Circadian rhythm of glomerular filtration rate in normal individuals

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SUMMARY

1. In a group of 11 normal individuals we measured glomerular filtration rate (GFR) by inulin clearances and effective renal plasma flow (ERPF) by p-aminohippurate clearances during a period of 24 h and a regimen of bedrest, identical food intake per 3 h and normal sleep/wake and light/dark cycles.

2. All subjects had a circadian rhythm for GFR with a maximum of 122 ml/min (SD 22) in the daytime, a minimum of 86 ml/min (SD 12) at night and with a relative amplitude of 33% (SD 15).

3. ERPF had a circadian rhythm with a similar relative amplitude as the GFR rhythm, but with a different phase. Because of this difference in phase, the calculated filtration fraction (GFR/ERPF) followed a circadian rhythm as well.

4. The circadian rhythms of urine volume and sodium excretion were in phase with the GFR rhythm, but the potassium rhythm had a different phase, probably because urinary potassium is largely derived from tubular secretion.

5. Urinary albumin and β₂-microglobulin excretion had a circadian rhythm in phase with the GFR rhythm.

6. The highest quantity of sodium, water and β₂-microglobulin was reabsorbed in the daytime; tubular reabsorption, expressed as percentage of the filtered load (fractional reabsorption), had a rhythm with a reversed phase.

Key words: albumin, circadian rhythm, effective renal plasma flow, electrolytes, filtered load, glomerular filtration rate, β₂-microglobulin.

Abbreviations: ERPF, effective renal plasma flow; GFR, glomerular filtration rate; PAH, p-aminohippurate.

INTRODUCTION

It is uncertain whether glomerular filtration rate (GFR) has a circadian rhythm in normal humans. In 1950, Sirota et al. [1] reported a mean night/day ratio of inulin clearance in 16 normal individuals of 0.96 (SD 0.07). In a later study of Wesson [2] in 12 normal subjects, inulin clearance during the day was 23% larger than during the night. Data on diurnal changes in creatinine clearances are conflicting, as some authors [1, 3, 4] observed differences but others [5-7] did not. Similarly, a day/night difference in effective renal plasma flow (ERPF) was found in some studies [2, 8, 9], but not in the study of Sirota et al. [1].

Recently, it has been shown that a high dietary protein intake [10-14] or the parenteral infusion of amino acid solutions [15, 16] enhance GFR (and ERPF) in normal individuals. In none of the studies on a possible day/night difference in GFR and ERPF was the diet strictly standardized. Therefore, any increase in GFR during the daytime might, in part, be due to the consumption of meals and it remains to be established that GFR and/or ERPF have an endogenous rhythm in normal humans.

In the present study GFR and ERPF were determined for 24 h in 11 normal individuals during bedrest and an identical intake of protein every 3 h, and the data were analysed statistically for the presence of circadian rhythms. Subsequently, filtered loads of various solutes were compared with urinary excretion to determine the contribution of tubular reabsorption to the circadian rhythmicity.

METHODS

Subjects

Eleven normal human volunteers (six males and five females, age 19-37 years) were studied in the metabolic ward of this hospital during a period of 28 h. Every 3 h during the day and night a standardized small meal, each
time of the same composition, was eaten. A dietician
determined the composition of the meals according to the
personal preference and need of calories of each indi-
vidual. A typical meal consisted of a buttered slice of
bread covered with 15 g of cheese, together with 150 ml
of milk and 150 ml of tea. With each meal 500 mg of
sodium bicarbonate was administered to maintain urinary
pH above 6.0 (required for the determination of $\beta_2$-
microglobulin). All individuals were kept strictly in bed.
To maintain normal light/dark and sleep/awake cycles
lights went out during the night (23.00–08.00 hours) and
the subjects were allowed to sleep between sample and
meal times during this period. The study started at 17.00
hours. At this time a cannula for intravenous infusion was
put in one arm and sampling device in the other. Loading
doses of inulin (Inutest, Laevosan Gesellschaft, Linz,
Austria) and $p$-aminohippurate (PAH; Aminohippurate-
sodium; Merck Sharp and Dohme, Haarlem, The Nether-
lands) were administered followed by continuous infusion
via a volumetric infusion pump (IMED-micro 965). The
first meal was given at 18.00 hours. After an equilibration
period, observations started at 21.00 hours and continued
until 21.00 hours the next day. Every 3 h urine was col-
clected by spontaneous voiding and blood samples were
taken. Urine volumes were measured with an accuracy of
5 ml. The study was approved by the Medical Ethics
Committee of the University of Amsterdam.

Laboratory methods

GFR and ERPF were measured as standard clear-
ances: $(U,V)/P$, where $U$ is urinary concentration, $V$
urine volume and $P$ is plasma concentration. Standard
clearances of inulin were also compared with standard
clearances of creatinine. Furthermore, the urine samples
of all individuals were analysed for albumin, $\beta_2$-micro-
globulin, sodium and potassium. The concentrations of
these substances in the serum were determined every
3 h in six individuals. Albumin in the urine was measured by a
nephelometric method as previously described [17].
$\beta_2$-Microglobulin in blood and urine was measured by a
radioimmunoassay (Phadebas, Pharmacia). Inulin was
determined with the method of Fjelbø & Stamy [18]. PAH
was measured by h.p.l.c. [19].

Analysis of circadian rhythms

Each set of eight observations per 24 h was fitted by a
sine wave with 24 h periodicity, using a cosinor analysis
[20]. This is illustrated in Fig. 1. The data were defined as
a circadian rhythm when a sinus fitted the data better than
its baseline (variance ratio $F$ test; $P<0.05$).

Phase and amplitude of the rhythms were calculated
from the actually measured data and not deduced from
the fitted sinus. The amplitude ($A$) of a rhythm was taken
as the difference between the highest (maximum) and
lowest (minimum) value of the day. The amplitude
expressed as percentage of the mean ($M$) of the eight
observations of the day is referred to as the relative ampli-
tude ($A/M$). The time of the maximum value is the ortho-
phase of the rhythm, the time of the minimum the bathy-
phase. Subsequently, average values ($\pm$ sd) were
determined for the whole group of 11 individuals for
mean, maximum, minimum, amplitude, relative ampli-
itude, orthophase and bathyphase. For calculation of dif-
ferences between phase or relative amplitude of various
renal rhythms, Student's $t$-test for paired data was used.
RESULTS

Circadian rhythm of GFR, ERPF and filtration fraction

All individuals had a circadian rhythm for GFR with a maximum in the daytime and a minimum during the night. In six subjects the orthophase was in the afternoon, in three in the morning and in two in the evening. The amplitude was at least 20 ml/min. The mean amplitude of the rhythms was 36 ml/min or 33% relative to the mean (Table 1).

When the creatinine clearance was taken as a marker of GFR instead of the inulin clearance, a significant rhythm was found in eight of 11 individuals (Table 2). The phase of the rhythm was similar to the phase of the inulin rhythm, but the amplitude and relative amplitude were lower. This was mainly due to an overestimation of GFR by the creatinine clearance during the night. Circadian variations in urinary excretion of creatinine were less obvious. Only three of the 11 individuals had a significant rhythm with an orthophase in the daytime.

ERPF had a circadian rhythm in all individuals (Table 1). The orthophase and bathyphase occurred later than in the GFR rhythm \((P<0.01)\). The amplitude \((214\pm 101\) ml/min) was much higher than observed for GFR, but the changes relative to the mean were similar: \(A/M\) (GFR), 33%; \(A/M\) (ERPF), 34%. Because of this difference in phase filtration fraction (GFR/ERPF) also had a circadian rhythm with a maximum in the daytime and a minimum at night in nine of 11 individuals. The orthophase was even earlier than for GFR \((P<0.05)\;\text{Table 1}\).

By subtracting the GFR from the total clearance of PAH the tubular clearance of PAH was obtained. This tubular clearance of PAH also varied over the day with a similar phase as the rhythm for total PAH clearance (ERPF). When the tubular clearance of PAH was expressed relative to the total clearance of PAH we found that the contribution of tubular secretion to total PAH clearance was larger during the night than during the day in nine of 11 individuals.

Circadian rhythms of urinary excretion of water, electrolytes and proteins

Circadian rhythms for urinary water and electrolyte excretion were present in all individuals (Table 3). The relative amplitudes were much higher than found for GFR. The orthophase of the rhythm of potassium excretion was earlier than the orthophase of the GFR rhythm \((P<0.02)\) and showed only minor variations between individuals. Orthophases and bathyphases of individual rhythms of water and sodium excretion could not be shown to be different from the phase of the GFR rhythm \((P<0.05)\).

A circadian rhythm of urinary albumin excretion was present in eight of 11 individuals. In the others urinary albumin excretion decreased over the 28 h without expression of circadian variations. When a rhythm was present the phase was similar to the phase of the GFR rhythm, but the relative amplitude was higher.

### Table 1. Circadian rhythm of renal function in 11 normal individuals

Data are expressed as means ± SD. Statistical significance: *\(P<0.01\), **\(P<0.05\) vs GFR. Abbreviation: FF, filtration fraction.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Maximum</th>
<th>Minimum</th>
<th>Amplitude</th>
<th>(A/M) (%)</th>
<th>Orthophase (h)</th>
<th>Bathyphase (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min)</td>
<td>105 ± 14</td>
<td>122 ± 22</td>
<td>86 ± 12</td>
<td>36 ± 18</td>
<td>33 ± 15</td>
<td>16.60 ± 3.40</td>
<td>2.90 ± 2.40</td>
</tr>
<tr>
<td>ERPF (total PAH clearance) (ml/min)</td>
<td>612 ± 135</td>
<td>713 ± 167</td>
<td>526 ± 124</td>
<td>214 ± 101</td>
<td>34 ± 13</td>
<td>19.90 ± 4.25*</td>
<td>6.40 ± 3.60*</td>
</tr>
<tr>
<td>GFR/ERPF (FF)</td>
<td>0.182 ± 0.043</td>
<td>0.217 ± 0.047</td>
<td>0.151 ± 0.047</td>
<td>0.060 ± 0.024</td>
<td>37 ± 13</td>
<td>11.00 ± 3.80**</td>
<td>1.30 ± 2.20**</td>
</tr>
<tr>
<td>Tubular PAH clearance/total PAH clearance</td>
<td>506 ± 127</td>
<td>607 ± 166</td>
<td>396 ± 107</td>
<td>211 ± 113</td>
<td>41 ± 17</td>
<td>20.90 ± 3.25*</td>
<td>6.55 ± 3.50*</td>
</tr>
</tbody>
</table>

† Reversed rhythm.

### Table 2. Comparison of the rhythms of inulin clearance and creatinine clearance in those subjects \((n = 8)\) who had a significant circadian rhythm for both

Data are expressed as means ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Maximum</th>
<th>Minimum</th>
<th>Amplitude</th>
<th>(A/M) (%)</th>
<th>Orthophase (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inulin clearance (ml/min)</td>
<td>117 ± 18</td>
<td>133 ± 24</td>
<td>97 ± 16</td>
<td>36 ± 13</td>
<td>31 ± 9</td>
<td>14.40 ± 2.95</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>126 ± 23</td>
<td>138 ± 23</td>
<td>113 ± 23</td>
<td>25 ± 8</td>
<td>20 ± 6</td>
<td>15.20 ± 3.35</td>
</tr>
<tr>
<td>Serum creatinine concentration (µmol/l)</td>
<td>71.2 ± 6.2</td>
<td>74.8 ± 6.4</td>
<td>66.8 ± 6.6</td>
<td>8.0 ± 0.8</td>
<td>9.4 ± 1.7</td>
<td>1.00 ± 3.40</td>
</tr>
</tbody>
</table>
Table 3. Urinary excretory circadian rhythms in 11 normal individuals
Data are expressed as means ± so. Statistical significance: *P<0.02 vs orthophase of all other rhythms (including GFR).

<table>
<thead>
<tr>
<th></th>
<th>Maximum</th>
<th>Minimum</th>
<th>A/M (%)</th>
<th>Orthophase (h)</th>
<th>Bathyphase (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (ml/h)</td>
<td>211 ± 67</td>
<td>60 ± 31</td>
<td>119 ± 26</td>
<td>14.00 ± 2.25</td>
<td>3.40 ± 2.00</td>
</tr>
<tr>
<td>Sodium (mmol/h)</td>
<td>19.0 ± 5.2</td>
<td>6.0 ± 2.9</td>
<td>108 ± 22</td>
<td>15.15 ± 3.10</td>
<td>3.55 ± 1.70</td>
</tr>
<tr>
<td>Potassium (mmol/h)</td>
<td>5.41 ± 1.84</td>
<td>0.79 ± 0.32</td>
<td>183 ± 40</td>
<td>11.00 ± 1.20*</td>
<td>3.20 ± 1.70</td>
</tr>
<tr>
<td>Albumin (mg/h)</td>
<td>0.43 ± 0.27</td>
<td>0.16 ± 0.07</td>
<td>75 ± 29</td>
<td>14.40 ± 2.65</td>
<td>4.00 ± 1.50</td>
</tr>
<tr>
<td>β2-Microglobulin (μg/h)</td>
<td>8.4 ± 3.4</td>
<td>4.1 ± 1.1</td>
<td>68 ± 26</td>
<td>12.90 ± 3.70</td>
<td>3.70 ± 2.80</td>
</tr>
</tbody>
</table>

Table 4. Circadian rhythms of filtered load (FL) and fractional tubular reabsorption (TR/FL) of water, sodium and β2-microglobulin in six normal individuals
Data are means ± so.

<table>
<thead>
<tr>
<th></th>
<th>Maximum</th>
<th>Minimum</th>
<th>Amplitude</th>
<th>A/M (%)</th>
<th>Orthophase (h)</th>
<th>Bathyphase (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water FL (ml/h)</td>
<td>8050 ± 1472</td>
<td>5630 ± 697</td>
<td>2420 ± 1372</td>
<td>35.4 ± 17.4</td>
<td>15.75 ± 3.25</td>
<td>3.50 ± 2.45</td>
</tr>
<tr>
<td>TR/FL (%)</td>
<td>98.97 ± 0.41</td>
<td>97.14 ± 0.61</td>
<td>332 ± 187</td>
<td>34.9 ± 15.9</td>
<td>16.00 ± 3.50</td>
<td>3.50 ± 2.45</td>
</tr>
<tr>
<td>Sodium FL (mmol/h)</td>
<td>1123 ± 200</td>
<td>791 ± 91</td>
<td>3094 ± 1023</td>
<td>35.0 ± 12.3</td>
<td>16.00 ± 2.95</td>
<td>5.00 ± 3.50</td>
</tr>
<tr>
<td>TR/FL (%)</td>
<td>99.15 ± 0.40</td>
<td>98.02 ± 0.55</td>
<td>200 ± 12</td>
<td>3.50 ± 2.45</td>
<td>11.25 ± 1.25</td>
<td>3.50 ± 2.45</td>
</tr>
<tr>
<td>β2-Microglobulin FL (μg/h)</td>
<td>10 423 ± 857</td>
<td>7329 ± 636</td>
<td>19 420 ± 857</td>
<td>15.75 ± 3.25</td>
<td>3.50 ± 2.45</td>
<td>14.50 ± 3.65</td>
</tr>
<tr>
<td>TR/FL (%)</td>
<td>99.952 ± 0.015</td>
<td>99.918 ± 0.029</td>
<td>204 ± 12</td>
<td>3.50 ± 2.45</td>
<td>11.25 ± 1.25</td>
<td>3.50 ± 2.45</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>134 ± 25</td>
<td>94 ± 12</td>
<td>35.4 ± 17.4</td>
<td>15.75 ± 3.25</td>
<td>3.50 ± 2.45</td>
<td>14.50 ± 3.65</td>
</tr>
</tbody>
</table>

Table 5. Circadian rhythm of urinary potassium excretion compared with circadian variations in its filtered load in six normal individuals
Data are means ± so. Statistical significance: *P<0.05 vs GFR and filtered load.

<table>
<thead>
<tr>
<th></th>
<th>Maximum</th>
<th>Minimum</th>
<th>A/M (%)</th>
<th>Orthophase (h)</th>
<th>Bathyphase (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma concentration (mmol/l)</td>
<td>4.06 ± 0.19</td>
<td>3.64 ± 0.13</td>
<td>10.9 ± 6.1</td>
<td>10.75 ± 1.50</td>
<td>23.50 ± 1.80</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>134 ± 25</td>
<td>94 ± 12</td>
<td>35.4 ± 17.4</td>
<td>15.75 ± 3.25</td>
<td>3.50 ± 2.45</td>
</tr>
<tr>
<td>Filtered load (mmol/h)</td>
<td>31.90 ± 5.30</td>
<td>21.43 ± 2.91</td>
<td>39.6 ± 15.0</td>
<td>15.25 ± 3.85</td>
<td>2.75 ± 2.00</td>
</tr>
<tr>
<td>Excretion (mmol/h)</td>
<td>5.41 ± 1.84</td>
<td>0.79 ± 0.32</td>
<td>183 ± 40</td>
<td>11.00 ± 1.20*</td>
<td>3.20 ± 1.70</td>
</tr>
</tbody>
</table>

(75% ± 29%; P<0.01). Urinary excretion of β2-microglobulin showed a circadian rhythm in all individuals with a higher mean relative amplitude (68% ± 26%) than the GFR rhythm (P<0.01). The orthophase and bathyphase were not different from the orthophase and bathyphase of the GFR rhythm.

Circadian variations in plasma concentrations, filtered load and tubular reabsorption of solutes
A circadian rhythm was found for plasma potassium concentration and serum albumin concentration in each of the six individuals in which the plasma concentration was measured. Both rhythms had a relative amplitude around 10% but the orthophase of the potassium rhythm (10.75 h) was earlier than that of the albumin rhythm (16.75 h; P<0.05). Data in four of the six individuals also suggested a circadian rhythm for plasma sodium concentration and serum β2-microglobulin concentration with a highest value during the night on visual appearance, but a sinus could not be fitted significantly.

Circadian variations in filtered load of solutes with unrestricted glomerular transport are given in Table 4 (water, sodium, β2-microglobulin) and Table 5 (potassium). The differences in absolute quantities between day and night were large. Circadian variations in serum concentrations did not change the phase of the rhythm of the filtered loads when compared with the GFR rhythm. The relative amplitudes were only slightly modified. The most pronounced change was observed for the relative amplitude of the rhythm for filtered load of potassium (39.6% vs 35.4% for GFR; Table 5).
Tubular reabsorption also had a circadian rhythm. The largest quantity of water, sodium and $\beta$-microglobulin was reabsorbed during the day at the same time as filtered load had its maximum. The relative amplitudes of these rhythms were slightly lower than that of the filtered load. The percentage of the filtered load that was reabsorbed (fractional reabsorption) was highest during the night (Table 4).

Most of the filtered load of potassium is reabsorbed in the proximal parts of the nephron, but potassium is also secreted from the blood into the tubular lumen by the cells of the cortical part of the collecting duct. Therefore, tubular reabsorption of potassium cannot be measured by subtracting excretion from the filtered load. The orthophase of the rhythm of urinary potassium excretion was earlier than the orthophase of the rhythm of GFR ($P < 0.02; n = 11$) and the filtered load of potassium ($P < 0.05; n = 6$; Table 5), corresponding with the orthophase of the rhythm of plasma potassium concentration.

**DISCUSSION**

In the present study we have shown that GFR has a circadian rhythm in normal individuals with an orthophase in the daytime. The rhythm is not due to day/night differences in posture or protein intake. Both exogenous factors were kept constant around the clock. This study, as well as our previous studies on circadian rhythms [21, 22], were performed during a normal light/dark cycle and the subjects were allowed to sleep during the night. The possibility that sleep per se changes GFR and has an influence on the rhythm cannot be excluded. However, this does not seem to be an important exogenous factor for the following reasons. First, the subjects in this study only slept a few hours between 23.00 and 08.00 hours. Because of the sampling and consumption of meals every 3 h, sleep periods at best were light and short and alternated with periods of wakefulness. Secondly, as is illustrated in Fig. 1, GFR started to decrease during the late afternoon or evening before the subjects went to sleep and often rose before the day period began.

The amplitude of the GFR rhythm (mean 36 ml/min) has such an order of magnitude that practical consequences do arise. For example, glomerular filtration can be important in the elimination of drugs and it should be realised that excretion during the night is lower than during the day. Also when measurements of GFR are mentioned, the time of the day should be stated, particularly when repeated determinations were performed. Furthermore, when a comparison is made of GFR before and after an intervention, e.g. the administration of a drug, the natural course of the GFR during that period of the day should be taken into account. Otherwise the change in GFR could be interpreted as being caused by the drug while it simply could represent the natural course of the circadian rhythm.

Creatinine is not only filtered in the glomerulus, but, for a small part, is also secreted by the tubules. Therefore, creatinine clearance tends to overestimate GFR. Our observations show that this overestimation is most pronounced during the night. The contribution of tubular secretion to the overall clearance of creatinine also depends on the time of the day. As a consequence the circadian rhythm of creatinine clearance had a lower amplitude and relative amplitude than the rhythm of inulin clearance. Furthermore, three subjects with a significant rhythm for the clearance of inulin did not have such a rhythm for the clearance of creatinine. When rhythms for both clearances were present, the phase was similar. The overestimation of GFR by the creatinine clearance in this study was lower than has been reported by others [23]. Possibly this was due to the simultaneous infusion of PAH, because it was found in an earlier study [24] that the tubular secretion of creatinine and PAH are competitive.

The question arises as to whether observations during a single day are sufficient to decide upon the presence, phase and amplitude of a circadian rhythm. For the detection of a GFR rhythm in normal volunteers a single day was apparently long enough. In a cosinor analysis, a method frequently used in chronobiology [20], a significant rhythm was present in all individuals. However, a study period of only 24 h will have its limitations for the detection of rhythms of lower amplitude. Sampling over 3 h periods will imply that small differences in phase between various rhythms remain undetected. Day to day variations in phase and amplitude depend on the type of rhythm studied as well as on the study conditions. The variations are large in predominantly exogenous rhythms, especially when conditions are variable, but are less pronounced in strongly endogenous rhythms and during constant conditions around the clock. In earlier studies on circadian rhythms of renal solute excretion, we have analysed day to day variation, both in phase and amplitude, of the potassium rhythm in individual patients. In these studies urine was collected in 3 h samples over 3 consecutive days. During similar conditions to this study (bedrest, identical meals every 3 h and sleep during the night), the amplitude (and relative amplitude) of the rhythm appeared to have a coefficient of variation of 13% and the orthophase an average sd of 1.25 h (M. G. Koopman et al.; unpublished work).

PAH clearance also showed a circadian rhythm with a relative amplitude similar to the GFR rhythm, but with a different phase. This phase difference could indicate that circadian variations in renal circulation (renal blood flow) and GFR have a different phase. However, it was shown in the present study that the orthophase of the PAH clearance is determined by the orthophase of the tubular secretion of PAH. Thus an alternative explanation is that GFR and renal blood flow do have rhythms in phase with each other, but that the extent to which PAH secretion is a reflection of renal blood flow is different at various times of the day.

The phase difference between GFR and ERPF also causes a circadian rhythm in the calculated filtration fraction, characterized by an earlier orthophase than the orthophase of GFR and ERPF. In patients with renal disease a low filtration fraction has been advocated as a useful marker of disease activity, for example in patients...
with systemic lupus erythematoses [25] or with kidney
transplant rejection [26]. To obtain meaningful sequential
data in these patients, the time of the day should be the
same for each determination of filtration fraction.

It is well known that sodium excretion and urine
volume have a circadian rhythm in normal subjects [2–4,
27–29] and that this rhythm persists during recumbency
and constant dietary sodium intake per 3 h. Plasma
sodium concentration did not show a significant circadian
rhythm, but the filtered load of sodium had a rhythm
caused by the GFR rhythm. The phase of the rhythms for
both filtered load and urinary excretion of sodium was the
same as the phase of the GFR rhythm. The amplitude of
the rhythms for sodium and water excretion was higher
than the amplitude of the GFR rhythm, suggesting that
variations in tubular reabsorption contribute to the ampli-
tude of the excretory rhythms. By subtracting urinary
sodium excretion from the filtered load, the reabsorbed
quantity was obtained. This quantity also had a circadian
rhythm with an orthophase and amplitude similar to the
rhythm of the filtered load. Fractional reabsorption of
sodium followed a circadian rhythm with a reversed
phase, or in other words, the highest percentage of the
filtered load of sodium was reabsorbed during the night.
For water similar calculations can be made. It can there-
fore be concluded that the circadian rhythms of urinary
volume and sodium excretion are the consequence of
circadian changes in functional activity both at the
glomerular and the tubular level.

For potassium different results were found. In accord-
cance with the observations of other authors [2, 30, 31], a
circadian rhythm was found for plasma potassium con-
centration. This rhythm slightly enhanced the circadian
rhythm for the filtered load of potassium. However, in all
individuals the circadian rhythm for urinary potassium
excretion had a completely different orthophase, con-
sistently several hours earlier than the GFR rhythm.
Filtered potassium is largely reabsorbed and urinary
potassium is mainly derived from a secretory process in the
cortical part of the collecting duct. The activity of this
secretory process is, in part, dependent on plasma potas-
sium concentration and plasma aldosterone concentra-
tion. During the early part of the night these determinants
of renal potassium secretion are low and tubular secretion
is probably minimal, but later during the night and in the
early morning plasma potassium and aldosterone con-
centrations are high and have their orthophase. The dif-
fERENCE in orthophase between the GFR rhythm and the
urinary potassium rhythm can be explained by the
assumption that urinary potassium is almost entirely
derived from a secretory process, that is partly controlled
by plasma potassium and aldosterone, factors that are
independent of GFR.

The two proteins in this study, β2-microglobulin and
albumin, also had a circadian rhythm in their urinary
excretion. However, in three subjects such a rhythm could
not be demonstrated for albumin, because the institution
and continuation of bedrest caused a strong decrease in
urinary albumin excretion. This pronounced 'orthostatic'
influence in these subjects may have masked the circadian
rhythm. It is of interest that the rhythm of GFR and that
of the urinary excretion of β2-microglobulin, sodium and
potassium were normal and apparently not influenced by
the institution of recumbent posture. Further studies are
needed to answer the question as to whether this dif-
ference between albumin and β2-microglobulin is caused
during their transport in the glomeruli or their reabsorp-
tion in the tubular cells. A similar decrease in the urinary
excretion of serum proteins after the institution of bedrest
is sometimes found in patients with the nephrotic
syndrome [21, 22].

The presence of a circadian rhythm in the urinary
excretion of albumin and β2-microglobulin in normal
subjects confirms earlier observations [22, 32–34],
although diet and posture were not kept constant in most
of the studies or only day/night comparisons were made.
For albumin it is difficult to separate the glomerular and
tubular component of the circadian rhythm because
glomerular passage is highly restricted. For β2-micro-
globulin the glomerular transport is unrestricted, but
more than 99.9% of the filtered load is reabsorbed and
metabolized by the proximal tubules. This reabsorption
process in the proximal tubules has a circadian rhythm
that follows the GFR rhythm, in a similar manner to the
sodium rhythm.

In conclusion, GFR does have a circadian rhythm in
normal subjects that is not the result of day/night dif-
fences in posture or protein intake. Its magnitude is
such that it may have practical consequences. The clear-
ance of PAH (ERPF), which is determined by glomerular
filtration as well as tubular secretion, has a rhythm with a
similar amplitude, but with a different phase. A difference
in phase was also found between the rhythms of GFR and
urinary potassium excretion, probably because potassium
in the urine is also markedly derived from secretion. For
sodium, water and β2-microglobulin no phase differences
are seen, but the amplitude of these rhythms is higher than
for the GFR rhythm.

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