Variations of Ambulatory Blood Pressure With Position in Patients With Type 1 Diabetes

Influence of disease duration and microangiopathy in a pilot study

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OBJECTIVE — To study the influence of position changes on 24-h ambulatory blood pressure (ABP) in normotensive or mildly hypertensive normoalbuminuric patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — A cross-sectional evaluation of patients was staged according to the duration of diabetes (DD) and the presence of microangiopathy. We recruited 37 patients (30 men and 7 women), aged 38 ± 12 years, who were normotensive or mildly hypertensive (diastolic blood pressure [DBP] <105 mmHg) and free of antihypertensive treatment and microalbuminuria. They were included according to DD (group 1, <5 years; group 2, ≥10 years). An additional group of seven diabetic patients with microalbuminuria and mild untreated hypertension was also investigated. We recorded 24-h ambulatory blood pressure every 15 min with a position sensor, which allowed for the discrimination between standing or supine/sitting position in the patient.

RESULTS — Mean daytime (10:00 A.M. to 8:00 P.M.) ABP in supine/sitting position did not significantly differ between groups 1 and 2. However, standing ambulatory systolic blood pressure (ASBP) and ambulatory DBP (ADBP) were significantly higher than supine/sitting ASBP and ADBP in group 1 (ΔSBP 4 ± 5, ΔDPB 4 ± 6 mmHg, $P < 0.01$) but not in group 2 (ΔSBP 2 ± 8, ΔDBP 2 ± 4 mmHg, P = NS). Patients free of microangiopathy presented with significantly higher ABP in standing position than in sitting/lying position, whereas patients with retinopathy and/or nephropathy exhibited no significant increase of ABP during standing.

CONCLUSION — The monitoring of position during ambulatory measurement of blood pressure in type 1 diabetic patients shows different patterns in relation to disease duration and the presence of microangiopathy.

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The prediction of diabetic microangiopathy is an important challenge in current diabetes research. Currently, it relies solely on the assessment of blood glucose control and blood pressure (BP) load. Elevated BP is recognized as a risk factor for the development of diabetic nephropathy, and it also contributes to the progression of retinopathy. However reliable detection of hypertension is frequently hampered by the "white-coat" effect. This outlines the advantage of 24-h ambulatory BP measurement (ABPM) in the early diagnosis of hypertension in diabetic patients. Disturbances in ABPM profiles were linked to diabetic nephropathy and retinopathy (1–3). Thus, type 1 diabetic patients who were strictly normotensive by casual BP assessments were found to exhibit increased ambulatory BP load in parallel with the development of microalbuminuria (4).

Although ABPM has gone into routine clinical practice, one limit at an individual level is the reproducibility of the recorded values (5). This reproducibility is questionable when recordings cover periods shorter than 24 h. Thus, detection of the loss of the nocturnal BP fall may fail from one recording to another (6–7). One factor that may cause the BP to vary is the position of the patient during the recording.

Technical progress in the devices used to record ABP now allows us to monitor the position of the patient and to discriminate between standing BP and supine or sitting BP (8). Using such a device, the aim of this pilot study was to address the following questions: *1*) What is the normal pattern of ABP according to the position in a population of young, recent and uncomplicated type 1 diabetic patients? and *2*) Is there an influence of duration of diabetes (DD) or microangiopathy on this pattern ?

RESEARCH DESIGN AND METHODS

Patients. The study was performed in 37 patients who were consecutively recruited from the diabetic outpatient clinic according to the following inclusion criteria: type 1 diabetes as defined by the American Diabetes Association, DD <5 years or >10 years, normotensive according to World Health Organization

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Abbreviations: ABP, ambulatory blood pressure; ABPM, ambulatory blood pressure management; ADBP, ambulatory diastolic blood pressure; AHR, ambulatory heart rate; ANOVA, analysis of variance; ASBP, ambulatory systolic blood pressure; BP, blood pressure; DBP, diastolic BP; DD, duration of diabetes; HR, heart rate; SBP, systolic BP; UAE, urinary albumin excretion; VH, vertical/horizontal; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

(WHO) criteria (BP <140/90 mmHg) or mildly hypertensive (diastolic BP [DBP] <105 mmHg), and age between 18 and 60 years old. Exclusion criteria were the presence of moderate or severe hypertension, a recent episode of major metabolic disturbances, the use of any antihypertensive treatment or vasoactive medication, any history of nondiabetic autonomic failure, permanent microalbuminuria (>20 μg/min), and renal insufficiency (plasma creatinine >150 μmol/l). Results of the study were analyzed according to DD: <5 years in group 1 and ≥10 years in group 2. Seven patients with type 1 diabetes were also investigated as an additional group (group 3); these patients were recruited using the criteria of permanent microalbuminuria (between 20 and 200 μg/min), and they corresponded to all of the other inclusion and exclusion criteria for groups 1 and 2.

HbA_{1c} was measured by high pressure liquid chromatography (normal values 4–6%), and urinary albumin excretion (UAE) was measured by immunoturbidimetry (Behring, Marburg, Germany). Microalbuminuria was defined by the presence of a UAE rate consistently between 20 and 200 μg/min, as assessed by three 24-h urine samples collected at least 6 weeks after any urinary tract infections or acute hyperglycemic events, and after exclusion of all other causes of albuminuria. Diabetic retinopathy was assessed by an experienced ophthalmologist through dilated pupils with direct ophthalmoscopy and biomicroscopy using a Goldman three-mirror lens. Grading of retinopathy was based on the Early Treatment Diabetic Retinopathy Study report, which allowed for the discrimination between retinopathic and retinopathy-free patients. Patients gave their informed consent to participate in this study, which was approved by the ethical committee of Grenoble University Hospital.

Measurements. Just before fitting the subject with the ABPM device, clinical BP was measured by means of a mercury sphygmomanometer using a correctly sized cuff. Three recordings were made after 10 min rest in the lying position, and then BP was recorded once, and again after 1, 3, and 6 min in the standing position. The Diasys Integra monitor (Novacor, Rueil-Malmaison, France) was used to record 24-h ABP with the same-sized cuff, and it was calibrated by a simultaneous measurement on the other arm with a mercury sphygmomanometer. This oscillometric automatic device is equipped with a position sensor placed on the thigh and is capable of detecting whether the patient is standing (first option) or lying or sitting (second option). Preliminary experiments were conducted to validate the accuracy of the sensor (8). The device is programmed to measure BP every 15 min over 24 h. The auscultatory method is the default mode, but a defective quality of the Korotkoff sounds drives the unit to opt for the oscillometric mode. Mean ABP was calculated for 24 h and for the period between 10:00 A.M. and 8:00 P.M., which was designated as the activity period, and the period between 12:00 A.M. and 6:00 A.M., which was designated as night. Usual daytime activities were maintained, since measurements were performed on an outpatient basis. Daytime activities were recorded in a diary log. Patients were requested to maintain their routine activity and diet and to avoid intensive physical stress. The current software provides the average ABP and ambulatory heart rate (AHR) cumulated in the supine/sitting position and in the standing position.

Statistical analysis. The comparisons of the differences between BP measures sitting and standing in the clinic setting were performed by the paired *t* test. This was also used to compare the seated versus standing BP and heart rate (HR) in the ambulatory recordings. All of the comparisons between groups were performed by analysis of variance (ANOVA) with Student-Newman-Keuls test, except when the variances were heterogeneous, as was the case when dippers were compared with nondippers. In the latter case, nonparametric Wilcoxon's rank-sum test was used. Data were computed with SPSS (SPSS, Chicago, IL). Results are means ± SD. Supine/sitting versus standing differences are given with 95% CIs. $P < 0.05$ was considered significant.

RESULTS

Demographic and clinical data. The population included 37 patients with type 1 diabetes (30 men and 7 women), aged 38 ± 12 years, with BMI 24 ± 3 kg/m^2. The mean age was 37 ± 12 in group 1 ($n = 16$) and 39 ± 12 in group 2 ($n = 21$) (P = NS). Patients in group 1 were free of retinopathy, except for one patient presenting with slow type 1 diabetes; 16 of 21 patients in group 2 presented with retinopathy. Clinical systolic BP (SBP), DBP, and HR did not differ significantly between group 1 and group 2 in resting position or standing for 1, 3, and 6 min (Table 1). Based on consensus definition (decline in SBP ≥20 mmHg and/or DBP ≥10 mmHg within the first 3 minutes), two patients in group 1 and six patients in group 2 presented with orthostatic hypotension. All patients were normotensive (BP <140/90 mmHg), with the exception of one patient in group 1 and three patients in group 2 with mild hypertension (149/99, 146/86, 163/96, and 127/95 mmHg, respectively). HbA_{1c} did not differ significantly between groups 1 and 2. Daytime activities recorded in a diary log were similar in both groups.

Influence of position on ABP and AHR and influence of DD on position-induced changes in ABP and AHR. Mean daytime (10:00 A.M. to 8:00 P.M.) ABP and AHR in supine/sitting position did not differ significantly between groups 1 and 2 (ASBP 115.3 ± 12.5 vs. 118.9 ± 12.3 mmHg, ADBP 78.0 ± 90 vs. 79.7 ± 7.5 mmHg, AHR 80.0 ± 12.0 vs. 78.9 ± 14.6 bpm). However, standing ASBP and ADBP were significantly higher than supine/sitting ASBP and ADBP in group 1 (ΔSBP 4.2 ± 4.5 [95% CI 1.8–6.6] mmHg; ΔDBP 4.3 ± 6.3 [1.0–7.7] mmHg; $P < 0.01$) but not in group 2 (ΔSBP 2.0 ± 7.9 [−1.6 to 5.6] mmHg); ΔDBP 1.5 ± 4.0 [−0.3 to 3.3] mmHg; P = NS). Standing AHR was significantly higher than supine/sitting AHR ($P < 0.001$) in group 1 (ΔHR 13.2 ± 7.3 [9.3–17.0] bpm) and in group 2 (ΔHR 12.8 ± 9.7 [8.4–17.2] bpm) (Table 1).

Relation between microangiopathy and position-induced changes in ABP and AHR. To study the links between microangiopathy and position-induced changes in ABP, the population was analyzed according to the presence of retinopathy and divided into group R^- (free of any retinopathy; $n = 20$, including 15 patients from group 1 and five patients from group 2) and group R^+ (presenting with retinopathy; $n = 17$, including 1 patient from group 1 and 16 patients from group 2). During daytime hours (10:00 A.M. to 8:00 P.M.), patients in group R^- exhibited a significant increase in SBP, DPB, and HR while moving from the sitting/lying position to the standing position (ΔSBP 5.5 ± 5.2 [95%CI 3.0–7.9]

Table 1—*Clinical description of the population and position-induced changes in ABP and HR in patients without diabetic nephropathy, according to DD*

	Group 1 (n = 16) DD <5 years	Group 2 (n = 21) DD >10 years
Patient characteristics (n = 37)		
Sex (M/F)	13/3	17/4
Age (years)	36.8 ± 12.1	38.7 ± 11.6
BMI (kg/m^2)	23.7 ± 2.9	23.4 ± 2.9
DD (years)	3.4 ± 1.4	17.4 ± 7.0
HbA_{1c} (%)	8.1 ± 2.0	9.2 ± 2.1
Retinopathy (R^-/R^+)	15/1	5/16
SBP (mmHg)	120.8 ± 12.1	122.3 ± 15.6
Standing	114.9 ± 14.4	115.9 ± 20.7
DBP (mmHg)	77.5 ± 12.1	82.2 ± 8.5
Standing	82.6 ± 9.7	83.2 ± 9.1
HR (bpm)	70 ± 11.1	70.3 ± 11.1
Standing	80.6 ± 14.1	83.7 ± 15.4
ABPM		
ASBP (mmHg)		
Horizontal, sitting/lying	115.3 ± 12.5	118.9 ± 12.3
Vertical, standing	119.5 ± 13.5*	120.9 ± 13.5
ΔVH	4.2 ± 4.5	2.0 ± 7.9
ADBP (mmHg)		
Horizontal, sitting/lying	78.0 ± 9.0	79.7 ± 7.5
Vertical, standing	82.4 ± 9.1†	81.2 ± 7.2
ΔVH	4.3 ± 6.3	1.5 ± 4.0
AHR (bpm)		
Horizontal, sitting/lying	80.0 ± 12.0	78.9 ± 14.6
Vertical, standing	93.1 ± 14.1‡	91.8 ± 18.8‡
ΔVH	13.2 ± 7.3	12.8 ± 9.7

Data are means ± SD or n. *P < 0.01; †P < 0.05; ‡P < 0.001, vertical versus horizontal.

mmHg; ΔDBP 4.6 ± 5.6 [2.0–7.2] mmHg; ΔHR 13.1 ± 6.4 [10.1–16.1] bpm). By contrast, patients in group R^+ exhibited a single significant increase of HR during standing (ΔSBP 0.0 ± 7.1 [−3.6 to 3.7] mmHg; ΔDBP 0.5 ± 3.9 [−1.5 to 2.5] mmHg; ΔHR 12.8 ± 10.9 [7.1–18.4] bpm) (Table 2). Patients in group R^- presented with a significantly higher vertical/horizontal (VH) difference for systolic and diastolic ABP (ANOVA, P < 0.05) when compared with group R^+ (Table 2). The distribution of ΔSBP and ΔDBP according to the status of retinopathy and DD (categorized as <5 years, 10–20 years, and >20 years) is plotted on Fig. 1. Although retinopathy and DD are two closely dependent variables, it appears that patients in the 10–20 years category who are free of retinopathy have significantly higher ΔSBP (9.8 ± 4.9 [3.8–15.9] vs. −0.4 ± 7.2 [−5.5 to 4.7] mmHg, multifactorial ANOVA, P < 0.05) and nonsignificantly higher ΔDBP (3.9 ± 3.6 [−0.5 to 8.4] vs. 0.8 ± 4.6 [−2.5–4.1] mmHg) compared with patients with diabetic retinopathy and similar disease duration.

Comparison of position-induced changes in ABP and dipper/nondipper status. Nondippers were defined by a day-to-night fall in either SBP or DBP of <10%. A nondipper pattern was previously described as a good predictor of diabetic retinopathy or nephropathy. Therefore, we compared the distribution of both indicators (i.e., position-induced changes in ABP and dipper/nondipper status) among our study population (Table 2). ΔSBP and ΔDBP were not different when dippers were compared with nondippers. Dippers with retinopathy exhibited less variation in ABP upon standing than dippers without retinopathy, although the difference did not reach statistical significance. Similarly, nondippers without retinopathy conserved variation of ABP upon standing, as opposed to nondippers with retinopathy, and the difference between these two subgroups was significant (P < 0.05, Table 2).

Influence of diabetic nephropathy. Patients in group 3 were older (46 ± 14 years), had a longer disease duration (22 ± 3 years), exhibited retinopathy (n = 7) and permanent microalbuminuria (121 μg/min, range 44–164) but a preserved renal function (creatinine clearance 104 ± 20 ml/min), and had higher SBP (145 ± 27 mmHg) and HR (77 ± 16 bpm). ASBP was higher in group 3 than in group 1 or group 2 (135 ± 24 mmHg, P < 0.05). For these reasons, group 3 was not included in the main statistical analysis of our study. DBP, ADBP, and AHR were 82 ± 13 mmHg, 81 ± 13 mmHg, and 83 ± 17 bpm, respectively. Standing ASBP and ADBP did not significantly increase when compared with supine/sitting ASBP and ADBP (ΔSBP 2 ± 11, ΔDBP 0 ± 5; P = NS). Standing AHR was significantly higher than supine/sitting AHR (ΔHR 9 ± 6 bpm, P < 0.001). Of note, only three patients in this group were nondippers, and four remained dippers.

CONCLUSIONS

— BP measures taken in the doctor's office remain the reference values for the diagnosis and follow-up of hypertension in diabetic patients in usual practice. The most recent WHO recommendations in 1999 (9) define the conditions of BP measurement and recommend BP to be measured both in the sitting and the standing position. In borderline circumstances, ambulatory measurements can be performed. ABP monitoring is now well codified for modes of measurement (10), although reference values are available for the nondiabetic population (11). We now report the first data describing the variations of ABP with position in type 1 diabetic patients.

To avoid possible disturbances of metabolic events on circadian BP, this study was conducted on ambulatory patients who were free of any recent acute metabolic events. In our study, no differences were observed between groups for insulin dosage or insulin scheme distribution (data not shown).

We first observed that young-adult recent-onset patients (<5 years) who were normotensive and free of any microangiopathy (group 1) exhibited a statistically significant variation of BP according to position, with higher levels

Table 2—*Distribution of position-induced changes in ABP and dippers/nondippers status according to the presence of diabetic retinopathy in patients without nephropathy*

	Group R^- (n = 20) DD 5.6 ± 5.3 years			Group R^+ (n = 17) DD 17.8 ± 7.8 years		
	H	V	Δ VH	H	V	Δ VH
ASBP (mmHg)	113.2 ± 11.2	118.7 ± 12.2*	5.5 ± 5.2	122.1 ± 12.2	122.1 ± 14.7	−0.0 ± 7.1‡
ADBP (mmHg)	76.3 ± 8.1	80.9 ± 8.6†	4.6 ± 5.6	82.2 ± 7.1	82.7 ± 7.2	0.5 ± 3.9‡
AHR (bpm)	77.8 ± 12.1	91.0 ± 14.8*	13.1 ± 6.4	81.2 ± 14.9	94.0 ± 19.1*	12.8 ± 10.9

	Dippers			Nondippers		
	R^- (n = 13)	R^+ (n = 7)	Total (n = 20)	R^- (n = 7)	R^+ (n = 10)	Total (n = 17)
Δ SBP (mmHg)	4.7 ± 5.4§	1.4 ± 7.3	3.5 ± 6.2	6.5 ± 5.0§	−1.1 ± 7.0‡	2.0 ± 7.2
Δ DBP (mmHg)	3.4 ± 4.6§	1.9 ± 5.4	2.9 ± 4.8	6.5 ± 7.1§	−0.6 ± 2.1‡	2.4 ± 5.9

Data are means ± SEM. Group R^-, retinopathy-free patients; Group R^+, patients with retinopathy. Nondippers were defined by a day-to-night fall in either SBP or DBP of <10%. *$P < 0.001$; †$P < 0.01$; ‡$P < 0.05$, vertical versus horizontal. §$P < 0.05$ group R^+ versus R^- (ANOVA), and group R^+ nondippers versus group R^- nondippers (Wilcoxon test).

of both SBP and DBP in the standing position. This difference was of the order of 4 mmHg for both SBP and DBP. The values of standing HR are also higher by ~13 beats/min. These variations are of the same order of magnitude as results obtained in a nondiabetic population of healthy normotensive young to middle-age individuals (8). These BP and HR variations may be caused by a modification in peripheral resistance and an increase in cardiac output, and they may be physiological changes mediated by the autonomic nervous system.

We next observed that in group 2 patients, who were similar in age and clinical BP and who were free of nephropathy but had a longer DD (≥10 years), these position-induced changes in ABP could not be found, although the increase in HR during standing persisted. Because a prolonged disease duration is closely associated with an increased incidence of diabetic retinopathy, we observed that the pattern of position-induced changes in ABP tended to disappear in patients suffering from retinopathy. This pattern was also observed in a third group of patients remarkable for the presence of permanent microalbuminuria. Overall, the data suggest that the development of microangiopathy is associated with changes in the regulation of BP during standing. The clinical implications of this pilot investigation are still speculative, but promising.

ABPM has now become an established clinical tool, but despite intensive studies performed in diabetic patients, no index has emerged from ABP as a reliable predictor of microangiopathy or other abnormalities. Many studies converged to show an increased ambulatory pressure load during the course of type 1 diabetes (12,13). Various features were described, among which an elevation in systolic values over 24 h and a nocturnal increase in systolic and diastolic levels were predominant. Several determinants are invoked, including the duration of the disease, the modality of insulin therapy, and the presence of a permanent microalbuminuria and dysautonomia.

The development of permanent microalbuminuria in normotensive type 1 diabetic patients is associated with an increase in ambulatory BP (1,2,4,14). Progressors to overt nephropathy are found among "high normal" albuminuric patients (15), but no difference in initial 24-h ABPM could be found between progressors and nonprogressors (16). Consequently, no ABP threshold could ever be set. Thus, any marker of a disturbed BP regulation could be useful in the early detection of these patients, before they progress to the microalbuminuric stage. This progression was previously suggested to be predicted by the loss of nocturnal decline in diastolic BP (17,18). However, the lack of prospective studies, the discrepancies in defining night period (19), and a large overlap in the night-to-

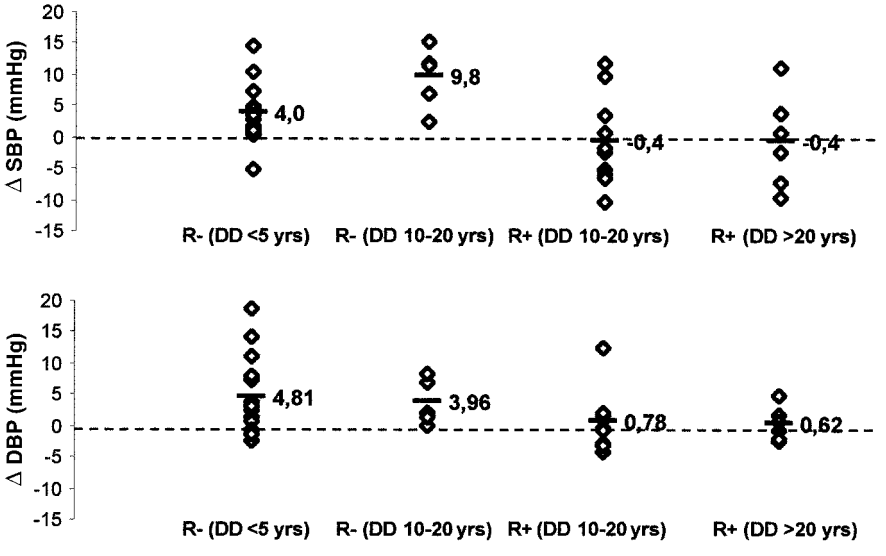

Figure 1—*Distribution of position-induced changes in ambulatory BP according to the status of retinopathy and disease duration. R^-, patients free of any retinopathy; R^+, patients presenting with retinopathy.*

day ratio of diastolic BP between the different groups of patients prevented the definition of a clinically relevant threshold. Therefore, the monitoring of the position of the patient, which can affect the reproducibility of ABP, may help in defining a predictive index.

Whether some degree of dysautonomia contributes to our findings in patients with microangiopathy and long DD is unknown. Indeed, the presence of neuropathy is related to DD, and blunted circadian or exercise-induced variations in ambulatory BP in type 1 diabetic patients are related to dysautonomia (20). Links between nephropathy as well as retinopathy and dysautonomia have been suggested (21–22).

The role of BP elevation in the incidence and progression of diabetic retinopathy is not clearly established, and few studies have addressed this issue with ABPM. A study performed in strictly normoalbuminuric type 1 diabetic patients found increased diastolic night BP and night-to-day ratio of diastolic BP among patients with retinopathy (3). In our patients with retinopathy, the role of DD and/or subclinical autonomic neuropathy in the disturbances in position-induced BP changes cannot be excluded.

In conclusion, ABPM coupled with a position sensor displays a loss of position-induced changes in BP in patients with longer disease duration and diabetic microangiopathy. This pilot study suggests the need for further investigation to determine whether the screening of patients at risk for microangiopathy could be improved. Through greater reproducibility, these studies may favor the search for a better correlation between ABP patterns and organ damage. Future investigations may involve the detection of subclinical dysautonomia, the evaluation of the effectiveness and tolerance of an antihypertensive treatment, and the assessment of patients, mostly adolescents, presenting with transient microalbuminuria.

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