Association Between Albumin:Creatinine Ratio and 24-Hour Ambulatory Blood Pressure in Essential Hypertension

Vladimir A. Boulatov, Aud Stenehjem, and Ingrid Os

Microalbuminuria (MAU) is often found in essential hypertension (EH) and represents a sign of renal and cardiovascular damage. In the present study, we aimed to look at the association between ambulatory blood pressure (BP) and urinary albumin excretion (UAE). We studied 140 patients aged 50.1 ± 11.6 years referred for 24-h ambulatory blood pressure monitoring (ABPM) and, separately, 46 untreated subjects with newly diagnosed EH. Urinary albumin excretion was evaluated by determination of the albumin-to-creatinine ratio (ACR) in the first voided morning urine sample taken the same day as the ABPM was started. According to the ACR, patients were categorized as having normoalbuminuria (ACR <1.5 mg/mmol), borderline MAU (1.5 ≤ ACR <3.0 mg/mmol), and overt MAU (ACR ≥3.0 mg/mmol).

Mean ACR was significantly higher in hypertensive than normotensive individuals (2.17 ± 2.67 mg/mmol and 1.72 ± 2.97 mg/mmol, respectively, P = .012). Average 24-h, daytime and nighttime systolic BP and diastolic BP were lower in patients with normoalbuminuria than in the other two groups and did not differ among the two microalbuminuric groups. Univariate regression analysis showed a close relationship between ACR and ambulatory BP. Strong correlation between BP and ACR in the normoalbuminuric and borderline microalbuminuric range was also obtained in the group of 46 newly diagnosed hypertensive patients.

In conclusion, the threshold level of ACR ≥3.0 mg/mmol currently used to define microalbuminuria may be not applicable to EH. Instead, a threshold level of ACR ≥1.5 mg/mmol may be more appropriate. Am J Hypertens 2001;14:338–344 © 2001 American Journal of Hypertension, Ltd.

Key Words: Microalbuminuria, essential hypertension, ambulatory blood pressure.
pronounced atherosclerosis, and major electrocardiographic changes and retinal vascular changes.

However, in spite of an increased interest in the significance of MAU and EH, several aspects of hypertensive microalbuminuria still remain uncertain and await elicitation. The mechanisms underlying the observed predictive role of UAE with regard to cardiovascular morbidity are not clear. Furthermore, several methods can be used for the evaluation of UAE, and the threshold level of significant UAE remains debatable.

In the present study, we aimed to look at the association between ambulatory BP and UAE using the albumin-to-creatinine ratio (ACR) in patients referred to 24-h blood pressure monitoring.

Methods
Subjects
At the first stage of the research we studied 140 patients who were referred to the Department of Nephrology for 24-h ambulatory BP monitoring. All patients included in the study had SBP $\geq 140$ mm Hg or DBP $\geq 90$ mm Hg in the sitting position after 5 min of rest as measured by the general practitioner in duplicate or triplicate. Patients with serum creatinine level $>130$ µmol/L, positive urine albumin dipstick, glucose, or culture were excluded from the study. Patients with type 2 (non-insulin dependent) diabetes mellitus ($n = 6$) and subjects receiving antihypertensive therapy at the moment of the study, that is, insufficiently treated patients ($n = 34$), were not excluded.

For the second stage of the study, of these 140 patients we recruited 46 subjects with newly diagnosed EH who had never received antihypertensive medications. Patients with diabetes mellitus, severe hypertension (defined as daytime SBP $\geq 180$ mm Hg or DBP $\geq 110$ mm Hg) and MAU (albumin-to-creatinine ratio $\geq 3.0$ mg/mmol) were excluded.

Urinary Albumin Excretion
Urinary albumin excretion was evaluated by determination of the ACR in the first voided morning urine sample taken the same day as the BP monitoring was started. In some patients, those who met the inclusion criteria for the second stage of the study ($n = 46$), repeated measurements were taken (ie, ACR was measured also on the second day of the BP monitoring). The mean between the two measurements was used for calculation. According to the ACR, patients were categorized as having normoalbuminuria (ACR < 1.5 mg/mmol), borderline MAU (1.5 $\leq$ ACR < 3.0 mg/mmol), and overt MAU (ACR $\geq 3.0$ mg/mmol). Albumin levels in the urine were measured by immunoturbidimetry and urine creatinine on Integra Analyser (Roche, Basel, Switzerland).

Ambulatory Blood Pressure Monitoring
The 24-h ambulatory blood pressure monitoring (ABPM) was performed using an oscillometric-based device (mod-
hypertensive patients (55.6%) were normoalbuminuric. Borderline MAU with ACR between 1.5 and 3.0 mg/mmol was found in 7 normotensive and 32 hypertensive subjects (17.1% and 32.3%, respectively). The prevalence of overt MAU with ACR $\geq$ 3.0 mg/mmol was 4.9% in the group of patients with normal BP and 12.1% in patients with EH (Fig. 1).

### Twenty-Four-Hour Blood Pressure According to Albumin-to-Creatinine Ratio

Table 2 shows demographic characteristics and ABPM parameters of the patients grouped by ACR. All three groups were similar in age, gender, and serum creatinine level. Average 24-h, daytime, and nighttime SBP and DBP were higher in patients with overt MAU than in those with normal albumin excretion rate and borderline MAU, but did not differ between the two microalbuminuric groups. Fig. 2 presents daytime SBP and DBP of the three groups of patients according to ACR. Heart rate for 24-h and separately for daytime and nighttime periods were similar in the three groups. No significant difference was observed in SBP and DBP decrease during the night (data not presented).

Comparisons of the ambulatory BP values performed on the patients who fulfilled the inclusion criteria for the second stage of the study ($n = 46$) showed similar results. Patients with borderline MAU showed higher

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Comparisons of the ambulatory BP values performed on the patients who fulfilled the inclusion criteria for the second stage of the study ($n = 46$) showed similar results. Patients with borderline MAU showed higher
levels of 24-h, daytime, and nighttime SBP and DBP than normoalbuminuric individuals (24-h SBP 148.6 ± 13.1 mm Hg v 135.4 ± 21.1 mm Hg, P = .003; 24-h DBP 96.1 ± 6.8 mm Hg v 88.4 ± 8.6 mm Hg, P = .005; daytime SBP 153.2 ± 13.0 mm Hg v 140.5 ± 13.2 mm Hg, P = .007; daytime DBP 98.7 ± 6.4 mm Hg v 92.1 ± 9.4 mm Hg, P = .02; nighttime SBP 141.4 ± 14.0 mm Hg v 127.2 ± 11.7 mm Hg, P = .002; nighttime DBP 91.6 ± 8.3 mm Hg v 82.2 ± 8.1 mm Hg, P = .001).

Relationship Between Albumin/Creatinine Ratio and Blood Pressure

Table 3 shows the univariate correlations between log ACR and ambulatory BP performed in the entire study population. It revealed significant positive relationship between log ACR and 24-h, daytime, and nighttime SBP and DBP (r = 0.282 to 0.415, P < .0005, except for nighttime DBP). Correlation seems to be better for log

![Daytime blood pressure (mmHg)](https://example.com/daytime-blood-pressure.png)

**FIG. 2.** Daytime ambulatory blood pressure in patients grouped by albumin/creatinine ratio. HR = average heart rate during daytime; ACR = albumin/creatinine ratio.

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**Table 2.** Characteristics of the 140 patients grouped by the albumin:creatinine ratio

<table>
<thead>
<tr>
<th>Albumin:Creatinine Ratio (mg/mmol)</th>
<th>&lt;1.5</th>
<th>≥1.5 and &lt;3.0</th>
<th>≥3.0</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/%</td>
<td>87/62.1</td>
<td>39/27.9</td>
<td>14/10.0</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>49.2 ± 11.1</td>
<td>52.0 ± 12.2</td>
<td>50.0 ± 13.7</td>
<td>NS</td>
</tr>
<tr>
<td>Men/women</td>
<td>48/39</td>
<td>22/17</td>
<td>6/8</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>79.6 ± 12.6</td>
<td>77.7 ± 13.3</td>
<td>78.9 ± 13.6</td>
<td>NS</td>
</tr>
<tr>
<td>Urine albumin (mg)</td>
<td>11.86 ± 5.04</td>
<td>24.13 ± 14.03</td>
<td>66.14 ± 49.37</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Urine creatinine (mmol)</td>
<td>12.04 ± 5.03</td>
<td>11.59 ± 5.70</td>
<td>8.06 ± 3.60</td>
<td>.015</td>
</tr>
<tr>
<td>Albumin:creatinine ratio (mg/mmol)</td>
<td>1.02 ± 0.26</td>
<td>2.05 ± 0.42</td>
<td>8.26 ± 5.62</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>24-h systolic blood pressure (mm Hg)</td>
<td>135.0 ± 12.7</td>
<td>145.7 ± 13.1</td>
<td>148.7 ± 18.4</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>24-h diastolic blood pressure (mm Hg)</td>
<td>96.1 ± 6.8</td>
<td>91.7 ± 10.8</td>
<td>92.2 ± 11.3</td>
<td>.004</td>
</tr>
<tr>
<td>24-h pulse pressure (mm Hg)</td>
<td>48.5 ± 9.0</td>
<td>53.9 ± 9.0</td>
<td>56.5 ± 11.6</td>
<td>.002</td>
</tr>
<tr>
<td>24-h heart rate (beats/min)</td>
<td>74.6 ± 9.1</td>
<td>75.9 ± 9.3</td>
<td>74.8 ± 12.4</td>
<td>NS</td>
</tr>
<tr>
<td>Daytime systolic blood pressure (mm Hg)</td>
<td>139.9 ± 13.2</td>
<td>149.8 ± 13.9</td>
<td>152.6 ± 18.0</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Daytime diastolic blood pressure (mm Hg)</td>
<td>90.3 ± 8.9</td>
<td>95.2 ± 11.2</td>
<td>95.8 ± 11.0</td>
<td>.019</td>
</tr>
<tr>
<td>Daytime pulse pressure (mm Hg)</td>
<td>4.96 ± 9.1</td>
<td>54.7 ± 9.6</td>
<td>56.8 ± 11.6</td>
<td>.006</td>
</tr>
<tr>
<td>Daytime heart rate (beats/min)</td>
<td>77.8 ± 10.1</td>
<td>79.2 ± 10.0</td>
<td>77.8 ± 12.7</td>
<td>NS</td>
</tr>
<tr>
<td>Nighttime systolic blood pressure (mm Hg)</td>
<td>126.8 ± 13.4</td>
<td>138.6 ± 13.2</td>
<td>139.9 ± 20.1</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Nighttime diastolic blood pressure (mm Hg)</td>
<td>79.8 ± 9.3</td>
<td>85.7 ± 11.6</td>
<td>85.0 ± 12.0</td>
<td>.005</td>
</tr>
<tr>
<td>Nighttime pulse pressure (mm Hg)</td>
<td>47.0 ± 10.0</td>
<td>53.0 ± 9.4</td>
<td>51.0 ± 18.9</td>
<td>.005</td>
</tr>
<tr>
<td>Nighttime heart rate (beats/min)</td>
<td>69.1 ± 8.6</td>
<td>70.0 ± 9.0</td>
<td>69.5 ± 11.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant.

Data are means ± SD.

* P shows the significance level of multiple comparison between the three groups.

† P < .0005 v group 1; †† P = .01 v group 1; †‡ P < .005 v group 1; ††† P < .001 v group 1.
ACR and 24-h SBP (r = 0.415, P < .0005). There was no significant correlation between log ACR and heart rate.

We also performed the correlation analysis between average ACR measured in two morning urine samples and ambulatory BP on newly diagnosed untreated hypertensive patients with normal UAE (Table 4). The ACR was significantly related to 24-h, daytime, and nighttime SBP and DBP (r = 0.470 to 0.585, P < .0005).

**Discussion**

The gold standard method of determination of UAE involves collection of 24-h urine sample. However, it seems to be inconvenient for the patients and often unreliable due to inaccurate volume collection. Recently, more practical and easier methods have been proposed. One of these includes determination of the ACR in a single morning urine sample. In contrast to random spot urine sample, morning urine is less likely to be influenced by activity and posture. The measurement of ACR in the first voided morning urine sample was shown to be an accurate and sensitive alternative to measurement of the UAE in timed collections, when screening for MAU.37–39 We have shown that ACR measured in a single morning urine sample correlated with 24-h, daytime, and nighttime SBP and DBP (r = 0.470 to 0.585, P < .0005).

**Table 4.** Univariate correlation between albumin:creatinine ratio and 24-h ambulatory blood pressure in newly diagnosed untreated hypertensive patients

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h SBP</td>
<td>0.576</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>0.518</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Daytime SBP</td>
<td>0.554</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Daytime DBP</td>
<td>0.470</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Nighttime SBP</td>
<td>0.585</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Nighttime DBP</td>
<td>0.555</td>
<td>&lt;.0005</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 3.

In conclusion, the present study confirms a higher prevalence of microalbuminuria in patients with essential hypertension and a close relationship between ambulatory BP and ACR. Moreover, we have shown that the threshold levels of ACR ≥3.0 mg/mmol currently used to define MAU may not be applicable to hypertension. This lends support to the study by Palatini et al,4 who suggested a new threshold level of UAE of ≥15 mg/24 h for defining MAU in hypertensives instead of the traditionally used level of UAE ≥30 mg/24 h.

At least two mechanisms are currently discussed for the increased UAE in hypertensive patients.40,41 First, there is a functional transmission of an elevated BP to the glomeruli and an increased permeability in the glomerular basement membrane. The existence of the functional component is supported by the observations that pharmacologic reduction of BP pressure leads to a decrease in UAE.42,43 Second, there seem to be structural alterations that appear in long-standing disease. We showed a strong correlation between ACR and ambulatory BP on the population of 46 newly diagnosed hypertensive patients. These subjects had never been treated with antihypertensive drugs, thus eliminating any treatment-induced changes in UAE. Patients with diabetes mellitus, urologic and renal pathology were excluded for better estimation of the damage produced by hypertension. Thus, a close relationship between ABPM and ACR in the normoalbuminuric and borderline microalbuminuric range could mean that elevated UAE already exists in the early stages of essential hypertension, probably reflecting the functional alterations in renal hemodynamics.

In conclusion, the present study confirms a higher prevalence of microalbuminuria in patients with essential hypertension and a close relationship between ambulatory BP and ACR. Moreover, we have shown that the threshold levels of ACR ≥3.0 mg/mmol currently used to define microalbuminuria may not be applicable to hypertension and deserve further investigation.

**Acknowledgment**

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References


