Autonomic dysfunction in cardiovascular disease
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Heart rate variability and baroreflex sensitivity in diabetic patients with peripheral neuropathy are indices of both neural and vascular disease.

Submitted.

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SUMMARY

Aims: Cardiovascular autonomic neuropathy (CAN) assessed by conventional tests, is variably related to the presence of diabetic peripheral neuropathy (DPN). Power spectral analysis of heart rate variability (HRV) and noninvasive measurement of baroreflex sensitivity (BRS) are advanced measures of CAN. It is unknown whether HRV and BRS measurements are impaired in the presence of clinical DPN, and may be useful as indicators of an increased cardiovascular risk in these patients. Therefore, we studied HRV and BRS in carefully selected diabetic patients with and without DPN, and healthy controls.

Methods: Eighteen diabetic patients with DPN (DN) were individually matched with 18 diabetic patients without DPN (DC) and healthy controls (C). Patients with cardiac and peripheral arterial occlusive disease were excluded. HRV and BRS were calculated by spectral analysis of continuous heart rate and blood pressure recordings by non–invasive Finapres measurements. The HRV was analyzed among the different frequency bands, the BRS was defined as the mean gain between blood pressure variability and heart rate variability in the 0.07–0.14 Hz frequency band.

Results: Total power in HRV was lower in DN (7.1 ± 0.3 ln(ms²) [mean ± SEM], P<0.001 for both) compared to DC (8.9 ± 0.3 ln(ms²) and C (9.3±0.3 ln(ms²)). BRS was similarly impaired in DN (3.0 ± 0.7 ms/mmHg, P<0.01 for both) compared to DC (6.0 ± 0.6 ms/mmHg) and C (6.7 ± 1.1 ms/mmHg). In a multiple regression analysis, peripheral neuropathy and an elevated urinary albumin excretion rate (UAE) were the main determinants of a lower HRV, whereas the presence of an elevated UAE almost uniquely explained the variance BRS. It was further discovered that the lower HRV and BRS in patients with DN appeared to be limited to those patients who had concomitant elevated urinary albumin excretion (UAE) (HRV, 6.2 ± 0.4 ln(ms²) and BRS, 1.7 ± 0.6 ms/mmHg, n=9) vs. normal UAE (HRV 8.0 ± 0.4 ln(ms²) and BRS 5.2 ± 1.1 ms/mmHg, n=9, p<0.01 for both).

Conclusions: Elevations in UAE are important independent determinants of a lower HRV and BRS in diabetic patients with peripheral neuropathy. We suggest that the presence of vascular abnormalities should to be taken into account while interpreting these measurements of cardiovascular reflex function.
INTRODUCTION

Foot ulceration in patients with diabetes mellitus is associated with a high morbidity and mortality (1). Distal peripheral neuropathy (DPN) and peripheral vascular disease play a dominant role in the multifactorial etiology of this complication (2). The coexistence of cardiovascular autonomic neuropathy (CAN) has been proposed to contribute to the high mortality rate in these patients, as the presence of CAN is a determinant of a poor prognosis in diabetic patients (3).

There is, however, a variable relation between CAN and DPN, and CAN is frequently observed in the absence of DPN (4–6). This contrasts with the possibility that the sensory and motor nerves of the lower extremities and the unmyelinated post–ganglionic sympathetic and parasympathetic vagal nerves to the heart are equally vulnerable to neuronal damage by the diabetic milieu. It has even been suggested that CAN and DPN are distinct entities with differences in pathogenesis as different risk factors have been described for the development of CAN and DPN (6,7).

The lower than expected concordance between CAN and DPN may be also attributable to the methodology employed to diagnose CAN (3). More advanced evaluation of CAN by power spectral analysis of heart rate variability (HRV) and non–invasive measurement of baroreflex sensitivity (BRS) have shown to be highly sensitive to detect CAN at an early stage in diabetic patients (8–10). While HRV evaluates the efferent part of the baroreflex arc, BRS measures both its afferent and efferent function by cross–spectral analysis of heart rate and blood pressure variations (9–12). Interestingly, HRV was evidently lowered patients with DPN and foot ulceration, and it was suggested that this parameter could be of additional value for cardiovascular risk stratification (13).

In the present study, we compared HRV and BRS measurements in diabetic patients, carefully selected for the presence or absence of clinical DPN, and healthy control subjects. We evaluated the possibility that these measures of CAN are more consistently abnormal in diabetic patients in whom neuropathy is manifested at the feet than what has been reported for conventional CAN testing.
**Materials and Methods**

*Subjects.* The study consisted of three groups: 18 diabetic patients with peripheral neuropathy (DN), 18 diabetic patients without peripheral neuropathy (D), and 18 control subjects with normal glucose tolerance (C). Patients were recruited from the Diabetes Outpatient Clinic (University Hospital Groningen) and the Rehabilitation Center Beatrixoord Haren on the basis of hospital records were checked for previous foot ulceration of neuropathic in origin and in whom peripheral vascular disease was not considered to have contributed to the foot ulcers. After this screening, they were recruited in a randomized order.

The first group consisted of 24 diabetic patients known to have had neuropathic foot ulcers (DU group). These ulcers were purely neuropathic by origin, as confirmed by their localization (plantar surface of the foot at high-pressure points) and the absence of peripheral arterial disease, as described below. In the second group, 24 diabetic patients without clinical neuropathy or foot ulcers (DC group) were included. To confirm this, the 10–g Semmes Weinstein monofilament was tested on the plantar surface of the hallux and central at the heel. The ability to correctly sense the monofilament in six trials on both locations was defined as normal, whereas the inability to sense the monofilament correctly in one or more trials was defined as disturbed. The third group consisted of 21 control subjects with normal glucose tolerance (C group). All groups were matched for sex and age (within 5 years), and the diabetic groups were also matched for duration and type of diabetes (type 1/type 2 diabetes; type 1 diabetes was considered on clinical grounds when the onset of the disease was a ketoacidosis or before the age of 40 years). Subjects with a history of or clinically apparent cardiac disease, with electrocardiographic abnormalities, or who used ß–blockers or calcium antagonists were excluded. Peripheral arterial disease was excluded by normal ankle–arm indexes (>0.90), toe–arm indexes (>0.70), and normal plethysmography (crest time 0.22 s) in all groups. Normal glucose tolerance of the control subjects was demonstrated by a fasting capillary blood glucose <6.1 mmol/l and a blood glucose 2 h after a 75–g oral glucose tolerance test. Details of the clinical characteristics of each group are given in
The study was approved by the local medical ethics committee and written informed consent was obtained from all participants after explanation of the purpose of the study.

The patients were recruited from the outpatient clinic of the University Hospital Groningen and the Rehabilitation Centre Beatrixoord. Healthy control subjects were recruited by an advertisement in a local newspaper.

The study consisted of three groups: 18 diabetic patients with peripheral neuropathy (DN), 18 diabetic patients without peripheral neuropathy (D), and 18 control subjects with normal glucose tolerance (C). All participants were recruited from the Diabetes Outpatient Clinic (University Hospital of Groningen) and from the Beatrixoord Rehabilitation Center in Haren, The Netherlands. Three groups of subjects were studied. The first group consisted of 18 diabetic neuropathic patients with a previous history of neuropathic foot ulceration (group DN); the second group of 18 diabetic patients without neuropathy (group DC); and the third group of 18 control subjects with normal glucose tolerance (group C). All groups were individually matched for sex and age (within 5 yr), and the diabetic groups for type of diabetes (type 1/ type 2) as well. Eligible subjects were 35 to 70 years of age. Subjects with a history of or clinically apparent cardiac disease, electrocardiographic abnormalities or using betablockers or calcium antagonists were excluded. Peripheral arterial disease was excluded by normal ankle–arm indices (>0.90), toe–arm indices (>0.70) and normal plethysmography (crest time 0.22 sec). Normal glucose tolerance of the control subjects was demonstrated by a fasting capillary blood glucose < 6.1 mmol/l and a blood glucose < 7.8 mmol/l 2h after a 75 gr oral glucose tolerance test.

The protocol was approved by the local Ethical Committee and all participants gave written informed consent. Blood glucose was measured on APEC glucose analyzer (APEC Inc., Danvers, MA, USA), HbA1c was measured by HPLC (Bio–Rad, Veenendaal, The Netherlands, normal range 4.6 to 6.1%), serum creatinine and cholesterol by a SMA(C) autoanalyzer (Technicon Instruments Inc. Tarrytown, N.Y., USA), and urinary albumin by radioimmuno–assay (Diagnostic Products Corporation, Apeldoorn, The Netherlands). A urinary albumin creatinine ratio lower than 2.5 mg/µmol in fresh voided morning urine excluded
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microalbuminuria. In case of a positive test, a 24h urine collection was made to quantify albumin excretion (elevated when > 30 mg/day).

Details of the clinical characteristics of each group are given in Table 1. All groups were comparable for sex, age, systolic and diastolic blood pressure, body mass index and number of smokers. The diabetic

| Table 1 Clinical characteristics of study subjects. |
|-----------------|-----------------|-----------------|
|                  | Neuropathic diabetic subjects (DN) | Diabetic control subjects (DC) | Healthy controls (C) |
| N                | 18              | 18              | 18              |
| Male/Female      | 9/9             | 9/9             | 9/9             |
| Age (years)      | 57 ± 3          | 56 ± 2          | 57 ± 2          |
| Systolic blood pressure (mmHg) | 146 ± 4        | 139 ± 3         | 133 ± 3         |
| Diastolic blood pressure (mmHg) | 80 ± 2         | 81 ± 2          | 86 ± 2          |
| Number of antihypertensives (0/1/2) | 7/7/4*        | 9/7/2H          | 17/1/0          |
| Body mass index (kg/m²) | 30.4 ± 1.2      | 28.0 ± 1.0      | 27.3 ± 1.3      |
| Smokers (yes/no) | 10/8            | 6/12            | 5/13            |
| Type of diabetes (1/2) | 4/14           | 4/14            | —/—/—          |
| Diabetes duration (years) | 17 ± 3         | 12 ± 2          | —/—/—          |
| Hba1c (%)        | 8.4 ± 0.3I      | 7.6 ± 0.2H      | 5.7 ± 0.1H      |
| Blood glucose (mmol/l) | 9.8 ± 1.0      | 8.8 ± 0.6H      | 5.8 ± 0.2H      |
| Serum creatinine (mmol/l) | 96 ± 5         | 89 ± 3          | 89 ± 2          |
| Normo– / micro– / albuminuria | 9/7/2H         | 17/1H/0         | 18/0/0         |
| Urinary albumin excretion rate (mg/day) in albuminuric patients (n=9) | 164 (54 – 616) | 102 | — |
| Retinopathy (absent/background/proliferative) | 4/10/4H | 13/5/0H | 18/0/0 |
| Serum cholesterol (mmol/l) | 4.9 ± 0.2H | 5.0 ± 0.2H | 6.2 ± 0.4 |
| Patients on cholesterol lowering agents | 12± | 8± | — |
| DNE | 8.9± 0.5H | 1.2± 0.4 | 0.5± 0.2 |
| NSS | 5.6± 0.7H | 0.8± 0.3 | 1.2± 0.4 |
| Semmes–Weinstein monofilaments | 6.6± 0.1H | 5.1± 0.1 | 5.1± 0.1 |

Hand: motor conduction n. medianus

|                  | Measurable | 17/18          | 16/18          | 18/18          |
| Velocity (ms)    | 47.8 ± 1.3I & <br>7.2 ± 0.6=I | 54.5 ± 0.7      | 58.0 ± 1.1      |
| Amplitude (mV)   | 32.4 ± 1.5I &<br>8.5 ± 1.7I | 40.6 ± 1.1      | 42.5 ± 1.6      |

Hand: sensory conduction n. medianus

|                  | Measurable | 17/18          | 15/18          | 18/18          |
| Velocity (ms)    | 44.2 ± 1.6I <br>6.3 ± 0.8I | 56.0 ± 1.7      | 54.6 ± 2.0      |
| Amplitude (mV)   | 37.8 ± 1.1I <br>1.8 ± 0.3I | 44.2 ± 1.3      | 47.2 ± 0.8      |

Foot: motor conduction n. peroneus

|                  | Measurable | 18/18          | 18/18          | 18/18          |
| Velocity (ms)    | 44.2 ± 1.6I <br>6.3 ± 0.8I | 56.0 ± 1.7      | 54.6 ± 2.0      |
| Amplitude (mV)   | 37.8 ± 1.1I <br>1.8 ± 0.3I | 44.2 ± 1.3      | 47.2 ± 0.8      |

Foot: sensory conduction n. suralis

|                  | Measurable | 9/18          | 17/18          | 18/18          |
| Velocity (ms)    | 37.8 ± 1.1I <br>1.8 ± 0.3I | 44.2 ± 1.3      | 47.2 ± 0.8      |
| Amplitude (mV)   | 1.8 ± 0.3I <br>7.6 ± 0.8I | 1.3 ± 0.2       | 0.7 ± 0.2       |

Peripheral neuropathy score

|                  | 3.0 ± 0.2I <br>0.2 ± 0.2I | 1.3 ± 0.2       | 0.7 ± 0.2       |

Data are number or means ± SE. *urinary albumin excretion is given as median (range). Microalbuminuria denotes an urinary albumin excretion of 30 – 300 mg/day, albuminuria was present in 2 patients but did not exceed 1000 mg/day. DNE: diabetic neuropathy examination score, NSS: neurological symptom score. Only of measurable nerves, the mean velocities and amplitudes are given. If there was no detectable nerve function, the nerve was classified as abnormal. Peripheral neuropathy score is the number of abnormal nerves (conduction velocity or amplitude) of the n. medianus (motor), n. medianus (sensory), n. peroneus and n. suralis. *p<0.01 vs. C, Hp<0.05 vs. C, Ip<0.05 vs. DC, &p<0.001 vs. C, ≡p<0.01 vs. DC, &p<0.001 vs. DC.
groups were comparable for type and duration of diabetes. HbA1c was higher and retinopathy was more severe in the DN compared to the DC group. Elevated UAE was highly prevalent in DN; 7 patients had microalbuminuria (30 – 300 mg/day) and 2 had albuminuria between 300–1000 mg/day (Table 1). Blood glucose was higher in the diabetic groups. The use of antihypertensive drugs was more frequent in the diabetic patients. Cholesterol lowering agents were also more frequently used in both groups of diabetic patients. As a result, serum total cholesterol was lower in both groups of diabetic patients compared to healthy subjects.

Assessment of neuropathy. Diabetic neuropathy was diagnosed according to the San Antonio Consensus Statement criteria (14). Clinical neuropathy signs were scored by means of the Diabetic Neuropathy Examination (DNE) score (15) that has a maximum score of 16 and is a modification of Neuropathy Disability Score. Neurological symptoms were scored by a modification of the Neurological Symptom Score (NSS) (16) with a maximum score of 12. Quantitative sensory testing was performed with Semmes–Weinstein monofilaments. Motor nerve conduction velocities and amplitudes were measured in the median and peroneal nerves (tibialis anterior), and sensory nerve conduction velocities and amplitudes in the median (first digit) and sural nerves. An overall peripheral neuropathy score (PNS) was defined as the number of these four nerves that had an abnormal conduction velocity and amplitude, ranging from 0 (all normal) to 4 (all abnormal). Since it was the goal of the present study to evaluate cardiovascular autonomic function, autonomic neuropathy was not assessed before selection of the patients. The neuropathy scores are given in Table 1. As expected from the selection procedure, severe neuropathy was present in the DN group, while neuropathy scores did not differ between the DC and C groups.

Evaluation of cardiovascular autonomic function. Cardiovascular autonomic function was assessed by analysis of heart rate variability (HRV) and baroreflex sensitivity (BRS). All participants were studied in the late morning, 2 hours after they had used a light breakfast and the diabetic patients taken their oral hypoglycemic agents or insulin dose. All measurements took place in a quiet room with the temperature kept constant at 22°C. Blood pressure was monitored by a Finapres (Ohmeda 2300, Inglewood, Col., USA) and heart rate by an ECG monitor.
(Hewlett-Packard 78351T, Palo Alto, Ca., USA). After 30 min of supine rest, the Finapres and ECG signal were sampled at 100 Hz and stored on a personal computer during 15 min. Offline, 300 seconds of each recording was analyzed by the CARSPAN program (IEC ProGamma, Groningen, the Netherlands), as described previously (12,17). After artifact correction and stationarity check, discrete Fourier transformation of systolic blood pressure and RR interval length was performed. HRV was analysed in accordance with the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (18). The power spectrum of HRV was divided into very low frequency (VLF) (0.02–0.06 Hz), low frequency (LF) (0.07–0.14 Hz) and high frequency (HF) (0.15–0.40 Hz) bands and expressed in ln(ms²) (12). The total power frequency band (TP) was defined as 0.02–0.40 Hz. BRS was determined by the transfer function method and defined as the mean modulus between systolic blood pressure and heart rate variability in the 0.07–0.14 Hz frequency band with at least 0.5 coherence, expressed in ms/mmHg (10,12,17).

**Heart Rate Variability**

![Graph](image-url)

*Figure 1. Heart rate variability in diabetic patients with peripheral neuropathy (DN), diabetic patients without peripheral neuropathy (DC) and healthy control subjects (C). Data are shown as mean (SEM).

- Very Low Frequency Power (VLF, 0.02–0.06 Hz),
- Low Frequency Power (LF, 0.07–0.14 Hz),
- High Frequency Power (HF, 0.15–0.40 Hz),
- Total Power (TP, 0.02–0.40 Hz).

*p<0.001 versus DC and versus C.*
Statistical analysis. The Statistical Package for Social Sciences for Windows version 9.0 (SPSS, Chicago) was used for the statistical analysis. Group differences were sought with analysis of variance and post–hoc comparisons with Bonferroni correction. The spectral parameters that have a $\chi^2$–distribution and BRS that has an $F$–distribution were normalized by log transformation. For nonparametrically distributed data, the Kruskal–Wallis test was used. The $\chi^2$ test was used for comparison of dichotomous variables. Multiple linear regression was used to evaluate the independent contribution of clinical variables to the variance in HRV and BRS. A $P$–value $\leq 0.05$ was considered significant.

Results

The total power, an overall index of HRV, was lower in the DN group compared to the DC and C groups (DN $7.1 \pm 0.3$ vs DC $8.9 \pm 0.3$ and C $9.3 \pm 0.3 \ln(\text{ms}^2)$, $P<0.001$ for both, Figure 1). These differences were present in all frequency ranges, VLF, LF and HF (DN < D and C, $P<0.001$ for all frequency ranges, Figure 1). Similar, BRS was depressed in the DN group ($3.0 \pm 0.7$) compared to the DC group ($6.0 \pm 0.6$, $P=0.003$) and the C group ($6.7 \pm 1.1 \text{ ms/mmHg}$, $P=0.001$).

Multiple regression analysis in the combined groups ($n=54$), disclosed that an elevated UAE ($P<0.001$), peripheral neuropathy score ($P<0.02$), diastolic blood pressure ($P<0.05$) and blood glucose level ($P<0.05$) independently contributed to $22\%$, $8\%$, $4\%$ and $4\%$, respectively, to the variance in HRV ($r^2=0.89$, $P<0.001$). The analysis showed that an elevated UAE ($P<0.001$) and blood glucose level ($P<0.02$) contributed to $27\%$ and $8\%$, respectively, to the variance in BRS ($r^2=0.62$, $P<0.001$), while diastolic blood pressure ($P=0.07$) and peripheral neuropathy score ($P=0.20$) did not significantly contribute to the model.

The large effects of the presence of an elevated UAE on the HRV and BRS measurements is further illustrated in Figure 2A, B. The HRV (total power) in the patients of the DN group with an elevated UAE ($6.2 \pm 0.4 \ln(\text{ms}^2)$, $n=9$) differed from the patients in the DN group with a normal UAE ($8.0 \pm 0.4 \ln(\text{ms}^2)$, $n=9$, $P<0.01$, Figure 2A). Similarly, BRS in the patients of the DN group with an elevated UAE ($1.7 \pm 0.6$, $n=9$) differed from the patients in the DN group with a normal UAE ($5.2 \pm 1.1 \text{ ms/mmHg}$, $n=9$, $P<0.01$, Figure 2B).
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**DISCUSSION**

The present study shows that cardiovascular autonomic function, assessed by HRV and BRS, is impaired in diabetic patients with peripheral neuropathy, and is in agreement with a previous report on HRV in such a patient group (13). Interestingly, multiple regression analysis indicated...
that HRV and BRS were particular abnormal in the patients in whom peripheral neuropathy was complicated by an elevated UAE. Thus independent from compounding variables, like duration of diabetes, blood glucose, HbA1c, blood pressure and need for antihypertensive medication and degree of retinopathy, which all directed towards a more severely complicated diabetes in the neuropathic patients, the presence of an elevated UAE allocated for abnormalities in HRV and BRS.

Although not anticipated on beforehand, elevations in UAE were highly prevalent in the diabetic patient with neuropathy, and this notion is in line with recent observations showing that a large portion of patient with abnormal CAN tests have elevated UAE levels (7,10,19). Also, in the study Aso et al. (13), the DPN patients had an elevated UAE though this but was not further considered. It is unknown, how abnormal CAN tests either by conventional means (7,19) or by the presently used HRV and BRS (10) pathogenetically relate to elevations in UAE.

Elevations in UAE are associated with cardiovascular risk factors like dyslipidemia (20), hypertension (21), insulin resistance (22), increased intima media thickness and stiffness of the carotid arteries (23) and endothelial dysfunction (24), and are conceptually seen to reflect generalized vascular disease (25,26). The presence of vascular disease as indicated an elevated UAE may have affected the HRV and BRS. The baroreflex input is derived from blood pressure changes sensed by baroreceptors in the carotid arteries and aorta, and its output is modulation of heart rate, myocardial contractility and peripheral arterial resistance (17,27). Thus measurement of HRV and BRS do to certain extent depend on vessel wall properties. Subclinical atherosclerosis at the site of the baroreceptors, a diminished arterial compliance (23), subclinical cardiac contraction abnormalities (28,29) and an impaired vascular endothelial function (24) may all have contributed to the impairments in HRV and BRS, as these abnormalities have all been documented in the presence of UAE elevations in diabetic patients. Conversely, it is also possible that CAN precedes elevations in UAE and increases the likelihood of the development of microalbuminuria, as this has previously been suggested (10). Endothelial dysfunction could be an important denominator (30,31). The fact that neuropathy score related to HRV and not to BRS in the multiple regression analysis may be due to the fact that HRV is more close to autonomic nerve function than BRS, as HRV assesses heart rate modulations by the efferent vagal and the sympathetic nerves. It further
suggesststhat BRS, that evaluates both blood pressure and heart rate variations more than HRV depends on vascular function.

However, elevations in UAE were present in a small group of patients, in the DPN group 2 had albuminuria, 7 had microalbuminuria and 9 had normo–albuminuria, and in the diabetic group without DPN, only 1 was found to have microalbuminuria. Therefore, we cannot exclude the possibility that the lack of independent association between neuropathy score and BRS was due to the rather restricted sample size of this post–hoc study observation. Finally the relation between a lower HRV and BRS and actual blood glucose level has recently been given attention in several reports (32,33), and this intriguing inverse relationship is still awaiting for an explanation (34).

In conclusion, elevations in UAE are important independent determinants of a lower HRV and BRS in diabetic patients with peripheral neuropathy. As elevations in UAE are associated with many vascular abnormalities, we raise the hypothesis that impairments of these cardiovascular reflex measurements in diabetic patients reflect both vascular and neural disease. The role of vascular function in autonomic neuropathy testing deserves further investigation.

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