Nephrol Dial Transplant (1998) 13: 326–332

Nephrology
Dialysis
Transplantation

Original Article

Ambulatory blood pressures and autonomic nervous function in normoalbuminuric type I diabetic patients

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Abstract

Background. In insulin-dependent diabetes mellitus (IDDM) patients with normal urinary albumin excretion (UAE) controversy exists about the presence of blood pressure (BP) elevation and an attenuation of BP decline during sleep.

Subjects and methods. These issues were studied in 60 IDDM patients and 55 healthy control subjects with 24 h ambulatory blood pressure monitoring. In addition, in the IDDM patients two cardiovascular reflex tests were performed to study autonomic nervous function.

Results. 55 IDDM patients had 4.4/3.1 mm Hg higher 24 h systolic/diastolic pressures when compared with 55 healthy matched controls ($P=0.005/0.009$). The diastolic BP decline during sleep was significantly attenuated in IDDM patients compared to healthy volunteers (18.9 vs 22.2%, $P=0.01$). The maximum/minimum (max/min) ratio of the RR′ interval of the lying to standing test (lower values indicating (incipient) parasympathetic dysfunction) was positively related to the decline of the diastolic BP during sleep in the diabetic patients. This relationship did not persist after adjusting for decline of heart rate during sleep.

Conclusions. IDDM patients with normal UAE, compared with healthy control subjects, have higher BPs during both the waking and sleeping periods and a decreased diastolic BP decline during sleep. In these patients both the diastolic BP decline and the heart rate decline during sleep were related to the max/min ratio. These findings are consistent with the hypothesis that attenuation of diastolic BP decline during sleep is at least partly due to (incipient) damage to the parasympathetic nervous system, which, through a blunted heart rate decline, leads to a decreased decline of cardiac output during sleep.

Key words: ambulatory blood pressure; autonomic nervous function; insulin-dependent diabetes

Introduction

Insulin-dependent diabetes mellitus (IDDM) is accompanied by an increased risk of morbidity and mortality, which is mainly due to cardiovascular disease and renal failure. Microalbuminuria, defined as urinary albumin excretion (UAE) of 30–300 mg/24 h, identifies patients at risk for these complications at an early stage. Elevation of blood pressure plays an important role in the progression of established renal disease and cardiovascular complications of IDDM [1]. At an earlier stage, i.e. before the presence of microalbuminuria, small elevations of the systemic blood pressure during the entire day or a blunted decline of blood pressure during sleep (considered by some authors as an independent cardiovascular risk factor in essential hypertension) [2] may be important in the development of diabetic nephropathy (DN), since it is thought [3] that renal autoregulation of blood pressure is impaired in IDDM patients, and thus higher systemic pressures will lead to higher intraglomerular pressures.

It is controversial whether blood pressure elevation in IDDM patients is already present in the normoalbuminuric state or whether it emerges in the microalbuminuric state. Studies using ambulatory blood pressure monitoring (ABPM) have shown higher blood pressures during both the waking and the sleeping periods and a diminished decline of blood pressure during sleep in microalbuminuric IDDM patients when compared with both normoalbuminuric counterparts and with healthy controls [4–7]. Studies in normoalbuminuric IDDM patients have not been conclusive, but

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have generally shown tendencies towards higher blood pressures during the entire 24 h period and towards an attenuation of blood pressure decline during sleep [4–10].

In healthy volunteers, it has been suggested that the blood pressure decline during sleep is due to a decrease in cardiac output, mainly caused by a decrease in heart rate [11]. In addition, attenuation of the decline in blood pressure during sleep in elderly healthy subjects and patients with hypertension is associated with an impaired decline in heart rate during sleep [12]. In diabetes, available studies suggest that the presence of (incipient) diabetic autonomic neuropathy (DAN) is the main cause of a diminished blood pressure decline during sleep [13–18]. However, these studies are difficult to interpret as mixed groups of patients (with IDDM and NIDDM, with and without increased albuminuria, and with and without antihypertensive treatment) were studied and thus several confounding factors may play a role.

Therefore, we wished, firstly, to elucidate the controversy about blood pressure elevation and blood pressure decline during sleep in normoalbuminuric IDDM patients by studying a large group of patients and carefully matched healthy control subjects, and, secondly, to test the hypothesis that (incipient) DAN, possibly through a blunted decrease of heart rate during sleep, is associated with a disturbance of the blood pressure decline during sleep in IDDM in the absence of confounding factors such as albuminuria and antihypertensive therapy.

Subjects and methods

Between January 1994 and January 1996, a cross-sectional study of IDDM patients was performed in the outpatient clinics of the Departments of Medicine of five secondary referral centres: the IJsselland Ziekenhuis in Capelle aan de IJssel, the Sint Jans-Gasthuis in Weert, the De Weverziekenhuis in Heerlen, the Franciscus Ziekenhuis in Roosendaal, and the Sint Franciscus Ziekenhuis in Rotterdam. IDDM was defined as the onset of diabetes before the age of 30 and the necessity of insulin therapy within 6 months after the onset of the disease. Since it was aimed to investigate IDDM patients with normal UAE, without renal insufficiency and without antihypertensive treatment, the following inclusion criteria were formulated: age <65 years; no pregnancy; body mass index (BMI) <29 kg/m^2; absence of clinical atherosclerotic disease; serum creatinine <120 μmol/l; UAE <30 mg/24h; serum total cholesterol <8 mmol/l and no treatment with antihypertensive drugs. All IDDM patients who fulfilled these criteria and gave informed consent were included in the study. The protocol had been approved by the appropriate medical ethics committees.

Determinations of serum creatinine and cholesterol were performed by routine methods. UAE was defined as the median of three 24 h urine collections and measured with an immunoturbidimetric technique (Behring, Germany). Glycated haemoglobin A (HbA1c) was determined with a high pressure liquid chromatography technique (normal range, 3.4–6.5%).

A total of 60 IDDM patients (37 men, 23 women) were included and underwent the investigations described below. To compare ABPM data between IDDM patients and controls, we matched 55 IDDM patients for age and gender with 55 healthy controls, allowing an age difference of ± 5 years. We did not match for BMI. Since BMI is positively correlated with blood pressure and since attempts at improved metabolic control in IDDM are associated with slight increases in BMI [19], we wished to study whether body mass is an intermediate between IDDM and hypertension. Control subjects did not have a history of hypertension, renal disease or any metabolic or endocrine disorder, and did not use any medication or special diet. Both patients and controls were included equally over the seasons.

Ambulatory blood pressure measurements (ABPM)

ABPM was performed with a Spacelabs 90207 monitor (Spacelabs Inc, Redmond, WA, USA). At the start of each ABPM registration, three measurements were taken with the SpaceLabs monitor in the outpatient clinic. The means of these three blood pressure readings were considered as office blood pressures. Thereafter, blood pressure readings were taken at 15 min intervals from 07:00 to 22:00 and at 20 min intervals from 22:00 to 07.00. Results of blood pressure measurements were not displayed on the monitor. ABPM was repeated in patients who had ABPM recordings with $>25\%$ missing values or more than two missing consecutive hours. Mean systolic and diastolic blood pressure values and mean heart rates of the waking and sleeping periods were calculated as means of hourly averages. The waking period was taken from 10:00 till 23:00; the sleeping period from 01:00 to 07:00 (i.e. 6 h). This method provided good estimates of blood pressures during the waking and sleeping periods, especially with a traditional sleep pattern (i.e. going to bed in the evening before 01:00 and awaking in the morning before 10.00 [20]. The blood pressure decline during sleep (mm Hg) was calculated as the difference of the mean systolic or diastolic blood pressures during the waking period (BPawake), and the mean systolic or diastolic blood pressures during the sleeping period (BPasleep). The proportional systolic and diastolic blood pressure declines (DipBPsys or DipBPdia) during sleep were calculated as: DipBP (%) = (BPawake − BPasleep)*100/BPawake. Declines of heart rates during sleep were calculated in a similar way.

Autonomic nervous function

Autonomic function tests were performed before the start of the ABPM measurements. Autonomic function was estimated from two cardiovascular reflex tests: the heart rate variability during deep breathing and the lying to standing test [21]. Execution of these tests and analysis of heart rate variability (HRV) were performed using a computer device 'CARE' developed by the Department of Medical Physics, Vrije Universiteit, Amsterdam, The Netherlands.

Heart rate variability during deep breathing (IE test)

The subjects were instructed to breath deeply at a frequency of 6 cycles/min in a supine position. The inspiration and expiration intervals were both 5 s. This rhythm was achieved by acoustic signals of the computer, which indicate that one has to change from inspiration to expiration and *vice versa*. An electrocardiogram (ECG) was recorded during the entire procedure. For each breathing cycle, the duration of the

longest interval between two R waves of the ECG (RR′ interval, longest: RR_{max}) and the duration of the shortest RR interval (RR_{min}) of the ECG were determined by the computer. From at least three breathing cycles the mean IE difference was calculated as: mean IE (ms) = mean RR_{max} − meanRR_{min}.

Lying to standing test (LS test)

Prior to the test the subjects rested in a supine position for 4 min. An ECG was recorded during the last 30 s. Subsequently, the computer provided an acoustic signal instructing the subject to rise quickly. Thereafter the computer recorded the ECG signal for another 60 s. From this registration the (RR_{max} (in ms), defined as the difference between the shortest RR interval in the first 15 s after standing up and the mean RR interval in the 30 s before standing up, was calculated. In addition, the RR_{max}/RR_{min} ratio (or max/min ratio or 30 : 15 ratio) was defined according to Ewing [21] the ratio, after standing up, of the duration of the longest RR intervals around the 30th and the 15th heart beat.

Statistical analysis

Groups were compared using unpaired Student's *t*-tests. Blood pressure differences between the groups were analysed with multiple linear regression analysis using diabetes and BMI as independent variables. The difference between the proportions of subjects in each group having a blood pressure decline $<10\%$ was tested with χ^2 analysis. Pearson's correlations were used to explore relationships among several variables. The relationships among systolic and diastolic blood pressures, diastolic blood pressure decline, and the max/min ratio were analysed with multiple linear regression using the max/min ratio as independent variable. All testing was two-sided, with $P<0.05$ considered to be statistically significant. All tests were performed with the Statistical Package of Social Sciences (SPSS) software package.

Results

Blood pressures

Ambulatory (not office) blood pressures and ambulatory heart rates were higher in normoalbuminuric IDDM patients than in control individuals (Table 1). Diastolic, but not systolic, blood pressure decline during sleep was significantly reduced in IDDM patients compared to control subjects. Recently, it has been demonstrated that blood pressures can be overestimated by oscillometric devices when compared with values obtained with a sphygmomanometer, especially in diabetic patients [22]. In the present study, analysis of simultaneous blood pressure measurements with the Spacelabs device and a sphygmomanometer, using the same blood pressure cuff, revealed that the differences in blood pressure among the groups could not be explained by this phenomenon (data not shown).

Regression analysis was performed to determine whether the blood pressure difference between the groups could be ascribed to the difference in BMI. For all blood pressure estimates, the presence of diabetes was more closely related to blood pressures than was BMI (e.g. 24 h systolic blood pressure = 105.7 + 4.0*DM + 0.55*BMI, where $\beta_1=4.0$, $P=0.011$ and $\beta_2=0.55$, $P=0.11$). The relationship between BMI and blood pressure was not statistically significant in any of these analyses (data not shown). Associations among HbA1c, insulin dose and blood pressure variables were also not statistically significant.

A recent study concluded that blood pressure differences between IDDM patients and control individuals are confined to women [23]. Table 2 shows the characteristics of the study groups according to gender. In women, blood pressures were higher in the IDDM group than in the control group during the waking period. However, in diabetic men, blood pressures were higher during the sleeping period and therefore the diastolic blood pressure decline was significantly blunted in the IDDM men. The diastolic blood pressure decline (%) did not differ significantly between the IDDM men and women ($P=0.13$).

Autonomic function

Median values and ranges of the two autonomic function test in the 60 IDDM patients were 217 (23–614) ms for the IE value, 253 (28–581) ms for the ΔRR_{max} value and 1.39 (1.01–2.08) for the max/min ratio. Significant correlations between the autonomic function tests and systolic and diastolic blood pressures and heart rates are given in Table 3. Blood pressures during the waking period did not correlate significantly with the results of the autonomic function tests, whereas heart rates during both the waking and sleeping periods did. The max/min ratio showed significant correlations with the diastolic, but not with the systolic, blood pressure decline during sleep in the IDDM group. The decline in heart rate during sleep was significantly related to the max/min ratio, the ΔRR_{max} value and the IE value. After adjusting for the decline of the heart rate during sleep, the partial correlation between the max/min ratio and the diastolic blood pressure decline during sleep was not statistically significant. A significant correlation was found between HbA1c and the (RR_{max} value (Pearson's $r=-0.31$, $P=0.02$), but not the max/min ratio or the IE value.

Discussion

The present study was performed to elucidate the controversy about blood pressure and abnormalities in 24 h blood pressure profiles in normoalbuminuric IDDM patients. We found that such patients had $\sim$4 mm Hg higher systolic blood pressures during the waking and the sleeping periods, 2.4 mm Hg higher diastolic blood pressure during the waking period, and 4.4 mm Hg higher diastolic blood pressure during the sleeping period than did matched healthy controls. Previous studies have not shown consistent differences in blood pressures, as measured by ABPM, between normoalbuminuric IDDM patients and healthy con-

Table 1. Patient characteristics and results of 24 h ambulatory blood pressure measurements of 55 normoalbuminuric IDDM patients matched with 55 control subjects. Values given are means with SD in parentheses unless otherwise indicated

	Controls	Normoalbuminuric patients	*P* value
Number (m/f)	55 (32/23)	55 (32/23)	
Age (years)	30.3 (11.0)	31.4 (10.6)	0.6
BMI (kg/m^2)	22.4 (2.3)	23.1 (2.3)	0.10
IDDM duration (years)	–	14.6 (10.0)	–
Serum creatinin (μmol/l)	–	76.3 (10.8)	–
Insulin dose (units/day/kg body weight)	–	0.79 (0.21)	–
HbA1c (%)	–	8.1 (1.3)	–
Successful ABPM (%)	95.8 (4.4)	94.2 (6.5)	0.1
Office blood pressures			
BPsys (mm Hg)	124.3 (9.9)	128.1 (11.0)	0.09
BPdia (mm Hg)	75.6 (8.5)	78.4 (8.5)	0.06
Hypertensives (%)	11	13	0.74
24 h period			
BPsys (mm Hg)	118.1 (8.1)	122.5 (8.1)	0.005
BPdia (mm Hg)	71.0 (6.6)	74.1 (5.4)	0.009
HR (b/min)	71.1 (9.0)	81.8 (8.5)	<0.0001
Waking period			
BPsys (mm Hg)	124.3 (8.6)	128.2 (8.4)	0.02
BPdia (mm Hg)	76.9 (6.3)	79.3 (6.0)	0.04
HR (b/min)	76.4 (10.3)	87.7 (9.1)	<0.0001
Sleeping period			
Bpsys (mm Hg)	106.9 (8.5)	111.3 (8.5)	0.007
Bpdia (mm Hg)	59.8 (7.0)	64.2 (6.5)	0.001
HR (b/min)	60.0 (9.6)	69.8 (9.7)	<0.0001
Declines during sleep			
Dipsys (mm Hg)	17.4 (6.1)	16.9 (6.7)	0.7
Dipdia (mm Hg)	17.1 (5.1)	15.1 (6.2)	0.08
DipHR (b/min)	16.4 (7.9)	18.0 (7.7)	0.29
Dipsys (%)	13.9 (4.5)	13.1 (4.9)	0.3
Dipdia (%)	22.2 (6.3)	18.9 (7.3)	0.01
DipHR (%)	21.1 (9.1)	20.4 (8.5)	0.67
Dipsys $<10\%$ (%)	18	24	0.48
Dipdia $<10\%$ (%)	0	11	0.01

BMI = body mass index; ABPM = 24 h ambulatory blood pressure monitoring; BPsys = systolic blood pressure; BPdia = diastolic blood pressure; HR = heart rate; Hypertensives = systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg; Dipsys = systolic decline of blood pressure during sleep; Dipdia = diastolic decline of blood pressure during sleep; Dip HR = decline of heart rate during sleep.

trols, although tendencies towards higher blood pressures in IDDM patients have usually been observed [4,5,7,10]. Since the present study is the largest study that compares ambulatory blood pressures in normoalbuminuric IDDM patients with those in healthy controls, lack of statistical power in the earlier studies may provide an explanation for these discrepant findings, although genetic differences among populations may also be relevant [4,5,7,10]. Recently, higher blood pressures have been observed in female, but not in male IDDM patients [23]. The present study confirms these results for the waking period, but blood pressures during the sleeping period differed between IDDM patients and controls in males, but not in females. There was a tendency towards higher blood pressure during sleep in females as well. Therefore, the present study indicates that the blood pressure elevation is not limited to male or female IDDM patients, although we cannot exclude that gender differences play a role.

Attenuation of the blood pressure decline during sleep occurs more frequently in diabetic patients than in healthy controls [7,8], but whether this phenomenon is or is not limited to patients with increased UAE is controversial [4,5,8–10]. We found a significant attenuation of the diastolic blood pressure decline during sleep in normoalbuminuric IDDM patients, mainly in male IDDM patients Two earlier studies showed slight, but not significant tendencies towards a diminished nocturnal diastolic blood pressure decline [4,5]; one other study showed a significant attenuation of both systolic and diastolic blood pressure decline [10]. In a recent study in patients with IDDM of short duration (3.9 (SD 2.5) years) and tight metabolic control (HbA1c 7.0 (SD 1.0)%), we have shown that the blood pressure decline during sleep is not different compared with controls [24]. An abnormal blood pressure decline may therefore be acquired during the course of the disease. Although we found no relationship between the diastolic blood pressure decline during sleep and diabetes duration, we did observe a relationship with (incipient) autonomic neuropathy, an acquired complication of IDDM.

Gender differences in blood pressure decline during sleep have not been reported before. Possibly, the male IDDM patients in the present study have relatively more autonomic nervous system dysfunction than the

Table 2. Characteristics of 55 normoalbuminuric IDDM patients and 55 control subjects according to gender. Values given are means with SD in parentheses unless otherwise indicated

	Men		*P* value	Women		*P* value
	Controls	IDDM		Controls	IDDM	
Number	32	32		23	23	
Age (years)	28.5 (10.5)	31.5 (10.4)	0.27	32.8 (11.3)	31.3 (11.1)	0.66
BMI (kg/m^2)	22.4 (2.1)	23.2 (2.2)	0.12	22.3 (2.5)	22.9 (2.4)	0.45
IDDM duration (years)	–	13.8 (9.4)		–	15.7 (10.9)	
Insulin dose (units/day/kg body weight)	–	0.73 (0.19)		–	0.87 (0.20)	
HbA1c (%)	–	8.0 (1.3)		–	8.2 (1.3)	
Successful ABPM (%)	95.9 (4.8)	93.9 (7.3)	0.21	95.6 (3.8)	94.6 (5.2)	0.45
24 h period						
BPsys (mm Hg)	119.5 (8.4)	123.6 (8.5)	0.06	116.1 (7.4)	121.0 (7.3)	0.03
BPdia (mm Hg)	71.7 (6.9)	74.3 (5.6)	0.12	70.1 (6.3)	74.0 (5.3)	0.03
HR (b/min)	68.5 (9.3)	80.6 (8.5)	<0.0001	74.7 (7.3)	83.5 (8.3)	<0.0001
Waking period						
BPsys (mm Hg)	126.0 (9.0)	129.2 (9.0)	0.16	122.0 (7.6)	127.0 (7.5)	0.03
BPdia (mm Hg)	77.5 (6.3)	78.7 (6.4)	0.47	76.0 (6.4)	80.2 (5.6)	0.02
HR (b/min)	73.8 (10.7)	86.5 (8.8)	<0.0001	79.9 (8.7)	89.4 (9.4)	0.001
Sleeping period						
BPsys (mm Hg)	107.5 (9.0)	112.3 (8.1)	0.03	106.0 (7.7)	110.0 (9.0)	0.11
BPdia (mm Hg)	59.7 (7.1)	64.7 (6.2)	0.004	60.0 (7.1)	63.5 (7.0)	0.10
HR (b/min)	57.5 (9.7)	68.3 (9.9)	<0.0001	63.5 (8.5)	71.9 (9.2)	0.003
Declines during sleep						
Dipsys (mm Hg)	18.4 (6.2)	16.9 (6.1)	0.3	16.0 (5.8)	16.9 (7.5)	0.63
Dipdia (mm Hg)	17.8 (4.8)	14.0 (5.6)	0.005	16.0 (5.5)	16.7 (6.7)	0.70
DipHR (b/min)	16.3 (8.9)	18.3 (7.7)	0.36	16.4 (6.5)	17.6 (7.9)	0.60
Dipsys (%)	14.6 (4.5)	13.0 (4.3)	0.15	13.0 (4.5)	13.3 (5.7)	0.87
Dipdia (%)	23.0 (5.8)	17.7 (6.6)	0.001	21.0 (7.0)	20.7 (8.0)	0.89
DipHR (%)	21.6 (10.2)	21.1 (8.7)	0.82	20.4 (7.5)	19.4 (8.4)	0.67
Dipsys <10% (%)	16	22	0.52	22	26	0.73
Dipdia <10% (%)	0	9	0.08	0	13	0.07

BMI = body mass index; ABPM = 24 h ambulatory blood pressure monitoring; BPsys = systolic blood pressure; BPdia = diastolic blood pressure; HR = heart rate; Dipsys = systolic decline of blood pressure during sleep; Dipdia = diastolic decline of blood pressure during sleep; Dip HR = decline of heart rate during sleep.

Table 3. Correlations among autonomic function tests, blood pressures and heart rates, and blood pressure decline during sleep in 60 normoalbuminuric IDDM patients

Variables		Pearson's *r*	*P* value
Blood pressures and heart rate			
BPdia asleep (mmHg)	IE value	−0.29	0.03
	ΔRR_{max} value	−0.29	0.03
	Max/min ratio	−0.18	0.17
Heart rate awake (b/min)	ΔRR_{max} value	−0.30	0.02
	BPdia awake (mm Hg)	0.26	0.04
Heart rate asleep (b/min)	IE value	−0.33	0.009
	ΔRR_{max} value	−0.53	<0.0001
	Max/min ratio	−0.37	0.004
Blood pressure and heart rate declines			
Dipdia (%)	Max/min	0.26	0.044
	ΔRR_{max} value	0.11	0.39
	IE value	0.21	0.12
DipHR (%)	Max/min	0.40	0.001
	ΔRR_{max} value	0.42	0.001
	IE value	0.26	0.045
Dipdia (%) adjusted for DipHR (%)	Max/min	−0.21	0.12

BPdia = diastolic blood pressure; b/min = beats per min; IE value = mean IE-difference (calculated from the deep breathing test); Dipdia = diastolic blood pressure decline during sleep; DipHR = decline of heart rate during sleep; IE value = mean IE difference (calculated from the deep breathing test); ΔRR_{max} value = ΔRR_{max} from the lying to standing test; max/min = max/min ratio derived from the lying to standing test.

female IDDM patients when compared with their male and female controls respectively. This issue cannot be elucidated with the data of the present study, since autonomic function tests were not performed in the control group. Within the IDDM group, the diastolic blood pressure decline during sleep did not differ significantly between men and women and thus the determinants of gender differences in this decline cannot be analysed within the IDDM group. Therefore, further studies are needed to analyse the determinants of these gender differences.

In the IDDM patients, the IE value and the ΔRR_{max} value [lower values indicating (incipient) DAN] were negatively correlated with both the diastolic blood pressure during sleep and the heart rate during sleep, compatible with the hypothesis that damage to the autonomic nervous system is related to higher blood pressures and heart rates during sleep. Both the diastolic blood pressure decline and the heart rate decline during sleep were positively correlated with the max/min value of the LS test. After adjusting for the decline of heart rate during sleep, the correlation between the max/min ratio and the diastolic blood pressure decline during sleep was not significant anymore. Although analysis of correlations cannot establish a cause and effect relation, these data are consistent with the hypothesis that (incipient) DAN in normoalbuminuric patients contributes to a diminished decline of blood pressure during sleep by a diminished decline in heart rate during sleep. This interpretation is consistent with the results of a recent study, in which both a blunted diastolic blood pressure and a blunted heart rate decline during sleep were associated with deterioration of autonomic nervous system function (established with spectral analysis of RR-interval oscillations) in normoalbuminuric IDDM [25]. We were unable to study whether this relationship also exists in healthy controls, but this does not detract from our findings in normoalbuminuric IDDM patients, in whom incipient neuropathy is likely to be much more frequent than in healthy control subjects of similar age [21].

Whether the abnormal blood pressure decline during sleep is a consequence of damage to the parasympathetic or to the sympathetic nervous system is difficult to determine. The max/min ratio of the LS test depends on a vagal reflex, which occurs after recovery or overshoot of blood pressure after standing up caused by sympathetically mediated vasocontriction [26]. Therefore, an abnormal max/min ratio may reflect both parasympathetic and sympathetic dysfunction. In general, damage to the parasympathetic nervous system in IDDM patients is believed to occur earlier in the course of the disease than damage to the sympathetic nervous system [21]; in addition, in non-diabetic subjects the sympathetic nervous system is thought not to play an important role in the decline of blood pressure during sleep [11,27]. However, a recent study [25], using spectral analysis concluded that the attenuation of the diastolic blood pressure decline during sleep in normoalbuminuric IDDM patients was due to a combined dysfunction of both the sympathetic and the parasympathetic nervous systems, but the remaining influence of the sympathetic nervous system after adjusting for the decline in heart rate during sleep was not analysed. We therefore favour the hypothesis that the abnormal diastolic blood pressure decline during sleep is related to damage of the parasympathetic nervous system. The fact that the decline of heart rate during sleep was related to the ΔRR_{max} value and to the IE value (Table 3), which both depend on parasympathetic nervous function, is consistent with this hypothesis.

In conclusion, in the present study, the largest in comparing ambulatory blood pressures in IDDM with normal UAE with those in healthy controls, IDDM patients, compared to healthy control subjects, had higher blood pressures and heart rates during the entire 24 h, the waking and the sleeping periods; in addition, the diastolic blood pressure decline during sleep was blunted, mainly in diabetic men, when compared with control subjects. In the IDDM patients higher diastolic blood pressures during sleep were negatively related to the IE value and the ΔRR_{max} value; the attenuation of the diastolic blood pressure decline during sleep was related to the max/min ratio of the LS test, but not after adjusting for the decline in heart rate during sleep. These data are consistent with the hypothesis that the diminished decline in diastolic blood pressure during sleep is at least partly due to (incipient) damage of the parasympathetic nervous system, leading to an impairment of the heart rate decline and thus the decline of cardiac output during sleep.

Acknowledgements. We thank J. W. F. Elte, MD, PhD, from the Sint Franciscus Gasthuis in Rotterdam, J. G. S. Breed, MD, PhD, from the Sint Jans-Gasthuis in Weert, and P. Biemond, MD, PhD, from the Franciscus Ziekenhuis in Roosendaal for their willingness to ask their patients to participate in the study and for their hospitality to perform the measurements in their department. C. D. A. Stehouwer, MD, PhD, is supported by a Clinical Research Fellowship from the Diabetes Fonds Nederland and the Netherlands Organisation for Scientific Research (NWO).

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Received for publication: 9.6.97
Accepted in revised form: 17.9.97