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ORIGINAL ARTICLE

Factors determining the 24-h blood pressure profile in normotensive patients with type 1 and type 2 diabetes

V Spallone[1], MR Maiello[1], E Cicconetti[1], A Pannone[1], A Barini[2], S Gambardella[1] and G Menzinger[1]

[1]*Department of Internal Medicine, Tor Vergata University, Rome, Italy;* [2]*Institute of Biochemistry, Catholic University, Rome, Italy*

Some controversy still exists about factors involved in the abnormal circadian pattern of blood pressure (BP) in diabetes, while prognostic value of non-dipping condition is being increasingly recognised. This study was aimed at evaluating the relative influence of autonomic neuropathy (AN) and albumin excretion on 24-h BP profile in type 1 and type 2 diabetes. We measured AN cardiovascular tests, 24-h ambulatory BP, and urinary albumin excretion rate (UAE) in 47 type 1 and 34 type 2 normotensive non-proteinuric diabetic patients. In type 1 diabetic patients day–night differences (Δ) in systolic and diastolic BP were lower in those with AN than in those without (3 ± 9 *vs* 10 ± 6%, $P < 0.01$, and 8 ± 9 *vs* 16 ± 6%, $P < 0.001$), and in univariate regression analysis they were inversely related to both autonomic score, index of degree of AN ($r = -0.61$, $P < 0.001$ and $r = -0.65$, $P < 0.001$), and to 24-h UAE ($r = -0.39$, $P < 0.01$ and $r = -0.46$, $P < 0.001$). In type 1 diabetic patients AN was also associated with lower nocturnal decrease in UAE (patients with AN *vs* without AN: −37 ± 214 *vs* 49 ± 37%, $P < 0.05$), and with a stronger relationship between simultaneous 24-h UAE and 24-h BP (for systolic BP patients with AN *vs* without AN: $r = 0.62$, $P < 0.01$ *vs* $r = 0.28$, NS). In type 2 diabetic patients Δ systolic BP was reduced in patients with AN compared to those without (4 ± 7 *vs* 10 ± 4%, $P < 0.01$), and it was related only to autonomic score ($r = -0.42$, $P < 0.01$). Using a stepwise regression analysis, in type 1 diabetic patients autonomic score was the variable of primary importance for Δ BP, while in type 2 diabetic patients it was the unique determinant not only of Δ systolic BP but also of 24-h systolic BP. In conclusion, AN is the pivotal factor of blunted nocturnal fall in BP in both type 1 and type 2 diabetic patients. In type 1 diabetic patients AN is associated with attenuated circadian pattern of albuminuria and with a steeper relationship between albuminuria and BP, in type 2 diabetic patients AN is the only factor related to elevated 24-h BP levels. Longitudinal studies are needed to establish the potential role of autonomic dysfunction as a progression promoter for nephropathy and hypertension in type 1 and type 2 diabetes respectively.
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Keywords: ambulatory blood pressure monitoring; autonomic neuropathy; albuminuria; circadian rhythm; type 1 diabetes; type 2 diabetes

Introduction

Non-invasive ambulatory blood pressure (BP) monitoring has allowed a better and easier definition of the circadian rhythm of BP under different pathophysiological conditions. Thus, blunted nocturnal decrease in BP has been described in diabetic patients and associated with autonomic neuropathy (AN)[1,2] or with nephropathy.[3–6] Moreover, the loss of nocturnal dipping in BP has been burdened with prognostic value with regard to end-organ damage and vascular events in both hypertensive and diabetic patients.[7]

Factors involved in the 24-h BP abnormalities are not completely known and probably play a different role in type 1 and type 2 diabetes. Moreover, different relationships seem to exist between BP and albuminuria in type 1 and type 2 diabetes. More information on this relationship might lead to a better pathogenetic understanding of diabetic nephropathy.

The aim of this study was to evaluate the relative influence of AN and albumin excretion on 24-h BP profile in normotensive type 1 and type 2 diabetic patients without overt nephropathy.

Correspondence: Vincenza Spallone, PhD, Dipartimento di Medicina Interna, Università di Tor Vergata, Complesso Integrato Columbus, via della Pineta Sacchetti 506, 00168 Rome, Italy. Fax: 0039 6 3050172
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Materials and methods

Patients

Forty-seven subjects with type 1 diabetes (age 39 ± 11, diabetes duration 18 ± 8 years) and 34 subjects with type 2 diabetes (age 53 ± 6, diabetes duration 13 ± 6 years) were consecutively recruited at the diabetic clinic of the University of Rome 'Tor Vergata'. Informed consent was obtained from all participants. Inclusion criteria were age under 60 years and diabetes duration more than 5 years for type 1 and age under 65 years for type 2, values of casual BP in the normal range (≤140/90 mm Hg) without antihypertensive treatment, and an urinary albumin concentration on three early morning urine collections in the range of normo- or microalbuminuria (0–200 mg/l). Exclusion criteria were: macroalbuminuria (urinary albumin concentration >200 mg/l), impaired renal function (serum creatinine >115 μmol/l), haematuria, urinary infection, clinically significant abnormality of hepatic, haemopoietic, respiratory or endocrine function, history and/or evidence of cerebrovascular or coronary heart disease, arrhythmias, antihypertensive treatment and use of any other medication affecting cardiovascular or autonomic nervous function. Among patients with type 2 diabetes 21 were under treatment with oral agents (sulfonyluraes and/or biguanides) and 13 with insulin.

Methods

Autonomic assessment: Autonomic function was assessed by four cardiovascular tests, performed and evaluated according to standard procedure and normality criteria proposed by Ewing *et al*.[8] Heart rate response to deep breathing was obtained by measuring the mean of the three greatest differences between maximum and minimum heart rate during each breathing cycle at six breaths/min (normal values ≥15 bpm, borderline values >10 bpm, abnormal values ≤10 bpm). Heart rate response to standing up was the ratio of the longest R-R interval around the 30th beat after standing to the shortest R-R interval around the 15th beat after standing (30:15 ratio) (normal values >1.03, borderline values >1.01, abnormal values ≤1.00). Heart rate response to the Valsalva manoeuvre was measured as the ratio of the longest R-R interval after the manoeuvre of breathing against a resistance of 40 mm Hg for 15 s to the shortest R-R interval during the manoeuvre (normal values >1.2, borderline values >1.1, abnormal values ≤1.1). Postural hypotension was defined as a fall in systolic BP upon standing of at least 30 mm Hg (borderline values 20–29 mm Hg). An autonomic score was obtained from the sum of scores given to each of the four tests (0 for a normal result, 1 for a borderline result, and 2 for an abnormal result),[8,9] and was used as an index of degree of autonomic dysfunction. Type 1 and type 2 diabetic patients were divided according to autonomic tests results into two groups with AN (one or more abnormal test) and without AN (less than one positive test).

BP monitoring: Non-invasive 24-h ambulatory BP monitoring (ABPM) was performed using an oscillometric recorder (SpaceLabs 90207, Redmond, WA, USA), satisfying the validation requirements for ABPM systems.[10] Standard sized cuff or when needed, 'obese' sized cuff was used for BP recordings. The device was programmed to measure BP every 20 mins for 24 h. Patients were hospitalised and were requested to comply with hospital routines. This allowed a better standardisation of recording conditions in particular with regard to physical activity. Only the 24-h recordings that contained a percentage of measurement errors <30% were accepted as valid. Systolic (SBP) and diastolic BP (DBP) measurements were averaged for the day and the night periods, according to reported time of waking up and going to bed. In addition, the percentage change from day to night in BP (Δ day–night BP) was calculated as: (day BP–night BP) × 100/day BP.

Albuminuria assessment: Albumin concentration was measured by a double antibody radioimmunoassay (Albumin RIA 100, Pharmacia AB, Uppsala, Sweden) on timed day and overnight urine collections. Samples were simultaneous to 24-h BP monitoring, and were stored at −20°C until the test procedure. Urinary albumin excretion (UAE) was calculated for the day and the night periods, and for the 24-h period. In addition, the percentage change from day to night in UAE (Δ day–night UAE) was calculated as: (day UAE–night UAE) × 100/day UAE.

Statistical analysis

Data are expressed as mean ± s.d. Unpaired Student's *t*-test and analysis of variance (ANOVA) were used as tests of significance for means, and the χ^2-test was used for categorical variables with Yates' correction if indicated. Mann–Whitney U test was used for UAE, a non-parametric variable. Linear regression analysis was used to relate different variables. Logarithmic transformation was applied to UAE before using linear regression analysis. Stepwise multiple regression analyses were performed to determine the relative contribution of different independent variables, both main clinical parameters and all those variables found to be related in univariate analysis, to Δ BP and 24-h BP values. All statistical analyses were done using the program StatView II (Abacus Concepts, Berkeley, CA, USA) on a Macintosh IIcx computer. $P < 0.05$ was considered as statistically significant.

Results

According to cardiovascular tests results 22 patients with type 1 diabetes had AN and 25 did not have

Table 1 Clinical parameters of type 1 and type 2 diabetic patients without and with autonomic neuropathy (AN) (mean ± s.d.)

	type 1 patients		*type 2 patients*	
	without AN	*with AN*	*without AN*	*with AN*
n	25	22	17	17
Sex (M:F)	12:13	10:12	9:8	11:16
Age (years)	38 ± 11	39 ± 10	52 ± 7	55 ± 6
Diabetes duration (years)	16 ± 9	19 ± 8	13 ± 7	14 ± 6
Body mass index (kg/m²)	24 ± 3	23 ± 3	26 ± 3	25 ± 3
Insulin dosage (U/kg/24-h)	0.6 ± 0.2	0.7 ± 0.2	—	—
HbA_{1c}(%)	7.4 ± 1	8.4 ± 2	7.8 ± 1.5	7.9 ± 1.3
Serum creatinine (μmol/l)	74.9 ± 20	68.2 ± 15	67.1 ± 18	70.2 ± 19
Cholesterol (mmol/l)	4.7 ± 1	4.9 ± 1	5.0 ± 0.7	5.1 ± 1
Triglycerides (mmol/l)	1.2 ± 0.6	1.3 ± 0.5	2.1 ± 1.4	1.6 ± 0.6
With retinopathy (absent/background/proliferative)	16/6/3	6/12/4*	10/5/2	8/5/4
Casual SBP (mm Hg)	117 ± 13	113 ± 13	124 ± 15	122 ± 11
Casual DBP (mm Hg)	72 ± 6	72 ± 9	76 ± 9	75 ± 9

*$P < 0.05$ *vs* type 1 without AN.

AN, 17 patients with type 2 diabetes were neuropathic and 17 were not. Clinical data of type 1 and type 2 diabetic patients with and without AN are given in Table 1. No significant differences of any clinical parameter were found, apart from a significantly higher percentage of retinopathy in type 1 diabetic patients with AN than in those without. Casual BP did not differ between patients with and without AN and was in the normal range for both type 1 and type 2 patients.

BP pattern in type 1 diabetic patients

Among type 1 diabetic patients ABPM showed significantly lower Δ day–night SBP and DBP in patients with AN compared to those without AN (Table 2).

In univariate regression analysis Δ day–night SBP and DBP were found to be related to each cardiovascular test, ie, to deep breathing ($r = 0.47$, $P < 0.001$ and $r = 0.57$, $P < 0.0001$, respectively), to lying to standing ($r = 0.42$ and $r = 0.40$, $P < 0.005$), to Valsalva ratio (*vs* Δ day–night DBP: $r = 0.35$, $P < 0.05$), to postural hypotension ($r = –0.60$ and $r = -0.59$, $P < 0.001$), and then to autonomic score ($r = -0.61$ and $r = –0.65$, $P < 0.0001$) (Figure 1). On the other hand, Δ day–night SBP and DBP were also inversely related to 24-h UAE ($r = -0.36$, $P < 0.05$ and $r = -0.43$, $P < 0.001$, respectively).

UAE assessment showed no significant differences between patients with and without AN regarding percentage of microalbuminuric patients, day, night and 24-h UAE (Table 3). The only difference was observed for Δ day–night UAE, which despite its wide range of values was significantly lower in type 1 diabetic patients with AN than in those without AN (Table 3). Δ UAE was positively related to Δ DBP ($r = 0.30$, $P < 0.05$).

Figure 2 shows individual values of Δ day–night SBP in type 1 diabetic patients according to the pres-

Table 2 Average 24-h, day, night and Δ day–night of BP in type 1 and type 2 diabetic patients without and with autonomic neuropathy (AN) (mean ± s.d.)

	type 1 patients		*type 2 patients*	
	without AN	*with AN*	*without AN*	*with AN*
n	25	22	17	17
SBP				
24-h (mm Hg)	114 ± 10	114 ± 14	117 ± 9.5	121 ± 10
day (mm Hg)	119 ± 10	115 ± 14	122 ± 9.5	123 ± 9.1
night (mm HG)	107 ± 11	111 ± 17	110 ± 10	118 ± 13
Δ day–night (%)	9.7 ± 5.6	3.4 ± 9.3*	9.7 ± 4	4.4 ± 7.4†
DBP				
24-h (mm Hg)	71 ± 6.4	71 ± 7.7	73 ± 6.5	74 ± 6.1
day (mm Hg)	76 ± 5.8	74 ± 7.8	77 ± 6.7	77 ± 6.2
night (mm Hg)	64 ± 7.5	68 ± 9.2	68 ± 6.6	70 ± 7.9
Δ day–night (%)	16 ± 6	8.3 ± 9.2**	13 ± 5.8	9.3 ± 8.6

*$P < 0.01$ **$P < 0.001$ *vs* type 1 diabetic patients without AN. †$P < 0.01$ *vs* type 2 diabetic patients without AN.

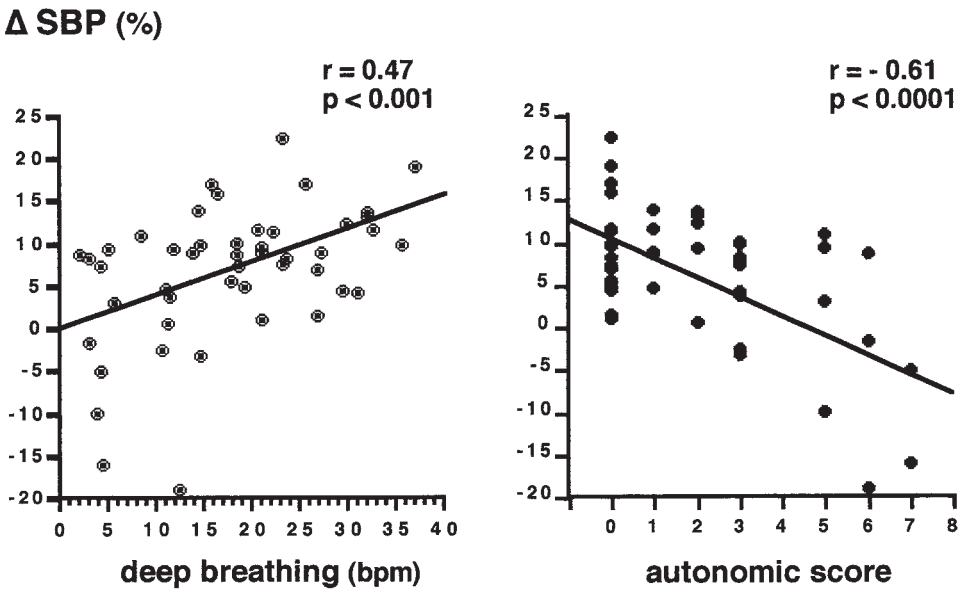

Figure 1 Correlation between Δ day–night SBP and deep breathing test or autonomic score in type 1 diabetic patients.

Table 3 Average 24-h, day, night, and Δ day–night of UAE in type 1 and type 2 diabetic patients without and with autonomic neuropathy (AN) (mean ± s.d. or median, range)

	type 1 patients		*type 2 patients*	
	without AN	*with AN*	*without AN*	*with AN*
n	25	22	17	17
UAE				
24-h (μg/min)	6 (0.1–146)	8.8 (1.7–185)	2.5 (0.1–137)	3.3 (0.1–56)
day (μg/min)	7 (0.1–183)	10.9 (0.6–209)	2.7 (0.2–108)	4.1 (0.1–73)
night (μg/min)	2 (0.1–131)	5.7 (0.4–316)	1.9 (0.1–178)	3.2 (0.1–33)
Δ day–night (%)	49 ± 37	−37 ± 214*	21 ± 59	16 ± 55

*$P < 0.05$ *vs* type 1 diabetic patients without AN.

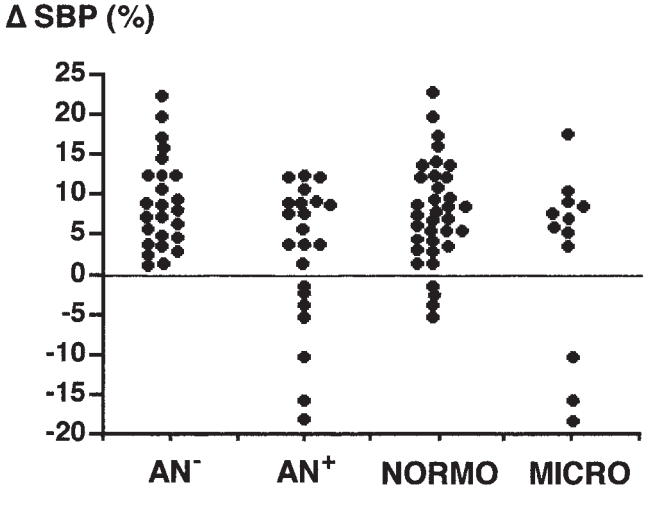

Figure 2 Individual values of Δ day–night SBP in type 1 diabetic patients according to the presence of autonomic neuropathy (AN) or microalbuminuria.

ence of AN or microalbuminuria. The seven subjects with reversed circadian rhythm of BP, ie a negative value of Δ day–night SBP, were all neuropathic but both normo- and microalbuminuric.

In addition, we used a stepwise multiple regression analysis including sex, age, body mass index, smoking, diabetes duration, HbA1c, cholesterolaemia, triglyceridaemia, 24-h UAE, and autonomic score as independent variables and Δ day–night BP as dependent variables. With this model we found that autonomic score was the variable of primary importance for both Δ day–night SBP and DBP (step 1 for Δ SBP: $r = 0.64$, $\beta = -2.53$, $P < 0.01$).

BP pattern in type 2 diabetic patients

ABPM in type 2 diabetic patients displayed significantly lower Δ day–night SBP in patients with AN than in those without ($P < 0.01$) (Table 2).

Δ day–night SBP was related to deep breathing ($r = 0.35$, $P < 0.05$), to lying to standing ($r = 0.40$, $P < 0.05$), and to autonomic score ($r = -0.42$, $P < 0.01$), while Δ day–night DBP was related to

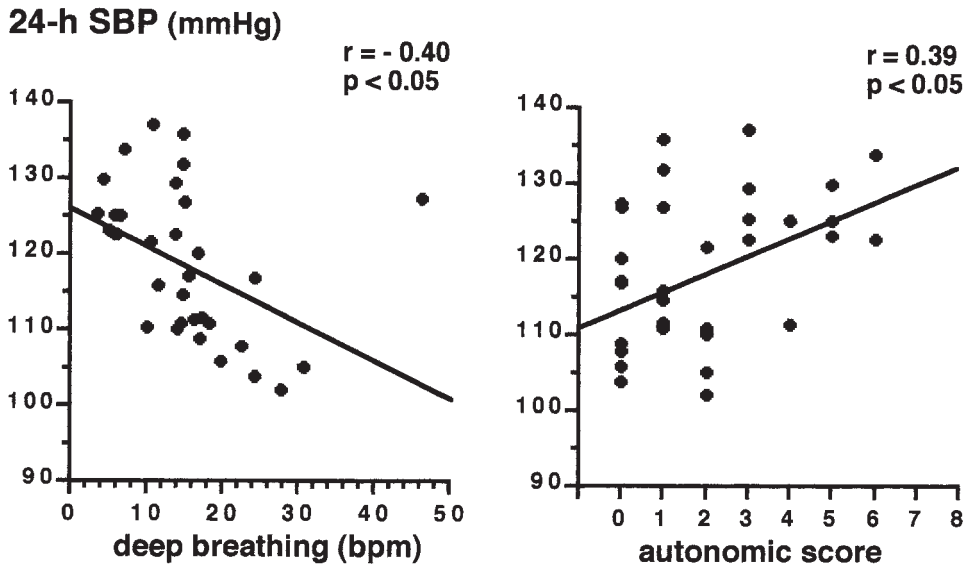

Figure 3 Correlation between 24-h SBP and deep breathing test or autonomic score in type 2 diabetic patients.

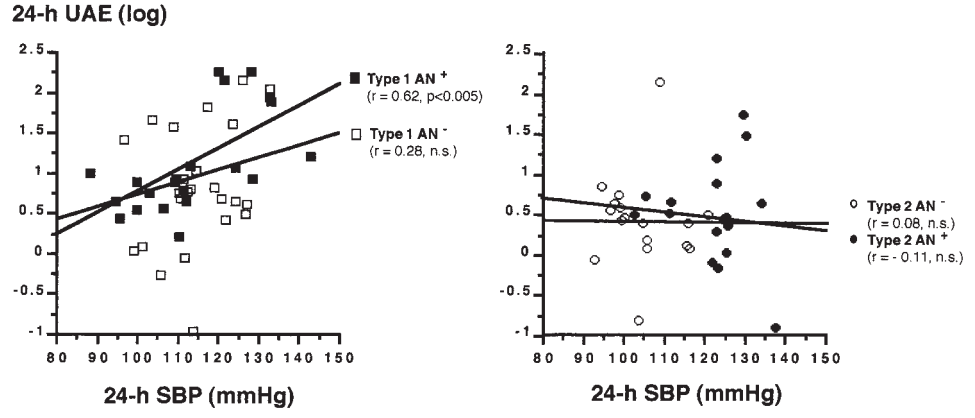

Figure 4 Correlation between simultaneous 24-h UAE (after log transformation) and 24-h SBP in type 1 (on the left) and type 2 (on the right) diabetic patients without (AN^-) and with autonomic neuropathy (AN^+).

lying to standing ($r = 0.34$, $P < 0.05$). No relationship was found between Δ day–night BP and postural hypotension.

No significant differences were found between type 2 diabetic patients with and without AN regarding day, night and 24-h UAE, or Δ day–night UAE (Table 3). Mean levels of 24-h SBP in type 2 diabetic patients in univariate analysis were inversely related to deep breathing ($r = -0.40$, $P < 0.05$) and positively related to autonomic score ($r = 0.39$, $P < 0.05$) (Figure 3). No significant correlations were found between 24-h DBP and the other variables.

In a stepwise multiple regression analysis with the same model used in type 1 diabetes, we found that in type 2 diabetic patients autonomic score was the variable of primary importance not only for Δ SBP (step 1: $r = 0.41$, $\beta = -1.44$, $P < 0.05$), but also for 24-h SBP (step 1: $r = 0.38$, β 2.0, $P < 0.05$), while no preminent factor was identified for DBP.

Relationship between BP and UAE in type 1 and type 2 diabetic patients

Whereas no significant relationship was found between UAE and casual BP in type 1 diabetic patients, both 24-h SBP and DBP were significantly related to simultaneous 24-h UAE in the whole group ($r = 0.42$, $P < 0.01$ and $r = 0.50$, $P < 0.001$, respectively). When considering separately type 1 diabetic patients with and without AN, 24-h UAE was found to be more strongly related to synchronous 24-h SBP and DBP ($r = 0.62$, $P < 0.005$ and $r = 0.65$, $P < 0.001$) in neuropathic patients than in non-neuropathic patients ($r = 0.28$, NS and $r = 0.42$, $P < 0.05$) (Figure 4). However, a significant difference between the slopes of the two regression lines between UAE and BP was not reached.

In type 2 diabetic patients no significant relationship was found between simultaneous BP and UAE neither in patients with AN nor in those without AN (Figure 4) nor in the whole group.

Discussion

In this study we observed in normotensive non-proteinuric type 1 diabetic patients that AN is clearly associated with impaired nocturnal fall in BP. Day–night change in BP was strongly related to cardiovascular tests and to autonomic score. When using stepwise multiple regression analysis the slight relationship between day–night change in BP and albumin excretion present at univariate analysis, was no longer present. Thus, autonomic score was the variable of primary importance for day–night change in SBP and DBP in these patients.

Some studies have described in type 1 diabetic patients with clinical nephropathy a reduction in day–night change in BP.[3,6,11] This abnormality in the absence of assessment of autonomic function was attributed to both nephropathy, through fluid retention, and presumably to AN.[3–5,11] Impaired nocturnal fall in BP has also been found in microalbuminuric patients although with some discrepancies and without clear identification of factors responsible.[5,12–14] In our study the evaluation of AN allowed us to demonstrate a prominent relationship between day–night change in BP and AN. Similarly, Poulsen *et al*[15] found in normoalbuminuric type 1 diabetic patients a correlation between day–night change in BP and the low-frequency component of spectral analysis of heart rate variability, index of sympathetic activity. In a previous study we have already shown in a group of type 1 and type 2 diabetic patients that the day–night profile of BP was related to the circadian pattern of sympathovagal balance, suggesting that in diabetic patients with AN an impaired increase of vagal activity during the night could lead to an abnormal nocturnal sympathetic prevalence with consequent blunted fall in BP and heart rate.[16]

The evidence in neuropathic type 1 diabetic patients of a lower nocturnal fall in UAE deserves some comment. The determinants of the circadian rhythm of albumin excretion, characterised by a nocturnal decrease of about 35%[17] are not fully understood. The correlation between day–night change in BP and day–night change in UAE observed in previous reports[18,19] and in the present study might support the role of diurnal changes in systemic BP and in the glomerular capillary hydraulic pressure. Nevertheless, another potential mechanism, the circadian redistribution of blood flow to nephrons with different protein permeability,[20,21] could be directly affected by AN, given the sympathetic control of regional intrarenal blood flow.[22] Thus, the abnormality in the circadian rhythm of UAE observed in the present study in neuropathic type 1 diabetic patients could be a direct consequence of AN.

Moreover, we found in type 1 diabetic patients that the relationship between simultaneous BP and UAE was stronger in the presence of AN. Given a certain BP value, neuropathic patients seem to develop a greater UAE, indicating a sort of increased renal vulnerability to BP. Whether AN is a non-specific marker or a cause of this vulnerability through the deprivation of defensive regulatory mechanisms is not yet known. Nevertheless, it is possible that a higher albumin excretion during the night and an enhanced vulnerability to haemodynamic effects of BP could accelerate the progression of diabetic nephropathy in neuropathic type 1 diabetic patients, according to previous suggestions.[18,23]

Limited data are available on the factors involved in 24-h BP pattern in type 2 diabetic patients.[24–27] These studies generally include both normotensive and hypertensive patients with or without clinical nephropathy, and most of them do not perform any assessment of AN. Thus, a conclusive link between blunted circadian rhythm of BP and autonomic neuropathy or nephropathy has not been reached.

The present study has considered only normotensive type 2 diabetic patients mostly normoalbuminuric showing a blunted nocturnal fall of BP in those with AN, although affecting only SBP. In a multivariate regression analysis autonomic score was found to be the only factor still related to day–night change in SBP, whereas no overriding factor was identified for day–night change in DBP.

In our study the decision to exclude type 2 diabetic patients with hypertension or other cardiovascular disease and/or proteinuria was based on the need to avoid factors potentially interfering with autonomic function assessment such as drugs or diseases affecting cardiovascular system.[28] Moreover, by the time of overt nephropathy it is more difficult to dissociate the effects on BP pattern of nephropathy and neuropathy which are commonly associated. Thus, we cannot exclude that with the progression of diabetic nephropathy or the occurrence of cardiovascular disease, further factors beyond AN could affect BP circadian pattern in type 2 diabetic patients.

In the present study no relationship was found between day–night change in BP and albumin excretion. Moreover, there was no correlation at all between simultaneous BP and albumin excretion in these normotensive type 2 diabetic patients irrespective of presence of AN. Regarding this finding, only a modest association has been observed between BP and albuminuria in type 2 diabetic patients.[26,29,30] Similarly, the link between SBP and the rate of progression of albuminuria in type 2 diabetes is weaker than in type 1 diabetes.[31–34] In the present study the absence of any significant relationship between ABPM and albuminuria could be due either to the characteristics of the type 2 diabetic patients, all normotensive and mostly normoalbuminuric, that might minimise any possible effect of BP on UAE, or to the peculiar implications of BP and albuminuria in type 2 diabetes. In type 2 diabetes albuminuria is not a simple marker of diabetic nephropathy but also reflects general vascular damage and BP is

just one element of a multifactorial metabolic syndrome.[35] Moreover, since we used albuminuria as the only marker of diabetic nephropathy, we cannot exclude that using other indexes such as glomerular filtration rate, a closer relationship between renal function and 24-h pattern of BP or autonomic dysfunction could be disclosed.

Rather surprisingly in type 2 diabetic patients AN was found to be related in both univariate and multivariate regression analysis to mean 24-h SBP. Recent data tend to delineate a significant relationship between hypertension and neuropathy in diabetes both in the sense of a correlation of SBP to autonomic test impairment[36,37] and in the suggestion of hypertension as a risk factor for peripheral neuropathy.[38] Moreover, recent evidence from the UKPDS study points to the efficacy of lowering SBP in reducing the risk of complications in type 2 diabetes.[39] Data from the present study based on 24-h BP recording originally supports a link between autonomic dysfunction and 24-h BP levels in type 2 diabetic patients.

Qualitative and quantitative differences in daily activities or nocturnal sleep can affect BP monitoring. In this study day and night periods were not fixed intervals but based on individual times for going to bed and rising. Moreover, ABPM was performed when patients were hospitalised, thus allowing a better standardisation of recording conditions in particular with regard to physical activity.

In conclusion, the present study found that AN is the pivotal factor of blunted nocturnal fall in BP in both type 1 and type 2 diabetic patients. In type 1 diabetic patients AN is associated with attenuated circadian pattern of albuminuria and with a steeper relationship between BP and albuminuria, and through these changes it potentially could affect the progression of diabetic nephropathy. In type 2 diabetic patients AN is the only factor related to elevated 24-h BP levels. Thus, in addition to its effects on circadian rhythm of BP, autonomic dysfunction might be a progression promoter for nephropathy and hypertension in type 1 and type 2 diabetes respectively. Large longitudinal studies are needed to establish the potential role of autonomic dysfunction as additional risk factor for nephropathy and hypertension in diabetic patients.

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