Altered Blood Pressure During Sleep in Normotensive Subjects With Type I Diabetes

Ampar Lurbe, Josep Redón, Jose M. Pascual, Jose Tacons, Vicente Alvarez, and Daniel C. Batlle

This study was designed to examine the circadian pattern of blood pressure in children and young adults with type I diabetes who were completely normotensive by standard criteria. Forty-five patients and the same number of age- and sex-matched control subjects were studied. In diabetic children of 10-14 years of age, the nocturnal fall in systolic and diastolic blood pressures was intact. In diabetics of 15-20 years of age, the fall in systolic blood pressure was blunted; in diabetics of 21-37 years of age, the fall in both systolic and diastolic blood pressures during sleep was blunted. When data from all diabetic subjects were pooled and analyzed in a multiple linear regression model, mean blood pressure during sleep correlated best with urinary albumin excretion ($r=0.60$). On the basis of this finding, we subdivided our patients into two groups: a microalbuminuric group (urinary albumin excretion >30 mg per 24 hours; mean, 160.3±29.7; $n=11$) and a normoalbuminuric group (urinary albumin excretion <30 mg per 24 hours; mean, 6.6±6.5; $n=34$). Both systolic and diastolic blood pressures during sleep were higher in microalbuminuric diabetic children (121.1±3.3 and 69.3 ±2.5 mm Hg, respectively) than in normoalbuminuric diabetics (114.2±1.8 and 60.1 ±1.2 mm Hg, $p<0.05$). Although most microalbuminuric patients (nine of 11) had a blunted fall in blood pressure during sleep, this alteration was also seen in normoalbuminuric subjects (14 of 34 patients). We conclude that in many "normotensive" patients with type I diabetes, the physiological nocturnal fall in blood pressure is blunted. This abnormality can antedate the development of microalbuminuria, suggesting that it may prove to be a sensitive marker for renal disease and eventual progression to overt hypertension.

Key Words • diabetes mellitus, type I • diabetic nephropathies • albuminuria • awake blood pressure • ambulatory blood pressure

The presence of hypertension is considered to be the major determinant in the progression of diabetic nephropathy toward end-stage renal disease.1-4 Because diabetic nephropathy develops in only 30-40% of patients with insulin-dependent diabetes mellitus, there is increasing interest in defining ways to identify patients susceptible to nephropathy early in the course of diabetes.5,6 Microalbuminuria usually develops in type I diabetics before the onset of clinically overt nephropathy.7 This subclinical stage of nephropathy has been shown to antedate hypertension8 or to develop in parallel with increasing blood pressure (BP).9-11 Whether subtle alterations in BP control antedate or follow the microalbuminuric stage in patients with insulin-dependent diabetes mellitus remains to be determined.12 The use of 24-hour ambulatory BP recordings provides an integrated BP profile over time and permits the exploration of circadian BP patterns.13-16 The fall in BP, which is normally seen during the sleep period both in normotensive and hypertensive subjects, may provide insight into mechanisms involved in BP regulation and also may have more predictive value than office BP in defining the potential for end-organ damage.17 Two recent studies have used 24-hour BP monitoring in patients with type I diabetes.18,19 Weigman et al18 reported that in adult subjects with type I diabetes, the fall in nocturnal BP was blunted. In their study, daytime BP was also increased, and many of their subjects had borderline hypertension. Hansen et al19 studied diabetics with microalbuminuria with and without hypertension and found an increase in both day and night BPs that correlated with urinary albumin excretion (UAE) better than office BP, but they observed no abnormalities in the night/day ratio. In the present study, we examined the 24-hour pattern of BP in children and young adults with type I diabetes who were completely normotensive by standard criteria.

Methods

Selection of Study Participants

The 45 patients of this study were recruited from the pediatric and diabetic outpatient clinics of the Hospital...
General of Valencia (Spain) and the Sagunto Hospital (Sagunto, Spain). All patients were diagnosed as having type I diabetes mellitus based on standard criteria of juvenile onset and insulin dependency, and all were normotensive. None of the patients had ever received antihypertensive medications, and office BP was <140/90 mm Hg in adults and less than the 95th age-specific percentile for children according to the Second Task Force report on blood pressure.20 BP was measured during three consecutive office visits at approximately 7-day intervals using a Korotkoff phase IV for diastolic BP in children and phase V in adults. Inclusion criteria included the absence of clinical evidence of complications of diabetes such as proliferative retinopathy, neuropathy, or overt nephropathy, defined by the presence of proteinuria (>300 mg per 24 hours). None of the female patients was pregnant or receiving contraceptive or estrogen treatment. Control subjects were 45 healthy normotensive individuals of similar age and sex distribution randomly recruited from the outpatient pediatric clinics and from the medical center. All participants gave informed consent to enter the study.

Twenty-four-Hour Blood Pressure Monitoring

BP readings were obtained automatically at 20-minute intervals from 6 AM to midnight and at 30-minute intervals from midnight to 6 AM using a portable oscillometric recorder (Spacelabs 90207, Redmond, Wash.). Mean values for every hour, daytime (6 AM to 10 PM) and nighttime (midnight to 6 AM), were calculated for each subject. BP load was expressed as the percentage of elevated BP over the 24-hour period (age >18 years, BP > 140/90 mm Hg; age <18 years, BP >95th age-specific percentile).20

The ratio between sleep BP, taken from midnight to 6 AM, and activity BP, taken from 8 AM to 10 PM, was considered abnormal when higher than the 90% confidence interval observed in the age-matched control group. Based on this criterion, the ratio was arbitrarily considered abnormal if >1.00 for systolic BP and >0.90 for diastolic BP.

Analytical Procedures

Three consecutive 24-hour urine collections were obtained for the measurement of UAE and glomerular filtration rate (GFR). Albumin concentration was measured in fresh urine specimens with a nephelometric assay (Behring).21 UAE was expressed as milligrams per 24 hours using the mean values of the three 24-hour urine collections. Microalbuminuria was defined as a UAE between 30 and 299 mg/day (normal UAE value in our laboratory, 4.2±0.4 mg per 24 hours) in the three collections. GFR was estimated from the clearance of endogenous creatinine. Patients were asked to avoid vigorous exercise during the time of urine collections. Glycosylated hemoglobin (HbA1c) was determined by high-performance liquid chromatography.

Statistical Analysis

Two-way analysis of variance was used to search for statistical differences in BP between two or more groups over the time interval of interest. Differences in the mean BP or pulse for a given time interval were analyzed using Student’s t test (unpaired data analysis). Within-group differences in BP or pulse between awake and sleep readings were sought by analysis of variance with repeated measures. Correlations between the clinicobiological parameters of interest and BP indexes were sought using single and multiple linear regression analysis when appropriate. Data are expressed as mean±SEM.

Results

General Data

Table 1 shows the general characteristics of the two study populations (control subjects and type I diabeticics). There were no significant differences between the two groups with respect to age, sex distribution, body mass index, and office BP and heart rate. In the diabetic group, the disease was diagnosed at the mean age of 13.7±1.0 years, and the mean disease duration at the time of study was 7.1±0.9 years. The mean insulin dose was 0.82±0.04 units/kg per day. Hyperglycemic control was considered reasonably satisfactory as judged by a
mean HbA1c level of 9.1±0.3% (range, 7.8–10.1%). The mean GFR was 112±4.5 ml/min per 1.73 m² (82–156 ml/min per 1.73 m²), and the mean UAE was 42.2±11.9 mg per 24 hours (range, 0–299 mg per 24 hours).

Twenty-four-Hour Blood Pressure Profile

Data from the 24-hour BP profile (a total of 68±1.5 valid readings per patient) for the two groups are shown in Table 1. Over the entire 24-hour period, mean systolic and diastolic BPs and mean BP were not significantly different between patients and control subjects. In both groups, BP load was well below the level characteristic of hypertensive individuals (30% or more readings over a 24-hour period).22 The mean BP for the entire sleep period (data pooled from midnight to 6 AM) was also not significantly different between the two groups. Thus, by all conventional criteria, our diabetic subjects considered as a group were normotensive.

The integrated heart rate profile over the whole 24-hour period was virtually the same in the two groups (Figure 1). The integrated BP profile over the 24 hours of observation is shown in Figure 1. While subjects were
Relation of 24-Hour Blood Pressure and Microalbuminuria

When age at the time of diagnosis, daily dose of insulin, GFR, HbA₁c levels, and UAE were correlated with BP, a strong positive correlation emerged between sleep mean BP and UAE (r=0.60, p<0.01) (Figure 2, left panel) and sleep diastolic BP and UAE (r=0.64, p<0.01). Systolic BP during sleep also correlated positively with UAE although not as strongly (r=0.35, p<0.05). In contrast, systolic, diastolic, or mean BPs during the 24-hour period or during daily activities correlated only weakly with UAE (Figure 2, right panel). Years of disease duration also correlated positively with sleep diastolic BP (r=0.34, p<0.05). No significant correlation was observed between age at the time of diagnosis, daily dose of insulin, GFR, or HbA₁c with any of the ambulatory BP parameters. When a multiple linear regression analysis was performed with sleep diastolic BP as the dependent variable, only UAE remained significant.

The strong positive correlation between sleep BP and UAE suggested to us that the abnormal nocturnal BP observed in diabetic subjects could be a feature limited to or more apparent in subjects with microalbuminuria. Accordingly, type I diabetics were subdivided into two groups based on whether they had microalbuminuria (Table 2). Mean age and body mass index tended to be higher in the group with microalbuminuria, but these differences did not reach statistical significance between the two subgroups. Disease duration was significantly higher in diabetics with microalbuminuria than in diabetics without microalbuminuria. GFR was also not significantly different between the two groups. No significant differences were found in terms of office BP and heart rate or ambulatory BP and heart rate. Mean BP during daily activities was also not significantly different between the two groups. In contrast, sleep mean BP and sleep heart rate were significantly higher in microalbuminuric than normalalbuminuric patients (Table 2). This is best illustrated in Figure 3, which shows that individuals with a UAE <30 mg per 24 hours displayed the expected nocturnal fall in BP and pulse, whereas those with microalbuminuria (UAE >30 mg per 24 hours) did not. Diabetics with microalbuminuria also tended to have a blunted fall in heart rate during sleep, but the difference did not achieve statistical significance as compared with either control subjects or diabetics with a UAE <30 mg per 24 hours (Figure 3).

Relation of 24-Hour Blood Pressure and Age and Disease Duration

The diabetic study group was composed of individuals with a wide age range and thus disease duration; therefore, the patient group and the control group were subdivided into three age subgroups: 10–14, 15–20, and 21–37 years of age. Age and body mass index were virtually identical between each diabetic subgroup and the corresponding control subgroup (Table 3). As expected, disease duration was dependent on the age of each diabetic subgroup (Figure 4, top panel). UAE was only slightly increased in the two younger groups and clearly elevated in the older group (Figure 4, middle panel). GFR was slightly reduced in the older group, although the difference was not statistically significant as compared with the two younger age groups (Figure 4, bottom panel).

No differences in either office or ambulatory 24-hour BP were observed among each age diabetic subgroup and the corresponding control subgroup (Table 3). In
the youngest subgroup, BP during sleep was virtually identical between diabetics and control subjects in terms of both systolic and diastolic BP (Figure 5A). In the intermediate group, the fall in systolic BP during sleep was blunted in diabetics, whereas the fall in diastolic BP was similar to that observed in control subjects (Figure 5B). In the older diabetic age group, the nocturnal fall in both systolic and diastolic BPs was markedly blunted. Consequently, both systolic and diastolic BPs during sleep were significantly higher in the older diabetic subgroup than in age-matched controls (Figure 5C).

Twenty-four-Hour Blood Pressure Patterns in Normoalbuminuric and Microalbuminuric Subjects

Among patients without microalbuminuria (34 patients), we found that as many as 14 had an abnormal BP pattern during sleep in either systolic or diastolic BP (Table 4). Among microalbuminuric patients (11 patients), the night/day ratio was altered in nine patients. In other words, only two of 11 patients retained the physiological nocturnal fall in both systolic and diastolic BPs.

We further examined the distribution of alterations in the day to night BP pattern in patients subdivided into three age subgroups (Table 4). Among normoalbuminuric subjects, 17 belonged to the youngest subgroup and 11 to the intermediate subgroup. There were several patients in these two subgroups in whom either the systolic or diastolic night/day ratio was altered, reflecting an inability to lower BP during sleep in the face of normal UAE (Table 4). All six normoalbuminuric subjects in the oldest age group had retained a normal night/day ratio, suggesting that individuals in whom nephropathy is less likely to develop retain the normal circadian BP rhythm in the face of increased disease duration.

Most of the patients in the microalbuminuric group belonged to the older group (10 of 11). Nine of these had an abnormal night/day ratio in either systolic or diastolic BP, and in seven the night/day ratio was increased for both systolic and diastolic BPs.

Discussion

The present study shows that the physiological nocturnal fall in BP is blunted or absent in some individuals with type 1 diabetes who are completely normotensive by conventional criteria. This abnormality in the circadian BP rhythm was found to be prevalent in patients with type 1 diabetes who had microalbuminuria, but it was also noted in many normoalbuminuric subjects (Table 4). Our study is unique in that it included patients in whom normotension was strictly defined by both mean 24-hour BP and office BP as compared with age- and sex-matched control subjects. BP load (i.e., the percentage of readings above the normal range over a 24-hour period) also was not significantly different between diabetics and age- and sex-matched control subjects (Table 1).

When the data from all of our diabetic subjects were pooled, a direct and strong correlation was found between UAE and mean BP during sleep ($r=0.60$, $p<0.01$). Weaker correlations were found between UAE and mean 24-hour BP over 24 hours ($r=0.40$, $p<0.05$).
TABLE 3. General Characteristics and Blood Pressure Data From Type I Diabetics and Control Subjects Subgrouped by Age

<table>
<thead>
<tr>
<th>Age group</th>
<th>10–14 years</th>
<th>15–20 years</th>
<th>21–37 years</th>
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<tbody>
<tr>
<td></td>
<td>Diabetics</td>
<td>Controls</td>
<td>Diabetics</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>17</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Body mass index (g/m²)</td>
<td>18.0±0.9</td>
<td>18.9±1.2</td>
<td>21.6±0.5</td>
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<tr>
<td>Office</td>
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<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>116.4±3.1</td>
<td>115.8±2.9</td>
<td>120.1±3.0</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>64.6±2.6</td>
<td>64.2±2.5</td>
<td>69.3±2.1</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>81.9±2.8</td>
<td>81.4±2.8</td>
<td>86.2±2.6</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>86.1±4.2</td>
<td>82.9±3.7</td>
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<tr>
<td>Ambulatory</td>
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<tr>
<td>Mean of 24 hours</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>108.1±1.5</td>
<td>110.8±1.7</td>
<td>120.2±2.1</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>63.6±1.3</td>
<td>62.1±1.6</td>
<td>66.3±1.9</td>
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<td>MBP (mm Hg)</td>
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<td>83.7±2.1</td>
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<td>HR (bpm)</td>
<td>84.9±2.5</td>
<td>80.2±2.3</td>
<td>79.0±2.9</td>
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<td>Mean daily activities (8 AM to 10 PM)</td>
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<tr>
<td>SBP (mm Hg)</td>
<td>111.4±1.5</td>
<td>113.2±1.9</td>
<td>121.1±1.9</td>
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<td>69.3±1.8</td>
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<tr>
<td>MBP (mm Hg)</td>
<td>80.4±1.3</td>
<td>83.8±1.8</td>
<td>86.6±1.9</td>
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<tr>
<td>HR (bpm)</td>
<td>89.2±2.7</td>
<td>84.9±2.8</td>
<td>85.7±3.1</td>
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<td>Mean sleep period (midnight to 6 AM)</td>
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<tr>
<td>SBP (mm Hg)</td>
<td>107.8±1.5</td>
<td>108.6±1.5</td>
<td>119.8±1.9</td>
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<tr>
<td>DBP (mm Hg)</td>
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<td>59.7±1.2</td>
<td>59.7±1.5</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>73.3±1.4</td>
<td>77.0±1.6</td>
<td>79.7±1.7</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>76.1±0.3</td>
<td>72.3±0.3</td>
<td>72.7±0.4</td>
</tr>
<tr>
<td>Night/day ratio</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.94±0.01</td>
<td>0.96±0.01</td>
<td>0.96±0.02</td>
</tr>
<tr>
<td>DBP</td>
<td>0.81±0.02</td>
<td>0.83±0.02</td>
<td>0.83±0.02</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; bpm, beats per minute.

*Statistically significant difference between diabetes and corresponding control group by Student's t test (unpaired analysis).

By including individuals with a wide age range (10–37 years), our study provides information regarding the natural history of BP changes that occur in patients with type 1 diabetes and, to our knowledge, is the first of its kind in providing 24-hour data in children afflicted with the disease. When we grouped our diabetic patients by age, we were able to make some interesting observations. However, our findings in children of 10–14 years of age as compared with age-matched control subjects. In the intermediate age group (15–20 years), the fall in systolic BP during sleep was blunted in diabetics as compared with control subjects. The fall in diastolic BP was similar in both subgroups. In the oldest age group (20–37 years), the nocturnal fall in both systolic and diastolic BPs was markedly blunted. In the two oldest groups, the duration of diabetes was, of course, more prolonged than in the youngest group.

We were able to identify several patients in the intermediate and younger groups in whom the nocturnal fall in systolic and diastolic BPs was markedly blunted. In the oldest age group (20–37 years), the nocturnal fall in both systolic and diastolic BPs was markedly blunted. In the two oldest groups, the duration of diabetes was, of course, more prolonged than in the youngest group.

Because the presence of microalbuminuria reflects, by definition, the presence of incipient diabetic nephropathy, we infer that in type I diabetics, there is an early association between BP dysregulation during sleep and incipient nephropathy. Recent studies have suggested that hypertensive individuals whose BP remains high at night are likely to have more left ventricular hypertrophy and/or more extensive vascular disease than those with a preserved circadian rhythm. Our findings of elevated UAE in many of our patients who had a blunted physiological nocturnal BP fall suggest a potential value of this alteration for predicting renal end-organ damage in diabetic subjects.
nal fall in either systolic or diastolic BP was blunted even though microalbuminuria had not developed (Table 4). Thus, blunting of the physiological BP reduction during sleep can antedate microalbuminuria in some cases. This alteration in BP regulation may prove even more sensitive than microalbuminuria in predicting those individuals who will develop nephropathy and other cardiovascular complications that often follow when overt hypertension is associated with diabetes.

The physiological fall in BP during sleep is retained by the majority of patients with essential hypertension. However, certain hypertensive groups, including older hypertensive patients,25 Afro-American blacks,26 and...
patients with chronic renal failure or malignant hypertension, have a blunted fall in BP during sleep. The absence of a normal fall in BP during sleep in normotensive diabetic patients may reflect, however, early autonomic dysfunction at a preclinical stage. Of possible relevance to our findings are previous observations that an abnormal BP pattern during sleep has been described in both normotensive and hypertensive individuals with autonomic dysfunction as well as in diabetic patients selected on the basis of autonomic neuropathy.30,31 In such individuals, BP during sleep may be even higher than during the day. In our patients, there was no overt clinical evidence of autonomic dysfunction, but this was not investigated in any detail. It is possible that evaluation of BP after a standard carbohydrate meal or heart rate and BP responses to standing or tilt and other provocative maneuvers could have uncovered subtle abnormalities consistent with autonomic dysfunction. Baroreceptor hyporesponsiveness in diabetes with early autonomic neuropathy could manifest itself by a higher heart rate and BP during recumbency, as observed during the sleep period in some of our diabetic subjects.

Altered BP control by an altered renal mechanism in patients with incipient diabetic nephropathy should also be considered. It is well appreciated that coexisting hypertension exacerbates diabetic nephropathy and that nephropathy, in turn, results in an increased risk of hypertension.34 That the majority of our diabetic patients with microalbuminuria and thus incipient nephropathy had developed alterations in BP during sleep in the face of normotension during daily activities could be interpreted as evidence for an early connection between nephropathy and BP dysregulation. The finding that some subjects without microalbuminuria already had an abnormal BP pattern during sleep, however, suggests a mechanism of BP dysregulation unrelated to renal impairment. In any event, both alterations could coexist at a subclinical level and not necessarily be related to each other.

Expansion of extravascular volume, as reported in patients with type 1 diabetes, could result in mobilization of fluid during recumbency, leading to an increase in nocturnal intravascular volume and an increase in BP. This volume regulatory dysfunction would be expected to have a greater effect on systolic than on diastolic BP. Interestingly, we observed an alteration in systolic BP but a normal pattern of diastolic BP during sleep in the intermediate age group of diabetics. Older subjects had developed alterations in both systolic and diastolic BPs (Figure 5). The mechanisms underlying these sequential, age-dependent alterations in the nocturnal BP rhythm cannot be discerned from the data reported in the present study and will require further examination.

In summary, the major finding of our study is that a subgroup of normotensive patients with type 1 diabetes lost the physiological fall in BP that normally occurs during sleep. Although many of such individuals had persistent microalbuminuria, others had an abnormal BP pattern during sleep, mostly in systolic BP, at a time when UAE was normal. Our data thus suggest that loss of the physiological nocturnal fall in systolic BP may be a sensitive marker for early renal involvement in patients with type 1 diabetes and likely a predictor of progression to overt hypertension as well.

### References

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