Ambulatory Blood Pressure and Urinary Albumin Excretion in Clinically Healthy Subjects

Peter Clausen, Jan S. Jensen, Knut Borch-Johnsen, Gorm Jensen, Bo Feldt-Rasmussen

Abstract—A slightly elevated urinary albumin excretion rate (UAER) is a predictor of atherosclerotic cardiovascular disease. The mechanism is unknown, but moderate office blood pressure elevation has been demonstrated as part of a clustering of known atherosclerotic risk factors in subjects with elevated UAER. Because 24-hour ambulatory blood pressure is a superior predictor of hypertensive target organ involvement, we aimed to investigate blood pressure profile in clinically healthy subjects with elevated UAER. Ambulatory blood pressure monitoring was performed with a portable recorder in 27 subjects with an elevated UAER (>6.6 \text{ \mu g/min}, overnight urine collection) and 46 normoalbuminuric control subjects. Mean±SD systolic and diastolic ambulatory blood pressures (24-hour) were significantly higher in subjects with elevated UAER than in normoalbuminuric controls (134±12 versus 128±11 mm Hg and 78±7 versus 75±6 mm Hg, \(P<0.05\)), as were systolic and diastolic blood pressure loads [median (range): 42% (6 to 94%) versus 23% (1 to 89%) and 20% (0 to 68%) versus 6% (0 to 62%), \(P<0.05\)]. The circadian variation of blood pressure was normal in subjects with elevated UAER. However, the increased urinary loss of albumin could not be solely related to the higher blood pressure. In conclusion, apparently healthy subjects with elevated UAER had slightly but significantly higher 24-hour systolic and diastolic blood pressure levels in addition to increased blood pressure loads but normal circadian variation. The demonstrated differences in blood pressure may offer a partial explanation for the association between elevated urinary albumin excretion and atherosclerotic cardiovascular risk.

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Key Words: blood pressure, ambulatory ■ atherosclerosis ■ cardiovascular disease ■ risk factors ■ albuminuria

A slightly elevated UAER is an independent predictor of cardiovascular disease in major population-based studies.\(^1\)\(^-\)\(^4\) The reason for this association is unknown but may in part be related to BP. Thus, among hypertensive subjects, the prevalence of elevated UAER is increased and associated with a poor prognosis.\(^5\)\(^-\)\(^\text{11}\) UAER also has been shown to correlate with office BP in hypertensive and diabetic subjects,\(^9\)\(^-\)\(^\text{12}\)\(^-\)\(^\text{14}\) as well as the general population,\(^15\)\(^\text{16}\) and pharmacological treatment often reduces the UAER concomitantly with the reduction in BP.\(^17\)\(^\text{18}\)

In cross-sectional studies of nondiabetic subjects with elevated UAER, office BP elevation has been demonstrated to be part of a clustering of known atherosclerotic risk factors.\(^19\)\(^-\)\(^\text{20}\) However, both the BP elevation and the changes in plasma lipoproteins of nondiabetic subjects with elevated UAER have been slight in these studies and do not alone explain the impact of elevated UAER on cardiovascular risk. Therefore, more extensive studies of BP and UAER are warranted; in particular, studies of 24-hour BP and UAER would be of interest for a number of reasons.

In normal subjects, the circadian variation of BP shows highest values during the morning, a gradual decrease during the course of the day, and a nocturnal drop during sleep.\(^21\) Ambulatory BP has been shown in cross-sectional studies to correlate better with indices of hypertensive cardiovascular complications than office BP,\(^22\) and in prospective studies ambulatory BP is superior to office BP in predicting target organ damage.\(^23\) Absence of the normal nocturnal BP fall has been shown to be of particular significance in some studies.\(^24\)\(^\text{25}\)

UAER has been demonstrated to correlate more strongly to ambulatory BP than to office BP among hypertensive and diabetic subjects.\(^26\)\(^\text{27}\) UAER has been shown to correlate in short-term urinary collections to concomitant BP measurements in a study of 13 healthy subjects.\(^28\) Furthermore, a blunted nocturnal BP fall has been demonstrated in diabetic patients with microalbuminuria (UAER, 15 to 150 \text{ \mu g/min}) or diabetic nephropathy.\(^29\)\(^\text{30}\)

We hypothesized that elevated ambulatory BP and a disturbed circadian variation of BP were present in clinically healthy subjects with elevated UAER. This would partly account for the independent predictive value of elevated UAER for later atherosclerotic cardiovascular disease. The present study aimed to test this hypothesis by correlating UAER to 24-hour mean BP values, BP loads, and nocturnal BP reduction.
Flow diagram showing the selection of candidates with elevated UAER for the present study from the CCHS and the reasons for the reduction in numbers.*Number of participants in the CCHS. †Exclusion criteria: atherosclerotic disease, hypertension, renal disease, diabetes, inflammatory rheumatic disease, coagulation disorder, or regular consumption of medicine based on information from the CCHS. ‡Excluded based on criteria met at re Interview.

Methods

Study Population

All subjects were recruited from the CCHS, 1992–1994, a longitudinal epidemiological survey of cardiovascular disease and its known and potential risk factors. In total, 11,290 inhabitants aged 30 to 70 years who lived in a well-defined area surrounding the State University Hospital were invited to a health examination that included collection of a timed overnight urine sample for measurement of UAER. Within the first 10 months of the study, 1011 participants from 30 to 70 years of age had delivered an overnight urine sample with a negative urinalysis (Nephur Test + Leuco, Boehringer Mannheim). On this basis, a reference group was established in which the median (10th to 90th percentile range) UAER was 2.3 (0 to 6.6) mg/g/min. UAER above the 90th percentile (6.6 mg/min) was considered elevated in this population. Of a total of 7089 participants, 3645 (51%) collected a timed overnight urine sample, and 2946 had a negative urinalysis (Figure 1). Among these, all participants from 40 to 65 years old with an UAER >6.6 mg/min (90th percentile in the reference group) and <150 mg/min (to avoid patients with subclinical nephrological disease) were identified. Any subject with a history of atherosclerotic disease (myocardial infarction, angina pectoris, stroke, or intermittent claudication), hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥95 mm Hg or use of antihypertensive medication), renal disease, diabetes, inflammatory rheumatic disease, coagulation disorder, or regular consumption of medicine was excluded to avoid preexisting disease as a confounder; this exclusion procedure left 85 of 248 subjects identified as eligible for study. However, at subsequent reinterview, 14 had developed medical conditions that excluded them on the basis of the original exclusion criteria established since their participation in the CCHS.

The remaining 71 subjects were invited to participate in the present study, and 51 (72%) answered positively. Before entrance into the study, the elevation of UAER in each of these potential participants was confirmed because of the known large intraindividual variation of UAER. Because the mean urine flow in the reference population was 1 mL/min, we chose an albumin concentration in the range of 6.6 to 150 mg/L in at least 1 of 2 mailed first morning–voided spot urine samples, with a negative urinalysis as entrance criterion to the study; thus, 29 eligible subjects were left, comprising the group with elevated UAER. At the examination day, 1 additional subject was excluded because of a fasting blood glucose concentration of 10 mmol/L, and 1 subject was excluded because of repeated hematuria in 2 separated timed urine collections and a blood hemoglobin concentration of 5.3 mmol/L. A flow diagram (Figure 1) illustrates the reduction in numbers and the reasons for these reductions in the selection of the candidates with elevated UAER for the study.

A normalalbuminuric control group (n=46) was established by random and consecutive invitation of 1 to 3 age- and gender-matched subjects with an UAER of ≤6.6 mg/L for each subject with elevated UAER. In the 2 first morning–voided spot urine samples, the requirement for entrance in this control group was an albumin concentration of ≤6.6 mg/L and negative urinalysis in both. All subjects studied were white. Basic characteristics of nor malalbuminuric controls and subjects with elevated UAER are given in Table 1.

All subjects included gave their informed consent to participation. The study was performed in accordance with the Second Helsinki Declaration and was approved by the regional ethics committee.

Protocol

Between the first and second day of examination, the participants collected a repeated overnight urine sample, and the urinary albumin concentration was measured with an enzyme-linked immunosorbent assay technique as previously described. The intraassay and interassay coefficients of variation were both 5.5%. UAER was calculated from urinary albumin concentration, urine volume, and urine assay technique as previously described. The intraassay and interassay coefficients of variation were both 5.5%. UAER was calculated from urinary albumin concentration, urine volume, and urine collection time and designated “current UAER.”

Height and weight were recorded, BMI was calculated (weight/height²), and concentrations of albumin, creatinine, potassium, and sodium in plasma as well as hemoglobin in blood were measured using standard laboratory methods.

Diastolic (Korotkoff phase V) and systolic office BP were measured in duplicate with a standard mercury sphygmomanometer (Trimline, PyMaH Corp) and an appropriately sized cuff after 10 minutes of supine rest. The mean of the two readings was taken as office BP.

Ambulatory BP was measured concomitantly with the urine collection with a portable automatic BP monitor (TM 2421, A&D), which has been validated according to the protocols of the Association for the Advancement of Medical Instrumentation and of the British Hypertension Society. The device automatically rejects readings with a heart rate <35 or >200 bpm, systolic BP <60 or >280 mm Hg, diastolic BP <40 or >160 mm Hg, or pulse BP (systolic–diastolic) <10 or >150 mm Hg. No additional editing was performed. The device was programmed to measure BP every 15th minute during daytime and every 30th minute at night as previously recommended. Two 24-hour BP recordings were unsuccessful because of technical errors (1 in a subject with elevated UAER and 1 in a subject with normalalbuminuria), and the oscillographic measurements in the remaining subjects [98% (79 to 100%) successful readings] are presented. The participants recorded actual
time points for going to bed and rising in the morning for accurate appraisal of awake and sleep BPs. Values were averaged for each hour before the awake, sleep, and 24-hour BPs and pulse pressures were calculated. BP load was calculated as the proportion of the recorded pressures exceeding 140/90 awake or 120/80 at sleep. This parameter has been shown to be superior to mean 24-hour BP values in correlation with different hemodynamic parameters.\cite{37}

Information was recorded regarding present and prior smoking and drinking habits. Study subjects were divided into smokers and nonsmokers, and in each subject, present cigarette consumption and lifetime cigarette consumption was estimated. As lifetime cigarette consumption, the number of “pack-years” (20 cigarettes per day in 1 year) was estimated. Only a few subjects consumed no alcohol, and an estimate of present alcohol consumption and lifetime consumption (1 drink-year=one drink per day in 1 year) was made.

**Statistical Analysis**

Normally distributed continuous variables are given as mean±SD and nonnormally distributed continuous variables as median (range). Comparison of variables between groups was made with unpaired Student’s $t$ test or Mann–Whitney $U$ test for normally and nonnormally distributed variables, respectively. $\chi^2$ tests were used to compare distribution of categorical variables. Correlations were determined by Spearman’s nonparametric test. Differences with a probability value of <0.05 were considered significant.

All tests were performed using Statistica version 5.0 (StatSoft Inc).

**Results**

Office systolic BP was significantly higher in subjects with elevated UAER, whereas no difference in office diastolic BP could be demonstrated. The resulting “pulse pressure” (systolic–diastolic BP) was significantly higher in subjects with elevated UAER.

These differences were confirmed by ambulatory BP monitoring that demonstrated significantly higher systolic, diastolic, and pulse BPs in subjects with elevated UAER. Even though a greater difference in BP was demonstrated between the groups while asleep than awake, no significant difference in the nocturnal reduction of either systolic or diastolic BP between subjects with elevated UAER and subjects with normoalbuminuria was found. Both systolic and diastolic BP loads were significantly higher in subjects with elevated UAER than in subjects with normoalbuminuria. All BP values are given in Table 2. As shown in a graphic presentation, the circadian variation of BP in subjects with elevated UAER is identical to the variation in normoalbuminuric subjects but is displayed at a higher level (Figure 2). In normoalbuminuric subjects, UAER was significantly correlated to most BP estimates (Table 3, Figure 3). In contrast, no significant correlations were found between UAER and any of the BP estimates in subjects with elevated UAER (Table 3, Figure 4).

A negative correlation between UAER and nocturnal BP reduction could not be demonstrated in either normoalbuminuric subjects or subjects with elevated UAER.

Ten of the subjects originally classified as having an elevated UAER excreted albumin in the normoalbuminuric range when reexamined [3.9 (2.8 to 6.3) $\mu$g/min]. Five of the subjects originally classified as being normoalbuminuric had a current UAER exceeding 6.6 $\mu$g/min [12.0 (7.8 to 20.3) $\mu$g/min]. If these subjects were excluded from the analysis, the difference between the 2 groups in 24-hour mean systolic BP was 137±13 versus 125±9 mm Hg, $P<0.0005$, and 24-hour mean diastolic BP 80±8 mm Hg versus 74±7, $P<0.02$.

No significant differences in BMI, smoking habits, or alcohol consumption were present between the 2 groups (Table 1). A significant positive correlation between BMI and UAER was found within the normoalbuminuric group ($r=0.48$, $P<0.001$) but not within the group with elevated UAER ($r=0.34$, NS).

Current UAER confirmed that the selection procedure successfully had identified 2 groups with differing UAER: 3.5 (0 to 20.3) $\mu$g/min versus 22.5 (2.3 to 147.8) $\mu$g/min, $P<10^{-6}$.

**Discussion**

This study has confirmed a previously reported slight elevation of office BP in clinically healthy normotensive subjects

<table>
<thead>
<tr>
<th>Basal Characteristic</th>
<th>Normoalbuminuria</th>
<th>Elevated UAER</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±7</td>
<td>58±7</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>26/20</td>
<td>17/10</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.9±3.8</td>
<td>27.5±3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Smokers/nonsmokers</td>
<td>23/23</td>
<td>13/14</td>
<td>NS</td>
</tr>
<tr>
<td>Present cigarette consumption, cigarettes/d</td>
<td>0.7 (0–35)</td>
<td>0 (0–28)</td>
<td>NS</td>
</tr>
<tr>
<td>Lifetime cigarette consumption, pack-years</td>
<td>18 (0–58)</td>
<td>18 (0–51)</td>
<td>NS</td>
</tr>
<tr>
<td>Present alcohol consumption, drinks/d</td>
<td>2 (0.1–11)</td>
<td>2 (0–6)</td>
<td>NS</td>
</tr>
<tr>
<td>Lifetime alcohol consumption, 1 drink-year</td>
<td>63 (3–334)</td>
<td>55 (2–226)</td>
<td>NS</td>
</tr>
<tr>
<td>Current UAER, $\mu$g/min</td>
<td>3.5 (0–20.3)</td>
<td>22.5 (2.3–147.8)</td>
<td>$=10^{-6}$</td>
</tr>
<tr>
<td>Plasma albumin, g/L</td>
<td>43 (33–48)</td>
<td>43 (36–50)</td>
<td>NS</td>
</tr>
<tr>
<td>Blood hemoglobin, mmol/L</td>
<td>8.7±0.7</td>
<td>8.6±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma creatinine, $\mu$mol/L</td>
<td>88±12</td>
<td>88±13</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma potassium, mmol/L</td>
<td>3.8±0.2</td>
<td>3.9±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma sodium, mmol/L</td>
<td>143±2</td>
<td>143±2</td>
<td>NS</td>
</tr>
</tbody>
</table>
with elevated UAER by demonstrating higher BP levels in subjects both during the daytime and while asleep, and higher BP loads using ambulatory BP monitoring. However, no disturbances in the circadian BP variation was found. The demonstrated higher BP is likely to contribute to the increased cardiovascular risk in subjects with elevated UAER.

Elevated UAER is an independent risk factor for later atherosclerotic cardiovascular disease in nondiabetic subjects, and the purpose of this study was to investigate whether differences in BP loads and circadian variation of BP could explain this association independently of any preexisting morbidity. As a consequence, we decided to examine a selected group of clinically healthy subjects with an elevated UAER, which was confirmed in spot urine samples. Hence, the conclusions of this study may not be valid for the total nondiabetic population with elevated UAER. However, we hypothesize that elevated UAER reflects a generalized vascular dysfunction and precedes later atherosclerotic cardiovascular disease.

Table 2. Systolic and Diastolic Office and Ambulatory BP Measurements in Clinically Healthy Subjects With Normoalbuminuria or Elevated UAER

<table>
<thead>
<tr>
<th>BP Estimate</th>
<th>Normoalbuminuria</th>
<th>Elevated UAER</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP, mm Hg</td>
<td>131±15</td>
<td>140±14</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>82±8</td>
<td>83±8</td>
<td>NS</td>
</tr>
<tr>
<td>Office pulse pressure, mm Hg</td>
<td>49±10</td>
<td>56±12</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>24-Hour ambulatory SBP, mm Hg</td>
<td>128±11</td>
<td>134±12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>24-Hour ambulatory DBP, mm Hg</td>
<td>75±6</td>
<td>78±7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>24-Hour ambulatory pulse pressure, mm Hg</td>
<td>52±3</td>
<td>56±3</td>
<td>&lt;0.00005</td>
</tr>
<tr>
<td>Awake ambulatory SBP, mm Hg</td>
<td>133±11</td>
<td>139±14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Awake ambulatory DBP, mm Hg</td>
<td>79±7</td>
<td>82±8</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep ambulatory SBP, mm Hg</td>
<td>114±12</td>
<td>122±12</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Sleep ambulatory DBP, mm Hg</td>
<td>65±7</td>
<td>69±7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nocturnal SBP, reduction, %</td>
<td>14±6</td>
<td>12±7</td>
<td>NS</td>
</tr>
<tr>
<td>Nocturnal DBP reduction, %</td>
<td>17±7</td>
<td>15±8</td>
<td>NS</td>
</tr>
<tr>
<td>SBP load (%)</td>
<td>23 (1–89)</td>
<td>42 (6–94)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>DBP load (%)</td>
<td>6 (0–62)</td>
<td>20 (0–68)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

SBP indicates systolic BP; DBP, diastolic BP.

Figure 2. Twenty-four-hour profile of hourly mean systolic and diastolic BPs in clinically healthy subjects with elevated UAER (n=26, □) and normoalbuminuric controls (n=45, ○). Vertical bars are standard deviations.

The 2 groups were well matched for age, gender, BMI, smoking, and alcohol consumption. A significant positive correlation between BMI and UAER was seen within the

Table 2.
normoalbuminuric group. However, this correlation was not found within the group of subjects with elevated UAER, and the differences in UAER and BP measurements between the two groups are not likely to be explained by the slight insignificant difference in mean BMI between the groups.

In studies of patients with diabetes, a negative association between UAER and nocturnal BP reduction has been demonstrated, which was not the case in our study of healthy subjects. This might be explained by a coexistence in diabetic patients of elevation of UAER and other diabetic complications, such as autonomic neuropathy or impaired renal function caused by nephropathy. Both of these conditions are known to cause blunted nocturnal BP reduction.

A significantly higher pulse pressure (systolic–diastolic BP) was demonstrated in subjects with elevated UAER by office BP measurement as well as ambulatory BP monitoring. Elevated systolic BP without parallel elevations in diastolic BP may be ascribed to reduced aortic compliance, owing to the stiffening of the vessel wall that is often seen in association with aortic atherosclerosis. This in turn reflects general atherosclerosis and predicts clinical cardiovascular disease. The finding is in accordance with the hypothesis that elevated UAER is an indicator of preclinical atherosclerosis.

In normoalbuminuric subjects, we found a significant correlation between UAER and office systolic BP but not between UAER and office diastolic BP. This is in accordance with earlier reports of weak correlations between UAER and office BP in the general population, even though these correlations are not confirmed in all studies. However, more precise correlations between UAER and 24-hour BP levels were demonstrated in normoalbuminuric subjects with regard to both systolic and diastolic BP, confirming earlier reports of superiority of 24-hour BP monitoring to office BP measurements in illustrating the renal effect of the BP level. When the correlations were calculated within the normoalbuminuric group excluding subjects with a current UAER exceeding the original grouping criterion, the correlations between UAER and BP were weakened because of the reduction in numbers, and the correlations to office BP values as well as 24-hour

![Figure 3. Correlation between 24-hour mean systolic ambulatory BP and current UAER in normoalbuminuric clinically healthy subjects (n=45; r=0.44, P<0.005 by Spearman).](image1)

![Figure 4. Correlation between 24-hour mean systolic ambulatory BP and current UAER in clinically healthy subjects with elevated UAER (n=26; r=0.14, NS by Spearman).](image2)
systolic BP lost significance. However, all other ambulatory BP estimates still correlated significantly to UAER.

UAER has a high intraindividual variation with higher values in daytime and is influenced by upright posture and physical activity. As a consequence, we collected overnight urine samples to measure UAER in this study, and as expected, the highest correlation coefficient between BP and UAER was found between nighttime systolic BP and UAER. However, similar correlations were demonstrated between 24-hour or daytime systolic BP values and UAER, confirming the association between UAER and the overall BP level in normal subjects. Calculation of BP loads revealed similar correlation coefficients to UAER, but these values were not greater than other estimates of ambulatory BP.

These positive correlations between current UAER and BP may very well indicate a direct causal relationship between systemic (and thus possibly intrarenal) BP and transglomerular transport of albumin in healthy subjects with normal UAER.

In contrast, among subjects with elevated UAER, much higher UAER was seen at identical BP levels, and no significant correlations between BP and UAER were found. This was also the case when the correlations were calculated excluding the subjects with a current UAER in the normoalbuminuric range. In these subjects, the increased urinary loss of albumin therefore might be caused by changes in the properties of the glomerular filter rather than hemodynamic changes. This would be in accordance with a number of previous observations. First, the glomerular filtration of albumin is partly dependent on properties of the glomerular filter, and in diabetes mellitus the combination of microalbuminuria and loss of glomerular charge and size selectivity, and increased transcapillary escape rate of albumin has been proposed to indicate a generalized vascular dysfunction.

Second, in reports from our group, generalized transvascular albumin leakiness, as well as reduced glomerular size and charge selectivity, has been demonstrated in clinically healthy subjects with elevated UAER.

The participants in the study will be followed up to investigate the possible influence of the elevated UAER on the later risk for hypertension, atherosclerotic cardiovascular disease, or nephropathy.

In conclusion, this study demonstrated that apparently healthy subjects with elevated UAER had slightly but significantly higher 24-hour systolic and diastolic BP levels in addition to increased BP loads compared with normoalbuminuric control subjects. The nocturnal reduction of BP was, however, normal. Furthermore, higher pulse pressure was demonstrated in subjects with elevated UAER, which may be an indicator of reduced aortic compliance as a consequence of subclinical atherosclerosis. The demonstrated differences in BP may offer a partial explanation for the association between elevated urinary albumin excretion and atherosclerotic cardiovascular disease.

Acknowledgments

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References

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