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Interictal cardiac autonomic dysfunction in temporal lobe epilepsy demonstrated by [^{123}I]metaiodobenzylguanidine-SPECT

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Summary

We studied the post-ganglionic cardiac sympathetic innervation in patients with chronic temporal lobe epilepsy (TLE) by means of [^{123}I]metaiodobenzylguanidine-single photon computed tomography (MIBG-SPECT) and evaluated the effects of carbamazepine on cardiac sympathetic innervation. TLE is frequently associated with dysfunction of the autonomic nervous system. Autonomic dysregulation might contribute to unexplained sudden death in epilepsy. Anticonvulsive medication, particularly with carbamazepine, might also influence autonomic cardiovascular modulation. MIBG-SPECT allows the quantification of post-ganglionic cardiac sympathetic innervation, whereas measuring the variability of the heart rate provides only functional parameters of autonomic modulation. Antiepileptic drugs, especially carbamazepine (CBZ), can affect cardiovascular modulation. We determined the index of cardiac MIBG uptake (heart/mediastinum ratio) and heart rate variability (HRV) using time and frequency domain parameters of sympathetic and parasympathetic modulation in 12 women and 10 men (median age 34.5 years) with a history of TLE for 7–41 years (median 20 years). Myocardial perfusion scintigrams were examined to rule out deficiencies of MIBG uptake due to myocardial ischaemia. To assess the possible effects of CBZ on autonomic function, we compared MIBG uptake and HRV in 11 patients who had taken CBZ and 11 patients who had not taken CBZ, and in 16 healthy controls. In order to identify MIBG uptake defects due to myocardial ischaemia, all patients had a perfusion scintigram. Cardiac MIBG uptake was significantly less in the TLE patients (1.75) than in the controls (2.14; $P = 0.001$), but did not differ between subgroups with and without CBZ treatment. The perfusion scintigram was normal in all patients. Time domain analysis of HRV parameters suggested the predominance of parasympathetic cardiac activity in the TLE patients, but less parasympathetic modulation in the patients treated with CBZ than in those not treated with CBZ ($P < 0.05$), whereas frequency domain parameters showed no significant difference between the subgroups of patients or between patients and controls. MIBG-SPECT demonstrates altered post-ganglionic cardiac sympathetic innervation. This dysfunction might carry an increased risk of cardiac abnormalities.

Keywords: temporal lobe epilepsy; cardiac autonomic dysfunction; [^{123}I]MIBG-SPECT; heart rate variability

Abbreviations: b.p.m. = beats per minute; CBZ = carbamazepine; CV = coefficient of variation; HF = high frequency; H/M = heart/mediastinum ratio; HR = heart rate; HRV = heart rate variability; LF = low frequency; MIBG-SPECT = metaiodobenzylguanidine–single photon emission computed tomography; MSA = multiple system atrophy; ROI = region of interest; RMSSD = root mean square of successive differences; TLE = temporal lobe epilepsy

Introduction

Temporal lobe epilepsy (TLE) may be associated with alterations of autonomic function, such as hyperventilation, apnoea and changes in blood pressure and heart rate (HR), including bradycardia and transient heart rest (Wannamaker, 1985). In 1941, Penfield described a patient with TLE who presented episodes of tachycardia during seizures (Penfield

Table 1 *Clinical data and antiepileptic drugs in 22 patients with TLE*

Patient	Age (years)	Sex	Age at onset (years)	Seizure type and frequency per month	Type of medication and daily dose (mg)	Interictal/ ictal EEG	MRI studies
1	38	F	32	SP (9), CP (2.5), SG (1)	CBZ (1200)	l-TL	Atrophy HF
2	51	F	35	SP (5), CP (5), SG (0.1)	CBZ (1200), VPA (2100)	l-TL	Am cavernoma
3	42	F	1	SP (4.5), CP (1), SG (1)	LTG (400), CLB (20)	r-TL	Gliosis HF
4	36	F	11	SP (2.5), CP (10), SG (1)	CBZ (1200)	l-TL	Atrophy HF
5	23	M	3	SP (4), CP (4)	CBZ (2000), TGB (10)	r-TL	Atrophy Am
6	25	F	6	SP (8), CP (8)	CBZ (1200), TGB (40)	r-TL	Gliosis HF
7	27	F	20	SP (10), CP (10), SG (1)	VPA (1200)	l-TL	Lesion, temporomesial
8	30	F	11	SP (7), CP (5), SG (0.5)	LTG (400)	r-TL	Gliosis HF
9	35	F	1	SP (4), CP (4), SG (1.5)	0	r-TL	Gliosis HF
10	32	M	12	SP (3), CP (3), SG (0.5)	LTG (300)	r-TL	Gliosis HF
11	38	M	16	SP (10), CP (10), SG (10)	LTG (200)	l-TL	Resection of haemangioma
12	35	M	4	SP (10), CP (10), SG (1.5)	LTG (150)	r-TL	Enlargement HF, Am
13	20	F	1	SP (1.5), CP (1.5), SG (0.3)	CBZ (1800)	l-TL	Cystic lesion HF, Am
14	30	M	1	SP (4), CP (12), SG (0.5)	LTG (400)	r-TL	Enlargement HF, Am
15	34	F	6	CP (10)	CBZ (1800), LTG (25)	l-TL	Atrophy HF
16	39	M	7	CP (3)	LTG (400)	r-TL	Atrophy HF
17	46	M	29	SP (0.1), CP (0.1)	CBZ (1000)	r-TL	Gliosis HF
18	30	F	18	SP (3), CP (3), SG (0.1)	CBZ (1200), TGB (20)	r-TL	Gliosis HF, cavernom
19	43	F	43	SP (1), CP (7), SG (7)	CBZ (1200)	r-TL	Gliosis HF, neocortical
20	40	M	1	CP (3)	LTG (500)	r-TL	Gliosis HF
21	34	M	12	SP (5), CP (5), SG (0.1)	CBZ (1200)	l-TL	Gliosis HF, neocortical
22	29	M	11	SP (4), CP (4), SG (0.1)	0	l-TL	Gliosis HF

F = female; M = male; SP = simple partial; CP = complex partial; SG = secondarily generalized tonic–clonic; CBZ = carbamazepine; VPA = valproate; LTG = lamotrigine; TGB = tiagabine; CLB = clobazam; Am = amygdala; HF = hippocampal formation; l = left; r = right; TL = temporal lobe.

and Erickson, 1941). Marshall and colleagues observed ictal tachycardias of 120–180 beats per minute (b.p.m.) in 12 patients with temporal lobe seizures and Blumhardt and colleagues reported ictal cardiac arrhythmias in 42% of the 26 epileptic patients they investigated (Marshall *et al*., 1983; Blumhardt *et al*., 1986). The most frequently observed arrhythmia was an irregular series of abrupt changes in HR occurring towards the end of seizure discharges in the EEG. Nei and colleagues analysed ECG changes in a total of 51 partial seizures occurring in 43 patients with refractory epilepsy. Thirty-nine per cent had one or more abnormalities of rhythm and repolarization during or immediately after seizures (Nei *et al.*, 2000). More importantly, ictal autonomic changes, especially arrhythmias, might contribute to the pathogenesis of unexplained sudden death in epilepsy.

In addition, there is evidence of interictal cardiac autonomic dysfunction in patients with TLE (Frysinger *et al.*, 1993; Devinsky *et al.*, 1994; Diehl *et al.*, 1997; Massetani *et al.*, 1997; Isojärvi *et al.*, 1998; Tomson *et al.*, 1998; Ansakorpi *et al.*, 2000). Diehl and colleagues demonstrated an interictal increase in the sympathetic modulation of cerebral blood flow velocities in epilepsy patients (Diehl *et al.*, 1997).

Tomson and colleagues and Ansakorpi and colleagues showed impaired cardiovagal modulation of HR variability (HRV) in TLE patients (Tomson *et al.*, 1998; Ansakorpi *et al.*, 2000). Frysinger and colleagues reported an increase in primarily sympathetically mediated HR modulation in patients after anterior temporal lobectomy with unfavourable postsurgical outcome (Frysinger *et al.*, 1993). In contrast, Massetani and colleagues saw a significant decrease in HRV and sympathetically and parasympathetically mediated components in interictal epilepsy patients (Massetani *et al.*, 1997).

In addition to the epileptic disorder, anticonvulsive medication might affect cardiovascular regulation (Tomson *et al.*, 1998). Phenytoin has antiarrhythmic properties and depresses the hyperactivity of cardiac sympathetic nerves (Lathers and Schraeder, 1982). In contrast, carbamazepine (CBZ) increases the sympathetic tone of the autonomic nervous system (Devinsky *et al.*, 1994). CBZ is also known to slow atrioventricular conduction and thus might increase the risk of arrhythmias (Herzberg, 1987).

Cardiac autonomic modulation can be assessed non-invasively by means of HR recording and analysis of HRV (Mathias and Bannister, 1999). Whereas HRV analysis provides indices of functional autonomic modulation, the morphology of sympathetic cardiac innervation can be quantified by means of [^{123}I]metaiodobenzylguanidine–single photon emission computed tomography (MIBG-SPECT) (Dae *et al.*, 1989). MIBG-SPECT allows the assessment of the global and regional distributions of cardiac sympathetic innervation and denervation (Schnell *et al.*, 1996). MIBG uptake by myocardial sympathetic nerve terminals is qualitatively similar to physiological norepinephrine uptake (Dae *et al.*, 1989). The [^{123}I]MIBG scintigram has been used widely to assess the impairment of sympathetic cardiac

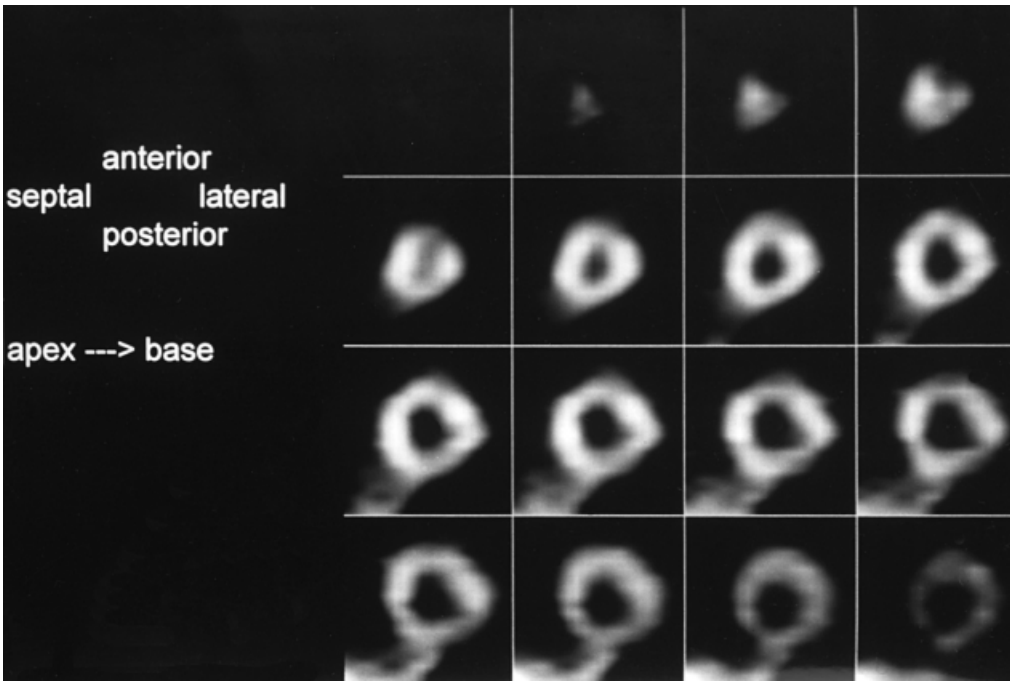

Fig. 1 Normal cardiac MIBG-SPECT showing homogeneous tracer uptake.

innervation in various diseases (Glowinak *et al.*, 1989; Stanton *et al.*, 1989; Druschky *et al.*, 2000). Minardo and colleagues were able to show sympathetic cardiac denervation in dogs after injection of latex into a coronary artery (Minardo *et al.*, 1988). MIBG showed regional sympathetic denervation in addition to myocardial perfusion deficits in patients after myocardial infarction (Stanton *et al.*, 1989). The method revealed global impairment of cardiac sympathetic innervation in diabetes mellitus and in patients after heart transplantation (Glowinak *et al.*, 1989). There is also evidence of deficient sympathetic cardiac innervation in patients with an increased tendency towards cardiac arrhythmias due to a prolonged refractory period of the heart (Calkins *et al.*, 1993).

[^{123}I]MIBG was approved as a diagnostic radiopharmacon by the Federal Institute for Drugs and Medical Devices (BfAvM) in 1997 and is widely used in routine diagnostic SPECT studies. So far, MIBG-SPECT has been used neither to assess the morphology of cardiac sympathetic innervation in epilepsy patients nor to study the effects of CBZ on sympathetic cardiac innervation. Since sympathetic cardiac innervation might be compromised as a result of both the seizure disorder and the anticonvulsive treatment, we performed this study to determine whether the morphology of sympathetic cardiac innervation is impaired in TLE patients and whether there is an additional effect of CBZ on cardiac sympathetic innervation, using MIBG-SPECT.

Patients and methods

We determined HRV and cardiac MIBG uptake in 12 women and 10 men (median age 34.5 years; upper and lower quartiles 29.7 and 39.2, respectively) with a history of TLE for 7–41 years (median 20 years; 16, 31). The clinical data of the patients are summarized in Table 1. To assess the influence of CBZ on HR modulation and on the morphology of sympathetic cardiac innervation, we studied HRV and MIBG uptake in a subgroup of 11 patients treated with 1000–2000 mg CBZ daily and compared these patients with a subgroup of 11 age-matched patients who had not taken CBZ for at least 1 year. To rule out short-term effects of CBZ on the cardiac MIBG-SPECT, patients were only included in the subgroup not treated with CBZ if they had not received CBZ within the 12 months preceding the study. Five patients receiving CBZ doses outside the range of 1000–2000 mg were not included in the study to prevent bias due to the effects of low or high CBZ doses. Informed consent was obtained from all patients according to the Declaration of Helsinki and biomedical studies involving human subjects (Somerset West Amendment).

A detailed history of the type and frequency of seizures was obtained from each patient or their legal guardian.

Patients were excluded from the study if they had concomitant diseases affecting the autonomic nervous system, such as infections, gammopathies, dysimmune or toxic neuropathies, alcoholism and diabetes mellitus. Patients with a history of ischaemic heart disease, especially myocardial infarctions, were also excluded from the study because cardiac perfusion defects are known to reduce MIBG uptake.

None of the patients had a history of cardiac or thyroid diseases or of arterial hypertension. None of the patients received any of ~80 substances that might interfere with [^{123}I]MIBG accumulation (Solanki *et al.*, 1992). The

medications used by the patients in the present study are listed in Table 1. Patient data were compared with previously published data from 16 healthy individuals (median age 30.0 years; 25, 44.5) (Fig. 1) (Claus *et al.*, 1994). In these control subjects, we had performed MIBG-SPECT for other medical reasons, not including cardiac disease or signs of polyneuropathy. For ethical reasons, we did not re-establish the MIBG-SPECT data in a new control group. The control subjects investigated previously had not received any concomitant medication. MIBG uptake in the control group had not been age-dependent (Claus *et al.*, 1994).

MIBG-SPECT

Sympathetic innervation of the heart was studied by means of MIBG-SPECT. In order to identify MIBG uptake defects related to previous myocardial infarction, all patients additionally had a myocardial perfusion scintigram with [^{99m}Tc]Sesta-methoxyisobutylisonitrile.

Following blocking of the thyroid gland with sodium perchlorate, [^{123}I]MIBG-SPECT was performed with commercially available [^{123}I]metaiodobenzylguanidine (Nycomed Amersham, Einthoven, The Netherlands) with a specific activity of 7.0–10.0 mCi/mg. The basic principles of the method have been reviewed by other authors (Claus *et al.*, 1994). The injected doses of MIBG ranged from 185 to 230 MBq. Four hours after the MIBG injection, 250 MBq of [^{99m}Tc]Sesta-methoxyisobutylisonitrile (Cardiolite; Dupont, Manati, Puerto Rico, USA) was administered intravenously. Recordings were made 5 h after administration of [^{123}I]MIBG. Early MIBG uptake, 1 h after injection, was not assessed because the myocardial, non-neuronal uptake decreases with increasing body mass index and diastolic blood pressure, even in patients without cardiac autonomic neuropathy (Mäntysaari *et al.*, 1996). In contrast, the myocardial uptake 5 h after injection can be ascribed to neuronal uptake alone and does not depend on parameters such as body mass index and blood pressure. Consequently, we only determined neuronal cardiac MIBG uptake 5 h after injection (Mäntysaari *et al.*, 1996). We conducted a double-nuclide SPECT study of MIBG uptake and MIBI perfusion (Orbiter 37 ZLC; Siemens, Erlangen, Germany). A MaxDELTA system (Siemens) was used for data acquisition, reconstruction and evaluation. Transverse slices were reconstructed by filtered back-projection with a Butterworth filter (cut-off 0.5, order 5) without interslice weighting. We used a single-head camera and consequently no attenuation correction was applied. Long- and short-axis slices were generated. Four rectangular regions of interest (ROIs) were drawn in the ninth (i.e. anterior) SPECT projection image of the ^{123}I energy channel. The ROIs consisted of the left ventricle, the right lung, the mediastinum and part of the liver. Relative myocardial MIBG uptake was computed after area normalization in comparison with the mediastinum, lung and liver. Cardiac MIBG uptake was expressed as the heart/mediastinum (H/M) ratio and heart/lung ratio. Lung MIBG uptake was expressed as the lung/mediastinum ratio (Druschky *et al.*, 2000).

On six short-axis sum slices from apex to basis, 33 ROIs were drawn semiautomatically and counts/voxel were calculated and expressed as the percentage of the maximum ROI. The large number of ROIs in our study allowed the assessment not only of global but also of regional deficits in cardiac sympathetic innervation. This approach enabled us to calculate the mean and standard deviation of the percentage values of each ROI in the normal group. In the patient group, the percentage values were compared with those of the normal group: the value x was added to the inhomogeneity index if the percentage value was x times outside the normal value and its standard deviation. The sum of all x values yielded the inhomogeneity index. This index is increased if the uptake pattern differs from that of a healthy person. Differences between myocardial blood flow and sympathetic innervation were evaluated visually in the reconstructed tomographic images and polar maps. The contrast between heart and adjacent lung tissue was assessed in addition to the subjective inhomogeneity index. Subjective homogeneity and subjective contrast were evaluated independently by two nuclear medicine physicians. Inhomogeneity was described as normal (no regions with low or absent MIBG uptake), intermediate (regions with slightly decreased MIBG uptake but no region with absent uptake) or pathological (regions with absent or massively decreased uptake) in the short-axis slices after 30% background subtraction. Similarly, the contrast between heart and lung was described as normal (high contrast of myocardium with respect to lung; lung not visible), intermediate (lung visible, myocardial uptake higher than lung uptake) and pathological (lower myocardial than lung uptake, or myocardium not visible). A global MIBG-SPECT score was calculated from the following parameters: MIBG uptake against mediastinum and lungs; the inhomogeneity index; subjective homogeneity; and subjective contrast. In order to increase specificity, only inhomogeneity indices >20 were considered abnormal. Depending on differences in the above parameters between patients and healthy control subjects, MIBG-SPECT results of TLE patients were defined as normal, borderline or abnormal.

HRV

HRV was recorded after patients had been in the supine position for 35 min. HRV was assessed at rest and during six cycles/min (0.1 Hz) of metronomic breathing using a commercially available computer-assisted system (ProSciCard; MediSyst, Linden, Germany) (Ziegler *et al.*, 1992). For HR analysis at rest, respiration was maintained at a frequency of 12 cycles/min (0.2 Hz) to rule out bias due to individual differences in respiration. HRV at rest was determined by calculating the mean HR, the coefficient of variation (CV) and the root mean square of successive differences (RMSSD) from 150 successive intervals of ECG R waves. To determine HRV during metronomic respiration,

a breathing rhythm of 6 s inspiration and 4 s expiration was achieved using a bar graph displayed on the computer screen. For analysis, HR, CV and RMSSD were computed from 100 R–R intervals (Ziegler *et al.*, 1992). The HR response to the Valsalva manoeuvre was recorded. We defined the Valsalva ratio as the ratio of the longest R–R interval after blowing into a mouthpiece at a pressure of 40 mmHg with the glottis open for 15 s to the shortest R–R interval during strain. (Isojärvi *et al.*, 1998). The HR response to active standing was assessed by calculating the ratio between the longest and the shortest R–R interval within the first 30 s after standing up (the 30 : 15 ratio) (Mathias and Bannister, 1999). Systolic and diastolic blood pressures were measured every 30 s after standing up. The lowest values were compared with the average of five measurements taken in the supine position at intervals of 1 min before the challenge.

To assess sympathetic and parasympathetic influences on HR modulation, we performed a fast Fourier transformation of the HR time series recorded over five min. The magnitude of HR modulation was derived from the powers of the frequency spectra in the ranges 0.04–0.15 Hz [low-frequency (LF) range] and 0.15–0.5 Hz [high-frequency (HF) range]; LF reflects sympathetic and parasympathetic influences and HF reflects the parasympathetic oscillatory influence of respiratory drive on HRV (Mathias and Bannister, 1999). The powers in the LF and HF ranges were calculated as the integral under the LF and HF curves and expressed as b.p.m.^{2}. From the powers, we calculated the LF/HF ratio as a measure of sympathovagal balance (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Power values below the 2.5th percentile and above the 97.5th percentile of healthy subjects were considered abnormal. Autonomic modulation of HR was considered abnormal if two or more parameters of (i) HR, CV and RMSSD at rest; (ii) HR, CV and RMSSD during metronomic respiration; (iii) LF, HF range; (iv) 30 : 15 ratio and (v) the Valsalva ratio were abnormal (Ziegler *et al.*, 1992).

Statistics

Because of the small number of cases, median values are given with upper and lower quartiles for the description of continuous data. The two-sided Mann–Whitney *U*-test was used for group comparisons of unpaired continuous data for which a normal distribution pattern could not be assumed because of the small number of cases. For the analysis of the target variables MIBG uptake ratio, HR, CV, RMSSD, 30 : 15 ratio, Valsalva ratio, lying and standing blood pressure, LF and HF powers, we adjusted for the confounding variable age by ANCOVA (analysis of covariance) with age as the continuous covariate. Logarithmic transformation of the main target variables was performed before ANCOVA in order to achieve an approximately normal distribution and homogeneous variances between subgroups.

The statistical assumptions for the analysis of covariance were checked before the analysis. Significance was assumed for P values $\leqslant 0.05$. A commercially available statistics software package was used for data analysis in the patients (SPSS for Windows; SPSS, Chicago, Ill., USA).

Results

MIBI scintigram showed normal myocardial perfusion in all TLE patients

Global MIBG-SPECT scores were classified as abnormal in one and as borderline in seven TLE patients. The H/M ratio of MIBG uptake was significantly smaller in the TLE patients than in the controls (Figs 2 and 3 and Table 2). In contrast, the lung/mediastinum ratio of MIBG uptake did not differ between TLE patients (0.71) and controls (0.72), indicating that the lower H/M uptake ratio of the patients was due to a decrease in specific cardiac neuronal MIBG uptake and not to generalized uptake deficiency.

In the 11 patients treated with CBZ, the H/M uptake ratio and lung/mediastinum uptake ratio did not differ from the ratio of the 11 patients not treated with CBZ, indicating similar cardiac neuronal MIBG uptake in the two groups (Table 3).

The HRV parameters HR, CV and RMSSD during metronomic breathing, LF and HF power, as well as the LF/HF ratio, the Valsalva ratio and the 30 : 15 ratio, are summarized in Tables 2 and 3. HRV showed more than two abnormal parameters in four of the 22 TLE patients. In comparison with the controls, these four patients had higher values for RMSSD during metronomic breathing and for the power of HR modulation at rest in the HF range. In three of these patients, the CV during metronomic breathing and in one patient the Valsalva ratio were higher than in the controls.

One TLE patient was excluded from the HR analysis because of tachyarrhythmia. In the TLE patients, RMSSD during metronomic respiration, the Valsalva ratio and the power of the LF modulation were higher in the TLE patients than in the controls ($P < 0.05$). Otherwise, parameters of HRV did not differ between the patient and control groups (Table 2). After active standing, the 30 : 15 ratio of R–R intervals did not differ between TLE patients (median 1.3; upper and lower quartiles 1.1, 1.5) and controls (1.4; 1.2, 1.6; $P = 0.13$). Similarly, systolic and diastolic blood pressure did not differ between the groups and remained stable during orthostatic challenge (Tables 2 and 3).

In the 11 patients treated with CBZ, median resting HR, LF and HF power did not differ from the values of the 11 patients without CBZ treatment, whereas the Valsalva ratio, CV and RMSSD during metronomic breathing were smaller in the subgroup treated with CBZ than in the subgroup without CBZ treatment (Table 3).

Discussion

Our study demonstrates for the first time a reduction in cardiac MIBG uptake in TLE patients. Since the MIBI

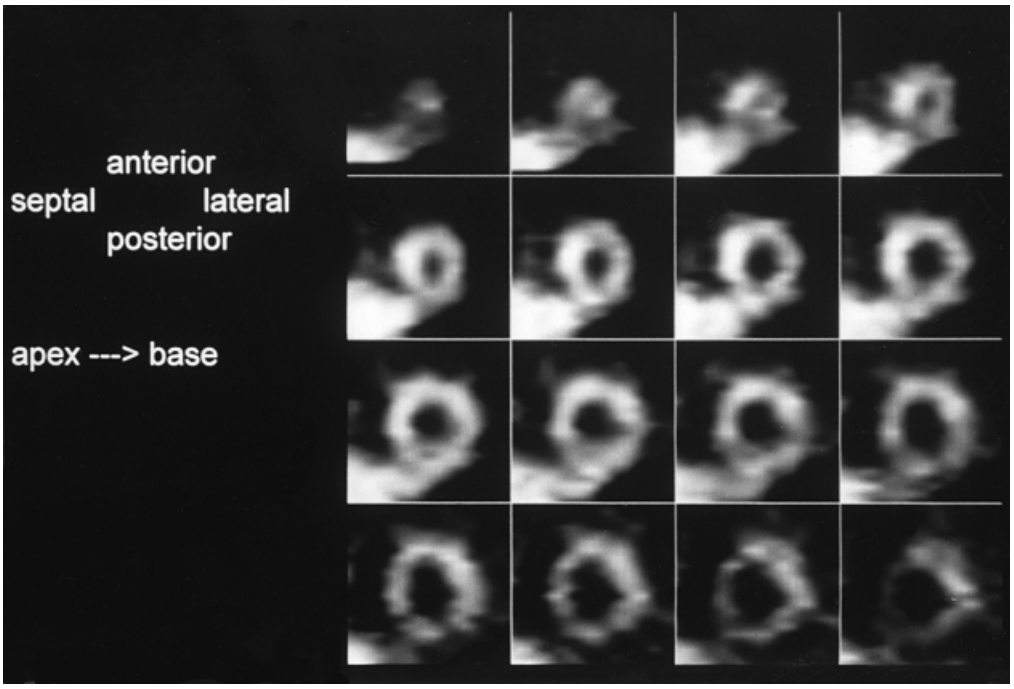

Fig. 2 MIBG-SPECT demonstrating non-homogeneous [^{123}I]MIBG accumulation in the heart in a 30-year-old man with a 29-year history of TLE.

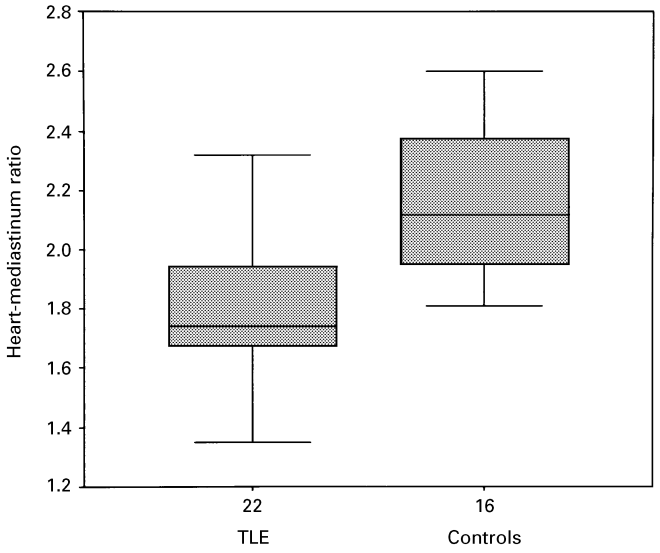

Fig. 3 Box plot of heart/mediastinum ratio in 22 TLE patients and 16 controls ($P = 0.001$).

scintigram showed normal myocardial perfusion in all patients, the reduced MIBG uptake might be ascribed to a reduction in post-ganglionic sympathetic innervation of the heart. It is unlikely that the lower H/M uptake ratio in the TLE patients resulted from relatively high MIBG uptake in mediastinal tissue due to increased sympathetic activity or from increased uptake in the lungs due to the higher respiratory drive of the patients. Previous studies (Dae *et al.*, 1989) demonstrated that there is rapid, non-neuronal MIBG uptake in the mediastinum, but also a swift washout within the first few hours after MIBG injection. The late-phase scintigram, taken 5 h after MIBG injection, is no longer biased by non-neuronal mediastinal or lung uptake. In contrast, the non-specific background activity of the mediastinum is considered to provide stable reference values for the comparison of cardiac uptake (Dae *et al.*, 1989). Increased MIGB uptake in the lungs due to respiratory differences, such as hyperventilation of the patients, also seems unlikely. The specific MIBG uptake and distribution into sympathetic vesicles occurs slowly, over several hours. Hyperventilation, even for up to 1 h, would have minimal influence on the process of neuronal MIBG uptake.

The findings of HRV with increased values for RMSSD, CV and Valsalva ratio suggest a functional predominance of parasympathetic modulation (Claus *et al.*, 1994; Mathias and Bannister, 1999). An autonomic imbalance towards increased parasympathetic activity might be explained by the deficient transmission of sympathetic activity due to morphological changes with a reduction of the post-ganglionic neurones.

As we found in our HRV study, Devinsky and colleagues found greater variation in blood pressure and HR during sympathetic challenge manoeuvres in their TLE patients than in controls (Devinsky *et al.*, 1994). According to these authors, this increased parasympathetic activity might have been due to several factors, such as anxiety, structural lesions and the chronic effects of epilepsy (Devinsky *et al.*, 1994).

Anxiety normally increases sympathetic output and is unlikely to account for a shift of autonomic modulation towards parasympathetic predominance (Friedman and

Table 2 *Autonomic cardiac investigations in TLE patients and in healthy subjects*

	TLE (n = 22)	Controls	P
Cardiac MIBG uptake (heart/mediastinum ratio)	1.75 (1.67, 1.95)	2.14 (1.94, 2.4)*	0.001
Age (years)	34.5 (29.7, 39.2)	30.0 (25, 44.5)* 52.5 (35.3, 59)†	0.46*, <0.005†
HR (b.p.m.)	78.8 (71.7, 86)	67.5 (60.3, 73)†	0.09‡
CV during metronomic respiration	8.2 (5.5, 11.7)	6.9 (5.6, 10.4)†	0.89‡
RMSSD during metronomic respiration	36.5 (17.2, 47)	25.6 (19.4, 36.6)†	0.01‡
LF (0.04–0.15 Hz) power (b.p.m.^{2})	1.3 (0.7, 3.2)	0.22 (0.07, 0.61)†	0.001‡
HF (0.15–0.5 Hz) power (b.p.m.^{2})	0.5 (0.3, 1.8)	0.23 (0.08, 0.65)†	0.50‡
LF/HF ratio	1.6 (1.3, 5,0)	1.3 (0.4, 4.2)†	0.13
Valsalva ratio	1.65 (1.3, 2.0)	1.3 (1.2, 1.6)†	0.02‡
30 : 15 ratio	1.3 (1.1, 1.5)	1.4 (1.2, 1.6)†	0.13‡
Systolic BP (mmHg) (supine position)	121 (113, 128)	119 (113, 128)†	0.66‡
Systolic BP (mmHg) (after standing up)	126 (116, 136)	120 (119, 138)†	0.62‡
Diastolic BP (mmHg) (supine position)	72 (68, 76)	73 (69, 79)†	0.94‡
Diastolic BP (mmHg) (after standing up)	83 (78, 91)	81 (78, 87)‡	0.86‡

Median values are given with upper and lower quartiles. BP = blood pressure; CV = coefficient of variation; HR = heart rate; HF = high frequency; LF = low frequency; TLE = temporal lobe epilepsy. *Controls, MIBG-SPECT (n = 16); †controls, HRV (n = 36). ‡Adjusted for age and carbamazepine treatment.

Table 3 *Autonomic cardiac investigations in TLE patients with and without carbamazepine*

	TLE with CBZ (n = 11)	TLE without CBZ (n = 11)	P
Cardiac MIBG uptake (heart/mediastinum ratio)	1.88 (1.7, 2.0)	1.75 (1.7, 1.8)	0.90‡
Age (years)	34 (26, 43)	35 (30, 39)	1.0‡
HR (b.p.m.)	85 (73, 89)	75 (66, 81)	0.09‡
CV during metronomic respiration	5.6 (4.8, 7.4)	9.9 (8.9, 12.3)	0.01‡
RMSSD during metronomic respiration	17.4 (15.7, 31)	44 (40, 54)	0.02‡
LF (0.04–0.15 Hz) power (b.p.m.^{2})	1.3 (0.6, 3.3)	1.1 (0.8, 1.8)	0.70‡
HF (0.15–0.5 Hz) power (b.p.m.^{2})	0.4 (0.2, 4.9)	0.7 (0.5, 1.6)	0.97‡
LF/HF ratio	1.0 (1, 3.1)	1.6 (1.3, 3.7)	0.34
Valsalva ratio	1.5 (1.3, 1.8)	1.8 (1.4, 2.2)	0.048‡
30 : 15 ratio	1.3 (1.1, 1.5)	1.3 (1.1, 1.4)	0.98‡
Systolic BP (mmHg) (supine position)	121 (114, 134)	120 (113, 125)	0.39‡
Systolic BP (mmHg) (after standing up)	126 (124, 138)	121 (110, 136)	0.53‡
Diastolic BP (mmHg) (supine position)	73 (68, 77)	75 (68, 76)	0.85‡
Diastolic BP (mmHg) (after standing up)	83 (77, 94)	83 (77, 89)	0.63‡

Median values are given with upper and lower quartiles. BP = blood pressure; CV = coefficient of variation; HR = heart rate; HF = high frequency; LF = low frequency; TLE = temporal lobe epilepsy; ‡adjusted for age.

Thayer, 1998). We assume that our MIBG finding of a reduction in post-ganglionic sympathetic neurones resulted from structural lesions caused by chronic epilepsy (Devinsky *et al.*, 1994; Ansakorpi *et al.*, 2000). Chronic TLE has been shown to induce structural lesions with neurone loss and sclerosis in brain areas involved in the central autonomic control and the modulation of the cardiovascular system, such as the amygdala and the hippocampus (Margerison and Corsellis, 1966; Babb *et al.*, 1984; Frysinger and Harper, 1990).

In TLE patients who underwent anterotemporal lobectomy, Frysinger and Harper found a loss of afferents to the amygdala ipsilateral to the seizure onset and loss of neurones in the amygdala (Frysinger and Harper, 1990). Similarly, Margerison and Corsellis observed nerve cell loss, gliosis and astrocytic proliferation in the amygdala of TLE patients (Margerison and Corsellis, 1966). Babb and colleagues described a reduction in anterior hippocampal neurones of 75% using volumetric measurements of cell density in the area of the epileptogenic focus (Babb *et al.*, 1984).

Hippocampal structures, in particular the amygdala, are among the centres at the highest level of cardiovascular autonomic control (Frysinger and Harper, 1990). Amygdalofugal fibres project to the hypothalamic area, medial parabrachial nuclei, locus coeruleus, the A5 region in the ventrolateral pons, and the raphe nuclei (Hopkins and Holstege, 1978; Kretteck and Price, 1978) as well as to the nucleus of the solitary tract and to the dorsal motor nucleus

of the vagus nerve (Hopkins and Holstege, 1978), and are therefore involved directly in the autonomic modulation of HR (Mathias and Bannister, 1999).

The amygdala and hippocampus regions are frequently involved in the ictal and interictal hyperexcitability of TLE patients. The activation of these cerebral structures contributes to cardiovascular dysregulation with arrhythmia and blood pressure changes and to respiratory and gastrointestinal irregularities (Wannamaker, 1985).

HF discharges of central neurones might be directly transferred onto cardiac autonomic nerve fibres (Lathers *et al*., 1987). Lathers and colleagues demonstrated that there is a synchronized, so-called lockstep transmission of cerebral, epileptogenic discharge frequencies onto cardiac sympathetic and vagal neurones (Lathers *et al*., 1987). Furthermore, Birks and colleagues showed that the preganglionic discharge frequency directly influences the discharge pattern of post-ganglionic sympathetic fibres (Birks *et al.*, 1981).

In pentylenetetrazol-treated cats, Lathers and Schraeder showed an imbalance of cardiac autonomic modulation related to epileptogenic and interictally increased cerebral discharge rates (Lathers and Schraeder, 1982). On the basis of these physiological and pathophysiological findings, we speculate that the long-lasting effects of increased interictal and excessive ictal neuronal discharge rates might first increase the activity of sympathetic cardiac fibres and finally contribute to transsynaptic degeneration of post-ganglionic neurones, which could explain the reduction in MIBG uptake. We also speculate that the long-term effects of chronic cerebral hyperexcitability with consecutive neurone loss and gliosis in regions such as the amygdala and hippocampus might induce such a transsynaptic degeneration. Similar mechanisms have been postulated for peripheral nerve degeneration in stroke patients (Caccia *et al.*, 1976; Pollock *et al.*, 1984).

Pollock and colleagues reported a significant reduction in myelin thickness and nerve fibre diameter in the sural nerves of post-stroke patients (Pollock *et al.*, 1984). Caccia and colleagues attributed changes in nerve conduction in patients after acute vascular brain lesions to the mechanisms of transsynaptic degeneration (Caccia *et al.*, 1976). The authors explained a decrease in maximum propagation velocity, an increase in the dispersion of velocity and increased distal motor latencies as the effects of transsynaptic degeneration (Caccia *et al.*, 1976). In patients with multiple system atrophy (MSA), transsynaptic degeneration of autonomic nervous system fibres has been identified as a factor contributing to orthostatic hypotension and impaired bladder, rectal and sexual function (Mathias and Bannister, 1999). Our previous study of cardiac MIBG uptake in MSA patients showed a reduction similar to that seen in our TLE patients (Druschky *et al*., 2000). In the MSA patients, there is a primarily central and preganglionic lesion of the structures mediating sympathetic outflow. As with TLE patients, the impairment of cardiac MIBG uptake seems to be due to trans-synaptic degeneration of cardiac sympathetic nerve fibres (Druschky *et al*., 2000). In patients with primary degeneration of peripheral sympathetic fibres, such as diabetics, the decrease in cardiac MIBG uptake is far more pronounced than in TLE and MSA patients (Claus *et al*., 1994). Because of the dying-back pathology of diabetic autonomic neuropathy (Dyck and Thomas, 1999), the sympathetic dysfunction is most pronounced in post-ganglionic fibres and results in more severe cardiac sympathetic denervation than in MSA and TLE patients.

Although we have no definite explanation for the structural impairment of sympathetic cardiac innervation, the cardiac MIBG findings suggest that there may be sympathetic post-ganglionic denervation and probably secondary β-adrenoreceptor hypersensitivity, which would contribute to an increased risk of arrhythmias and probably even sudden unexplained death in epilepsy patients. In ventricular tachycardia patients, Gill and colleagues showed reduced MIBG uptake and assumed that the increased tendency towards cardiac arrhythmias was due to denervation hypersensitivity of cardiac β-adrenoreceptors (Gill *et al.*, 1993).

Although several studies suggest that myocardial ischaemia may be a cause of cardiac arrhythmias and probably sudden death in epilepsy patients (Natelson *et al.*, 1998), our MIBI scintigram findings of regular myocardial perfusion support the conclusion that arrhythmias are more likely to be caused by an imbalance of sympathetic and parasympathetic cardiac modulation.

We cannot rule out the possibility that the abnormal cardiac MIBG uptake is related to long-term effects of anticonvulsive medication. Our patients had been on various anticonvulsive regimes. Among the substances used at the time of the study and during previous years were CBZ, valproate, lamotrigine, tiagabine and clobazam. Apart from CBZ, the anticonvulsive drugs used by our patients are, however, not known to have any side-effects on the autonomic cardiac innervation. Phenytoin is an antiarrhythmic drug that is thought to have protective, but not harmful, effects on cardiovascular function, although there is some risk of bradyarrhythmias when it is given intravenously (Ansakorpi *et al*., 2000). Isojärvi and colleagues did not see any influences of phenytoin and valproate on the modulation of HR (Isojärvi *et al.*, 1998). Similarly, phenobarbital does not seem to have negative effects on cardiac function and impulse conduction (Massetani *et al*., 1997). Vigabatrin also has no major effects on the autonomic control of the heart (Massetani *et al*., 1997). CBZ was the most common anticonvulsive medication in our patient group. However, the comparison of cardiac MIBG uptake between patients treated and not treated with CBZ indicated no significant difference in cardiac sympathetic innervation. Although this result does not exclude long-term effects of the convulsive medication on post-ganglionic sympathetic fibre function, our findings did not demonstrate a short-term influence of CBZ on MIBG uptake and post-ganglionic innervation. Otherwise there would have been a different uptake pattern in patients treated and those not

treated with CBZ during the 12 months preceding study. Although CBZ has no obvious effects on post-ganglionic sympathetic cardiac innervation, the drug might alter the functional modulation of HRV and might reduce the vagal influence on HR, as suggested by the reduction in the time domain parameters of HRV, RMSSD, CV and the Valsalva ratio in the patients receiving CBZ. CBZ is known to reduce HR and it decreases parasympathetic cardiac modulation (Isojärvi *et al.*, 1998; Tomson *et al.*, 1998; Ansakorpi *et al.*, 2000). In conformity with our findings, Isojärvi and colleagues demonstrated decreased HR responses to metronomic breathing in patients receiving CBZ (Isojärvi *et al.*, 1998). Tomson and colleagues reported a reduction in the standard deviation of the R–R interval, a parameter that primarily reflects parasympathetic cardiac modulation (Tomson *et al.*, 1998).

Our results show a discrepancy between the time domain values of RMSSD, CV and the Valsalva ratio and the LF/HF ratios derived from the frequency domain powers of sympathetically and parasympathetically mediated HR modulation. Perhaps this discrepancy results from the method and sensitivity of the algorithm used for the analysis of HRV. The HRV parameters of the controls were derived from a group that was older than the group of TLE patients. Although we considered age as a variable in the comparison of patient and control data, we cannot rule out the possibility that sympathetic activity was more pronounced in the controls because of their greater age (Ziegler *et al*., 1992). The LF/HF ratio can be used as a parameter of sympathovagal balance that is less biased by the effects of age. This ratio showed no significant difference between the groups but suggested similar sympathetic and parasympathetic modulation of HRV in the three groups, or slightly more pronounced sympathetic activity in the TLE patients and in the subgroup without CBZ.

This finding supports an alternative explanation of the difference between cardiac MIBG uptake in the TLE patients and the controls. Perhaps the reduced cardiac MIBG uptake did not arise from post-ganglionic sympathetic neurone degeneration but was caused by a continuous slight augmentation of sympathetic activity in the TLE patients. A subtle increase in sympathetic outflow might occur as a consequence of the above-mentioned increase in cerebral discharge rate and the lockstep phenomenon described by Lathers and colleagues (Lathers *et al*., 1987) and could impede cardiac MIBG uptake (Kuwahara *et al*., 1998; Ohya *et al*., 2001). In patients with chronic essential hypertension, there is abundant evidence of reduced cardiac MIBG uptake (Kuwahara *et al*., 1998; Ohya *et al*., 2001), although spectral analysis of HRV and microneurographic recordings and plasma catecholamine levels demonstrate increased sympathetic outflow (Jennings, 1998). In these patients, the discrepancy between the reduced cardiac MIBG uptake and a simultaneous increase in sympathetic cardiac modulation is attributed to competitive mechanisms of norepinephrine and MIBG uptake into the presynaptic vesicles (Merlet, 1995). In heart failure patients with increased sympathetic activity, Merlet and colleagues discuss similar competitive inhibition of cardiac MIBG uptake due to an elevated norepinephrine concentration in the synaptic cleft of post-ganglionic cardiac sympathetic fibres (Merlet, 1995). In hypertensive patients with cardiac hypertrophy, Kelm and colleagues found increased cardiac norepinephrine release and reduced MIBG uptake (Kelm *et al*., 1996). The authors assumed that hyperstimulation of the cardiac sympathetic nerves might induce increased MIBG release from the heart with decreased cardiac MIBG accumulation. Moreover, there might be competitive impairment of MIBG uptake due to the elevated norepinephrine levels (Nakajo *et al*., 1983; Merlet, 1995).

To summarize, our MIBG findings in chronic TLE patients suggest dysfunction of post-ganglionic cardiac sympathetic fibres with reduced MIBG uptake. This reduction may either reflect post-ganglionic trans-synaptic degeneration resulting from a prolonged increase in central sympathetic discharges or arise from competitive inhibition of MIBG uptake due to continuously enhanced sympathetic activity with increased synaptic norepinephrine levels. The MIBG results do not indicate short-term effects of CBZ on post-ganglionic sympathetic cardiac innervation. Analysis of HRV shows inconsistent findings for the parasympathetic time domain and the sympathetic frequency domain indices. There may be slightly less parasympathetic cardiac modulation in patients treated with CBZ than in patients not treated with CBZ. Therefore, CBZ may be particularly suited for the treatment of chronic TLE patients as it may counter-regulate sympathetic cardiac dysfunction.

The alteration of MIBG uptake in the TLE patients suggests sympathetic cardiac dysfunction in TLE patients and implies an increased risk of cardiac instability and arrhythmias. The MIBG findings, therefore, encourage consecutive monitoring of cardiac function and HRV in TLE patients.

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