Baroreflex Sensitivity and Its Response to Deep Breathing Predict Increase in Blood Pressure in Type 1 Diabetes in a 5-Year Follow-Up

Milla Rosengård-Bärlund, md[1,2]
Luciano Bernardi, md, dmsc[2,3]
Anna Sandelin, rn[1,2]
Carol Forsblom, dmsc[1,2]

Per-Henrik Groop, md, dmsc[1,2,4]
on behalf of the FinnDiane Study Group

OBJECTIVE—We have recently demonstrated that early autonomic dysfunction, defined as low baroreflex sensitivity (BRS), could be functional and reversible. However, potential temporal changes in BRS have not yet been addressed by longitudinal studies in type 1 diabetes. Moreover, it is not known whether low BRS predisposes to hypertension or other nonfatal diabetes complications.

RESEARCH DESIGN AND METHODS—We conducted a 5-year prospective study including 80 patients with type 1 diabetes. We measured ambulatory blood pressure and autonomic function tests. BRS was assessed by six different methods during spontaneous, controlled, and slow deep breathing at baseline and follow-up.

RESULTS—Spontaneous BRS declined over time ($BRS_{average}$ 16.2 ± 0.8 vs. 13.2 ± 0.8 ms/mmHg; $P < 0.01$), but the change was not significant when adjusted for time of follow-up. Low BRS at baseline did not progress to cardiac autonomic neuropathy but predicted an increase in the nighttime systolic blood pressure ($BRS_{average}$ $r = -0.37$; $P < 0.05$). Additionally, BRS response to deep breathing at baseline predicted an increase in 24-h ambulatory blood pressure (BRS-αLF $r = 0.323–0.346$; $P < 0.05$).

CONCLUSIONS—The decline in spontaneous BRS over time in patients with type 1 diabetes seems to be due to normal aging, which supports a functional etiology behind early autonomic derangements. Decreased resting BRS and the magnitude of improvement by deep breathing may be due to sympathovagal imbalance, a well-known mechanism in the development of hypertension. Early interventions aiming to reduce sympathetic overactivity in patients with low BRS might delay the development of hypertension.

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Cardiovascular autonomic neuropathy (CAN) has for a long time been a challenge for diabetologists because of the lack of easily available diagnostic methods and, thus, the difficulty in starting interventions at a stage when the disorder is still reversible. The importance of early diagnosis lies in the fact that established CAN is associated with increased risk of diabetes complications (1) and mortality (2). However, in our recent studies in patients with type 1 diabetes with short (3) or long (4) duration, we demonstrated that reduced baroreflex sensitivity (BRS), an early marker of autonomic impairment, was markedly improved by slow, deep breathing. Notably, the patients had, regardless of duration of diabetes, blunted BRS that could be restored by deep breathing, except in those with definite CAN.

The potential reversibility of BRS and low prevalence of definite CAN in our patients (3,4) is in line with observations that the prevalence of diabetes complications seems to decrease (5,6). The concept of functional autonomic dysfunction does not diminish the importance of an early diagnosis given that the prognostic value of reduced BRS has undoubtedly been proven in hypertension, renal failure, postmyocardial infarction, heart failure, and cerebral stroke (7–9)—conditions associated with functional alterations in the autonomic nervous system.

Autonomic imbalance plays a major role in the etiology of hypertension. Accordingly, the close relationship between reduced BRS and high blood pressure was already established decades ago (10), but whether low BRS is the cause or the consequence of elevated blood pressure is still not evident. While 24-h ambulatory blood pressure is considered a better predictor of target organ damage (11) than isolated clinic blood pressure measurements, studies have suggested that a lack of nocturnal systolic blood pressure (SBP) dipping is a sensitive marker for incipient diabetic nephropathy (12).

BRS is considered a more sensitive measure of autonomic function than conventional autonomic function tests (13), but whether low BRS predicts CAN is not known. Due to a possible functional etiology, reduced BRS might not necessarily progress to CAN but may still predispose to future diabetes complications. Studies in healthy subjects have suggested that BRS declines with age alongside other autonomic parameters (14), but whether such decline is more pronounced in patients with type 1 diabetes is unclear. Therefore, our purpose was to determine whether the autonomic indices decline more in patients with type 1 diabetes than in healthy subjects and whether baseline BRS predicts progression to CAN. Moreover, we aimed to elucidate the role of BRS as a potential predictor of the development of hypertension during a 5-year follow-up.

RESEARCH DESIGN AND METHODS

All patients participated in the IDentification of EArly mechanisms in the pathogenesis of diabetic Late complications (IDEAL) Study launched in 2003 as a substudy of the nationwide Finnish Diabetic Nephropathy Study (FinnDiane Study) (3). A total of 125 patients participated at baseline in 2003–2004, and 80 patients agreed to take part in the follow-up visit in 2008–2009. All patients gave their written informed consent before participation. The study protocols were approved by the ethics committee of Helsinki University Hospital.

Both at baseline and follow-up, patients underwent a clinical examination, resting electrocardiogram (ECG), laboratory testing, one 24-h urine collection, ambulatory blood pressure monitoring (ABPM), and assessment of spontaneous BRS and autonomic function tests. Each participant completed a detailed questionnaire on lifestyle, smoking habits, and family history.

Protocol for autonomic testing

The autonomic tests were performed in a quiet room at a temperature between 19 and 23°C between 8:00 A.M. and 2:00 P.M. under standardized conditions as previously described (3). The autonomic testing was postponed in cases of hypoglycemia within 24 h of the test. No medications were discontinued for the purpose of the study. ECG was recorded using a bipolar precordial lead. Continuous blood pressure was measured with Finapres 2300 digital plethysmograph (Ohmeda, Louisville, CO) from the middle finger of the right arm held at heart level. The Finapres device was self-calibrated before data acquisition. Recorded signals were digitized with 12-bit resolution at a sampling rate of 200 Hz (WinAcq data acquisition system; Absolute Aliens, Turku, Finland). Ectopic beats were recognized visually and corrected by linear interpolation. The subsequent off-line signal processing was performed using WinCPRS software (Absolute Aliens).

The autonomic function was evaluated in line with the recommendations of the recent European Diabetic Neuropathy Study Group (NEURODIAB) expert panel (15) by a set of four cardiovascular autonomic function tests: *1*) the expiration-to-inspiration ratio of RR interval (RRI) during slow deep breathing, *2*) the maximum-to-minimum 30-to-15 ratio of RRI during active standing, *3*) the SBP response to standing, and *4*) the maximum-to-minimum ratio of RRI during Valsalva maneuver. Each test was scored (0 if normal and 1 if abnormal) according to Finnish age-specific reference values (16), giving a total autonomic score between 0 and 4. The participants with type 1 diabetes were grouped as follows: CAN-0 (autonomic score = 0), CAN-1 (autonomic score = 1), and CAN-2 (autonomic score >1). CAN-2 corresponds to the established definition of cardiovascular autonomic neuropathy. The timing of breathing (controlled and deep breathing) was given by a signal from the WinCPRS software and verbal instructions by the technician. At the prospective visit, the respiration was monitored with respiratory inductance plethysmography (zRIP; Pro-Tech Services, Mukilteo, WA).

Assessment of BRS

ECG and continuous blood pressure were recorded in the supine position during 5 min of spontaneous breathing and 2 min of controlled breathing (15 breaths per min) and during 1 min of slow deep breathing (6 breaths per min). Time series of the RRI and the SBPs were constructed and saved for further analysis. Power spectral analysis of SBP and RRI was performed with Fast Fourier transformation to obtain the power in the low-frequency (0.04–0.15 Hz) and high-frequency (0.15–0.40 Hz) bands.

BRS was determined from the spontaneous fluctuations in the RRI and SBP during spontaneous, controlled, and deep breathing by six different methods and the average of these six methods ($BRS_{average}$). The sequence methods ($BRS^{+/+}$ and $BRS^{-/-}$) are based on identification of sequences of three or more consecutive heartbeats in which the SBP and the subsequent RRIs changed in the same direction at the minimum of 1 mmHg or 5 ms. The slopes of the regression lines between SBP and RR intervals were calculated for valid sequences with the correlation coefficient >0.85, and average was taken as a measure of $BRS^{+/+}$ and $BRS^{-/-}$, correspondingly. α-Coefficients were calculated as the square root of the ratio of the spectral powers of RRIs and SBP in the low-frequency range (BRS-αLF) (0.04–0.15 Hz) and high-frequency range (BRS-αHF) (0.15–0.4 Hz). Transfer function BRS was determined as the average of the SBP-RRI cross-spectrum divided by the SBP spectrum in the frequency range of 0.04–0.15 Hz, when coherence exceeded 0.5. Furthermore, we used a new method (BRS-SD) (17), based on the calculation of the ratio between the SD of the RRI divided by the SD of SBP as a measure of BRS. Finally, we determined the average of all six methods because none of the individual methods proved superior to the others (17). Because controlled breathing by forcing the patient to breathe 15 breaths per min is likely to induce sympathetic activation in some patients, the BRS during spontaneous breathing was used as the resting level. Deep breathing reduces sympathetic activity (18), and therefore we calculated the increase in BRS as a response to deep breathing.

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) was performed in a subset of 71 participants with a SpaceLabs 90207 monitor (Spacelabs, Redmond, WA). During the monitoring, patients were asked to avoid vigorous physical exercise and to keep their arm relaxed during measurements. Blood pressure readings were obtained every 20 min during the day (7:00 A.M.–11:00 P.M.) and every 30 min at night (11.00 P.M.–7:00 A.M.). Day- and nighttime periods were defined based on individual sleeping time. Patients with a nocturnal decrease of systolic or diastolic blood pressure <10% of the corresponding daytime value were defined as nondippers. The change in blood pressure over time was calculated as the baseline value subtracted from the follow-up value.

Laboratory tests

Venous blood samples were obtained after a light breakfast and analyzed for HbA_{1c}, lipids, and serum creatinine. HbA_{1c} concentrations were determined by immunoturbidimetric immunoassay (Medix Biochemica, Kauniainen, Finland). Serum lipids (total cholesterol, triglycerides, and HDL cholesterol) and creatinine were measured by enzymatic methods. Urinary albumin excretion rate was measured from one 24-h urinary collection.

Statistical analyses

All statistical analyses were performed using PASW Statistics 18. Data in tables are given as means ± SEM or median (range). Data were tested for distribution, and skewed variables were log transformed before analyses. Differences between groups were analyzed with χ^2 (for qualitative variables) or unpaired Student *t* test (for quantitative variables). Pearson correlation coefficients were used to evaluate associations. Statistical significance was defined as *P* value ≤ 0.05.

Age adjustment. From our database, we selected all available data on spontaneous breathing obtained in healthy subjects with an age range of 16–60 years ($n = 425$), and we calculated age regression curves for each BRS index, SD of all normal RRIs (SDNN), and mean RRI. For the autonomic function tests (E-to-I ratio, 30-to-15 ratio, Valsalva ratio, and lying-to-standing change in SBP), we obtained similar age regression slopes from a previous study in 120 healthy subjects aged 22–92 years (19). All age regressions were significant except that with RRI. Using equations obtained in healthy subjects, we calculated the physiologic age-dependent deterioration for each subject over the individual follow-up period. To obtain age-adjusted values, we added the age-dependent BRS deterioration value to the value of the follow-up result. Thus, the difference between baseline and age-adjusted follow-up value reflected changes not due to aging. To evaluate the change in BRS over time, we performed a paired t test between baseline BRS and both the measured BRS and age-adjusted BRS at follow-up.

RESULTS—Table 1 shows the clinical characteristics and ABPM data of the participants at baseline and follow-up. Duration at baseline was 8.8 ± 0.2 years and 13.8 ± 0.2 years at follow-up with a mean follow-up time of 5.0 ± 0.0 years. Of the 5 patients with antihypertensive treatment (AHT) at baseline, 1 terminated the medication and 17 new patients started AHT. Thus, a total of 21 patients were using AHT at the time of the follow-up visit, whereas none used β-blockers. Results are given separately for these groups. Office SBP did not change over time, but the patients with AHT had higher blood pressure both at baseline and follow-up. The patients who started AHT were older (35.6 ± 0.9 vs. 30.8 ± 0.7 years; $P < 0.001$) and had a later age at onset of diabetes (21.3 ± 1.0 vs. 17.2 ± 0.7 years; $P < 0.05$). These patients also had a higher total cholesterol level ($P < 0.05$). Four new patients were laser treated due to retinopathy during follow-up. The lipid concentrations remained unchanged, but 10 patients started lipid-lowering medication during follow-up. Urinary albumin excretion rate increased marginally ($P < 0.05$). No major cardiovascular events were reported during follow-up.

Autonomic score according to four cardiovascular autonomic function tests
At baseline, 68 patients had no signs of CAN (CAN-0), whereas 11 patients had borderline (CAN-1) and one had evident (CAN-2) CAN. At follow-up, 63 patients presented with CAN-0, 16 with CAN-1, and 1 with CAN-2. One of the patients progressed to CAN-2, and in 12 patients the CAN score worsened. The single patient with CAN-2 at baseline reversed to CAN-1, and seven patients improved their autonomic score. Thus, a total of 61 patients had an unchanged CAN score over time. BRS indices at baseline did not differ when patients were grouped by CAN score at follow-up.

Change in autonomic function tests and spontaneous BRS during follow-up
When all patients were analyzed together, the E-to-I ratio, SDNN, and all but one of the BRS indices declined significantly during follow-up, but after age adjustment only one BRS method (BRS-αHF) showed a significant decline ($P < 0.01$) (Table 2). In the group with AHT, there was a significant drop with time in E-to-I ratio, 30-to-15 ratio, SDNN, BRS-αHF, BRS$^{-/-}$, and BRS$_{average}$, but the changes in E-to-I ratio, 30-to-15 ratio, and BRS-αHF were significant even after age adjustment ($P < 0.01$). In those without AHT, E-to-I ratio and four of six BRS indices declined significantly during follow-up, but none of these changes were significant anymore after age adjustment.

BRS and blood pressure
Baseline. The association between spontaneous BRS and 24-h AMBP and office blood pressure at baseline were analyzed in patients with AMBP data available. Overall BRS correlated negatively with 24-h and daytime AMBP, predominantly with diastolic blood pressure (DBP) and mean arterial blood pressure (MAP). All BRS variables except BRS$^{+/+}$ correlated with 24-h DBP (r -0.238 to -0.331; $P < 0.05$) and daytime DBP (r -0.295 to -0.400; $P < 0.05$), whereas the correlations with nighttime AMBP were nonsignificant. Furthermore, office blood pressures (SBP, DBP, and MAP) correlated significantly with BRS-αLF (r -0.234 to -0.275; $P < 0.05$), and transfer function BRS (r -0.251 to -0.281; $P < 0.05$).
Follow-up. The correlations between baseline spontaneous BRS-variables and change in nighttime SBP are shown in Fig. 1. Only patients without AHT are included ($n = 50$). The lower BRS at baseline, the more the nighttime SBP increased over time ($r = -0.348$ to -0.381; $P < 0.05$). In addition to resting BRS, we also calculated the

increase in BRS induced by deep breathing at baseline (data not shown). Two of the BRS methods showed a significant correlation with the increase in blood pressure over time, mainly with 24 h (BRS-αLF $r = 0.323$–0.346, $P < 0.05$; BRS-SD $r = 0.352$–0.454, $P < 0.05$) and nighttime (BRS-αLF $r = 0.303$–0.434, $P < 0.05$; BRS-SD $r = 0.333$–0.481, $P < 0.05$) indices and with daytime MAP (BRS-αLF $r = 0.302$, $P < 0.05$; BRS-SD $r = 0.339$, $P < 0.05$). With the other BRS methods the correlations between the response in BRS and blood pressure variables were nonsignificant.

CONCLUSIONS—In a representative sample of patients with type 1 diabetes, we demonstrated that although the BRS is reduced at baseline, the decline in BRS during a 5-year follow-up is similar to that seen in healthy subjects. The low BRS at baseline does not progress to evident CAN but predicts an increase in nighttime SBP.

Cross-sectional studies have shown that cardiovagal BRS deteriorates with age in healthy subjects (14). As expected, there was a decline in the majority of the autonomic indices in patients with diabetes, but when the age-dependent deterioration was eliminated the decline, which could have been ascribed to the presence of diabetes, was no longer significant. However, in patients with AHT there was a significant drop in the E-to-I ratio, 30-to-15 ratio, and BRS-αHF even after age correction. Although these patients were older, the results still suggest that they are more likely to develop diabetes complications. This is further supported by increased prevalence of laser-treated retinopathy in this group.

In the current study, all but one of the BRS-variables correlated inversely with 24-h DBP and daytime DBP at baseline—in agreement with previous data (20). Importantly, baseline BRS predicted an increase in nighttime blood pressure at follow-up. Moreover, the BRS response to deep breathing correlated with the increase in 24-h blood pressure indices overall. A recent meta-analysis confirmed that nighttime SBP is a stronger predictor of cardiovascular and noncardiovascular mortality than daytime SBP both in hypertensive patients and in randomly selected populations (21). In contrast to some (12) but not all (22) previous studies, we could not detect any relationship between the increase in nocturnal blood pressure and the albumin excretion rate. Moreover, the non-dipping status was not related to baseline BRS and did not predict an increase in blood pressure or albumin excretion rate.

Table 1—Clinical characteristics and ambulatory blood pressure in patients with type 1 diabetes and according to antihypertensive treatment at follow-up

	All patients (n = 80)			AHT+ (n = 21)			AHT− (n = 59)		
	Baseline	Follow-up	P	Baseline	Follow-up	P	Baseline	Follow-up	P
Sex (male/female)	46/34	46/34	—	16/5	16/5	—	29/28	29/28	—
Age (years)	27.0 ± 0.6	32.0 ± 0.6	**	31.6 ± 0.9	35.6 ± 0.9	**	25.8 ± 0.7††	30.8 ± 0.7††	**
Diabetes duration (years)	8.8 ± 0.2	13.8 ± 0.2	**	9.2 ± 0.3	14.3 ± 0.3	**	8.5 ± 0.2	13.7 ± 0.2	**
Age at onset (years)	18.2 ± 0.6	—	—	21.3 ± 1.0	—	—	17.2 ± 0.7†	—	—
BMI (kg/m^2)	24.8 ± 0.4	25.7 ± 0.5	**	24.9 ± 0.7	25.3 ± 0.8	NS	24.7 ± 0.5	25.8 ± 0.6	**
Waist-to-hip ratio	0.86 ± 0.08	0.87 ± 0.01	NS	0.88 ± 0.02	0.91 ± 0.01	NS	0.85 ± 0.01	0.86 ± 0.01†	NS
Current smokers (%)	16.0	13.8	NS	25.0	20.0	NS	11.9	11.9	NS
AHT (%)	6.3	26.3	**	19.0	100.0	**	1.7	0.0	NS
Laser-treated retinopathy (%)	1.3	6.3	NS	0.0	19.0	*	1.7	1.7	NS
HbA$_{1c}$ (%)	7.5 ± 0.1	8.0 ± 0.1	**	7.5 ± 0.3	8.0 ± 0.2	*	7.4 ± 0.1	8.0 ± 0.1	**
Total cholesterol (mmol/L)	4.7 ± 0.1	4.5 ± 0.0	NS	5.0 ± 0.2	4.5 ± 0.2	*	4.6 ± 0.1†	4.5 ± 0.1	NS
HDL cholesterol (mmol/L)	1.71 ± 0.05	1.60 ± 0.05	*	1.63 ± 0.11	1.48 ± 0.08	*	1.73 ± 0.06	1.63 ± 0.06	*
LDL cholesterol (mmol/L)	2.4 ± 0.1	2.4 ± 0.1	NS	2.72 ± 0.18	2.44 ± 0.12	NS	2.33 ± 0.10	2.40 ± 0.09	NS
Triglycerides (mmol/L)	0.97 (0.47–5.17)	0.99 (0.40–4.59)	NS	0.99 (0.49–5.17)	0.99 (0.4–4.59)	NS	0.95 (0.47–3.00)	0.98 (0.40–3.33)	NS
UAER (mg/24 h)	3 (1–113)	4 (0–458)	*	3 (2–113)	5 (0–458)	NS	3 (1–31)	4 (0–28)	NS
Serum creatinine (µmol/L)	70 ± 1	69 ± 1	NS	73 ± 3	72 ± 2	NS	70 ± 2	68 ± 2	NS
Office SBP (mmHg)	134 ± 2	132 ± 1	NS	141 ± 3	137 ± 2	NS	131 ± 2†	131 ± 1.6†	NS
Office DBP (mmHg)	78 ± 1	78 ± 1	NS	81 ± 2	80 ± 2	NS	77 ± 1	77 ± 1	NS
24-h SBP	123 ± 1	126 ± 1	**	127 ± 1	127 ± 2	NS	122 ± 1	125 ± 1	**
24-h DBP	73 ± 1	76 ± 1	**	77 ± 1	78 ± 1	NS	72 ± 1	75 ± 1	**
24-h MAP	90 ± 1	92 ± 1	**	93 ± 1	94 ± 1	**	88 ± 1	92 ± 1	**
24-h heart rate	73 ± 1	74 ± 1	NS	72 ± 3	77 ± 2	**	73 ± 1	72 ± 1	NS
Daytime SBP	128 ± 1	131 ± 1	**	132 ± 2	132 ± 2	NS	127 ± 1	131 ± 1	**
Daytime DBP	78 ± 1	82 ± 1	**	82 ± 2	83 ± 2	NS	77 ± 1	81 ± 1	**
Daytime MAP	95 ± 1	98 ± 1	**	98 ± 1	99 ± 2	**	93 ± 1	97 ± 1	**
Daytime heart rate	77 ± 1	78 ± 1	NS	76 ± 3	82 ± 2	**	78 ± 2	77 ± 2	NS
Nighttime SBP	113 ± 1	114 ± 1	NS	118 ± 2	116 ± 2	NS	111 ± 1	114 ± 2	NS
Nighttime DBP	62 ± 1	64 ± 1	*	67 ± 2	66 ± 2	NS	62 ± 1	62 ± 1	*
Nighttime MAP	79 ± 1	81 ± 1	NS	84 ± 1	83 ± 2	NS	80 ± 1	80 ± 1	NS
Nighttime heart rate	63 ± 1	63 ± 1	NS	64 ± 2	67 ± 3	NS	62 ± 1	62 ± 1	NS

Data are means ± SEM or median (range). AHT+, antihypertensive treatment at follow-up; AHT−, no antihypertensive treatment at follow-up; UAER, urinary albumin excretion rate. *Significant at P < 0.05. **Significant at P < 0.01 for baseline vs. follow-up. †Significant at P < 0.05. ††Significant at P < 0.01 for baseline vs. follow-up. †Significant at P < 0.01 for AHT+ vs. AHT−. *Significant at P < 0.05.

Table 2—Autonomic function tests and spontaneous baroreflex sensitivity at baseline and follow-up

|	All patients (n = 80)			AHT⁺ at follow-up (n = 21)			AHT⁻ at follow-up (n = 59)		
	Baseline	Follow-up	Follow-up adjusted	Baseline	Follow-up	Follow-up adjusted	Baseline	Follow-up	Follow-up adjusted
Mean RRI (ms)	919 ± 13	936 ± 15	939 ± 15	922 ± 24	910 ± 28	913 ± 28	917 ± 16	945 ± 18	949 ± 18*
E-to-I ratio	1.38 ± 0.02	1.31 ± 0.02**	1.36 ± 0.02	1.38 ± 0.04	1.24 ± 0.03**	1.29 ± 0.03††	1.39 ± 0.02	1.33 ± 0.02**	1.38 ± 0.02
30-to-15 ratio	1.64 ± 0.03	1.59 ± 0.04	1.61 ± 0.04	1.66 ± 0.06	1.40 ± 0.05**	1.43 ± 0.05††	1.64 ± 0.04	1.65 ± 0.04	1.68 ± 0.04
Valsalva ratio	2.03 ± 0.05	1.97 ± 0.05	2.02 ± 0.05	2.10 ± 0.10	1.98 ± 0.09	2.03 ± 0.10	2.10 ± 0.06	1.98 ± 0.06	2.03 ± 0.1
Blood pressure response to standing (mmHg)	0.8 ± 1.1	2.1 ± 1.0	2.8 ± 1.0	0.6 ± 1.6	3.8 ± 2.1	3.8 ± 2.1	0.9 ± 1.3	1.7 ± 1.1	2.4 ± 1.1
SDNN (ms)	55 ± 2	51 ± 2*	55 ± 2	52 ± 5	45 ± 5*	49 ± 5	57 ± 3	53 ± 3	57 ± 3
BRS-αLF (ms/mmHg)	13.1 ± 0.8	11.2 ± 0.8*	13.4 ± 0.8	11.1 ± 1.0	9.9 ± 1.8	12.1 ± 1.8	13.8 ± 1.0	11.7 ± 0.8	13.9 ± 0.8
BRS-αHF (ms/mmHg)	23.5 ± 1.2	17.6 ± 1.4**	20.1 ± 1.4††	21.0 ± 3.0	13.7 ± 2.9**	16.2 ± 2.9††	24.5 ± 1.2	19.2 ± 1.6**	21.6 ± 1.6
Transfer function BRS (ms/mmHg)	12.2 ± 0.7	10.5 ± 0.7*	12.3 ± 0.7	10.3 ± 0.9	8.9 ± 1.4	10.7 ± 1.4	12.9 ± 0.9	11.1 ± 0.7	12.9 ± 0.7
BRS⁺/⁺ (ms/mmHg)	19.6 ± 1.4	15.3 ± 1.0**	16.8 ± 1.0	17.0 ± 1.7	13.3 ± 2.2*	14.8 ± 2.2	20.5 ± 1.8	16.0 ± 1.2*	17.4 ± 1.2
BRS⁻/⁻ (ms/mmHg)	19.1 ± 0.9	16.0 ± 1.1**	18.8 ± 1.1	17.7 ± 2.0	15.9 ± 3.2	18.7 ± 3.2	19.6 ± 1.1	16.0 ± 1.1**	18.8 ± 1.0
BRS SD (ms/mmHg)	9.8 ± 0.5	9.0 ± 0.5	10.6 ± 0.5	8.9 ± 0.8	8.0 ± 1.2	9.6 ± 1.2	10.2 ± 0.6	9.3 ± 0.6	11.0 ± 0.6
BRS$_{average}$ (ms/mmHg)	16.2 ± 0.8	13.2 ± 0.8**	15.2 ± 0.8	14.1 ± 1.3	11.3 ± 1.9*	13.4 ± 1.9	16.9 ± 0.9	13.9 ± 0.8**	15.9 ± 0.8

Data are means ± SEM. Follow-up values are adjusted for follow-up time. AHT⁺, antihypertensive treatment at follow-up; AHT⁻, no antihypertensive treatment at follow-up. *Significant at $P < 0.05$. **Significant at $P < 0.01$ for baseline vs. follow-up. †Significant at $P < 0.05$. ††Significant at $P < 0.01$ for baseline vs. follow-up adjusted for follow-up time.

This might be explained by the fact that future microalbuminuric patients are most likely those already on AHT. It is of note, though, that the predictive value of the nondipping phenomenon for microalbuminuria or especially in normotensive patients is still not clear.

Whereas spontaneous BRS was associated with an increase in nighttime blood pressure, the ΔBRS (SD and αLF), i.e., the BRS response to deep breathing, correlated with a general increase in blood pressure. During sleep, the renin-angiotensin system plays a more important role in blood pressure regulation than the sympathetic nervous system unless the sympathetic system is activated (23). It can be argued that nighttime blood pressure is better standardized than daytime blood pressure, and thus an increase in nighttime blood pressure may also be a more sensitive marker of sympathetic activation. Slow breathing is an intervention that reduces muscle nerve sympathetic activity and consequently increases BRS in patients with chronic heart failure, hypertension, and chronic obstructive pulmonary disease (18,24). We have recently demonstrated the same phenomenon in type 1 diabetes (3,4). Thus, the magnitude of improvement after an intervention aimed to reduce the sympathetic activation could reflect the level of functional impairment. The fact that the BRS response predicts an increase in nighttime blood pressure underlines the importance of a functional deficiency of the autonomic regulation.

Potential differences in the prognostic information that the different BRS methods provide are inadequately studied. In the current study, the deep breathing–induced BRS response correlated with the overall blood pressure in patients without AHT. Interestingly, a recent study demonstrated that reduced BRS in hypertension was most evident using the noninvasive BRS-αLF method (25). The similar behavior of BRS-SD and BRS-αLF is not surprising given that they are tightly correlated (17). Nonetheless, the single method that showed a persistent decline over time even after age adjustment was the BRS-αHF. This decline could be explained by reduced respiratory sinus arrhythmia in the high-frequency region due to diabetes. Yet, a more prominent change over time than the reduced high-frequency component of RRI (LnHF-RRI) (spontaneous breathing 6.21 ± 0.13 vs. 5.77 ± 0.15 ms², $P < 0.001$; controlled breathing 6.00 ± 0.11 vs. 5.99 ± 0.16 ms², P = NS) was the marked increase in the HF component of the SBP (LnHF-SBP) (spontaneous breathing 0.17 ± 0.08
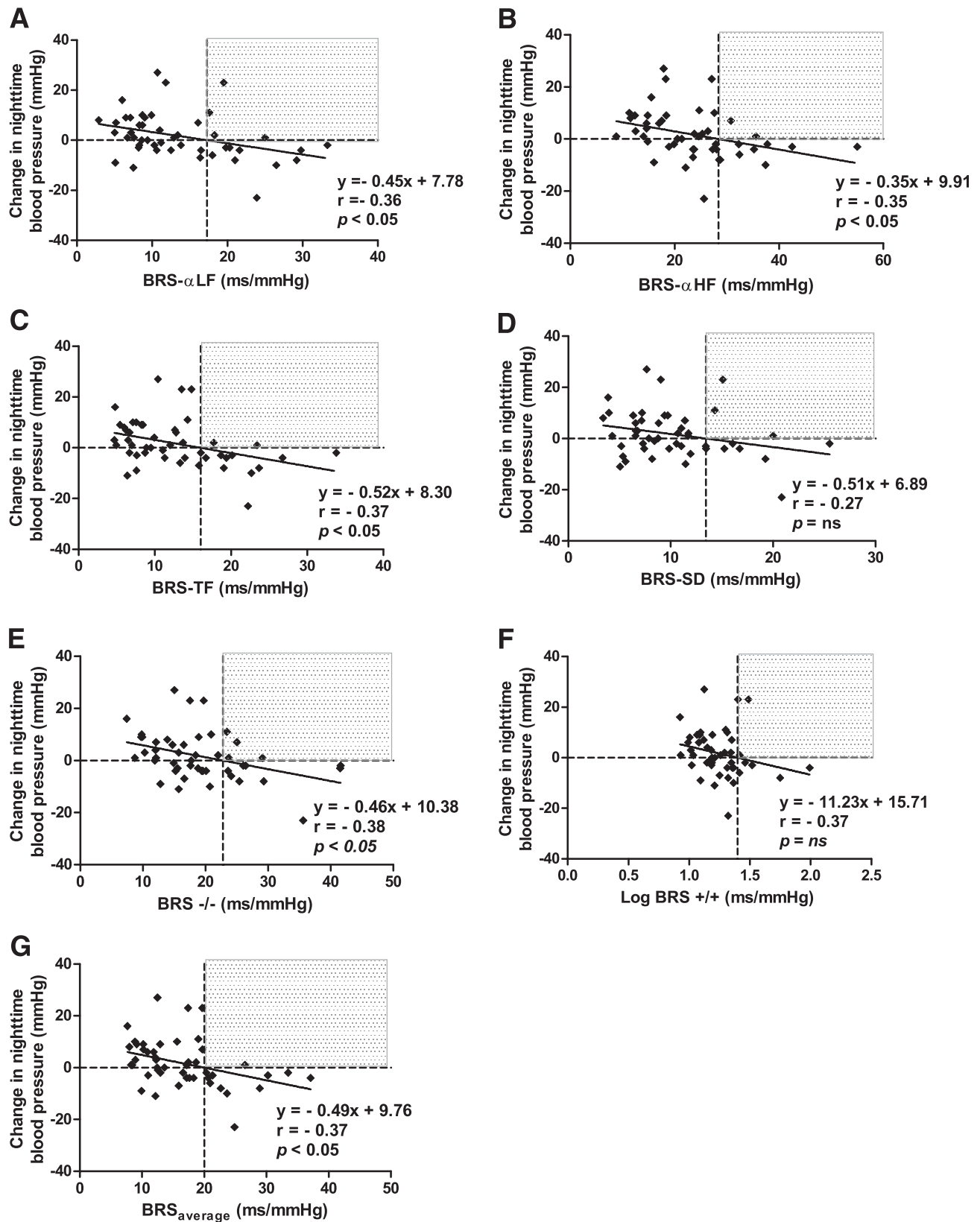
Figure 1—*Correlations between baseline spontaneous BRS and change in nighttime SBP during 5-year follow-up.*

vs. 0.59 ± 0.07 mmHg^2, $P < 0.001$; controlled breathing 0.21 ± 0.08 vs. 0.83 ± 0.08 mmHg^2, $P < 0.001$). Whether the decline in BRS-αHF is a cause or a consequence of the increase in SBP-HF remains unclear, but the ability of the BRS to buffer blood pressure changes in the HF region is obviously reduced. Further research is needed to establish the significance of this finding.

A major limitation of this study is the small sample size. Furthermore, the association between baseline BRS indices and the change in blood pressure over time was studied only in patients not treated with AHT, and thus the current study was not designed to assess the association between BRS and albuminuria.

In conclusion, although the decline in BRS over time appears to be physiological, a reduced BRS at baseline predicts an increase in blood pressure. The assessment of BRS could help to identify those patients with type 1 diabetes who would benefit from early interventions aiming to reduce sympathetic overactivity and to delay the development of hypertension.

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