Recognition of Hypertension and Abnormal Blood Pressure Burden With Ambulatory Blood Pressure Recordings in Type I Diabetes Mellitus

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Ambulatory blood pressure (AMBP) measurements were obtained at 20-min intervals for 24 h in 25 subjects with insulin-dependent (type I) diabetes mellitus and 21 control subjects. The diabetic patients had normal kidney function (glomerular filtration rate 112.1 ± 7.2 ml · min^{-1} · 1.73 m^{-2}, renal plasma flow 459.0 ± 23.4 ml · min^{-1} · 1.73 m^{-2}) and were normotensive according to standard sphygmomanometer examinations. Mean ± SE AMBP (systolic/diastolic in mmHg) measurements in diabetic patients (24 h, 131.7/77.2 ± 2.9/1.8; 0600–2200, 132.3/78.4 ± 2.9/3.4; 2200–0600, 125.1/75.7 ± 3.9/3.4) significantly exceeded control values during all times (24 h, 121.8/70.3 ± 2.9/1.9; 0600–2200, 120.7/71.8 ± 2.6/2.0; 2200–0600, 108.2/61.5 ± 6.6/2.7). Mean 24-h AMBP exceeded 135/85 mmHg in 49% of diabetic patients. The same threshold of 135/85 mmHg was used to determine the prevalence of abnormal measurements per time period (pressure burden). Pressure burden was increased twofold in diabetic patients compared with control subjects. Mean AMBP was significantly reduced at night in control subjects but not in diabetic patients. Changes in blood pressure were not related to kidney function in diabetic patients. AMBP recordings uncovered an increased prevalence of abnormal mean blood pressure, increased pressure burden, and a lack of diurnal variation of blood pressure in subjects with type I diabetes mellitus. These findings have important implications for early intervention strategies in diabetes mellitus because AMBP recordings correlate well with end-organ damage. *Diabetes* 39:1556–60, 1990

Noninvasive ambulatory blood pressure (AMBP) recordings gather numerous blood pressure measurements in the patient's natural environment, which avoids increased pressures due to the office environment or stress (alert reaction). The ambulatory technique defines patterns of blood pressure and circadian rhythms and provides an important opportunity to diagnose borderline hypertension (1–3). Increased blood pressure, determined by office readings, is a well-established determinant of vascular disease (4,5). AMBP recordings have also been shown to be related to cardiovascular events and end-organ damage (6–8). Furthermore, it has been suggested that end-organ damage is related to the frequency of abnormal pressure measurements rather than casual or average blood pressure (9,10). Treatment of hypertension has been shown to reduce cardiovascular morbidity (4,11). In diabetic patients, in whom hypertension and cardiovascular morbidity are common, treatment of hypertension inhibits progression of diabetic nephropathy (12–16).

Mean blood pressure and daily patterns have not been examined by ambulatory recordings in diabetic patients. This study determined mean blood pressure, prevalence of abnormal measurements, and day/night pattern in patients with insulin-dependent (type I) diabetes mellitus and control subjects who were diagnosed as normotensive by routine clinical blood pressure measurements.

RESEARCH DESIGN AND METHODS

The 25 patients in this study were recruited consecutively from the diabetic outpatient clinic at the University of Kansas Medical Center (Kansas City). All patients were diagnosed as having type I diabetes mellitus based on the standard criteria of juvenile onset and insulin dependency. All were normotensive (<140/90 mmHg) according to sphygmomanometer determinations during repeated clinic visits, and none took antihypertensive medications. Inclusion in the study was based on diagnosis, absence of hypertension, and treatment and absence of overt clinical evidence of

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chronic complications of diabetes (retinopathy, nephropathy, amputation, myocardial disease). Control subjects of similar age and sex distribution were healthy normotensive individuals, as confirmed by history and physical examination. These subjects were randomly recruited among the medical center staff and their relatives. All participants gave informed consent.

An oscillometric AMBP recorder (SpaceLabs 90202, Redmond, WA) was used to determine AMBP every 20 min for 24 h. Measurements were started between 0800 and 0900. Mean AMBP for each subject was calculated for 24 h and separately for the period between 0600 and 2200, which was designated as day, and the period between 2200 and 0600, which was designated as night. Casual blood pressure was determined at the beginning of each study as the mean of three sphygmomanometer readings, taken 5 min apart in the sitting position.

A blood pressure in excess of 140/90 mmHg was used for a standard World Health Organization definition of hypertension by sphygmomanometer readings in the office. A universal standard has not yet been defined for AMBP, which may be substantially lower than casual blood pressure. The mean difference can be as great as 27/15 mmHg (17,18). We used a threshold of 135/85 mmHg for mean 24-h AMBP, which is only 5 mmHg lower than the standard threshold. A mean AMBP of 135/85 mmHg exceeds mean 24-h AMBP, as reported previously in normotensive and borderline hypertensive subjects (Table 1). The threshold was used to determine the prevalence of hypertensive readings at different times. The prevalence of increased blood pressure, expressed as the percentage of total blood pressure readings, was designated as the pressure burden.

Kidney function was determined in diabetic patients. A 24-h collection of urine was used to measure urinary excretion of albumin (AER) during the period of AMBP monitoring. Urine was collected in standard plastic containers without additive. Patients were asked to avoid vigorous exercise during the time of urine collections. All participants received written and verbal instructions on the collection of timed day and night urine collections, which were combined to yield a 24-h collection. Collection times were recorded on prepared forms. The volumes of all collections were determined with graduated cylinders, and aliquots were frozen at −20°C until analyzed. Albumin concentration was measured in either fresh or thawed frozen urine specimens with a double-antibody radioimmunoassay (Diagnostic, Los Angeles, CA). AER was expressed as micrograms per minute corrected for a body surface area of 1.73 m^2. Glycosylated hemoglobin (HbA_{1c}) was determined in the university clinical laboratories (normal range 6.0–8.5%).

TABLE 1
Mean ambulatory blood pressure (mmHg) previously reported in normotensive and borderline hypertensive subjects

	Ref.
Normotensive	
103/64	19
122/76	20
115/71	21
116/74	22
125/70	23
123/79	24
Borderline hypertensive	
130/81	21
135/87	10
132/83	23

TABLE 2
Clinical characteristics in study subjects with (n = 25) and without (n = 21) insulin-dependent diabetes mellitus

	Diabetic	Control
Age (yr)	31.4 ± 2.8	27.4 ± 2.6
Weight (kg)	75.2 ± 2.8	73.3 ± 3.8
Height (cm)	178.6 ± 1.8	171.5 ± 3.5
Surface (m^2)	1.93 ± 0.03	1.80 ± 0.04
Duration of disease (yr)	11.2 ± 1.1	NA
Insulin (U/day)	58.4 ± 1.1	NA
HbA_{1c} (%)	11.6 ± 0.58	NA

Values are means ± SE. NA, not applicable.

Glomerular filtration rate (GFR) and renal plasma flow (RPF) were examined in diabetic patients at the end of AMBP monitoring. Determinations were conducted during water diuresis in the fasting state; half of the regular insulin dose was withheld the morning of the study. Blood glucose concentration was maintained between 5.6 and 13.3 mM during the clearance study. Diuresis was initiated with an oral water load (1% of body wt, limit 1 L) and maintained with 150 ml of water taken orally every 30 min. Patients remained in a comfortable sitting position for the duration of the study, except during micturition.

Baseline urine and plasma samples were obtained after initiation of stable diuresis. The clearance of ^{99}Tc represented GFR during each clearance period, whereas [^{131}I]iodohippurate (Squibb, Princeton, NJ) represented RPF. Urine and plasma samples were collected every 30 min in serial clearance periods (1–9). Specific activity of ^{99}Tc and [^{131}I]iodohippurate in urine and plasma were determined in a Hewlett-Packard dual-channel γ-scintillation spectrometer. Clearance was determined by the standard formula $U_x \times V/P_x \times t$, where U and P represent urine and plasma concentrations, V is urine volume, and t time in minutes. The average of clearance periods 6–9 was used to calculate GFR and RPF. Results were expressed as ml · min^{-1} · 1.73 m^{-2} body surface area.

Results are means ± SE. In the case of AMBP measurements, group results represent the mean of individual mean blood pressures. A t test for unpaired data was used in the comparison of subjects with and without diabetes, and a paired t test was used to compare data within a group. Analysis of variance was used for multiple comparisons, and correlation analysis was used to explore relationship between variables. $P < 0.05$ was significant.

RESULTS

Clinical characteristics of the study population are shown in Table 2. There were no statistically significant differences between groups with respect to age, body size, and sex distribution. GFR in diabetic patients was normal (112.1 ± 7.2, range 1.2–212.1 ml · min^{-1} · 1.73 m^{-2}). RPF in diabetic

TABLE 3
Mean ambulatory blood pressure (mmHg) and heart rate (beats/min) during different times in subjects with (n = 25) and without (n = 21) insulin-dependent diabetes mellitus

	Diabetic	Control
Systolic blood pressure		
24 h	131.7 ± 2.9*	121.8 ± 2.9
0600–2200	132.3 ± 2.9†	120.7 ± 2.6
2200–0600	125.1 ± 3.9†	108.2 ± 6.6
Diastolic blood pressure		
24 h	77.2 ± 1.8†	70.3 ± 1.9
0600–2200	78.4 ± 3.4*	71.8 ± 2.0
2200–0600	75.7 ± 3.4†	61.5 ± 2.7
Heart rate		
24 h	87.4 ± 2.4‡	80.2 ± 2.5
0600–2200	89.4 ± 2.4‡	81.7 ± 2.5
2200–0600	75.5 ± 2.7*	70.8 ± 3.7

Values are means ± SE.
*P < 0.05, †P < 0.005, ‡P < 0.01, vs. control.

patients was also normal (459.0 ± 23.4, range 271.0–746.5 ml · min^{-1} · 1.73 m^{-2}). AER over 24 h in 24 diabetic patients was 18.2 ± 3.4 μg · min^{-1} · 1.73 m^{-2} (range 3.0–62.3 μg · min^{-1} · 1.73 m^{-2}). One patient had overt proteinuria with an AER of 739 μg · min^{-1} · 1.73 m^{-2}. Clearance studies and AER determination were not conducted in control subjects, but kidney function was considered normal with individual serum creatinine concentrations <106 μM.

There was no statistically significant difference in casual blood pressure between diabetic patients (127.6/73.6 ± 2.3/2.4 mmHg) and control subjects (122.2/72.6 ± 2.9/2.3 mmHg). Mean AMBP readings were compared between groups. Altogether, 49% of the diabetic patients had a mean 24-h AMBP in excess of 135/85 mmHg compared with 24% in control subjects (P < 0.01). The mean systolic and diastolic blood pressures were significantly higher in patients during all time periods (Table 3). Furthermore, heart rates were higher in diabetic patients. The prevalence of abnormal blood pressure measurements (pressure burden) also differed significantly between groups (Table 4). The pressure burden, both systolic and diastolic, was increased to more than twice that of control subjects at all time periods. A comparison of mean AMBP in patients and control subjects during each hour showed significant differences between systolic and diastolic pressure for most time periods (Fig. 1).

TABLE 4
Mean prevalence (%) of increased blood pressure readings during different times in subjects with (n = 25) and without (n = 21) insulin-dependent diabetes mellitus

	Diabetic	Control
Systolic blood pressure >135 mmHg		
24 h	49.2 ± 5.9*	23.7 ± 6.9
0600–2200	50.6 ± 6.0†	29.4 ± 7.3
2200–0600	43.4 ± 6.9‡	16.1 ± 6.7
Diastolic blood pressure >85 mmHg		
24 h	27.3 ± 4.8†	11.4 ± 3.3
0600–2200	28.3 ± 4.9*	14.0 ± 3.4
2200–0600	24.7 ± 6.9†	8.6 ± 3.8

Values are means ± SE.
*P < 0.01, †P < 0.05, ‡P < 0.005, vs. control.

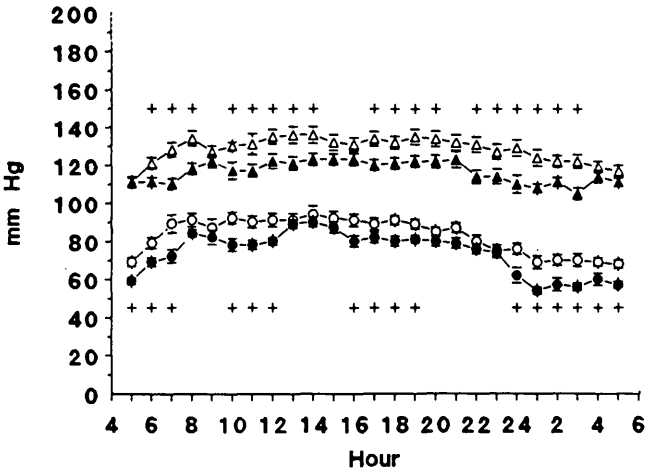

FIG. 1. Hourly comparison of systolic (*triangles*) and diastolic (*circles*) blood pressure in subjects with (*open symbols*) and without (*solid symbols*) insulin-dependent diabetes mellitus. Values are means ± SE. †P < 0.05 between groups.

The reduction of blood pressure and heart rate during the night compared with the day was examined also. The mean reduction in systolic pressure during the night was variable at 13.2 ± 6.6 mmHg (P < 0.1) in control subjects. The reduction in patients' blood pressure was smaller and less variable at 6.6 ± 2.7 mmHg (P < 0.05). Mean diastolic pressures were significantly reduced at night in control subjects (9.8 ± 1.8 mmHg, P < 0.0001), whereas there was no change in diabetic patients (2.6 ± 2.8 mmHg). Finally, the prevalence of systolic and/or diastolic measurements >135/85 mmHg was significantly reduced at night in control subjects, whereas there was no significant reduction in diabetic patients.

GFR and RPF were inversely related to various measures of blood pressure, but these relationships were weak (r < 0.20) and insignificant. We also divided the patients into two groups with <112 (n = 13) and >112 (n = 12) ml · min^{-1} · 1.73 m^{-2} GFR to determine whether blood pressures were related to any degree of glomerular hyperfiltration. There were no significant differences between groups with high and low GFR with respect to blood pressure, age, body size, or glucose control (not shown). Moreover, the correlation between AER and the kidney and various measures of blood pressure was weak (r < 0.30) and insignificant, both before and after logarithmic transformation. However, various measures of blood pressures were all related (r > 0.50) to duration of disease in a significant manner (P < 0.01).

DISCUSSION

With the use of the standard technique, there was no difference in blood pressure between diabetic patients and control subjects whose AMBP recordings confirmed readings previously obtained in studies of normotensive individuals (19–24). In contrast, AMBP recordings in diabetic patients showed significantly higher mean blood pressures during all time periods compared with control subjects. The values in the group with diabetes were similar or even higher than those obtained in previous studies of patients with bor-

derline hypertension without diabetes mellitus (10,21,23). Moreover, the normal nighttime decrease in systolic pressure was attenuated in patients, whereas the decrease in diastolic pressure was absent. Increases in blood pressure in diabetic patients could not be attributed to occult kidney disease because measures of kidney function were normal. Moreover, pressures were not related to glomerular hyperfiltration.

A threshold of 135/85 mmHg was used to ascertain the prevalence of increased pressure during different time periods because blood pressure measurements during ambulatory recordings were generally lower than measurements of casual blood pressure. In fact, some studies on essential hypertension have found a mean difference as large as 27/15 mmHg (17,18). In comparison, lowering the threshold for hypertension by 5 mmHg for AMBP is a conservative adjustment. In this study, half of the diabetic patients had a mean AMBP >135/85 mmHg. The prevalence of increased (>135/85 mmHg) pressure readings in the control group was similar to that reported for normotensive individuals. In contrast, there was a twofold increase in the prevalence of increased pressure measurements, both systolic and diastolic, during all time periods in subjects with diabetes. We designated this increased prevalence as the pressure burden. Others have defined this finding similarly and have shown a significant relationship to cardiovascular morbidity (10). The distribution of abnormal measurements throughout the 24-h period was also apparent in the hourly comparison of blood pressures (Fig. 1).

Increased mean pressure and increased prevalence of abnormal readings in our patients were similar to those found previously when comparing borderline and established hypertension (10). The findings could not be attributed to age, physical characteristics, or kidney function. However, disease duration was significantly related to pressure. Interestingly, diabetic patients failed to reduce blood pressure and blood pressure burden during the night. The absence of the normal fall in nighttime blood pressure probably represents evidence of autonomic dysfunction, which is a prominent characteristic of advanced diabetes mellitus (25). This notion is supported by the finding that heart rates were higher than those found in control subjects during all time periods.

The potential use of AMBP in the early detection of increased blood pressure was apparent in patients with diabetes. This increase in blood pressure met the definition of hypertension according to AMBP criteria. Twenty-four-hour ambulatory recordings determined a lack of nocturnal pressure reduction in patients. AMBP recordings may be more closely related to end-organ damage and are possibly a better predictor than casual blood pressure readings (6–8). However, these observations are restricted to patients with essential hypertension, but its use in the prediction of morbidity remains to be determined in diabetic patients. The ambulatory recording technique also established the presence of increased blood pressure burden, which may be of particular importance in end-organ damage (1,9). It remains to be seen whether increased blood pressure burden determines eventual vascular morbidity in diabetic patients.

This study also raises a question regarding which AMBP value should define hypertension and indicate the need for therapeutic intervention. Because blood pressure is a continuously distributed variable in the general population, established treatment threshold in reality represents the arbitrary criteria of a previous outcome study. Therefore, it is not clear whether a level of 140/90 mmHg by sphygmomanometer or 135/85 mmHg by ambulatory measurement is too high in diabetic patients. We believe that diabetic patients are at risk from early increased blood pressure below the standard levels defined as hypertension. Such early subclinical increase in pressure could be conceptualized as incipient hypertension. Random blood pressure measurements in a clinic setting may not identify these patients. Moreover, it has yet to be established whether antihypertensive therapy should be based on ambulatory measurements. Carefully designed prospective studies will be required to establish efficacy of early treatment.

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