

## 24-h blood pressure and autonomic function is related to albumin excretion within the normoalbuminuric range in IDDM patients

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**Summary** Significant changes in both blood pressure, autonomic function and kidney ultrastructure are observed in insulin-dependent diabetic (IDDM) patients with microalbuminuria. Intervention strategies are evaluated at even earlier stages of disease. Identification of patients at risk of developing microalbuminuria must be based on a thorough knowledge of the relations between key pathophysiological parameters in patients with normoalbuminuria. The aim of the present study was to characterize the interactions of urinary albumin excretion (UAE), 24-h ambulatory blood pressure (AMBP), and sympathovagal balance in a large group of normoalbuminuric IDDM patients. In 117 normoalbuminuric (UAE < 20 µg/min) patients we performed 24-h AMBP (Spacelabs 90207), with assessment of diurnal blood pressure and heart rate (HR) variation, and short-term (three times 5 min) power spectral analysis of RR interval oscillations, as well as cardiovascular reflex tests (HR variation to deep breathing, postural HR and blood pressure response). Patients with UAE above the median (4.2 µg/min) had significantly higher 24-h systolic and diastolic AMBP ( $125 \pm 10.1/76 \pm 7.2$  mmHg) compared to the low normoalbuminuric group ( $120 \pm 8.4/74 \pm 5.1$  mmHg),  $p < 0.01$  and  $0.02$ , respectively. Patients with UAE above the median had significantly reduced

short-term RR interval variability including both the high frequency component ( $5.47 \pm 1.36$  vs  $6.10 \pm 1.43$  ln ms<sup>2</sup>), and low frequency component ( $5.48 \pm 1.18$  ln ms<sup>2</sup> compared to  $5.80 \pm 1.41$  ln ms<sup>2</sup>),  $p < 0.02$  and  $p = 0.04$  (ANOVA). In addition, patients with high-normal UAE had reduced mean RR level (faster heart rates)  $916 \pm 108$  compared to  $963 \pm 140$  ms,  $p < 0.04$ . These differences were not explained by age, duration of diabetes, gender, level of physical activity, or cigarette smoking. HbA<sub>1c</sub> was significantly higher ( $8.6 \pm 1.2$  vs  $8.2 \pm 1.0$  %,  $p = 0.03$ ) in the group with high normal UAE. Comparing normoalbuminuric IDDM patients with UAE above and below the median value, we found significantly higher AMBP in combination with significant differences in sympathovagal balance and significantly poorer glycaemic control in the group with high-normal albumin excretion. Our data demonstrate interactions between albumin excretion, blood pressure, autonomic function, and glycaemic status, already present in the normoalbuminuric range and may describe a syndrome indicative of later complications. [Diabetologia (1997) 40: 718–725]

**Keywords** Ambulatory blood pressure, autonomic control, heart rate variability, spectral analysis, IDDM, microalbuminuria, diabetic nephropathy

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**Abbreviations:** AMBP, Ambulatory blood pressure; CCV HF, coefficient of component variance HF; CCV LF, coefficient of component variance LF; MSSD, mean square of successive R-R differences; N/D ratio, night/day ratio; Power HF, high frequency power (0.15–0.50 Hz); Power LF, low frequency power (0.05–0.15 Hz); UAE, urinary albumin excretion; IDDM, insulin-dependent diabetes mellitus.

The presence of microalbuminuria in insulin-dependent diabetes mellitus (IDDM) patients is a strong predictor of subsequent development of nephropathy [1–3]. Whereas renal function is preserved at this stage, recent data indicate that substantial pathophysiological changes have taken place: in microalbuminuric patients blood pressure is elevated [4–7] with an attenuated circadian rhythm [8]. Vagal function is impaired with an abnormal sympathovagal interaction [9, 10]. In addition, new ultrastructural findings [11, 12] indicate the presence of glomerular and arteriolar abnormalities in IDDM patients with incipient nephropathy. Prevention of progression to microalbuminuria would thus be a major clinical turning-point. A sound description of the relationship between urinary albumin excretion, blood pressure, and autonomic function in normoalbuminuric patients is a prerequisite for the identification of patients at increased risk of developing microalbuminuria.

Spontaneous beat-to-beat fluctuations in heart rate reflect ongoing modulation of sinus node activity through several cardiovascular control mechanisms. Quantification of fluctuations in RR intervals can be used to assess autonomic function [13], and based on 24-h recordings these measurements have proven to be more sensitive than ordinary bedside tests in the detection of early autonomic neuropathy [9, 14, 15]. The application of power spectral analysis, which calculates the frequency content of time varying signals, has provided a powerful tool in the assessment of sympathovagal balance [16, 17]. This technique permits the identification of two major components with different frequency bands: the respiratory dependent high frequency (HF; 0.15–0.50 Hz) oscillations are mediated purely by vagal activity [16, 18]. The power in this band is highest in the supine position [16, 17, 19], reduced in upright position, and abolished by atropine [16, 18]. The power of the HF component is linearly related to pharmacologically determined vagal activity [18]. Low frequency (LF) oscillations in the 0.05–0.15 Hz band are in the supine position highly dependent on vagal activity, whereas the LF oscillations in the upright position are mediated by interaction between sympathetic and vagal activity [16, 18]. The spectral power of the HF and LF component can be estimated in 5-min RR interval segments [16–18].

Attenuated circadian blood pressure rhythm with reduced night-time drop is a pathophysiological trait observed both in patients with autonomic neuropathy [20, 21] and in patients with increased UAE (urinary albumin excretion) [8]. The question of a possible causative role of autonomic neuropathy in the development of diabetic nephropathy has emerged [20, 22, 23]. The proposed pathophysiological mechanism is inappropriate renal vasodilatation permitting a more ready transmission of a higher night-time blood pressure to the glomeruli.

This hypothesis would be strengthened if normoalbuminuric patients at increased risk of progression to microalbuminuria proved to have disturbed autonomic function in combination with attenuated circadian blood pressure rhythm.

The aim of the present study was: i) to characterize a large group of normoalbuminuric IDDM patients according to UAE, 24-h ambulatory blood pressure, and sympathovagal balance; and ii) to determine whether disturbances in autonomic function and circadian blood pressure rhythm are detectable in normoalbuminuric patients at increased risk of progression to microalbuminuria.

## Subjects and methods

**Patients.** 117 IDDM patients were consecutively recruited from outpatient clinics at our and two nearby hospitals. Patients had to be normoalbuminuric (UAE < 20 µg/min in at least two out of three overnight collections) and without other chronic diseases. None received (or had earlier received) antihypertensive or other medical treatment apart from insulin. UAE was measured by RIA and expressed as geometric mean of three overnight collections made within 1 week. HbA<sub>1c</sub> was determined by HPLC (non-diabetic range 4.4–6.4%). Blood glucose was determined (Reflolux II; Boehringer Mannheim, Mannheim, Germany) in association with autonomic testing.

Patients were classified according to participation in leisure-time physical activity as: *passive* (not participants), *moderate* (physical exercise once or twice a week), and *active* (Physical exercise more than twice a week). Tobacco consumption was graded as *non-smokers* (without daily use of tobacco for at least the last year), *moderate smokers* (less than 15 cigarettes per day) and *heavy smokers* (More than 15 cigarettes per day). Five patients smoking one packet of pipe tobacco per week were classified as moderate smokers.

The study was approved by the local ethics committee and patients gave their written informed consent.

**Autonomic testing.** According to written and oral instructions, patients had to refrain from smoking, eating, and drinking 2 h before the examination which took place in a quiet room with subdued light, with none other than the laboratory technician who performed the examination present. Patients rested in the supine position for 15 min breathing quietly at their normal respiration rate and afterwards RR intervals were measured using an on-line telemetrical transmitter (VariaPulse TF3; Sima Media Olomouc [24]). Short-term power spectral analysis was obtained in three positions (supine-standing-supine) each of at least 5 min, resulting in three times 256 artifact-free heart beats. In addition to automatic filtering (using a recognition algorithm), each data set was visually scrutinized for ventricular ectopic beats. Frequent ventricular extrasystoles made power spectral analysis impossible in two patients (1.7%). In the calculations a modified fast Fourier transformation was used (Coarse-graining) which allows extraction of a broadband non-harmonic 'noise', contaminating particularly the lower frequencies (1/f component) [25]. Low frequency (LF; 0.05–0.15 Hz) and high frequency (HF; 0.15–0.50 Hz) components were determined and expressed as ln ms<sup>2</sup>. Coefficient of component variance (CCV; square root of power/mean RR) was calculated for the two components. This parameter accounts for a possible impact of the mean RR level on the

**Table 1.** Clinical characteristics

	All patients ( <i>n</i> = 117)	UAE > 4.2 µg/min ( <i>n</i> = 59)	UAE < 4.2 µg/min ( <i>n</i> = 58)	<i>p</i> value
UAE (µg/min)				
geometric mean $\times/\pm$ tolerance factor	4.4 $\times/\pm$ 1.7	6.6 $\times/\pm$ 1.4	2.9 $\times/\pm$ 1.4	NR
Age (years)	38 $\pm$ 9.6	38 $\pm$ 10.2	38 $\pm$ 9.0	NS
Duration (years)	18.6 $\pm$ 10.1	18.7 $\pm$ 9.8	18.5 $\pm$ 10.5	NS
Gender (% male)	45 %	39 %	52 %	NS
BMI (kg/m <sup>2</sup> )	23.9 $\pm$ 2.6	24.1 $\pm$ 3.0	23.7 $\pm$ 2.2	NS
Insulin (units/kg body weight)	0.63 $\pm$ 0.18	0.66 $\pm$ 0.18	0.60 $\pm$ 0.17	0.06
HbA <sub>1c</sub> (%)	8.4 $\pm$ 1.1	8.6 $\pm$ 1.2	8.2 $\pm$ 1.0	0.03
Blood glucose (mmol/l)	10.8 $\pm$ 5.6	11. $\pm$ 5.6	10.2 $\pm$ 5.6	NS
Smoking status (%)				
Non-smoking – moderate – heavy	69–8–23	68–7–25	70–9–21	NS
Physical activity (%)				
Not active – moderate – active	66–28–6	71–22–7	61–33–6	NS

(mean  $\pm$  SD, except when indicated)

NR: Not relevant. NS: not significant  $p > 0.25$

amplitude of the HF and LF component [18]. In addition MSSD (mean square of successive R-R differences) was calculated. Reproducibility of spectral power data was assessed in 27 healthy control subjects: The intra-individual coefficient of variation of two measurements performed within 1 week was for power LF: 15.9%, and for power HF 11.3%.

Three cardiovascular reflex tests were also performed: heart rate variation to deep breathing (inspiration/expiration difference, average of two determinations), heart rate response to standing up (30:15 ratio), and blood pressure response to standing up. The tests were performed and evaluated in accordance with the procedure described by Ewing et al. [26].

**24-h blood pressure measurements and circadian blood pressure variation.** Ambulatory blood pressure (AMBP) was measured by an oscillometric technique (Spacelabs 90207, Redmond, Wash., USA). Readings were obtained at 20-min intervals throughout 24 h. Measurements were performed during a day with normal activities at home or at work. Individually reported sleeping times were implemented in the calculation of day and night-time blood pressure. No records with more than 2 missing hours were accepted, on this basis measurements from two patients (1.7%) were excluded.

### Statistical analysis

Before analysis UAE and power spectral data were log transformed to approximate normal distribution. Differences between the two groups were tested by Student's *t* test (continuous parameters) and chi-square test (discrete variables). Repeated measurements were analysed by repeated measurements ANOVA. Correlations were analysed using Pearson's test. Multiple regression analysis was performed by stepwise linear regression analysis,  $\beta$  indicating the regression coefficient. Differences with  $2p$  greater than 0.05 were considered not significant (NS). Group results are given as mean  $\pm$  SD, except for UAE, which is presented as geometric mean  $\times/\pm$  tolerance factor.

### Results

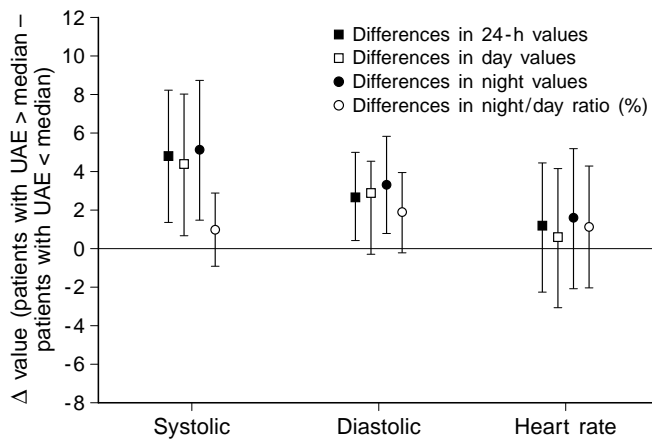
Clinical characteristics of the patients are given in Table 1. Patients were divided according to the median UAE (4.2 µg/min), and the groups were similar regarding age, duration of diabetes, gender, BMI, level of physical activity, and cigarette smoking. Eight out of the 59 patients (13.5%) in the higher UAE group had excretion rates exceeding 10 µg/min. Blood glucose at the time of examination was similar in the two groups, whereas long-term glycaemic control was poorer in the group with UAE above the median and insulin consumption tended to be higher. Ambulatory blood pressure data are given in Table 2, and differences between the two groups with 95% confidence intervals are depicted in Figure 1. The day for the blood pressure measurement was characterized according to either working or day off work, the two groups were similar in this respect. Systolic and diastolic blood pressure were significantly higher in the group with UAE above the median for both 24-h, day, and night measurements. Clinic blood pressure (mean of three random zero measurements) confirmed these results (124  $\pm$  16/83  $\pm$  9 mmHg in the high normal UAE group compared to 117  $\pm$  11/79  $\pm$  7 mmHg in the low normal group,  $p < 0.01$  and  $p < 0.02$ , respectively). There were no significant differences in heart rate between the two groups. As depicted in Figure 1 night differences were numerically bigger compared to day differences for both systolic and diastolic AMBP as well as heart rate, and diastolic night/day ratio tended to be higher (i.e. attenuated circadian rhythm) in the high normal UAE group (82.5  $\pm$  6.2 vs 80.6%  $\pm$  5.4,  $p = 0.08$ ). Six patients (5.2%) were non-dippers (five in the high-normal UAE group and one in the low-normal UAE group) when defined as systolic and diastolic night-time drop of less than 10% [27]. These patients had

**Table 2.** Ambulatory blood pressure data

		UAE > 4.2 µg/min (n = 58)	UAE < 4.2 µg/min (n = 57)	p value
Type of day for AMBP (%) (working – half of each – day off)				
		38–4–58	38–6–56	NS
Systolic AMBP (mmHg)	24 h	125 ± 10.1	120 ± 8.4	< 0.01
	Day	130 ± 10.7	126 ± 9.1	0.02
	Night	114 ± 10.7	109 ± 8.8	< 0.01
	Night/day ratio (%)	87.8 ± 5.0	86.9 ± 5.2	NS
Diastolic AMBP (mmHg)	24 h	76 ± 7.2	74 ± 5.1	0.02
	Day	81 ± 7.5	79 ± 5.5	0.08
	Night	67 ± 7.8	63 ± 5.4	< 0.01
	Night/day ratio (%)	82.5 ± 6.2	80.6 ± 5.4	0.08
Heart rate (beats/min)	24 h	77 ± 9.1	76 ± 9.1	NS
	Day	82 ± 9.4	81 ± 10.3	NS
	Night	67 ± 10.1	65 ± 9.6	NS
	Night/day ratio (%)	81.7 ± 8.2	80.6 ± 8.9	NS

(mean ± SD)

NS: Not significant  $p > 0.25$



**Fig. 1.** Δ Systolic AMBP, Δ diastolic AMBP, Δ heart rate, and Δ night/day ratio (%) between normoalbuminuric IDDM patients divided according to median UAE value (4.2 µg/min). Mean differences with 95 % confidence intervals

similar age, duration, glycaemic status and gender composition compared to the dipping patients. The non-dippers had significantly reduced indices for autonomic function (power HF:  $5.0 \pm 0.45$  vs  $5.8 \pm 1.44$  ln  $ms^2$  ( $p < 0.01$ ), power LF:  $4.6 \pm 0.87$  vs  $5.7$  ln  $ms^2 \pm 1.3$  ( $p = 0.02$ ) compared to the dippers. Furthermore, the non-dippers had higher UAE ( $6.4 \times \pm 1.46$  vs  $4.3 \times \pm 1.7$  µg/min,  $p < 0.05$ ) and attenuated night/day variation for heart rate ( $88.6 \pm 10.3$  vs  $80.8 \pm 8.3$ ,  $p < 0.03$ ). In this material, the 10% percentile for circadian blood pressure variation was demarcated by a systolic and diastolic night drop of 12.2%. With this cut off for reduced circadian variation, there were similar significant differences regarding autonomic indices, UAE, and night/day variation in heart rate (data not shown).

Table 3 shows the results of the autonomic tests in patients with low and high normal UAE. The group with UAE above the median had significantly

reduced power LF and power HF (depicted in Fig. 2),  $p = 0.01$  and  $p < 0.04$ . CCV-HF which accounts for differences in mean RR level was still significantly reduced in the high-normal UAE group. In addition, these patients had significantly reduced RR levels (faster heart rates), as well as reduced MSSD ( $p = 0.05$  and  $p = 0.01$ ). The conventional cardiovascular reflex tests revealed no statistically significant differences between the two groups, although indices were numerically reduced for the high normal UAE group (Table 4). Inspiration/expiration ratio and power HF were significantly correlated ( $r = 0.5$ ,  $p < 0.001$ ) and patients in the three groups of inspiration/expiration differences (abnormal/borderline/normal) segregated with respect to power HF ( $4.32 \pm 1.54$ ,  $5.43 \pm 1.16$ , and  $6.04 \pm 1.33$  ln  $ms^2$ ,  $p < 0.001$ ). Blood glucose (or HbA<sub>1c</sub>) and power HF or power LF were not associated ( $r < -0.13$ ,  $p > 15\%$ ).

Correlations between diurnal variation (heart rate and blood pressure), UAE, and autonomic indices are described in Table 5. Night/day ratio of heart rate and of arterial blood pressure were positively correlated. Night values for both heart rate and diastolic AMBP were inversely associated with HF and LF power and there were negative correlations between diurnal heart rate variation as well as diastolic AMBP and autonomic indices, i.e. attenuation in autonomic indices was associated with blunted diurnal variation (higher night/day ratios). There were no significant associations between UAE and autonomic indices. Correlations were significant between UAE and AMBP with the strongest positive association for night-time blood pressure leading to significant correlations between UAE and diastolic night/day ratio (Fig. 3).

Multiple, stepwise regression analysis was performed with diastolic night/day ratio as dependent variable. The following variables were entered as

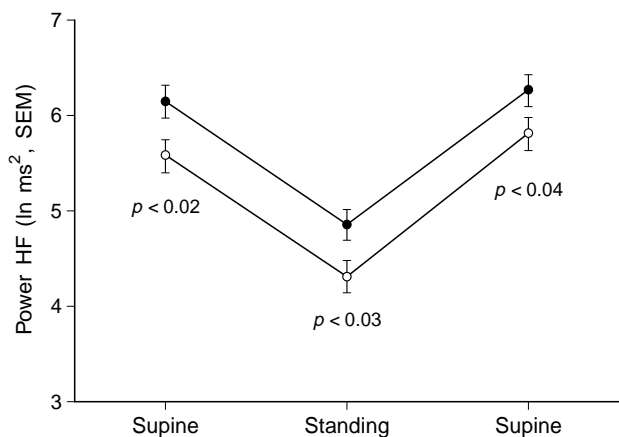
**Table 3.** Heart rate variability

		UAE > 4.2 µg/min (n = 58)	UAE < 4.2 µg/min (n = 57)	p (between groups)	ANOVA (repeated measurements)
Power HF (1n ms <sup>2</sup> )	Supine	5.47 ± 1.36	6.10 ± 1.43	< 0.02	Group effect: p = 0.01 Postural effect: p < 0.01
	Standing	4.15 ± 1.44	4.73 ± 1.29	< 0.03	
Power LF (1n ms <sup>2</sup> )	Supine	5.71 ± 1.39	6.23 ± 1.36	0.04	Group effect: p < 0.04 Postural effect: p = 0.11
	Supine	5.48 ± 1.18	5.80 ± 1.41	NS	
	Standing	5.53 ± 1.36	5.86 ± 1.23	NS	
CCV HF (%)	Supine	5.20 ± 1.13	5.79 ± 1.19	< 0.01	Group effect: p < 0.02 Postural effect: p < 0.01
	Supine	2.07 ± 1.6	2.68 ± 1.6	< 0.03	
	Standing	1.37 ± 1.1	1.68 ± 1.0	< 0.03	
CCV LF (%)	Supine	2.39 ± 2.0	2.82 ± 1.7	0.06	Group effect: p = 0.08 Postural effect: p < 0.01
	Supine	1.97 ± 1.1	2.33 ± 1.5	NS	
	Standing	2.66 ± 1.7	3.00 ± 1.9	NS	
Centerfreq. High (mHz)	Supine	1.70 ± 1.0	2.18 ± 1.2	0.01	Group effect: NS Postural effect: p < 0.01
	Supine	231 ± 47	226 ± 51	NS	
	Standing	209 ± 58	209 ± 47	NS	
Centerfreq. Low (mHz)	Supine	238 ± 51	234 ± 53	NS	Group effect: NS Postural effect: p < 0.01
	Supine	86 ± 24	94 ± 28	NS	
	Standing	80 ± 16	86 ± 20	NS	
Mean R-R (ms)	Supine	97 ± 29	96 ± 25	NS	Group effect: p = 0.05 Postural effect: p < 0.01
	Supine	916 ± 108	963 ± 140	0.04	
	Standing	743 ± 105	759 ± 116	NS	
MSSD (1n ms <sup>2</sup> )	Supine	921 ± 116	965 ± 145	0.07	Group effect: p = 0.01 Postural effect: p < 0.01
	Supine	6.54 ± 1.15	7.14 ± 1.27	0.01	
	Standing	5.60 ± 1.11	5.98 ± 1.08	0.06	
	Supine	6.77 ± 1.29	7.29 ± 1.24	0.03	

(mean ± SD)

Power HF, Power in the high frequency band (0.15–0.50 Hz); Power LF, Power in the low frequency band (0.05–0.15 Hz);

CCV, coefficient of component variance (square root of power/mean RR); MSSD, mean square of successive R-R differences. NS: Not Significant (p &gt; 0.10)

**Fig. 2.** Power HF (ln ms<sup>2</sup>) in 115 normoalbuminuric IDDM patients with UAE above (○), or below (●) median UAE (4.2 µg/min)

possible predictors: gender, age, duration of diabetes, UAE, HbA<sub>1c</sub>, smoking, power LF<sub>standing</sub>, power HF<sub>supine</sub>, type of day, and level of physical activity. Four variables were significantly associated with diastolic night/day ratio: type of day ( $\beta = 0.30$ ), UAE ( $\beta = 0.23$ ), Power LF<sub>standing</sub> ( $\beta = -0.24$ ), and level of physical activity ( $\beta = 0.20$ ), adjusted  $R^2$ : 0.18, ANOVA < 0.001). Reduced power LF<sub>standing</sub> and high levels of UAE were associated with high night blood

pressure, whereas days off and high physical activity were associated with relatively low daytime blood pressure and thus reduced diurnal variation.

## Discussion

Our study is the first to address autonomic function (assessed by spectral analysis) and 24-h AMBP in a large number of well characterized, strictly normoalbuminuric IDDM patients. Longitudinal studies [4, 5, 28–30] have shown that high normal UAE, poor glycaemic control and perhaps high blood pressure are predictors of progression to microalbuminuria. We have found that normoalbuminuric patients at increased risk of progression (characterized by significant elevations in all the three progression parameters mentioned above) have a sympathovagal balance significantly different from normoalbuminuric patients with low UAE. The two groups were very similar in respect to all factors known to influence autonomic function (age, gender, diabetes duration, smoking, and level of physical activity). The data obtained extends the work of Mølgaard et al. [9, 10] who have shown that at the microalbuminuric stage a significant autonomic dysfunction is already present. Hansen et al. [31] have recently described a positive correlation between circadian variation of heart

**Table 4.** Conventional cardiovascular reflex tests

	UAE > 4.2 $\mu\text{g}/\text{min}$ ( $n = 59$ )	UAE < 4.2 $\mu\text{g}/\text{min}$ ( $n = 58$ )	<i>p</i> value
Inspiratory-expiratory difference (beats/min)	20.9 $\pm$ 9.3	22.7 $\pm$ 9.1	NS
[abnormal ( $\leq 10$ )-borderline(11–14)-normal( $\geq 5$ )] (%)	[14–18–68]	[9–11–80]	
30 : 15 ratio	1.27 $\pm$ 0.18	1.29 $\pm$ 0.21	NS
[abnormal( $\leq 1.00$ )-borderline(1.01–1.03)-normal( $\geq 1.04$ )] (%)	[2–0–98]	[7–5–88]	
Postural blood pressure change (mmHg)	4.2 $\pm$ 8.9	4.3 $\pm$ 7.9	NS
[abnormal( $\geq 30$ )-borderline(11–29)-normal( $\leq 10$ )] (%)	[0–3–97]	[0–3–97]	

(mean  $\pm$  SD)NS, not significant ( $p > 0.10$ )**Table 5.** Correlations between AMBP data, spectral indices, and UAE ( $n = 115$ )

	<i>r</i>	<i>p</i> value
Heart rate N/D ratio ~		
systolic N/D ratio	0.31	< 0.01
diastolic N/D ratio	0.33	< 0.01
MSSD	– 0.23	0.01
Power HF (supine)	– 0.20	0.03
Power LF (standing)		NS
Night heart rate ~		
MSSD	– 0.31	< 0.01
Power HF (supine)	– 0.24	< 0.01
Power LF (standing)	– 0.25	$\pm$ 0.01
Diastolic N/D ratio ~		
UAE	0.22	0.02
MSSD		NS
Power HF (supine)		NS
Power LF (standing)	– 0.22	< 0.02
Diastolic Night AMBP ~		
UAE	0.27	< 0.01
MSSD		NS
Power HF (supine)	– 0.19	< 0.05
Power LF (standing)	– 0.33	< 0.01

N/D ratio, night/day ratio, Power HF, power in the high frequency band (0.15–0.50 Hz), Power LF, power in the low frequency band (0.05–0.15 Hz), MSSD, mean square of successive R-R differences, NS, not significant ( $p > 0.10$ )

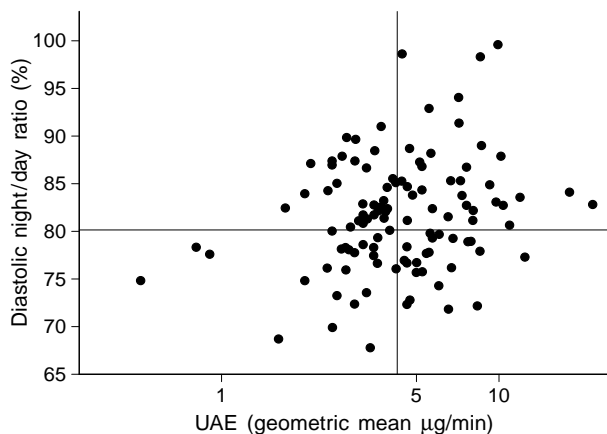
rate and of blood pressure in IDDM patients with nephropathy and suggests a relative lack of sympathetic withdrawal as a possible explanation for nocturnal hypertension, although no specific measures of sympathovagal function were performed. Our data extend this finding to normoalbuminuric patients and furthermore we found significant negative correlations between more specific indices of autonomic function (power LF and MSSD) and night-time heart rate as well as night-time blood pressure, i. e. attenuation in autonomic indices is associated with blunted diurnal variation in both heart rate and arterial blood pressure.

As to the differentiation between parasympathetic and sympathetic function by spectral analysis, the latter is thought to be mediated through RR interval oscillations in the LF band in the upright position [16]. The technique for specific assessment of sympathetic activity is at its present stage, however still

incomplete. Thus, the interpretation of the changes observed in our study is confined to combined para- and sympathetic disturbances. The combination of higher blood pressure and shorter mean RR intervals however, strongly suggests sympathetic overactivity in the putative high-risk group. Our data indicate that high normal UAE is accompanied by signs of autonomic dysfunction. Only longitudinal studies can reveal whether this represents coexistence of independent variables with a common background, or if autonomic disturbances play a pathogenetic role in the very early development of diabetic nephropathy [20, 22, 23, 32].

IDDM patients with autonomic neuropathy [20, 21] have an attenuated circadian BP rhythm with reduced night-time drop of blood pressure [20, 21]. The same is true for IDDM patients with increased UAE [8]. Recent data indicate that diabetic patients may have impaired circadian modulation of sympathovagal activity [19]. Lack of sympathetic withdrawal during sleep has been suggested as an important feature of nocturnal hypertension in IDDM patients with nephropathy [31]. Consequently, the question of a possible causative role of autonomic neuropathy in the development of diabetic nephropathy has been raised [20, 22, 23]. In our patients with high-normal UAE both blood pressure and heart rate elevations were greater numerically for the night period and diastolic night/day ratio tended to be higher. Furthermore, there was a significant correlation between UAE and diastolic night/day ratio and when dichotomizing patients into dippers and non-dippers, the non-dipping patients had significantly reduced indices of autonomic function, confirming that also in normoalbuminuric patients, attenuated circadian variation of blood pressure is associated with autonomic dysfunction.

The frequency of non-dippers was lower than reported in several other studies [27]. The reason is probably twofold: The patients in our study were all normoalbuminuric and their reported sleeping times were used in the calculation of day and night-time blood pressure thus avoiding erroneously overestimating the fraction of patients with abnormal circadian variation [33]. The use of the 10th percentile for abnormal circadian blood pressure variation might



**Fig. 3.** Association between diastolic night/day ratio and UAE in 115 normoalbuminuric IDDM patients. Dotted lines indicate median values

be more appropriate when patient-reported sleeping times are used. Patients with diurnal variation below the 10th percentile had significantly reduced autonomic indices confirming the results mentioned above.

With power spectral analysis significant differences in autonomic function were revealed between patients with high-normal and low-normal UAE, as well as significant differences between non-dipping and dipping patients. These differences were not detectable by conventional tests, confirming that power spectral analysis is more sensitive than ordinary bedside tests to detect early autonomic changes [9, 14, 34, 35].

The combination of a poorer glycaemic status and a trend towards higher insulin consumption in patients with UAE above the median could suggest insulin resistance in this group, as has been demonstrated in microalbuminuric patients compared to normoalbuminuric patients [36]. In addition, higher insulin requirement has been described in normoalbuminuric IDDM patients later progressing to micro- or macroalbuminuria [37]; however, we did not perform specific evaluations of this (e.g. glucose clamps).

Patients in this study were selected with regard to UAE (strictly normoalbuminuria) and blood pressure (no present or earlier antihypertensive treatment). Even so, we found clear associations between albumin excretion and blood pressure as well as autonomic indices. Our findings stress that albumin excretion should be considered as a continuum; although demarcation in the clinical situation is an operational necessity, changes both in blood pressure and autonomic function are demonstrable before transition to microalbuminuria, provided methods with sufficient sensitivity are implemented.

In conclusion, when comparing normoalbuminuric IDDM patients at increased risk of progression to

microalbuminuria (UAE above the median) with putative low-risk patients (UAE below the median value), we found significantly higher blood pressure in combination with significant differences in sympathovagal balance and higher HbA<sub>1c</sub> in the group with high normoalbuminuria. Autonomic dysfunction may interact with poor glycaemic control and blood pressure elevation in determining nephropathy risk in IDDM patients.

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