Early Disturbances of Ambulatory Blood Pressure Load in Normotensive Type I Diabetic Patients With Microalbuminuria

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OBJECTIVE— To compare 24-h ABP in normotensive type 1 diabetic patients with and without microalbuminuria.

RESEARCH DESIGN AND METHODS— The study was a retrospective comparison of cases and matched control subjects. The first phase included 35 type 1 diabetic patients, normotensive by OMS criteria. The 23 patients with normoalbuminuria (<15 μg/min) were compared with 12 patients with microalbuminuria (≥15 μg/min). In the second phase, the 12 microalbuminuric patients were paired by sex- and age-matched with 12 normoalbuminuric patients and 12 nondiabetic healthy control subjects. We measured casual systolic and diastolic BP and HR, 24-h ABP and AHR (recorded with a Spacelabs automatic recorder), and microalbuminuria.

RESULTS— No correlation between microalbuminuria and casual BP was observed. Microalbuminuria was correlated significantly with diastolic 24-h APR and nocturnal systolic and diastolic ABP ($r = 0.35$, 0.38, and 0.33, respectively; $P < 0.05$) and with AHR during all time periods (24-h, $r = 0.46$; day, $r = 0.39$; night, $r = 0.39$; $P < 0.05$). Normo- and microalbuminuric patients did not differ in casual BP and HR. However, microalbuminuric patients had a significant increase in systolic 24-h ABP (119.1 ± 8.2 vs. 113.1 ± 8.1, $P = 0.05$), diastolic 24-h ABP (74.9 ± 7.5 vs. 70.2 ± 5.7, $P = 0.04$), nocturnal systolic ABP (112.8 ± 7.1 vs. 105.8 ± 7.9, $P = 0.01$), and AHR during all time periods. The same results were observed when patients were paired by age and sex.

CONCLUSIONS— Normotensive microalbuminuric type 1 patients, although strictly comparable with normoalbuminuric patients for casual BP and HR, have an increased ABP and HR, especially during the night. This difference might reflect dysautonomia. Ambulatory measurement of BP and HR is more appropriate than casual measurements in hemodynamic studies of incipient diabetic nephropathies and could be proposed as an interesting tool for an early prediction of diabetic nephropathy.

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TYPE I, INSULIN-DEPENDENT DIABETES MELLITUS; ABP, AMBULATORY BLOOD PRESSURE; AHR, AMBULATORY 24-H HEART RATE; WHO, WORLD HEALTH ORGANIZATION; NDDG, NATIONAL DIABETES DATA GROUP; UAE, URINE ALBUMIN EXCRETION; ELISA, ENZYME-LINKED IMMUNOSORBENT ASSAY; SPSS, STATISTICAL PACKAGE FOR THE SOCIAL SCIENCES; ANOVA, ANALYSIS OF VARIANCE; BMI, BODY MASS INDEX; NS, NO SIGNIFICANCE; BP, BLOOD PRESSURE; HR, HEART RATE.

The pathogenesis of diabetic nephropathy remains unclear. A genetic susceptibility to hypertension has been implicated but still is controversial (1–3). The causal effect of hypertension is doubtful, and the temporal relationships with diabetic nephropathy is ill-defined. Thus, the question of a preexisting minimal rise in systemic and/or glomerular arterial BP is crucial and largely debated (4).

The introduction of microalbuminuria monitoring has improved the management of diabetic nephropathy. Microalbuminuria characterizes early diabetic nephropathy (5). A continuous increase of albuminuria can be observed from this early stage to end-stage renal disease. Until now, no better alternative to microalbuminuria has been proposed for the early detection of the patient at risk of nephropathy in diabetes (6). It is our purpose to revisit the interest in BP monitoring, through the techniques of ambulatory recordings, in the prediction of nephropathy.

At the microalbuminuric stage, casual BP can be normal according to WHO criteria. Cross-sectional studies of microalbuminuric type 1 patients have shown elevated casual BP compared with normoalbuminuric patients (7,8). Although it appears that mild microalbuminuric patients maintain normal casual BP, distinguishing them from normoalbuminuric patients is possible only above a certain level of microalbuminuria (9).

Recently, some preliminary studies emphasized the possible beneficial role of recording ABP in the management of hypertension (10), especially in diabetic patients (11). Such an approach looks extremely promising and could be as useful as the introduction of microalbuminuria monitoring was for the measurement of proteinuria.

Among strictly normotensive type 1 patients, differing in microalbuminuria but with similar casual BP, we questioned the discriminative value of

Table 1—*Clinical characteristics of type 1 diabetic subjects with and without persistent microalbuminuria*

	UAE < 15 μG/MIN	UAE ≥ 15 μG/MIN
	(N = 23)	(N = 12)
AGE (YR)	31.1 ± 8.6	31.1 ± 9.8
DURATION (YR)	9.9 ± 8.6	15.2 ± 5.2
SEX (MEN/WOMEN)	16/7	7/5
BMI (KG/M^2)	23 ± 3.1	21.5 ± 2.2
SERUM CREATININE (μMOL/L)	72.9 ± 13.7	71.8 ± 21
INSULIN DOSE (U/DAY)	46 ± 13	37 ± 6
UAE (μG/MIN)	4.7 (1.6–10.2)	56.3 (15–355)*
RETINOPATHY (ABSENT/BACKGROUND/ PROLIFERATIVE)	14/5/4	3/3/6
HbA_{1c} (%)	7.23 ± 1.6	8.76 ± 1.6†

*P < 0.001.
†P < 0.01.

ABP recording. By analogy with the concept of microalbuminuria, we intended to support the concept of microhypertension. Thus, the aim of our study was to compare the ABP load in two groups of normotensive type 1 diabetic patients with or without microalbuminuria.

RESEARCH DESIGN AND METHODS

— The first phase of this study dealt with 35 patients. These patients were recruited consecutively from the diabetic outpatient clinic. All of them had type 1 diabetes according to NDDG criteria. All patients were normotensive according to WHO criteria (<140/90 mmHg), as observed with repeated sphygmomanometer determinations. None took any medication other than insulin.

ABP and AHR measurements were taken with an oscillometric automatic recorder (Spacelabs 90207, Redmond, WA) every 15 min from 0700 to 1700 and every 30 min from 1700 to 0700. Measurements were started between 0800 and 0900. Mean ABP was calculated for 24-h and for the period between 0900 and 1900, which was designated day, and the period between 2300 and 0700, which was designated night (12,13). Usual daytime activities were maintained, but all patients were admitted to the hospital for the night. Casual BP was determined at the beginning of each study as the mean of three sphygmomanometer readings taken after a 5-min rest in the sitting position. Dietary sodium intake was restricted to 8 g/day.

The expression of ABP measurement results used mean values; SD of means of all recordings reflected interindividual variability, whereas mean SD of each recording reflected individual variability. Without a universal standard for ABP, a threshold of 135/85 mmHg was proposed as a way to determine the prevalence of hypertensive readings at different times (11). We tested this threshold and also attempted to define a more appropriate threshold as the 90th percentile of 24-h ABP of our normoalbuminuric patients.

UAE was determined with three consecutive nocturnal measurements with an ELISA. A cutoff value of 15 μg/min defined two groups of patients as normoalbuminuric (<15 μg/min) and microalbuminuric (≥15 μg/min). Patients with at least two of three samples above this value were defined as microalbuminuric. All but one of the microalbuminuric patients had UAE <200 μg/min. The intraindividual day-to-day variation in the nocturnal UAE was 30% in our clinic. HbA_{1c} was measured with microcolumn chromatography (Bio-Rad, Richmond, CA; range 4–5.5%).

In the second phase of this study, ABP and AHR were compared in the 12 microalbuminuric patients, who were sex- and age-matched with 12 normoalbuminuric patients recruited from the first-phase sample and with 12 nondiabetic, normotensive healthy control subjects randomly recruited from the medical center staff.

Results are means ± 1 SD for normally distributed data and median and range for nonparametrically distributed data. Data were computed with SPSS for comparison of groups (ANOVA), correlation between quantitative variables (correlation coefficient), and stepwise multiple regression. Microalbuminuria was log-transformed. $P < 0.05$ was significant.

RESULTS

First phase

Clinical, metabolic, renal, and BP features are shown in Tables 1 and 2. The two groups were comparable for age, duration of disease, and sex ratio (Table 1). Although no significant difference was observed for casual BP and HR between normo- and microalbuminuric patients, both systolic and diastolic 24-h ABP were significantly higher in the latter group. This tendency was more pronounced during the night. Furthermore, HR was significantly higher in microalbuminuric patients during all time periods. Microalbuminuria was correlated significantly with diastolic 24-h ABP, nocturnal systolic and diastolic ABP, and HR during all time periods, whereas no correlations were observed for casual measurements (Table 2). Stepwise multiple regression showed that microalbuminuria could be predicted by 24-h AHR (F 8.89), diastolic 24-h ABP (F 8.56), and HbA_{1c} (F 7.56), in a model including age, sex, HbA_{1c}, casual BP and HR, and ABP and AHR.

Questioning the temporal rela-

Table 2—*Mean casual BP and ABP and HR of type 1 diabetic subjects with and without persistent microalbuminuria*

	UAE < 15 μG/MIN* (*N* = 23)	ANOVA	UAE ≥ 15 μG/MIN* (*N* = 12)	CORRELATION WITH UAE
CASUAL				
SYSTOLIC BP (MMHG)	119.9 ± 10.2	NS	115.5 ± 12.7	*R* = −0.01, NS
DIASTOLIC BP (MMHG)	78.1 ± 11.1	NS	73.1 ± 9.6	*R* = 0.09, NS
HR (BEATS/MIN)	79.1 ± 13.3	NS	87.8 ± 12.1	*R* = 0.09, NS
24-H				
SYSTOLIC ABP (MMHG)	113.3 ± 8.1	*P* = 0.05	119.1 ± 8.2	*R* = 0.29, NS
DIASTOLIC ABP (MMHG)	70.2 ± 5.7	*P* = 0.04	74.9 ± 7.5	*R* = 0.35, P = 0.04
AHR (BEATS/MIN)	72.2 ± 7.7	*P* = 0.008	79.9 ± 7.5	*R* = 0.46, P = 0.005
DAYTIME				
SYSTOLIC ABP (MMHG)	119.1 ± 10.3	NS	124.1 ± 11.6	*R* = 0.17, NS
DIASTOLIC ABP (MMHG)	76.4 ± 6.9	NS	80.7 ± 8.9	*R* = 0.21, NS
AHR (BEAST/MIN)	78.9 ± 9.5	*P* = 0.02	86.4 ± 6	*R* = 0.39, P = 0.02
NIGHTTIME				
SYSTOLIC ABP (MMHG)	105.8 ± 7.9	*P* = 0.01	112.8 ± 7.1	*R* = 0.38, P = 0.02
DIASTOLIC ABP (MMHG)	63.4 ± 6.7	NS	67.7 ± 7.4	*R* = 0.33, P = 0.05
AHR (BEATS/MIN)	62.8 ± 8.5	*P* = 0.02	70.3 ± 9.8	*R* = 0.39, P = 0.02
DAY-NIGHT DIFFERENCE				
SYSTOLIC ABP (MMHG)	13.3 ± 8.5	NS	11.3 ± 9.9	*R* = −0.15, NS
DIASTOLIC ABP (MMHG)	13.0 ± 8.4	NS	13.0 ± 6.7	*R* = −0.09, NS
AHR (BEATS/MIN)	16.0 ± 9.5	NS	16.2 ± 6.9	*R* = −0.01, NS

Values are means ± SD.

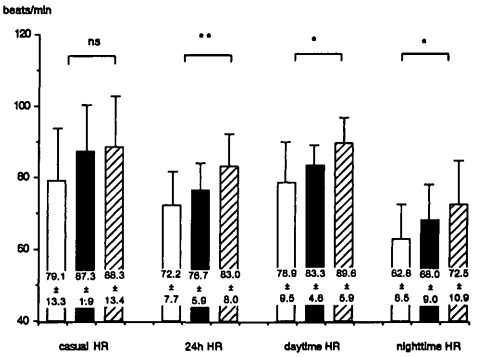

Figure 2—*Casual and ambulatory HR according to microalbuminuria level in 35 normotensive type 1 diabetic patients. Results are means ± SD. *P < 0.005; **P < 0.001.*

tionship between nephropathy and hypertension, we divided our population into three groups according to microalbuminuria: group 1 (<15 μg/min, *n* = 23), group 2 (15–50 μg/min, *n* = 6, values = 15.0, 16.2, 26.2, 42.2, 47.5, and 49.2 μg/min), and group 3 (>50 μg/min, *n* = 6, values = 51.7, 59.0, 100.1, 122.2, 123.0, and 355.0 μg/min).

A gradual increase of ABP was observed from group 1 to group 3, with a global significant difference between groups observed for nocturnal systolic ABP (ANOVA, *P* = 0.05), whereas no differences were observed for casual measurements (Fig. 1). Group 2 already had significantly increased values for nocturnal systolic ABP (112.7 ± 4.5 vs. 105.8 ± 7.9 mmHg, *P* = 0.05) compared with group 1. Differences between group 3 and group 1 were more significant: Systolic 24-h ABP was 120.4 ± 9.3 vs. 113.4 ± 8.1 (*P* = 0.05), diastolic 24-h ABP was 76.3 ± 7.1 vs. 70.2 ± 5.7 (*P* = 0.03), and systolic nocturnal ABP was 112.8 ± 9.6 vs. 105.8 ± 7.9 (*P* = 0.05). Groups 2 and 3 did not differ significantly (Fig. 1). The

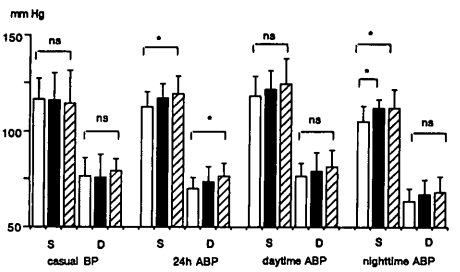

Figure 1—*Casual and ambulatory blood pressure by microalbuminuria level in 35 normotensive type 1 diabetic patients. Results are means ± SD. *P < 0.005.*

same gradual increase from group 1 to group 3 was observed for AHR, with a global significant difference between groups observed for 24-h AHR (ANOVA, *P* = 0.01), diurnal AHR (*P* = 0.03), and nocturnal AHR (*P* = 0.05), without any difference for casual measurements. Whereas groups 1 and 2 did not differ significantly, group 3, when compared with group 1, had a significantly increased value for 24-h AHR, diurnal AHR, and nocturnal AHR. Groups 3 and 2 did not differ significantly, except for diurnal AHR (Fig. 2).

Differences between day and night pressure load, expressed as absolute difference or related to day ABP, did not differ significantly between normo- and microalbuminuric patients (Table 2). Patients with <5 mmHg decrease in ABP during the night were defined as having abnormal nyctohemeral rhythm. The percentage of such patients did not differ significantly in each group (systolic ABP: 2/23 in normoalbuminuric group vs. 3/12 in microalbuminuric group; diastolic ABP: 2/23 vs. 1/12).

Second phase

To exclude any bias caused by the known influence of age and sex on ABP (12), we decided to pair the patients according to these variables. Age, sex, BMI, serum creatinine, and insulin dose were comparable in the two diabetic patient

Table 3—*Comparison of 12 microalbuminuric patients (group M) paired by sex and age with 12 normoalbuminuric patients (group N) and 12 nondiabetic normotensive healthy control subjects (group C)*

	Control subjects (N = 12)	C vs. N	UAE < 15 μg/min (N = 12)	N vs. M	UAE ≥ 15 μg/min (N = 12)	C vs. M
Casual						
Systolic BP (mmHg)	117.5 ± 15.3	NS	119.2 ± 11.6	NS	115.5 ± 12.7	NS
Diastolic BP (mmHg)	78.6 ± 10.8	NS	78.0 ± 10.8	NS	73.1 ± 9.6	NS
HR (beats/min)	88.2 ± 23.1	NS	78.3 ± 11.9	NS	87.8 ± 12.1	NS
24 h						
Systolic ABP (mmHg)	109.8 ± 4.9	NS	111.8 ± 7.8	*	119.1 ± 8.2	†
Diastolic ABP (mmHg)	71.0 ± 8.2	NS	71.3 ± 5.7	NS	74.9 ± 7.5	NS
AHR (beats/min)	77.3 ± 7.6	*	71.1 ± 6.9	†	79.9 ± 7.5	NS
Daytime						
Systolic ABP (mmHg)	115.9 ± 7.1	NS	117.9 ± 9.9	NS	124.1 ± 11.6	*
Diastolic ABP (mmHg)	76.2 ± 10	NS	77.5 ± 7.8	NS	80.7 ± 8.9	NS
AHR (beats/min)	85.3 ± 11.3	NS	78.6 ± 8.0	†	86.4 ± 6	NS
Nighttime						
Systolic ABP (mmHg)	99.9 ± 5.2	NS	103.2 ± 6.6	†	112.8 ± 7.1	†
Diastolic ABP (mmHg)	61.1 ± 5.8	NS	64.6 ± 7.4	NS	67.7 ± 7.4	*
AHR (beats/min)	63.8 ± 5.5	NS	61.2 ± 8.2	*	70.3 ± 9.8	*
Day-night difference						
Systolic ABP (mmHg)	16.1 ± 8	NS	14.8 ± 4.9	NS	11.3 ± 9.9	NS
Diastolic ABP (mmHg)	15.1 ± 6.2	NS	12.9 ± 10.5	NS	13.0 ± 6.7	NS
AHR (beats/min)	22.2 ± 10.2	NS	17.4 ± 6.8	NS	16.2 ± 6.9	NS
Variability						
Systolic BP (mmHg)	11.1 ± 3.1	NS	10.1 ± 2.6	NS	9.1 ± 3.5	NS
Diastolic BP (mmHg)	9.6 ± 2.4	NS	11.2 ± 6.2	NS	8.3 ± 2.4	NS
HR (beats/min)	14.6 ± 4.2	NS	11.9 ± 2.9	NS	11.8 ± 4	NS
Systolic ABP > 135 mmHg (%)	1.5 ± 2.2	NS	2.1 ± 2.8	NS	9.7 ± 12.2	NS
Diastolic ABP > 85 mmHg (%)	13.4 ± 19.8	NS	11.3 ± 11	NS	20.1 ± 18.4	NS

Results are means ± 1 SD.
*$P < 0.05$.
†$P < 0.01$.

groups, with normoalbuminuric patients having a shorter duration of disease (6.6 ± 6.3 yr, $P < 0.01$), better metabolic control (HbA_{1c} = 7.29 ± 1.73%, $P < 0.05$), and less severe retinopathy (7 patients with none, 4 with background neuropathy, and 1 with proliferative Table 1). Nondiabetic healthy control subjects were recruited randomly according to age and sex and were comparable for BMI.

Microalbuminuric patients still had significantly higher values for systolic 24-h and nocturnal ABP and AHR during all time periods compared with normoalbuminuric patients, whereas normoalbuminuric patients differed from nondiabetic control subjects only in having a lower 24-h AHR. No difference could be seen for casual measurements between all three groups (Table 3).

The three groups did not differ significantly for the day-night ABP and AHR difference, nor for the BP and HR individual variability, though a tendency toward a reduced systolic day-night difference and a reduced BP variability was observed in the microalbuminuric group (Table 3).

The prevalence of increased BP readings, using an arbitrary threshold of 135/85 mmHg, was increased nonsignificantly in the microalbuminuric group (Table 3). The 90th percentile of the normoalbuminuric group was 128.7/85.6 mmHg for day and 111.7/77.3 mmHg for night. ABP was considered abnormal when the 50th percentile of an individual exceeded this threshold. Using these thresholds, 6 of 12 microalbuminuric patients had abnormal ABP versus 1 of 12 normoalbuminuric patients.

CONCLUSIONS — Incipient diabetic nephropathy (stage 3) is characterized by a persistent increase of UAE in the range defining microalbuminuria (5). Although cross-sectional studies of microalbuminuric type 1 patients previously have shown elevated casual BP compared with normoalbuminuric patients (7,8), the

same authors did not find any more significant differences in a previous report (14). This result is probably because of heterogeneity inside the microalbuminuric phase, with mild microalbuminuric patients maintaining normal casual BP (9). This explanation was suggested by another study, in which differences in casual BP between microalbuminuric and normoalbuminuric patients were only revealed above a certain level of microalbuminuria. In this study, a cutoff value of 70 μg/min was suggested as the threshold for elevation of casual BP (9). This observation outlines the need for a more discriminating and sensitive tool of BP recording, such as ambulatory monitoring. Our study demonstrates a significant increase of ambulatory BP load in microalbuminuric type 1 diabetic patients compared with normoalbuminuric patients. Both groups were still normotensive according to casual measurements. Casual measurements could not make any distinction between normo- and microalbuminuric patients.

Few studies dealt with ABP recording with the same purpose as ours, i.e., the exploration of diabetic nephropathy. Indeed, until now, most studies only focused on day-night patterns of BP in diabetic patients and on dysautonomia. A recent case-control study reported a twofold increase of ABP load in normotensive type 1 diabetic patients compared with nondiabetic normotensive control subjects. However, no distinction between microalbuminuric and normoalbuminuric patients was established (11). More recently, an increase of ABP also was reported in microalbuminuric versus normoalbuminuric patients, though some of these patients already had pathological casual measurements (14).

This increase of ABP was observed predominantly during the night, both for systolic and diastolic load. Some researchers have suggested that abnormal daily patterns, and particularly the absence of the physiological fall in nighttime pressure load, were related to autonomic dysfunction (11,15–17). We did not observe a significant difference of nyctohemeral pressure rhythms between our two groups, but day-night differences and mean SD of recordings only grossly approximate dysautonomia. In fact, nyctohemeral heart rate was significantly higher in microalbuminuric patients during all time periods compared with normoalbuminuric patients and was well correlated with microalbuminuria. This result argues for some degree of autonomic dysfunction, which is a characteristic feature of long-duration diabetes, such as in the microalbuminuric stage (18,19). A preliminary study of our group revealed important disturbances of HR and BP variability as assessed by spectral analysis in some of these microalbuminuric patients compared with normoalbuminuric patients (data not shown).

The question of temporal relationship between nephropathy and hypertension is largely debated. Prospective studies demonstrated the association between the progression of microalbuminuria and the increase in casual BP (20). A recent prospective study showed evidence that elevation of UAE during the development of nephropathy in IDDM precedes the increase of systemic BP, as measured with the usual technique (21). However, the sensitivity and precision of a casual measurement and its ability to detect a small increase in BP is questionable. Because true BP is a continuously distributed variable, this is an indication to undertake large studies for the establishment of an arbitrary threshold defining ambulatory hypertension in diabetic patients. Thus, our results showed a good linear correlation of nocturnal systolic and diastolic load with microalbuminuria. Similarly, available data from transversal epidemiological studies suggest that ABP has better correlations than casual blood pressure with other target organs alterations (22). Currently, only relying on casual measurements to assess normotension in diabetic patients is questionable.

Diabetic nephropathy is characterized by a continuous gradual increase of UAE starting several years before the development of persistent microalbuminuria (21). By analogy, we suggest a gradual shift of pressure load parallel to the shift of albuminuria. Combining thresholds for both continuous spectra of albuminuria and ABP could help make a better and earlier prediction of nephropathy. The temporal links between these two conditions remain to be established with appropriate tools. Whereas much progress has occurred in the management of microalbuminuric patients in a clinical setting during the past few years, the same work has to be done to establish the clinical meaning of ABP measurements in the field of early detection of hypertension and nephropathy. Another interesting offshoot of ABP recording could be the evaluation of the hemodynamic effects of nephroprotective therapy (4). In conclusion, our study demonstrates an increase of ABP in normotensive type 1 microalbuminuric diabetic patients, arguing for the concept of microhypertension or incipient hypertension.

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