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ARTICLE

Impaired short-term blood pressure regulation and autonomic dysbalance in children with type 1 diabetes mellitus

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Abstract
Aims Because reduction in baroreceptor sensitivity (BRS) has been associated with hypertension in the normal population and with increased cardiovascular morbidity and mortality in patients with diabetes mellitus, we measured BRS in a patient cohort of children with type 1 diabetes mellitus.
Methods Two hundred and eight children (150 patients with type 1 diabetes mellitus, mean age 13.9±2.8 years, 70 boys, mean HbA_{1c} 7.8±1.4%; and 58 healthy controls, mean age 14.1±3.1 years, 32 boys) were studied. BRS and heart rate variability (HRV) were analysed from a short-time ECG and BP recording using the sequence method (BRS) and the frequency domain method (HRV).
Results There were 111 of 150 patients (74%) and 5 of 58 controls (8.6%) that showed impaired BRS. Mean BRS differed significantly between patients and controls (18.4±7.2 vs 25.8±8.2 ms/mm, $p<0.001$). BRS correlated inversely with systolic BP ($r=-0.23$, $p=0.009$) and was related to diabetes duration ($r=-0.194$, $p=0.027$). Analysis of HRV showed greater sympathetic and less parasympathetic influence in patients than in controls (low frequency/high frequency ratio 1.3±0.8 vs 0.9±0.6, $p<0.05$); the low frequency/high frequency ratio was inversely correlated with BRS ($r=-0.28$, $p=0.001$).
Conclusions/interpretation Diabetic children show reduced BRS. In our patient group, the single risk factor for this finding was found to be the disease duration. The degree of BRS impairment was related to the degree of autonomic dysbalance.

Keywords Autonomic neuropathy · Baroreceptor sensitivity · Blood pressure · Heart rate variability

Abbreviations

BRS	baroreceptor sensitivity
HF	high frequency
HFnu%	high-frequency normalised unit
HRV	heart rate variability
LF	low frequency
LFnu%	low-frequency normalised unit
SDS	standard deviation score
VLF	very low frequency

Introduction

Type 1 diabetes mellitus is an important risk factor for the development of cardiovascular disease [1]: adult patients with diabetes show a two- to tenfold risk of developing atherosclerotic lesions compared with the normal population [2, 3]. In this patient group increased morbidity and mortality due to coronary, cerebrovascular and peripheral arterial disease has been observed [4].

Systemic hypertension is seen as a major cofactor for cardiovascular disease in diabetic patients [3]. Data from adult diabetic patients indicate that an impairment in baroreceptor sensitivity (BRS) may be involved in the

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development of systemic hypertension in diabetes [5–7]. The baroreflex itself describes a complex regulatory circuit that consists of afferent receptors located in the aorta and carotid arteries (high-pressure baroreceptors) and in the right atrium and pulmonary artery (low-pressure baroreceptors) signalling through non-myelinated nerve fibres to the circulatory centres in the medulla oblongata. Here, a complex interaction of excitatory and inhibitory neurons together with local mediators process the afferent stimuli and modulates vagal and sympathetic efferent impulses. Thus, a short-term change in BP in the high- and low-pressure systems can be responded to within seconds with arteriolar dilatation or vasoconstriction, as well as an increase or decrease in heart rate. The efficacy of this circuit can be calculated as the regression line of changes in BP against heart rate and is given as BRS. Impairment of BRS has been shown to be a valuable predictor of future cardiovascular morbidity and mortality in a variety of diseases that are associated with disturbed autonomic function, such as myocardial infarction and diabetes mellitus [8, 9]. Impaired BRS has also been shown to be a precursor of hypertension in the general population [10]; in diabetic adults a reduced BRS has been observed preceding peripheral neuropathy [11–13]. The longitudinal assessment of BRS from beat-to-beat BP regulation and beat-to-beat heart rate fluctuations may therefore allow individual paediatric patients to be stratified with regard to risk.

Power spectral analysis of heart rate variability (HRV) with regard to sympathetic and parasympathetic influences is considered a valuable method for the assessment of sympathovagal balance [14]. When a power spectral analysis is performed, peaks in the low-frequency (LF) band (0.04–0.15 Hz) are considered to reflect predominantly sympathetic function with a contribution from the parasympathetic system, while the high-frequency (HF) band (0.15–0.4 Hz) is said to reflect mainly vagal or parasympathetic activity. The LF/HF ratio is indicative of sympathovagal balance. Autonomic dysbalance has been shown to precede autonomic neuropathy in adult diabetic patients [5] and has been attributed to abnormality of parasympathetic function.

The purpose of the present cross-sectional study was to assess the autonomic nervous system by testing both BRS and HRV in a paediatric patient group.

Methods

Patients The study was conducted in 208 children and adolescents: 150 patients with type 1 diabetes mellitus and 58 healthy children. From 166 eligible patients with type 1 diabetes mellitus and age >8 years, 150 children and adolescents were enrolled. All patients were recruited consecutively during their regular three-monthly visits as outpatients at a tertiary healthcare centre (Division of Endocrinology and Diabetology, University Children's Hospital, Munich, Germany). Patients were excluded if they had evidence of or a history of clinically relevant systemic disease (untreated hypothyroidism, untreated coeliac disease). Medical records were available for all patients (data on HbA_{1c} and insulin dosage as well as on diabetic complications) for the entire period between the diagnosis of diabetes and the time when BRS and autonomic balance measurements were made. The mean HbA_{1c} was calculated as the arithmetic mean value of all HbA_{1c} levels measured—excluding those immediately after the appearance of the disease—during the regular follow-up visits at the outpatient department, in most patients starting after the clinical manifestation of the disease. Twenty-five patients were hypertensive (standard deviation score [SDS] for systolic BP >2 [15]); this group was analysed separately and compared with the normotensive study participants. Five patients were receiving medication with ACE inhibitors (one for hypertension and four for microalbuminuria); this subgroup also underwent a detailed analysis. Participants did not differ in any clinical characteristics from the entire eligible diabetic clinic population of the same age.

The control group consisted of 58 children, some of whom were siblings of the diabetic patients and some presenting for cardiac evaluation for heart murmur at our institution. Measurements were performed after exclusion of an underlying chronic or cardiovascular disease by medical history, clinical assessment, electrocardiography and echocardiography.

The family history of coronary artery disease and stroke was determined by questionnaire. Written informed consent was obtained from all participants and from their legal guardians. The study was performed according to the Declaration of Helsinki; the study protocol was approved by the local ethics committee.

BP measurements BP measurement during the regular three-monthly follow-up visits was performed in a quiet room with the patient supine. BP was obtained using a conventional oscillatory measurement system positioned on the right upper arm (Dinamap; GE Systems, Freiburg, Germany). Standard deviation scores were calculated by adopting normative values from the literature [15].

Baroreflex sensitivity Beat-to-beat BP was measured with the patient supine for at least 10 min in a quiet room. A finger cuff measured online beat-to-beat BP on the second and third fingers of the right hand, using the vascular unloading technique (Task Force Monitor; CNS Systems, Graz, Austria). This technique has been validated by

Tanaka et al. [16]. The quality of the pulse signal obtained was controlled visually by one experienced reader. The system was calibrated with a conventional non-invasive BP cuff (Dinamap; GE Systems) positioned on the left upper arm; this was performed automatically every 2 min. A standard three-lead ECG was used to record heart rate. Visual control of ECG quality was performed as described above for the pulse waveform. The entire measurement was conducted over a time interval of 10 min. When premature beats were noted, the test was stopped and started again. For the calculation of BRS, the relative changes in BP (expressed in mmHg) and heart rate (expressed as the distance between the corresponding QRS complexes [RR interval] in ms) were considered according to the sequence method with a cut-off point of 1 mmHg and 3 ms respectively [17–19].

HRV During a short-term test, a six-lead ECG with a sampling frequency of 1000 Hz was recorded for 15 min, starting when the patient felt relaxed after a minimum of 15 min in a supine position. Calculation of HRV (see below for methods) was performed during the test and involved all RR intervals recorded. When the ECG recording was disturbed by artefacts or premature beats, the tracings recorded until that point were deleted and the test was started again. Repeated premature beats during recording led to exclusion from the study. As respiration may have a great influence on HRV, respiratory frequency was monitored visually during the test and data were not considered when the frequency fell below 15 breaths per min. HRV was calculated by the frequency domain method with a power spectral analysis of rhythmic oscillations of the RR interval. The relative contributions of the LF power (0.04–0.15 Hz; predominantly sympathetic influences on heart rate), HF power (0.15–0.4 Hz; vagal modulation of heart rate) and very-low-frequency (VLF) power (0–0.04 Hz) to total power were calculated as follows: $LF\ normalised\ units\ (LFnu\%) = LF\ absolute\ power\ (ms^2) / total\ power\ (ms^2) - VLF\ power\ (ms^2) \times 100$ *and* $HFnu\% = HF\ absolute\ power\ (ms^2) / total\ power\ (ms^2) - VLF(ms^2) \times 100$. The LFnu%/HFnu% ratio was considered to indicate sympathetic/vagal tone. All calculations and recordings were performed using a central computer device (Task Force Monitor; CNS Systems).

Laboratory methods Blood samples were taken during the patient's follow-up visit at the time when BRS/autonomic balance measurements were made. HbA_{1c}, triacylglycerol, total cholesterol, HDL-cholesterol and LDL-cholesterol were measured by standard laboratory methods.

Statistics Calculations were performed using the statistical package SPSS for Windows (version 14.0; SPSS, Chicago, IL, USA). Differences within the patient group and between the patient and control groups were tested using the independent samples *t* test and the non-parametric Mann–Whitney test. Correlations were analysed using Pearson's correlation coefficient. All significance testing was fixed at $p<0.05$ (two-sided). We used general univariate linear regression analysis (ANOVA) to evaluate the covariant effects. Values are given as mean±SD.

Results

The anthropometric characteristics of the groups are reported in Table 1. Though the diabetic patients had a slightly higher weight and BMI standard deviation score (SDS) than the healthy children, the differences were not statistically significant. Patients and controls did not differ significantly in their clinical details. BRS was significantly impaired in diabetic patients compared with healthy controls. The LF/HF ratio was significantly higher in the diabetic patients, indicating a prominent sympathetic and reduced vagal influence on the heart rate in diabetic patients: LFnu% was higher and HFnu% was lower in diabetic patients. LF/HF ratio and BRS were found to be negatively correlated ($r=-0.28$, $p=0.001$) in the entire patient group as well as in the normotensive ($r=-0.282$, $p=0.02$) and hypertensive ($r=-0.31$, $p=0.01$) patient subgroups. A negative correlation of BRS with systolic BP was also found ($r=-0.23$, $p=0.009$ in the entire patient group; $r=-0.25$, $p=0.02$ in the normotensive subgroup; $r=-0.35$, $p=0.005$ in the hypertensive subgroup). Comparing the BRS of our study population with normative data, 111 patients (74%) and five control patients (8.6%) showed a BRS SDS of <2 [20]. We explored the effects of disease-related factors, such as age at onset, height and weight, disease duration, daily insulin dose, HbA_{1c} concentration and total and LDL-cholesterol concentrations, by carrying out a multiple regression analysis. The model was adjusted for age and sex. A significant negative correlation of BRS with the duration of disease was found ($r=-0.194$, $p=0.027$). However, BRS was not significantly related to the mean HbA_{1c} as a single factor. Including the mean HbA_{1c} (which correlated significantly with the actual HbA_{1c} concentration in our patients; $r=0.856$, $p<0.001$) as well as the duration of disease as a covariate in a multilinear regression model, a significant influence of these two factors on the BRS emerged (β coefficient −0.361, $p=0.029$, 95% CI −0.685 to −0.038).

The LF/HF ratio was directly correlated with the duration of the disease (β coefficient 0.17, $p=0.017$, 95% CI 0.41–0.31). A combination of the factors of disease duration and mean HbA_{1c} (explored again by multilinear

Table 1 Characteristics of patients and controls

	Patient group (n=150)	Control group (n=58)
Sex	70 male, 80 female	32 male, 26 female
Age (years)	13.9±2.8 (8 to 19.5)	14.1±3.1 (8.5 to 22.4)
Weight (kg)	55.6±16.6 (22 to 96)	52.0±14.7 (29.8 to 83)
Height (cm)	160.5±15.8 (126 to 191)	159.9±14.7 (125 to 185)
BMI (kg/m^2)	21.0±3.6 (13.2 to 32.0)	20.0±3.5 (14.5 to 30.0)
BMI SDS	0.4±0.9 (−2.3 to 2.6)	0.1±1.1 (−2.7 to 2.3)
HbA_{1c} (%)	7.5±0.9 (5.3 to 11.2)	–
Heart rate at rest (beats per min)	79.4±10.5 (55.1 to 107.4)	75.4±12.0 (55.0 to 101.6)
Systolic BP (mmHg)	111.3±11.2 (89.8 to 146.3)	104.3±5.2 (94.4 to 119.1)
Diastolic BP (mmHg)	67.4±8.1 (52.1 to 97.2)	65.8±7.7 (54.0 to 82.0)
LFnu%	65.4±8.5 (49.3 to 82.1)	48.4±8.4 (35.2 to 53.4)[a]
HFnu%	33.6±10.3 (28.5 to 42.2)	52.3±6.4 (47.4 to 55.4)[a]
LF/HF	1.3±0.79 (0.2 to 6.0)	0.93±0.6 (0.33 to 2.5)[a]
BRS (ms/mmHg)	18.4±7.2 (4.9 to 42.7)	25.8±8.2 (6.0 to 44.3)[b]

Data are mean±SD (range)
[a] $p<0.05$; [b] $p<0.001$

regression analysis that included both factors as covariates) was again significantly related to the LF/HF ratio (β coefficient 0.001, p=0.02, 95% CI 0–0.002).

Twenty-five diabetic patients were found to have had a systolic BP SDS of >2 during their last three regular three-monthly follow-up visits (Tables 2 and 3). A comparison of these children with the rest of the diabetic group revealed a higher BMI SDS, a longer duration of disease, a higher daily insulin dose and a higher HbA_{1c} concentration. A significantly reduced BRS, a higher LFnu% and lower HFnu% and an increased LF/HF ratio was found in these patients even after correction for BMI SDS, duration of disease and mean HbA_{1c} concentration.

Eleven patients showed microalbuminuria, but a subgroup analysis failed to find any significant differences among these and the remaining patients. Five patients were on ACE inhibitors: four of them for microalbuminuria and one for hypertension. The number of patients in this subgroup was probably too small to detect any significant differences.

Discussion

The present study revealed signs of impaired BRS in a group of children and adolescents with type 1 diabetes mellitus. Moreover, evidence for disturbed autonomic function emerged.

The baroreceptor reflex describes the mechanism of interaction between BP receptors and the autonomic nervous system [21]. Normally, changes in BP cause activation of baroreceptors at various sites of the high and low BP systems. Afferent stimuli are transmitted via non-myelinated nerve fibres to the brainstem. These excitatory signals are processed in the nucleus tractus solitarii, in the caudal and rostral ventrolateral medulla oblongata. In a complicated

Table 2 Characteristics of patients (subgroup 1 including hypertensive patients and subgroup 2 including normotensive patients) and controls

	Patient group 1 (systolic BP SDS >2) (n=25)	Patient group 2 (systolic BP SDS ≤2) (n=125)	Control group (n=58)
Sex	16 male, nine female	54 male, 71 female	32 male, 26 female
Age (years)	15.1±2.8	13.5±2.7[a]	14.1±3.1[e]
Weight (kg)	64.1±15.9	53.1±15.9[a]	52.0±14.7[c,e]
Height (cm)	165.6±12.4	159.2±16.4[a]	159.9±14.7
BMI (kg/m^2)	23.2±4	20.5±3.3[a]	20.0±3.5[e]
BMI SDS	0.9±0.8	0.3±0.9[a]	0.1±1.1[e]
Heart rate at rest (beats per min)	85.7±11.1	77.6±9.7	75.4±12.0[e]
Systolic BP (mmHg)	122.2±12	108.2±8.7	104.3±5.2[e]
Diastolic BP (mmHg)	75.2±9	65.2±6.3	65.8±7.7[e]
LFnu%	56±12.4	48.7±16.2	48.4±8.4[e]
HFnu%	43.9±12.4	51.2±16.2	52.3±6.4[e]
LF/HF	1.44±0.61	1.14±0.81[a]	0.93±0.6[d,f]
BRS (ms/mmHg)	14.37±5.6	19.48±7.3[b]	25.8±8.2[e,f]

Data are mean±SD
[a] $p<0.05$, [b] $p<0.001$ between groups 1 and 2; [c] $p<0.05$, [d] $p<0.001$ between group 2 and controls; [e] $p<0.05$, [f] $p<0.001$ between group 1 and controls

Table 3 Clinical characteristics of hypertensive and normotensive patients

	Systolic BP SDS >2 (n=25)	Systolic BP SDS ≤2 (n=125)
BMI (kg/m^2)	23.1±4.2	20.5±3.3[a]
BMI SDS	0.96±0.8	0.37±0.95[a]
Duration of disease (years)	8.3±3.0	5.8±4.1[a]
Insulin dosage (IU kg^{-1} day^{-1})	0.96±0.25	0.8±0.31[a]
BRS (ms/mmHg)	14.37±5.6	19.48±7.3[b]
LFnu%	56±12.4	48.7±16.2[a]
HFnu%	43.9±12.4	51.2±16.2[a]
LF/HF ratio	1.44±0.61	1.14±0.81[a]
HbA_{1c} (%)	8.4±1.8	7.7±1.3[a]

Data are mean±SD
[a] $p<0.05$, [b] $p<0.001$

regulatory circuit involving also local neurotransmitters, finally efferent stimuli are activated and this results in acceleration or deceleration of the heart rate along with venous and arteriolar vasoconstriction or dilatation. By these means, short-term variations in systolic BP can be responded to immediately in order to keep systemic BP within physiological limits [17, 22, 23].

An impairment of this regulatory circuit has been found to precede the development of systemic hypertension in the general population [10]. A possible contribution of the impairment of the BRS to systemic hypertension has been hypothesised in children and adolescents after heart and heart–lung transplantation and in young adults born small-for-gestational-age [24, 25]. In people with disturbed autonomic function, such as after myocardial infarction and in diabetes mellitus, a reduced BRS is considered a precursor of morbidity and mortality [8, 9]. In type 2 diabetic patients, impaired BRS precedes the development of peripheral autonomic neuropathy [11–13].

In the entire patient group, a reduction of the BRS was found compared with healthy controls and normative data. A high percentage of diabetic patients showed impaired baroreflex function. Thus, the evidence from studies in adult patients may be comparable with that in paediatric patients with type 1 diabetes mellitus. An inverse correlation of BRS with systolic BP reflects the known correlation between hypertension and BRS. In essential hypertension, the reduced baroreflex activity was held to be the consequence of high systolic BP [26]. More recent studies indicate, however, that the reduction in BRS may precede the development of hypertension [5–7]. Thus, diabetic children with a reduced BRS may be at special risk of the development of hypertension. We consider that our hypothesis is confirmed by our subgroup analysis of the diabetic children with hypertension. Compared with normotensive patients, BRS was further reduced.

When considering the autonomic nervous system, we found a significantly elevated LF/HF ratio in diabetic patients. This is seen by some to be a marker of sympathetic function [27], while others consider it to include both sympathetic and parasympathetic influences [28]. Calculating the relative contributions of spectral power at the LF and HF peaks minimises the effects of total power and of the VLF component on the values of LF and HF power. We therefore consider that it would be useful to study the balance of sympathetic and parasympathetic influences.

Together with the slightly increased heart rate in our patient group, the elevation of the LF/HF ratio may represent a reduction in parasympathetic activity and a relative sympathetic predominance. We hypothesise that the elevation of the LF/HF ratio in our diabetic patients represents the first, discrete damage to the parasympathetic limb of the autonomic nervous system. Compared with data from adults [5], our patients showed a less severe LF/HF elevation. The explanation of this finding may be that, in our patient group, the degree of LF/HF elevation is directly related to the combination of diabetes duration and HbA_{1c} concentration. Thus, our findings may be indicative of the onset of damage to the autonomic nervous system at an early stage of the disease, tracking subsequently into adulthood. It is worth noting that none of our patients had clinical evidence of autonomic neuropathy.

As the parasympathetic autonomic nervous system forms part of the baroreflex circuit, we investigated a possible correlation between BRS and the autonomic dysbalance. In the entire patient group, we found a negative correlation between the two parameters. This may be indicative of the site of impairment of BRS: patients with decreased parasympathetic function (and increased LF/HF ratio) also showed decreased BRS. Thus, the damage in the vagal part of the autonomic nervous system may be responsible for the reduced efficacy of short-term BP regulation in diabetic children. Both parameters showed a significant relation to the combination of the time course of diabetes and the mean HbA_{1c} concentration. This suggests the hypothesis that a combination of a longer time course of diabetes mellitus with poor metabolic control results in impairment of the vagal limb of the baroreflex-mediated regulation of BP.

Abnormalities of BRS may in part explain the increased incidence of sudden death among adult diabetic patients with autonomic neuropathy [29, 30]. A reduced BRS has been associated with life-threatening ventricular arrhythmias following myocardial infarction [31]. Thus, impaired BRS may identify an at-risk group of diabetic children and adolescents at an early stage. During childhood, consecutive maturation of the autonomic nervous system has been

shown [20]. The baroreflex function improves gradually until the age of 16 years in healthy adolescents. In young adults a decline in BRS has been observed, and there is a continuous reduction throughout life. In our patient group, the reduction in BRS at a young age may represent a burden which may result in severe BP dysregulation and autonomic dysfunction later during the disease course.

Thus, in a patient group of children and adolescents with type 1 diabetes mellitus we were able to detect an impairment of the beat-to-beat BP control. BRS was significantly reduced compared with healthy controls. The function of the baroreflex circuit was inversely related to systolic BP in our patients, indicating a possible role of altered short-term BP control in the development of hypertension. The assessment of autonomic function by HRV analysis revealed a dysbalance in our patients, in whom we found increased sympathetic and decreased vagal activity. As there was an inverse relationship between BRS and autonomic dysfunction, we hypothesise that vagal impairment may be responsible for the reduced baroreflex function. The baroreceptor function and the sympathovagal balance were significantly influenced by the combination of diabetes duration and mean HbA_{1c} concentration. A reduced BRS and autonomic dysfunction have been linked with increased morbidity and mortality in adult diabetic patients. However, because a precise prediction of the development of hypertension in children with type 1 diabetes mellitus cannot be deduced at present from impaired BRS and autonomic function, longitudinal assessments are warranted to establish these parameters for the stratification of the risk of cardiovascular disease.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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