/g in Group 2 ($p < 0.05$ vs Group 1). Relative global MIBG uptake decreased by –1.7 (–3.4–9.4) % in Group 1 and by –4.7 (–17.4–1.3) % in Group 2 ($p < 0.05$ vs Group 1). No differences between the groups were noted for the changes in the automatic function tests, QTc interval, and QT dispersion. In conclusion, long-term poor glycaemic control constitutes an essential determinant in the progression of left ventricular adrenergic dysinnervation which may be prevented by near-normoglycaemia. Evaluation of susceptibility to metabolic intervention may be superior when CAN is characterized directly by MIBG scintigraphy rather than by indirect autonomic function testing. [Diabetologia (1998) 41: 443–451]

Keywords Diabetic cardiovascular autonomic neuropathy, MIBG scintigraphy, sympathetic denervation, autonomic function tests, glycaemic control.

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Abbreviations: AFTs, Autonomic function tests; MIBG, [^{123}I]metaiodobenzylguanidine; HRV, heart rate variability; ECG, electrocardiogram; CAN, cardiovascular autonomic neuropathy; ROI, region of interest; SPECT, single photon emission computed tomography; HED, [^{11}C]hydroxyephedrine; Sesta-MIBI, [^{99m}Tc]hexakis-2-methoxy-2-isobutyl-isonitrile; IDDM, insulin-dependent diabetes mellitus.

Cardiovascular autonomic neuropathy (CAN) characterized by reduced heart rate variability (HRV) is detected in approximately 20 % of diabetic patients [1–3] and represents a serious complication of diabetes as it carries an approximately fivefold increased risk of mortality [4], is associated with enhanced likelihood of sudden death [5], and may predict a deterioration in glomerular filtration rate [6] or even the development of stroke [7].

Although the unfavourable impact of long-term poor glycaemic control on the development and progression of CAN is now generally accepted [4, 8, 9], there is as yet no clear answer to the question of whether long-term near-normoglycaemia may

reverse CAN or prevent its progression [4]. Some authors consider autonomic neuropathy an irreversible process [10, 11]. On the other hand, it is conceivable that lesions to the autonomic nerves are less susceptible to intervention than those to the somatic nerves or that cardiovascular autonomic function tests (AFTs) based on HRV simply do not provide a measure sensitive enough to detect subtle effects of intervention on autonomic nerve function. Moreover, AFTs provide only an indirect measure of the integrity of the autonomic nervous system.

Radionuclide techniques for cardiac mapping have recently been introduced to directly quantify myocardial sympathetic innervation in various diseases including CAN. One of these techniques uses the non-metabolized guanethidine derivative [^{123}I]metaiodobenzylguanidine (MIBG), a radiolabelled analogue of norepinephrine which is taken up by the postganglionic presynaptic sympathetic nerve terminals and shares the same uptake and storage mechanisms with norepinephrine [12, 13]. Several studies have demonstrated decreased myocardial MIBG uptake in insulin-dependent (IDDM) [14–17] or non-insulin-dependent diabetic [18–22] patients with abnormal [23–26] or normal AFTs [14, 15, 27, 28] and those with silent [25, 29, 30] or painful myocardial ischaemia [30] predominantly in the left ventricular inferior and posterior segments [14–16, 18, 19]. Defects in MIBG uptake have been reported to correlate with the body mass index [24], systolic blood pressure [24], autoantibodies to sympathetic ganglia [16], disturbed left ventricular diastolic filling [14, 31], QT interval length [17], QT dispersion [20], and power spectrum of HRV [21].

A recent study included newly diagnosed IDDM patients, 77% of whom had reduced global myocardial MIBG uptake [32] which, however, did not change after 1 year of intensive insulin therapy [33]. To date there have been no prospective studies over several years that assessed the effects of glycaemic control on myocardial MIBG uptake compared with AFTs in longer-term diabetic patients. The aim of the present prospective 4-year study was to evaluate the effects of glycaemic control on myocardial sympathetic innervation in long-term IDDM patients.

Subjects and methods

Subjects. After obtaining written informed consent from all subjects and approval by the ethics committee of the Heinrich Heine University of Düsseldorf, 12 C-peptide negative IDDM patients, classified according to the criteria of the National Diabetes Data Group [34], admitted to the inpatient clinic of the Diabetes Research Institute consented to participate in the study and were followed up for 49 (40–60) months on an outpatient basis. Inclusion criteria were duration of diabetes 5 years or more, presence of polyneuropathy and/or CAN evidenced by 3 or more abnormalities among 7 parameters tested (see methods), and intensive insulin therapy either by multiple daily insulin injections or continuous subcutaneous insulin infusion. Patients were excluded if they had medication known to influence autonomic nerve function, neuropathies other than of diabetic origin, and coronary artery disease evidenced by positive exercise scintigraphy. MIBG scintigraphy and AFTs were performed in the absence of ketonuria/acidosis within 2 weeks prior to the baseline and follow-up visit. Prior to the study all subjects underwent a standardized 1 week teaching programme including dietary instructions, training in self-monitoring of blood glucose, and learning of self-adjustment of the insulin dose.

To evaluate the effect of long-term glycaemic control on autonomic function, the patients were grouped on the basis of their mean HbA_{1c} levels during the study according to the Consensus Guidelines for the Management of IDDM proposed by the European IDDM Policy Group [35]. Patients with mean HbA_{1c} levels less than 7.6% of months 6–60 who were considered to have good or borderline glycaemic control were allocated to Group 1 ($n = 5$), while those with mean HbA_{1c} levels 7.6% or more of months 6–60 were assigned to Group 2 ($n = 6$) representing subjects with long-term poor metabolic control. One patient who died 26 months after the baseline assessment was not included in the statistical analysis. This male patient aged 56 years (duration of diabetes: 22 years; initial HbA_{1c}: 7.6%) had retinopathy, peripheral neuropathy, and severe autonomic neuropathy presenting with a maximum CAN score, almost absent global MIBG uptake, postural hypotension, and diabetic diarrhoea. The patient died from a progressive space-occupying left hemispheric insult of the middle and posterior cerebral artery resulting in brain stem impaction.

Six subjects served as a healthy control group for MIBG scintigraphy performed at one time. They had no evidence of an acute organic or systemic disease as confirmed by medical history, clinical examination, and 12-lead electrocardiogram (ECG), and none of them was on any medication.

The clinical characteristics of both groups at entry into the study and those of the healthy control subjects are shown in Table 1. There were no significant differences between the groups regarding any of the parameters listed. The patients were not taking any antihypertensive medication, except for one patient of Group 2 who was treated with lisinopril and furosemide throughout the study.

Laboratory methods. Glycosylated haemoglobin (HbA_{1c}) was measured at hospital admission and thereafter at 6 month intervals by the HPLC technique (Diamat, Bio-Rad, Munich, Germany). The normal range for our laboratory is 4.2–6.2%. Capillary blood glucose was determined at the start and the end of the MIBG studies, and usually 1–3 additional values were measured in between. Samples were collected in heparinised capillaries (20 μl), and analysed by the hexokinase method on an ACP 5040 autoanalyzer (Eppendorf, Hamburg, Germany). C-peptide was analysed by RIA (RIAmat C-peptide, Byk-Mallinckrodt, Dietzenbach, Germany). Urinary albumin excretion rate was determined from 24-h samples using the immuno-nephelometric technique (Array Protein System, Beckman, Fullerton, Calif., USA). The reversed phase HPLC method with electrochemical detection was used to determine plasma epinephrine and norepinephrine (Beckman, München, Germany). Serum creatinine was measured by the para-aminophenazone (PAP) method (Boehringer, Mannheim, Germany). Serum triglycerides and cholesterol were determined by standard procedures.

Table 1. Clinical characteristics of the healthy subjects and diabetic patients studied

	Control	Group 1 Mean $HbA_{1c} < 7.6\%$	Group 2 Mean $HbA_{1c} \geq 7.6\%$
n	6	5	6
Male/female	4/2	5/0	5/1
Age (years)	54.5 (35–72)	42.0 (32–61)	38.0 (27–57)
Weight (kg)	76.5 (60–100)	82.0 (67–93)	76.5 (68–93)
Height (cm)	167 (154–184)	180 (168–196)	178 (159–188)
Heart rate (bpm)	64.0 (56–92)	83.0 (65–86)	69.0 (66–82)
Epinephrine (pg/ml)	42.0 (20–111)	26.0 (13–47)	93.0 (18–117)
Norepinephrine (pg/ml)	264 (104–361)	128 (35–334)	188 (53–428)
Triglycerides (mg/dl)	–	111 (79–208)	117 (60–151)
Cholesterol (mg/dl)	–	215 (167–253)	212 (191–240)
Creatinine (mg/dl)	–	0.8 (0.6–1.1)	0.9 (0.6–1.0)
Systolic BP (mm Hg)	–	134 (128–139)	144 (120–153)
Diastolic BP (mm Hg)	–	69 (66–81)	81 (68–84)
Duration of diabetes (years)	–	28.0 (7–32)	19.5 (15–37)
Insulin dose (IU/day)	–	37 (30–54)	42 (32–85)
Number of injections/day	–	4 (3–4)	4 (3–5)
CSII	–	1	1
Albuminuria (μg/min)	–	150 (3–185)	42.5 (4–4269)
Retinopathy	–	4	6
Polyneuropathy	–	4	6
CAN (≥ 3 tests abnormal)	–	2	3

Values are medians (ranges) or *n*. BP, Blood pressure; CSII, continuous subcutaneous insulin infusion; CAN, cardiovascular autonomic neuropathy

Cardiovascular autonomic function. Autonomic reflex tests based on HRV were performed using a ProSciCard computer system (MediSyst, Linden, Germany) as previously described [36]. The systolic blood pressure response to standing was performed using a Dinamap 1846 SX monitoring system (Critikon, Norderstedt, Germany). Normal ranges were established in 120 healthy subjects aged 32 (15–67) years [36]. We have previously suggested the following seven indices to be included in the test battery: 1) coefficient of R-R interval variation (CV) at rest, 2) spectral power in the low-frequency (LF) band and 3) mid-frequency (MF) band, 4) mean circular resultant (MCR) of vector analysis during deep breathing, 5) maximum/minimum 30:15 ratio to standing up, 6) Valsalva ratio, and 7) postural change in systolic blood pressure. Definite CAN was defined as 3 or more abnormalities among these seven indices [37]. The CAN score was defined as the ratio between the number of abnormal parameters divided by the total number of parameters tested in an individual patient (maximum score = 1).

Electrocardiographic assessment. Heart rate adjusted QT interval according to the Bazett formula $QTc = QT/\sqrt{R\text{-}R}$ [38] and QT dispersion [39] were employed as indirect measures of repolarization of the ventricular myocardium. Measurements of these indexes were obtained from a 12-lead resting ECG at a paper speed of 50 mm/s. All subjects were in sinus rhythm and had no conduction abnormalities of the QRS complex. QT interval was measured as previously described [17]. At least 9 of 12 analysable ECG leads were required for inclusion in data analysis and calculation of the mean QT and QTc interval. QT dispersion was defined as the difference between the maximum and minimum QT interval in any of at least 9 ECG channels, respectively. Measurements were obtained manually by one observer unaware of the subject's clinical status.

Peripheral nerve function. Electrophysiological tests, thermal and vibration sensation thresholds and neurological examination were performed as previously described [8].

Retinopathy assessment. Colour retinal photographs were taken after pupillary dilatation using a CR3-45NM non-mydriatic retinal camera (Canon, Tokyo, Japan) and were judged by an experienced examiner.

[^{123}I]metaiodobenzylguanidine (MIBG) SPECT. MIBG SPECT studies were performed as previously described [17]. All patients and control subjects received 900 mg sodium perchloride orally at 48 h, 24 h and 1 h before tracer injection to block possible uptake of free radioactive iodide by the thyroid gland. The specific activity of MIBG (CYGNE BV, Eindhoven, The Netherlands) was between 260 and 480 MBq/mmol, the radionuclide purity was more than 99.95%, and the radiochemical purity of MIBG was 98% or more. For the measurement of norepinephrine and epinephrine a fine gauge intravenous canula was placed in an antecubital vein of the left arm, and the patient remained in a supine position for 30 min for blood sampling. Thereafter, 370 MBq MIBG was injected via the intravenous canula. The injected amount of tracer radioactivity was determined exactly by measuring the radioactivity in the syringe before and after tracer injection. A first (early) SPECT study was performed from 15 to 45 min p.i., a second SPECT study from 120 to 150 min p.i. For the assessment of late MIBG-uptake the 2 h scan was chosen which has been shown to be representative for specific MIBG retention [40].

The studies were performed using a triple headed SPECT system (Trionix Triad, Twinsburg, Ohio, USA) equipped with high resolution parallel hole collimators. The SPECT data were reconstructed by filtered back projection in a 128×64 matrix with a pixel size of 3.56 mm using a butterworth filter (0.35 highcut, 3.0 roll-off). Data were corrected for attenuation [41] (first order $\mu = 0.1$) using a contour-finding procedure. No scatter correction was applied. Vertical and transversal long axis sections of the left ventricle were generated. Four slices in the centre of the vertical long axis and in the centre of the transversal long axis were added up yielding a slice thickness of 1.42 cm. The slices were evaluated by cubical regions of in-

Table 2. Follow-up of cardiovascular autonomic parameters

	Group 1 Mean $HbA_{1c} < 7.6\%$ ($n = 5$)	Group 2 Mean $HbA_{1c} \geq 7.6\%$ ($n = 6$)
CAN score		
Baseline	0.17 (0–1)	0.52 (0–1)
Follow-up	0.14 (0–0.85)	0.50 (0.14–0.86)
CV at rest (%)		
Baseline	3.24 (0.95–5.36)	2.62 (0.97–3.89)
Follow-up	2.05 (0.68–3.83)	2.35 (0.91–3.59)
Very low-frequency PS ($10^{-4}Hz^2$)		
Baseline	0.37 (0.14–3.53)	0.43 (0.15–0.77)
Follow-up	0.40 (0.09–2.33)	0.37 (0.18–0.76)
Low-frequency PS ($10^{-4}Hz^2$)		
Baseline	0.14 (0.05–2.35)	0.24 (0.11–0.63)
Follow-up	0.51 (0.04–1.61)	0.43 (0.05–0.51)
High-frequency PS ($10^{-4}Hz^2$)		
Baseline	0.36 (0.04–1.16)	0.11 (0.07–0.49)
Follow-up	0.39 (0.05–0.82)	0.11 (0.06–0.55)
Mean circular resultant		
Baseline	0.021 (0.01–0.052)	0.018 (0.007–0.029)
Follow-up	0.035 (0.01–0.041)	0.014 (0.007–0.02)
Max/min 30 : 15 ratio		
Baseline	1.08 (1.0–1.43)	1.08 (1.01–1.44)
Follow-up	1.04 (1.02–1.28)	1.07 (1.0–1.17)
Valsalva ratio		
Baseline	1.55 (1.08–2.01)	1.12 (1.08–1.15)
Follow-up	1.31 (1.11–1.58)	1.26 (1.04–1.39)
Postural change in SBP (△ mm Hg)		
Baseline	–13.0 (–28–12.5)	–19.0 (–32–[–12])
Follow-up	–15.0 (–32–[–11])	–27.0 (–33–[–9])
Postural change in DBP (△ mm Hg)		
Baseline	4.5 (–3–5)	–8.5 (–19–8)
Follow-up	–3.0 (–6–[–1])	–10.0 (–16–[–2])
QTc (ms)		
Baseline	384 (359–453)	416 (383–422)
Follow-up	403 (384–434)	405 (379–426)
QT dispersion (ms)		
Baseline	48 (15–71)	51.5 (20–59)
Follow-up	43 (36–62)	54.5 (21–87)

Values are medians (ranges). CAN, cardiovascular autonomic neuropathy; CV, coefficient of variation; PS, power spectrum; S/DBP, systolic/diastolic blood pressure

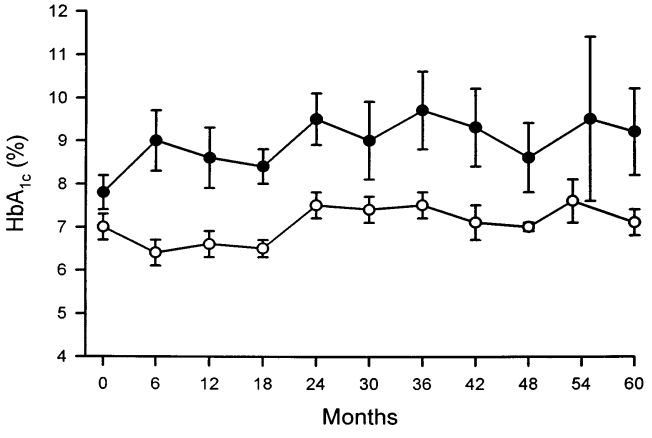

Fig. 1. Glycosylated haemoglobin (HbA_{1c}) levels (mean ± SEM) during the study in patients with mean HbA_{1c} of months 6–60 < 7.6% (Group 1) (○) and mean HbA_{1c} of months 6–60 ≥ 7.6% (Group 2) (●).

terest (ROI) of 4 × 4 × 4 (1.42 × 1.42 × 1.42 cm) pixel so that the ROI covered a cubic volume of 2.9 ml. These ROIs were placed on the following positions: 1) in the vertical long axis section: on the basal part of the anterior wall, apical part of the anterior wall, apex, apical part of the posterior wall, basal part of the posterior wall, 2) in the transversal long axis section: on the basal part of the septum, apical part of the septum, apex again, apical part of the lateral wall, and basal part of the lateral wall. For the apical ROI a mean value from the region in the vertical and transversal longitudinal sections was calculated. Thus, for each heart evaluation the data of 9 ROI were available. The following two parameters of MIBG scintigraphy were defined:

Absolute global MIBG uptake. Global myocardial MIBG uptake was quantified in counts · min^{-1} · ml^{-1} tissue normalized to injected dose and body weight. A mean value of the MIBG uptake in each cardiac ROI was calculated to estimate the global myocardial uptake. This evaluation involved both the early and late MIBG scans. Since there were no major differences in the outcome between early and late MIBG studies, only the results of the latter are presented here.

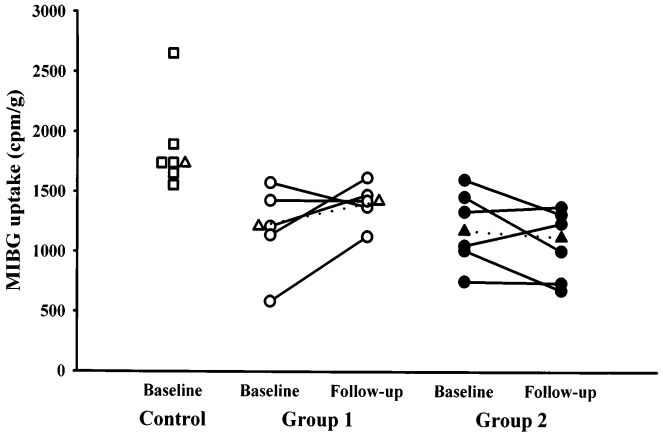

Fig. 2. Absolute global MIBG uptake in the control subjects (□) and in patients with mean HbA_{1c} of months 6–60 < 7.6 % (Group 1) (○) and mean HbA_{1c} of months 6–60 ≥ 7.6 % (Group 2) (●) at baseline and follow-up.
$p < 0.05$ for the median changes (dotted lines) from baseline to follow-up in Group 1 (△) vs Group 2 (▲)

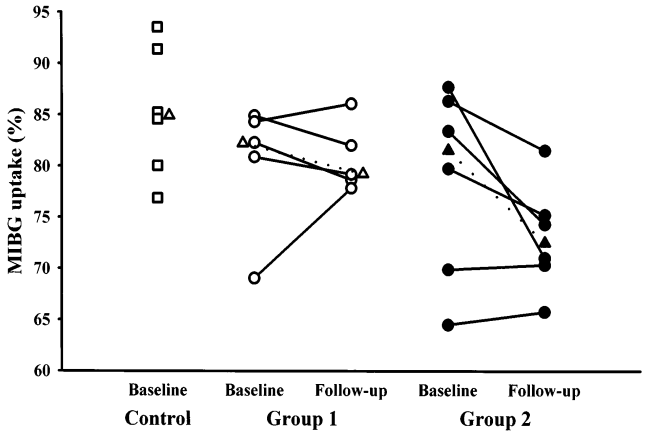

Fig. 3. Relative global MIBG uptake in the control subjects (□) and in patients with mean HbA_{1c} of months 6–60 < 7.6 % (Group 1) (○) and mean HbA_{1c} of months 6–60 ≥ 7.6 % (Group 2) (●) at baseline and follow-up.
$p < 0.05$ for the median changes (dotted lines) from baseline to follow-up in Group 1 (△) vs Group 2 (▲)

Relative global MIBG uptake. Relative global MIBG uptake was defined as the mean of the percentage uptake in each region in relation to the left ventricular maximum which was considered 100 %. Relative MIBG uptake was calculated as the mean value of all segments and was given in percent.

Sesta-MIBI SPECT. Myocardial perfusion scintigraphy after maximal bicycle exercise was performed a few days following the MIBG assessments using [^{99m}Tc]hexakis-2-methoxy-2-isobutyl-isonitrile (Sesta-MIBI) SPECT [42] to exclude significant coronary artery disease in all subjects with cardiac MIBG uptake defects.

Statistical analysis. Results are expressed as the median (range) and were tested using the Mann-Whitney U test, except for the HbA_{1c} levels shown in Figure 1 which are given as arithmetic mean ± SEM. The results obtained at follow-up were adjusted to their baseline values by calculating the changes from baseline to follow-up. By this adjustment, possible confounding factors were controlled during statistical testing inasmuch they may had exerted an influence prior to the study. These changes from baseline to follow-up were expressed as medians (ranges) which were analysed using the Mann-Whitney U test. The mean HbA_{1c} levels of months 6–60 were tested between the groups by the *t*-test for two independent samples. Qualitative data are given as absolute frequencies which were analysed by the Fisher's exact test. The level of significance was set at $\alpha = 0.05$.

Results

Glycaemic control. The HbA_{1c} levels at 6-month intervals in the two groups studied are shown in Figure 1. There was no statistically significant difference between the groups regarding HbA_{1c} at baseline (month 0). Mean HbA_{1c} levels of months 6–60 were 7.0 ± 0.2 % in Group 1 and 9.0 ± 0.5 % in Group 2 ($p < 0.05$) and remained relatively stable during the study, showing an average difference of about 2 % of HbA_{1c} throughout the study.

Capillary blood glucose levels during the MIBG studies were 5.7 (2.3–7.2) mmol/l at baseline and 5.9 (4.7–9.6) mmol/l at follow-up in Group 1. The corresponding values were 7.1 (2.1–18.6) and 8.5 (5.6–17.4) mmol/l in Group 2, without significant differences between the groups. No significant associations were noted between the blood glucose levels during the MIBG studies and absolute or relative MIBG uptake.

Cardiovascular autonomic parameters: The results of the autonomic function tests, QTc interval, and QT dispersion are shown in Table 2. No significant differences between the groups were noted for the changes from baseline to follow-up for any of the parameters listed.

MIBG scintigraphy: Absolute global MIBG uptake (Fig. 2) was 1733 (1554–2650) cpm/g at baseline in the control subjects, 1209 (584–1573) cpm/g in Group 1 ($p < 0.05$ vs controls), and 1173 (751–1600) cpm/g in Group 2 ($p < 0.05$ vs controls). It increased from baseline to follow-up by 260 (–190–540) cpm/g to 1421 (1124–1614) cpm/g in Group 1 and decreased by –150 (–450–224) cpm/g to 1122 (679–1376) cpm/g in Group 2 ($p < 0.05$ vs Group 1) (Fig. 2).

Relative global MIBG uptake (Fig. 3) was 84.9 (76.9–93.5) % at baseline in the controls, 82.2 (69.0–84.9) % in Group 1, and 81.5 (64.5–87.7) % in Group 2. There was a decrease by –1.7 (–3.4–9.4) % to 79.2 (78.4–86.0) % in Group 1 and by –4.7 (–17.4–1.3) % to 72.5 (65.8–81.5) % in Group 2 ($p < 0.05$ vs Group 1) (Fig. 3).

Figure 4 illustrates examples of a marked improvement in MIBG uptake in a patient who maintained

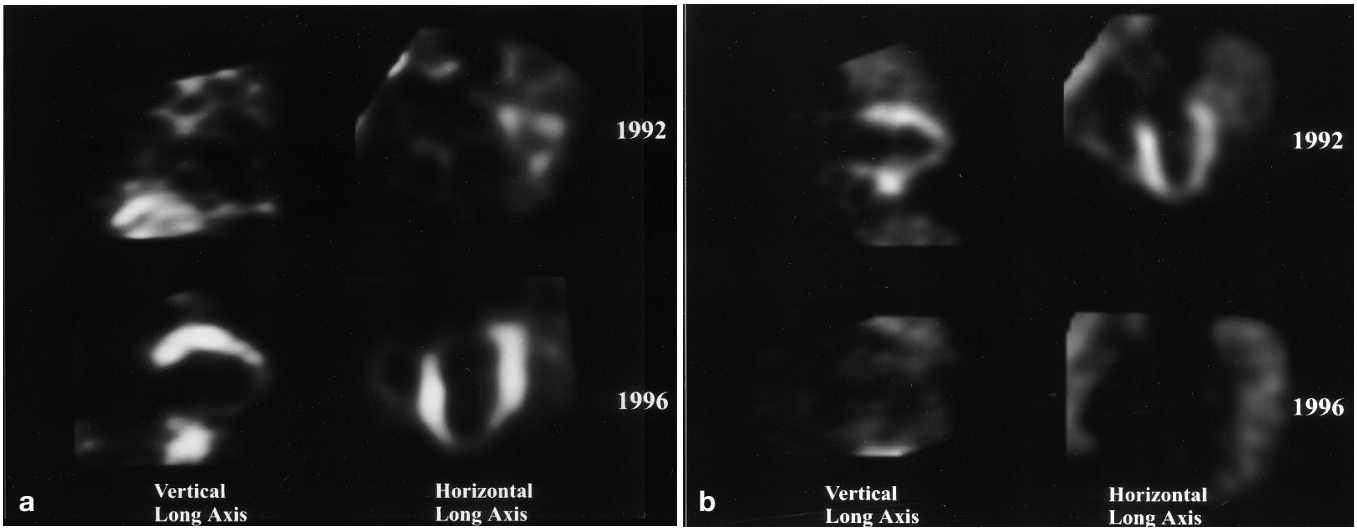

Fig. 4 a, b. Examples of a marked improvement in left ventricular MIBG uptake from the baseline to the follow-up visit in a patient who maintained near-normoglycaemia during the study (**a**) and marked deterioration in MIBG uptake in a patient who was poorly controlled (**b**)

near-normoglycaemia (Fig. 4 a) and a marked deterioration in a patient who was poorly controlled (Fig. 4 b) during the period studied.

Myocardial perfusion scintigraphy using sesta-MIBI and SPECT after maximal bicycle exercise did not reveal any abnormalities both at baseline and follow-up in the patients with cardiac MIBG uptake defects.

Discussion

The results of this study demonstrate that long-term poor glycaemic control constitutes an essential determinant in the progression of left ventricular adrenergic innervation defects as assessed by MIBG scintigraphy in IDDM patients. Both absolute and relative MIBG uptake deteriorated after 4 years in poorly controlled patients as compared with those who maintained near-normoglycaemia. In contrast, no such progression was noted for the AFTs, QTc interval, and QT dispersion, suggesting that direct assessment of myocardial innervation defects by MIBG scintigraphy may be more appropriate for evaluating the effect of metabolic intervention in CAN than indirect autonomic function testing.

The findings of the present study are novel in view of the notion that CAN represents an irreversible complication of diabetes [10, 11, 43]. Studies of the natural history of CAN have demonstrated that HRV either deteriorated at a slow rate or did not change over 4–10 years in longer-term IDDM and NIDDM patients [10, 44–49]. Given these slowly evolving abnormalities, any intervention aimed at near-normoglycaemia would presumably require many years to demonstrate slowing or cessation of progression of CAN assessed by tests based on HRV. Indeed, the non-randomized intervention studies over 3–4 years failed to show any significant effect of (near)-normoglycaemia on abnormalities in HRV [50–53], while the randomized trials over 6–8 years either showed no benefit [54] or have not reported serial assessment of HRV [55, 56]. Moreover, in the Diabetes Control and Complications Trial (DCCT), intensive insulin therapy prevented the deterioration in HRV over a mean of 6.5 years in the primary prevention cohort but not in the secondary intervention cohort selected on the basis of absence and presence of retinopathy, respectively [57]. In the DCCT the median HbA_{1c} levels at the final visit were 7.07 % in the intensive treatment group and 9.02 % in the conventionally treated group [58]. This difference of approximately 2 % was stable throughout the DCCT follow-up and corresponds exactly with the mean HbA_{1c} of 7.0 and 9.0 % observed in our study in the well controlled and poorly controlled patients grouped on the basis of the guidelines for the management of IDDM proposed by the European IDDM Policy Group [35]. Thus, the evidence from the DCCT and other long-term trials suggests that CAN diagnosed by AFTs may not be reversed or its progression halted by near-normoglycaemia. The results of the present study challenge this view by showing favourable effects of near-normoglycaemia maintained over 4 years on myocardial adrenergic innervation defects.

There are no published trials of similar duration with which to compare our findings. The only prospective study hitherto reported using MIBG scintigraphy was performed in 16 newly diagnosed IDDM patients who were treated by intensive insulin therapy for 1 year [33]. However, that study did not include a poorly controlled group for comparison. Despite a marked drop in mean HbA_{1c} from 11.5 to 6.3 %, an

improvement in MIBG uptake was noted only in the posterior and septal regions, but the mean global myocardial MIBG uptake score did not change after 1 year. Moreover, the prevalence of reduced MIBG uptake found in 77% of the newly diagnosed IDDM patients was striking [32]. It appears unlikely that these abnormalities at the time of diagnosis of IDDM reflect a myocardial denervation process [59]. Instead, increased sympathetic activity could have accounted for the reduced MIBG uptake. In patients with pheochromocytoma an inverse relationship between myocardial MIBG uptake and plasma norepinephrine concentration has been demonstrated [60]. In short-term experimental diabetes a similar inverse relationship has been observed between MIBG uptake and myocardial norepinephrine levels [61], and myocardial sympathetic activity has been found increased [62]. In contrast, post-mortem studies in long-term diabetic patients have demonstrated markedly reduced concentrations of norepinephrine in heart tissue indicating sympathetic denervation [63]. Thus, reduced MIBG uptake in early and longer-term IDDM may reflect different pathophysiological events.

Although the exact mechanism of attenuated myocardial MIBG uptake remains to be elucidated, sympathetic denervation has been suggested as its primary underlying substrate [64, 65]. In fact, myocardial sympathetic efferent denervation evidenced by loss of electrophysiologic responses has been shown to correlate with defects in MIBG uptake in the dog model [66]. Patients with spontaneous ventricular tachyarrhythmias following myocardial infarction showed regions of thallium-201 uptake indicating viable perfused myocardium, with no MIBG uptake [67]. In patients with a history of sustained ventricular tachycardia or aborted episodes of sudden death a prolonged effective ventricular refractory period was found in areas of myocardium that showed reduced retention of the norepinephrine analogue [^{11}C]hydroxyephedrine (HED) [68]. In diabetic patients attenuated HED retention was related to the severity of CAN [69]. However, because of the complex nature of sympathetic nervous system regulation, it is difficult to determine whether a given change in sympathetic function represents a pathologic or compensatory event [70].

Since apart from autonomic neuropathy regional sympathetic denervation in diabetic patients may be due to silent or symptomatic myocardial ischaemia [25, 29, 30], it may be argued that reduced myocardial perfusion could have accounted for the defects in MIBG uptake. However, this possibility has been excluded by exercise perfusion scintigraphy which showed that none of the patients who presented with abnormal MIBG scintigraphy had perfusion defects at baseline and follow-up. Thus, we believe that the reduction or absence in MIBG uptake found in the present study was exclusively due to innervation defects.

In conclusion, the results of this study indicate that long-term near-normoglycaemia may prevent the progression of left ventricular adrenergic dysinnervation in IDDM patients. Since indirect testing using AFTs, QTc interval, and QT dispersion did not result in such a favourable effect, we suggest that direct assessment of myocardial innervation defects by MIBG scintigraphy may be more appropriate for evaluating the effect of metabolic intervention on CAN than indirect autonomic function testing. Whether the effect on MIBG uptake is related to clinical endpoints of CAN or mortality remains to be established in long-term larger-scale prospective studies.

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