Nondipping of Nocturnal Blood Pressure Is Related to Urinary Albumin Excretion Rate in Patients With Type 2 Diabetes Mellitus

S. Equiluz-Bruck, C. Schnack, H.P. Kopp, and G. Schernthaner

Although cardiovascular and cerebrovascular morbidity and mortality in type 2 diabetic patients is closely related to urinary albumin excretion rate (UAER), the causative mechanisms are not yet identified. The aim of our study was to define the circadian variation of blood pressure (BP) in 72 type 2 diabetic patients (mean age 60 years, mean diabetes mellitus duration: 12 years) in comparison with 41 nondiabetic controls with essential hypertension (mean age 58 years) by using ambulatory blood pressure measurement. Thirty diabetic patients had normal UAER (<30 mg/24 h), 27 had microalbuminuria (30 to 300 mg/24 h), and 15 had persistent proteinuria (>300 mg/24 h). Systolic blood pressure during both nighttime and daytime was significantly elevated in type 2 diabetic patients with macroalbuminuria compared to controls and patients with normal UAER. During nighttime even type 2 diabetic patients with microalbuminuria had significantly elevated systolic blood pressure compared to controls with essential hypertension. We also observed a correlation of nocturnal blood pressure to UAER (systolic: \( r = 0.32, P < .007 \) and diastolic: \( r = 0.24, P < .04 \)). Nondipping (defined as a reduction of nocturnal BP <10%) was observed in 80% of the macroalbuminuric, 74% of the microalbuminuric, but only in 43% of the normoalbuminuric type 2 diabetic patients and in 37% of the controls (\( P < .04 \)). Since a loss of circadian variation of BP is closely related to vascular complications in nondiabetics, our findings may indicate an important relationship between nondipping of BP and the high morbidity and mortality rate in diabetic patients with increased UAER. Am J Hypertens 1996;9:1139–1143

KEY WORDS: Urinary albumin excretion, diabetes mellitus, circadian variation, nocturnal blood pressure drop, microalbuminuria, hypertension.

Hypertension and type-2 diabetes are frequently associated. Moreover, patients may have essential hypertension years before the diagnosis of diabetes mellitus is made. It is also known that increased albumin excretion rate is associated with a rise in blood pressure in type 2 diabetes mellitus. The information regarding 24-h blood pressure measurements in type 2 diabetics with normal and increased albumin excretion rate is very limited. Microalbuminuria is considered as a strong predictor of clinical overt nephropathy in type 1 diabetes mellitus; in type 2 diabetes mellitus end-stage renal disease develops in a much smaller number of patients. Undoubtedly, cardiovascular and cerebrovascular morbidity and mortality are frequent in type 2 diabetes mellitus and closely related to urinary albumin excretion rate (UAER) and hypertension. 

Usually the diagnosis of hypertension is done after
repeated single measurements of blood pressure, but these might be influenced by the phenomenon of "white-coat hypertension." Nowadays, ambulatory 24-h blood pressure measurements represent a well-established technique that allows the documentation of the circadian variation of blood pressure and the effectiveness of antihypertensive treatment. The aim of our study was to define the circadian variation of blood pressure in a representative number of type 2 diabetic patients and to evaluate the relationship to urinary albumin excretion rate.

PATIENTS AND METHODS

Seventy-two type 2 diabetic patients (43 men, 29 women) were compared to a group of 41 nondiabetic controls (17 men, 24 women) with essential hypertension (mean age: 58 years; mean body mass index: 27 ± 4 kg/m²). Patients with secondary hypertension were excluded from our study. The mean age of the diabetic patients (60 years), the mean duration of diabetes mellitus (12 years), and the mean body mass index (28 kg/m²) were not different between the three groups of diabetic patients and controls: thirty patients had a normal UAER (<30 mg/24 h), 27 had microalbuminuria (30 to 300 mg/24 h), and 15 persistent macroproteinuria (>300 mg/24 h). After the inclusion of 30 patients with normal UAER only, patients with increased UAER were further analyzed. Among the type 2 diabetics, mean albumin excretion was 15.1 ± 4.6 (range 8 to 24.9) mg/24 h in the normoalbuminuric patients, 1019 ± 592 (303 to 4180) mg/24 h in the patients with microalbuminuria, and 1019 ± 992 (303 to 4180) mg/24 h in the macroalbuminuric group. The mean UAER of the controls with essential hypertension was 17.3 ± 5.1 (8 to 27) mg/24 h. Only patients with normal UAER were included. Serum creatinine levels were similar in the normoalbuminuric patients (1.06 ± 0.2 mg/dL), in the microalbuminuric group (1.02 ± 0.5 mg/dL), and in the controls (1.01 ± 0.4 mg/dL), whereas the macroalbuminuric patients had significantly higher serum creatinine (1.67 ± 0.6 mg/dL) levels. The diabetic patients were treated with diet alone (n = 16), oral hypoglycaemic agents (n = 32), or insulin (n = 24). The antihypertensive treatment of the patients and controls is shown in Table 1.

Ambulatory 24 h blood pressure measurement (ABPM) was performed using an oscillometric recorder (SpaceLabs 90207, Redmond, WA); measurements with this device have a strong correlation to auscultation. This recorder satisfies the validation requirements of ABPM and has a proven accuracy. Blood pressure was measured in intervals of 20 min during the daytime and 30 min during the night.

Patients were hospitalized, but free to move in the hospital area during the daily measurements. Recordings were started between 08:00 and 09:00 and ended automatically. If the recordings had less than 90% of completed measurements, they were discarded. Systolic and diastolic blood pressure were averaged for each hour, and further separated into daytime, considered as 06:00 to 22:00, and nighttime, between 22:00 and 06:00. We also calculated the means and standard deviations for blood pressure and separated them into a daytime and nighttime period. In addition, the percentage of measurements higher than 140/90 mm Hg (defined normal range) and the heart rate profile were examined. Mean arterial blood pressure was calculated by the recorder as the quotient of the integrated area under the curve for systolic blood pressure divided by the duration of pulse rate.

Usually blood pressure is reduced during the night; the mean range is 10% to 15%. In our study "nondipping" was defined as a reduction of nocturnal blood pressure of <10%. Repeated single measurements of blood pressure were taken in the usual way during the daytime; each patient had 3 to 6 checks a day.

UAER was measured by an immunoturbidimetric test for the quantitative determination of human albumin in urine (Tina Quant, Boehringer Mannheim, Mannheim, Germany) using the Hitachi BM 704/717 system (Tokyo, Japan) (detection limit for urinary albumin concentration: 4 mg/L) and assessed as the mean of three 24-h urine samples. Blood samples were taken after an overnight fast; plasma glucose, hemoglobin Alc (by HPLC), serum cholesterol, triglycerides, HDL and LDL, and serum creatinine were analyzed with standard laboratory techniques.

Statistical Analysis Data were expressed as mean ± SD. Comparisons of subgroups with patients of the control group were performed using paired t tests for parametric data, with \( \chi^2 \) tests as appropriate. Simple linear regression analysis was used to evaluate the correlation between two parameters. Statistical significance was considered for \( P < .05 \). SAS Statistical Software was used for all calculations. (SAS Institute, Cary, NC)

| Table 1. Antihypertensive Treatment of the Diabetic Patients and Controls |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Antihypertensive Drugs**    | **Normo (n = 30)** | **Micro (n = 27)** | **Macro (n = 15)** | **Controls (n = 41)** |
| ACE inhibitor                  | 14              | 19              | 13              | 27              |
| Ca antagonist                  | 10              | 14              | 11              | 18              |
| α-Blocking agents             | 4               | 5               | 5               | 6               |
| β-Blocking agents             | 2               | 3               | 1               | 3               |
| Others                        | 3               | 3               | 3               | 6               |
| No treatment                  | 10              | 0               | 0               | 6               |
| Multiple treatment            | 10              | 14              | 12              | 19              |

* Diabetic patients.
The data for the blood pressure levels and heart rates for daytime and nighttime are shown in Tables 2 and 3, respectively.

During the time between 06:00 and 22:00 (Table 2), we found higher systolic and diastolic blood pressure values in patients with macroalbuminuria compared to controls and normoalbuminuric type 2 diabetic patients. Diastolic blood pressure was significantly elevated in type 2 diabetic patients with macroalbuminuria compared to controls. Mean arterial blood pressure was elevated in micro- and macroalbuminuric type 2 diabetic patients compared to controls (and in macroalbuminuric patients compared to type 2 diabetic patients with normoalbuminuria).

In the nighttime period (between 22:00 and 06:00), there was a significant increase of systolic blood pressure and mean arterial blood pressure in type 2 diabetic patients with macroalbuminuria compared to controls and normoalbuminuric type 2 diabetic patients. Systolic blood pressure was significantly elevated compared to controls also in type 2 diabetic patients with microalbuminuria. The differences in diastolic blood pressure were not significant (Table 3).

According to the definition of nondipping, 37% of the controls, 43% of the type 2 patients without albuminuria, 67% of the patients with microalbuminuria, and 80% of the patients with persistent macroalbuminuria were nondippers (Number of nondipping patients in the control group, diabetic patients with normal albumin excretion compared to diabetic patients with micro- and macroalbuminuria: \( \chi^2; P < .05 \)).

For the diabetic patients we observed a correlation during nighttime between both systolic \( (r = 0.32, P < .007) \) and diastolic \( (r = 0.24, P < 0.005) \) blood pressure and albumin excretion rate, whereas during daytime no significant relationship between blood pressure and albumin excretion was found. The analysis of correlation of albumin excretion rate to blood pressure values in the subgroups of diabetic patients with normo-, micro-, and macroalbuminuria were not significant.

The phenomenon of nondipping was not influenced by antihypertensive treatment or by the intake of ACE inhibitors, further the time of antihypertensive treatment did not influence our data.

Furthermore, heart rates were higher in the diabetic patients with macroalbuminuria compared to the patients with essential hypertension (Tables 2, 3). During the night time macroalbuminuric diabetic patients had significantly elevated heart rates compared to diabetic patients with normoalbuminuria (Table 3).

Repeated single measurements of blood pressure during the daytime showed significantly higher systolic blood pressure levels than those of the ambulatory blood pressure measurements \((152 ± 23 \text{ vs } 144 ± 18 \text{ mm Hg, } P < .001)\), but there was no significant difference in the diastolic blood pressure \((85 ± 11 \text{ vs } 84 ± 10 \text{ mm Hg})\). A strong correlation between ABPM and repeated single measurements was found \((r = 0.62; P < .0003)\).

**DISCUSSION**

The main findings of this study are threefold. First, there was a significant increase of arterial blood pressure during both daytime and nighttime in type 2 diabetic patients with macroalbuminuria compared to patients with essential hypertension (Controls). During the nighttime, even type 2 diabetic patients with microalbuminuria had a significantly elevated systolic

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**TABLE 2. ABPM DURING DAYTIME (06:00 TO 22:00)**

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>Mean Arterial BP</th>
<th>Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuric</td>
<td>139 ± 18*</td>
<td>82 ± 10</td>
<td>102 ± 12†</td>
<td>76 ± 11</td>
</tr>
<tr>
<td>Microalbuminuric</td>
<td>145 ± 15*</td>
<td>85 ± 10</td>
<td>107 ± 12†</td>
<td>79 ± 16</td>
</tr>
<tr>
<td>Macroalbuminuric</td>
<td>149 ± 19†</td>
<td>86 ± 10‡</td>
<td>108 ± 11</td>
<td>83 ± 16‡</td>
</tr>
<tr>
<td>Controls</td>
<td>137 ± 16‡</td>
<td>79 ± 13‡</td>
<td>100 ± 12</td>
<td>74 ± 10‡</td>
</tr>
</tbody>
</table>

* \( P < .01, † P < .001, ‡ P < .05. \)

**TABLE 3. ABPM DURING NIGHTTIME (22:00 TO 06:00)**

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
<th>Mean Arterial BP</th>
<th>Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoalbuminuric</td>
<td>125 ± 80*</td>
<td>72 ± 10</td>
<td>91 ± 12†</td>
<td>66 ± 9†</td>
</tr>
<tr>
<td>Microalbuminuric</td>
<td>137 ± 21*</td>
<td>75 ± 11</td>
<td>98 ± 13†</td>
<td>68 ± 7†</td>
</tr>
<tr>
<td>Macroalbuminuric</td>
<td>146 ± 21*</td>
<td>79 ± 10</td>
<td>104 ± 13†</td>
<td>73 ± 18†</td>
</tr>
<tr>
<td>Controls</td>
<td>129 ± 21*</td>
<td>72 ± 12</td>
<td>93 ± 14†</td>
<td>63 ± 10†</td>
</tr>
</tbody>
</table>

* \( P < .01, † P < .05. \)
blood pressure compared to patients with essential hypertension. Second, there was a high incidence of the phenomenon of nondipping of nocturnal blood pressure in type 2 diabetic patients with an elevated albumin excretion rate compared to patients with a normal albumin excretion rate or patients with essential hypertension. Third, a correlation of nighttime blood pressure (systolic and diastolic) to urinary albumin excretion rate was documented, although during daytime no correlation was found.

The circadian blood pressure rhythm is the result of various activities of the hypothalamus, which causes a number of hormonal actions. This regulation overlaps the influence of exogenous events, eg, sleep disturbance. Measurement of serum catecholamines shows the highest level in the early morning. Similarly, a circadian rhythm exists for heart constriction, ADP-induced aggregability of platelets, and the activity of the clotting system.

Steady stimulation of the renin-angiotensin system and serum catecholamines might be responsible for the lack of decreasing blood pressure at night. There are some events known to be associated with nondipping, eg, secondary hypertension, heart failure, sleep disturbances, shift working, autonomic neuropathy, left ventricle hypertrophy, and performed cardiac transplantation. Nondipping is potentially caused by several mechanisms, such as left ventricle hypertrophy, autonomic neuropathy, and overhydration, which have to be clarified in prospective studies.

In our study, the phenomenon of nondipping was frequently found in type 2 diabetic patients with elevated UAER. The diabetic patients with macroalbuminuria had higher heart rates than diabetic patients with normal albumin excretion rate and controls. Hausmann et al found an accumulation of silent ischemia as well as cardiac infarction in the early morning in nondiabetic patients. Pasqualetti et al showed in his study an increased frequency for cerebral strokes in nondiabetic patients. However, more of the patients with type 2 diabetes were dying from cerebral stroke and cardiac arrest. Our data suggest that the high frequency of nondipping in type 2 diabetic patients with an increased albumin excretion rate may partially explain the high cardiovascular morbidity and mortality in these patients. Further, the heart rate profiles of our patients also indicate a connection to autonomic neuropathy, as previously suggested.

It might further be speculated that the phenomenon of nondipping of nocturnal blood pressure might precede microalbuminuria in type 2 diabetes. If so, then it should be clarified in prospective studies as to whether intensified antihypertensive treatment prevents the development of microalbuminuria in these patients.

Schmitz et al described an increase of blood pressure in type 2 diabetic patients, regardless of the prevalence of microalbuminuria. Nevertheless, a correlation of 24 h systolic blood pressure to UAER in patients with microalbuminuria was described, whereas in patients with normal UAER no such correlation was found. However, day and night data were not separated. Nakano et al found a high presence of reversed circadian blood pressure variation with a peak value during night. However only normotensive type 2 diabetic patients were included. The prevalence and degree of autonomic neuropathy and nephropathy were greater in the diabetic patients with this disturbed circadian variation of blood pressure.

Very recently, a close relationship of increased UAER to the presence of hypertension (documented by ambulatory 24 h blood pressure measurements) was observed in type 2 diabetic patients. Albuminuria, however, was not related to the increased erythrocyte sodium-lithium countertransport, which is associated with diabetic nephropathy in type 1 diabetes, suggesting that different mechanisms determine microalbuminuria in type 1 and type 2 diabetes mellitus. In this study, however, the phenomenon of nondipping of nocturnal blood pressure was not observed, but only 20 patients with elevated albumin excretion rate (>15 µg/min) were analyzed.

Our data also show the high prevalence of the white-coat phenomenon and may indicate the more frequent use of ABPM. The use of ABPM, rather than single measurements, may result in early detection and optimized antihypertensive treatment in relation to the circadian variation of blood pressure of those patients.

In our study, it was demonstrated that albuminuria correlates with both systolic and diastolic blood pressure at night and with the phenomenon of nondipping in type 2 diabetic patients. Because of the high cardiovascular mortality of these patients, prospective long-term studies are necessary to evaluate the possible benefits of reduction of nocturnal blood pressure levels.

REFERENCES


