Kidney International, Vol. 59 (2001), pp. 1873–1880

Circadian rhythms in systemic hemodynamics and renal function in healthy subjects and patients with nephrotic syndrome

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Circadian rhythms in systemic hemodynamics and renal function in healthy subjects and patients with nephrotic syndrome.

Background. The resemblance of the circadian rhythm of glomerular filtration rate (GFR) to that of arterial blood pressure (BP) suggests that systemic hemodynamic factors contribute to this variation. In the present study, this was investigated using continuous BP monitoring and pulse wave analysis. The study was performed in eight healthy subjects and in seven patients with nephrotic syndrome who had normal or reversed rhythms of GFR.

Methods. Circadian variations of renal function (continuous infusion of inulin/paraaminohippuric acid), noninvasive finger arterial pressure (Portapres), and vasoactive hormone levels were monitored during 27 hours. With stepwise backward regression analysis, the contributions of the measured variables to the circadian variation of GFR were investigated.

Results. Both groups showed a reduction of BP at night. In the controls, this was related to a drop in cardiac output, while in the patients, total peripheral resistance decreased at night. None of the hemodynamic variables explained the circadian GFR variation in both groups. In the controls, only 6% of the effective renal plasma flow (ERPF) rhythm was associated with variations in cardiac output ($P = 0.03$). In the patients, atrial natriuretic peptide and plasma renin activity were responsible for 36% of the variation in GFR ($P < 0.01$).

Conclusions. These results indicate that the circadian variation of GFR does not result directly from changes in BP or cardiac output. An inverted GFR rhythm in patients with nephrotic syndrome may originate from hormonal mechanisms rather than directly from the hemodynamic effects of edema mobilization.

In healthy subjects, the glomerular filtration rate (GFR) displays a circadian rhythm with a maximum in the daytime and a nadir during the night [1–4]. In an earlier study, we observed a similar GFR rhythm in patients with a recently developed nephrotic syndrome [5]. In some patients, however, the orthophase was shifted toward the night. Irrespective of the timing of the GFR orthophase within the 24-hour cycle, the circadian rhythm of GFR paralleled that of urinary sodium excretion. We speculated that an increased nocturnal GFR and sodium excretion was related to entrance of edema into the circulation during recumbency at night. This hypothesis was supported by the observation that "inverted" rhythms occurred primarily in patients with extensive edema and marked hypoalbuminemia.

We questioned how a change in circulating volume could affect natriuresis and glomerular filtration in these patients. It is possible that circadian variations in blood pressure (BP) or cardiac output (CO) might, in a direct manner, influence renal blood flow (RBF) and intraglomerular pressure and thereby glomerular filtration [6, 7]. However, changes in vascular filling status are also associated with effects on the concentrations of various natriuretic substances, with possible effects on both sodium chloride excretion and GFR.

The present study examined the circadian variations of GFR in relationship to the changes in systemic hemodynamics. In preliminary studies, we found no relationship with intermittent BP measurements [8]. Therefore, we chose a machine that could record continuous noninvasive BP measurements (Portapres), which reliably detected variations in BP and heart rate (HR) without disturbing the patients' sleep. With this technique, beat-to-beat variations in stroke volume (SV), CO, and total peripheral resistance (TPR) were also assessed. The measurements were performed in nephrotic patients with either a normal-phased or a shifted GFR rhythm. These results were contrasted to a group of healthy individuals. We tested the hypothesis that changes in the circadian GFR rhythm in nephrotic patients are the consequence of changes in systemic hemodynamics.

Key words: glomerular filtration rate, blood pressure, cardiac output, finger arterial BP, edema.

Received for publication March 10, 2000
and in revised form October 23, 2000
Accepted for publication November 21, 2000

METHODS

Research settings

The study was performed in two groups of subjects. The first group consisted of eight healthy volunteers (4 males and 4 females) with a mean age of 25 years (range 23 to 30 years). The second group comprised seven patients with nephrotic syndrome (3 males and 4 females) with a mean age of 45 years (range 28 to 71 years). All patients were admitted with a newly diagnosed proteinuria with a decreased plasma albumin level, on average 9 g/24 h (range 6 to 13 g/24 h). None of the patients were hypertensive; the average BP was 130/79 mm Hg. Patients having diabetes mellitus were not included, since hemodynamic regulatory mechanisms may be altered because of autonomic neuropathy in these patients. If necessary, vasoactive medication was interrupted from three weeks prior to the start of the study until the end of the measurement period. None of the patients were treated with corticosteroids or cyclosporine during the study.

The experiments were conducted in the metabolic ward of the hospital. Experiments started at 5 p.m. and ended at 9 p.m. the following day. The circadian variations of finger arterial BP, renal function, and vasoactive hormones were simultaneously measured. In patients with nephrotic syndrome and generalized edema, a transition from an erect to a supine position has pronounced effects on urine flow and salt excretion because of the mobilization of edema into the intravascular space. To preclude that these effects would obscure the circadian variations in renal function and systemic hemodynamics, patients had kept bed rest during three days preceding the measurement in order to obtain stable measurement conditions. In the healthy subjects, we considered a much shorter equilibrium period of four hours sufficient, as Blomqvist et al have shown that the fluid shift to the thoracic region occurs after transfer from the standing to the minus 6° head-down tilt position within four hours [9]. We therefore expected that this also held true for a smaller change in body position. For the same reason, the head ends of the beds were kept in a fixed supine position during both day and night. However, it should be noted that minor changes in body position during the experiment could not be avoided, since participants used cushions during the day for reading and watching television.

Blood and urine samples were collected every three-hour period, starting at 9 p.m. The participants were allowed to sleep between 1 a.m. and 9 a.m. (nighttime), in between the planned collection times and meals (3 a.m. and 6 a.m.). To divide food intake over the observation period as much as possible, a standardized diet was provided with equal portions every three hours during both day and night. The volunteers' meals (given every 3 hours) comprised food choices that took into account their personal preference and caloric needs. A typical meal consisted of a slice of bread with cheese or marmalade and a glass of milk. Patients with nephrotic syndrome received a sodium-restricted diet (20 to 70 mmol/24 h). Fluid intake was at least 300 mL per three hours to ensure sufficient urine production. Smoking and the coffee consumption were not permitted during the study protocol.

Hemodynamic measurements

The finger arterial pressure signal was recorded continuously and noninvasively, alternating each 30 minutes between the third and fourth finger. Portapres Model 2, the portable version of TNO-BMI's Finapres, was used for this study [10, 11], and BP was measured using the volume clamp method of Peñaz [12]. The device was provided with a height-correcting system, which measured the position of the finger relative to heart level. The continuous BP waveform was sampled at 100 Hz with 0.25 mm Hg resolution and stored in a digital flash memory after data compression.

Off-line artifact rejection of the finger arterial pressure tracing was performed visually. Beat-to-beat values of systolic and diastolic BP (SBP and DBP), mean arterial pressure, and HR were determined from the continuous finger arterial pressure signal with the Beatfast-program (TNO-BMI, Amsterdam, The Netherlands) [13]. Left ventricular SV, CO, and TPR were estimated on a beat-to-beat basis using the "Modelflow" method [14]. The method computes aortic flow pulsations from central or peripheral arterial pressure waveform using a nonlinear, time-varying model of aortic input impedance, which consists of a characteristic impedance, an aorta "Windkessel," compliance, and peripheral resistance. Modelflow has been validated under various pathophysiological conditions and also in patients with arteriosclerotic disease. Recently, Harms et al showed that even after one hour of severe ortostatic stress induced by a 70° head-up tilt, a good correlation was present between Modelflow SV from the noninvasive finger tracings and thermodilution ($r^2 = 0.87$, $P < 001$) [15]. This was comparable to the Modelflow data from the intra-arterial signal.

Laboratory analyses

Blank urine and plasma samples were collected before a priming intravenous injection of inulin 60 mg/kg (Inutest, Laevosan Gesellschaft, Linz, Austria), and paraaminohippuric acid (PAH; 7.5 mg/kg, aminohippurate sodium; Merck Sharp and Dohme, Haarlem, The Netherlands) was administered at 5 p.m. After this bolus, a continuous infusion of inulin and PAH by a microvolumetric infusion pump (IMED-micro 965) was started to achieve stable plasma inulin concentrations of 400 mg/L and plasma PAH levels of 20 mg/L. After an equilibration period of more than four hours, the first collection period was from 9 p.m. to midnight and continued for 24 hours until 9 p.m. on the following day. Every three-hour urine

sample was collected by spontaneous voiding, and peripheral blood was sampled. Plasma and urine samples were frozen promptly at −20°C. Laboratory analyses of the aliquots were performed within three weeks after the experiment. Inulin and PAH were determined after deproteinization of the plasma using the Somogyi zinc precipitation method [16]. Inulin was determined by a modification of Walser's method with the color reagent diphenylamine [17]. Concentrations of PAH in urine and plasma were determined with the color reagent N-(1-Naphtyl)-ethylene-diammonium dichloride [18]. Plasma renin activity (PRA) was measured by radioimmunoassay (RIA) for angiotensin I generation. Plasma atrial natriuretic peptide (ANP) and cortisol concentrations were determined by commercial RIAs. The concentrations of the prostaglandins PGE_2, 6-keto-$PGF_{1\alpha}$, $PGF_{2\alpha}$, and thromboxane (Tx) B_2 (the stable metabolite of TxA_2) in the urine were determined by RIA according to the method of Thomas et al [19].

Statistical analyses and calculations

Glomerular filtration rate and ERPF were calculated for each three-hour period (8 values in each measurement period) as the clearance of inulin and PAH using the standard formula $UV/P \cdot \Delta t$, where U is the urinary concentration, V is urine volume, P is the arithmetic mean of the plasma concentrations at the beginning and the end of each clearance period, and Δt is the duration of the period. When appropriate, clearances were corrected for errors in urine collection and for unstable plasma concentrations. This method has been described previously [3, 4] and is based on Donker et al's observation that the constant infusion of PAH is identical to the renal clearance performed with an accurate urine collection [20]. This allows correction for errors in urine collection. As the value for a three-hour period, we averaged the plasma values at the start and the end of a particular sampling period. Filtration fraction (FF) was defined as GFR/ERPF, and RBF was defined as ERPF/(1 − hematocrit). To compute the Modelflow-derived parameters SV, CO, and TPR, no calibration with a reference method of CO determination was performed. Therefore, all values are presented as percentage deviations from individual 24-hour averages. Daytime was defined from 9 a.m. to 1 a.m., and nighttime was from 1 a.m. to 9 a.m.

For the hemodynamic parameters computed with Modelflow from the continuous BP tracings (SV, CO, and TPR), the average percentage of deviations from the individual 24-hour average levels were used (**Methods** section). Data from PGE_2, 6-keto-$PGF_{1\alpha}$, $PGF_{2\alpha}$, and Tx determined in the urine represented three-hour urinary clearances. The levels of the plasma hormones (PRA, cortisol, and ANP) were entered as the arithmetic means of the plasma concentrations measured at the beginning and end of the sampling period.

The following parameters were determined to describe the circadian rhythm: (*1*) the amplitude (A) was defined as the difference between the highest and lowest value observed in the 24-hour period. (*2*) The relative amplitude (A/M) was the amplitude (A) that was expressed as a percentage of the 24-hour mean (M). (*3*) The orthophase was defined as the time of the highest value during the study period. The percentage of day-to-night changes of the hemodynamic parameters were calculated as follows: [(nighttime average − daytime average)/daytime average] × 100%

All descriptive parameters are given as median values with corresponding ranges. Differences of mean values between both groups were tested nonparametrically with Wilcoxon's matched pairs signed rank test, with $P < 0.05$ indicating significance.

The influence of systemic hemodynamics on the circadian variability of GFR and ERPF was analyzed with a stepwise backward analysis of variance with repeated measurements (BMDP Statistical Software, program 2 version) [21]. For all dependent and independent variables, a logarithmic transformation was performed prior to further analysis to reduce residuals in the analysis of variance. Residual analyses from a repeated-measurement analysis of covariance (ANCOVA), with group (patients vs. controls) as between patient factor and time as within-patient factor including the group–time interaction, were used to detect possible outliers in the dependent variables. Compound symmetry was assumed for the covariance matrix. The same model was used to analyze whether variables changed during the day and whether the change differed between the patients and control subjects. The relationships between independent and dependent variables were analyzed in the two groups, both in combination and separately, using a repeated-measurement ANCOVA. In the combined analysis, a group was used as the between factor, while the interaction between group and time was also accounted for. First, for each dependent variable, ANCOVA's were performed with only one independent variable. Thereafter, all independent variables with a $P < 0.10$ for the within-patient correlation were selected. Only these variables were entered together in the repeated-measurement analysis of variance (ANOVA), in order to compute the extent to which the within-patient variation of the dependent variable was explained by a variation of these independent variables together. As a measure the ratio of the sum of squares (SS) was used of all within patient covariates to the total within patient SS. The latter total was calculated from the sum of the within-patient residual SS and the SS caused by time in a model without covariates. This is defined as the within-patient squared multiple correlation coefficient between the covariates and the dependent variables.

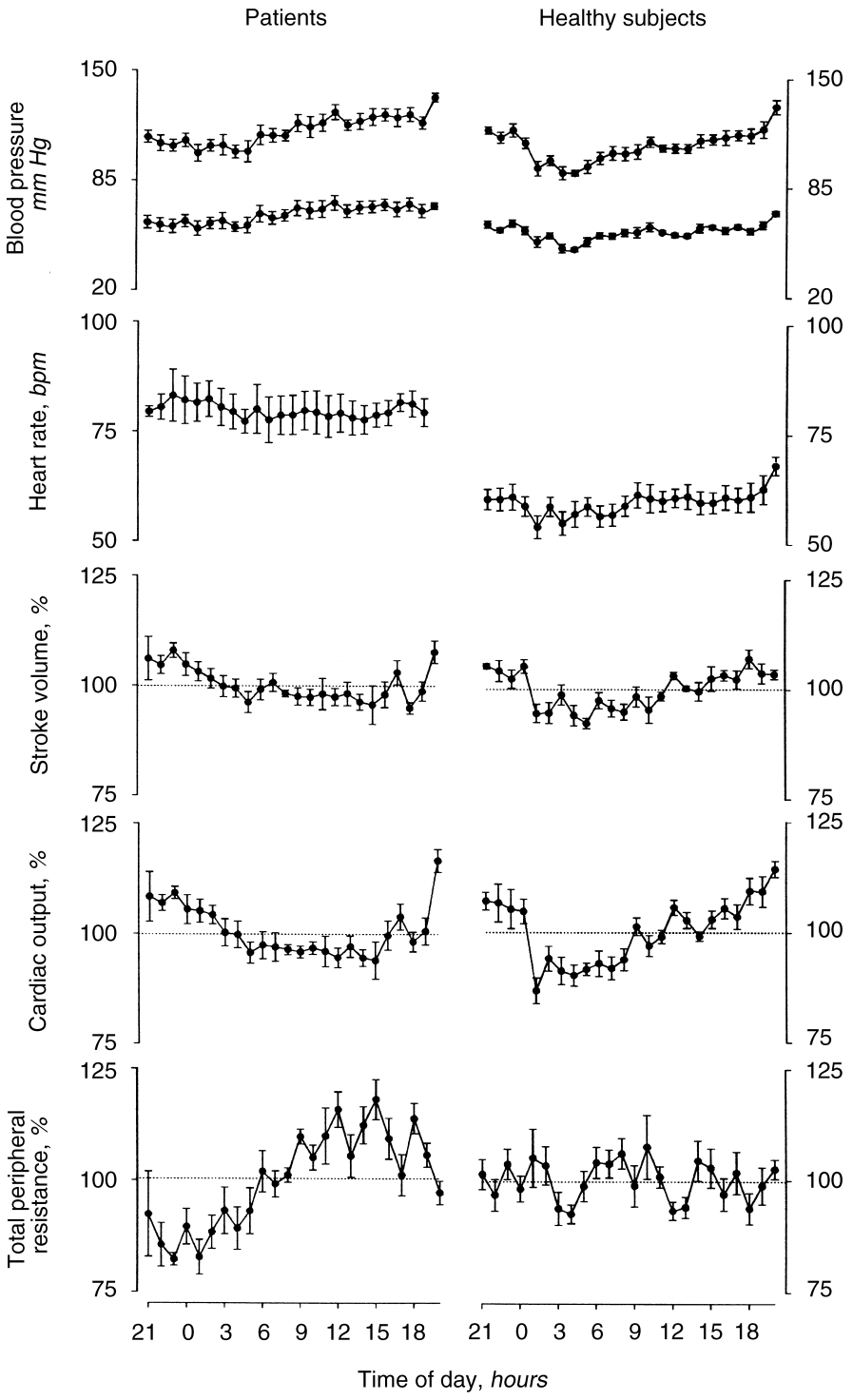

Fig. 1. Circadian profiles of systemic hemodynamics in the patients with nephrotic syndrome (N = 7) and in healthy controls (N = 8). Values are hourly averages ± SEM. The dashed area represents the night period.

RESULTS

Renal function

The 24-hour average GFR in the control group was 117 mL/min (104 to 134 mL/min). The average ERPF was 596 mL/min (525 to 718 mL/min), and the average FF was 14% (13 to 15%). In all healthy subjects, a circadian variation of GFR and ERPF was observed with a mean orthophase in daytime (on average at 12.12 hours for GFR and 16.42 hours for ERPF). The mean A/M of GFR was 43% (18 to 113%) and of ERPF 52% (28 to 70%). The 24-hour average levels of GFR and ERPF in the patients were significantly lower than in the control group: 56 mL/min (20 to 127 mL/min) and 399 mL/min

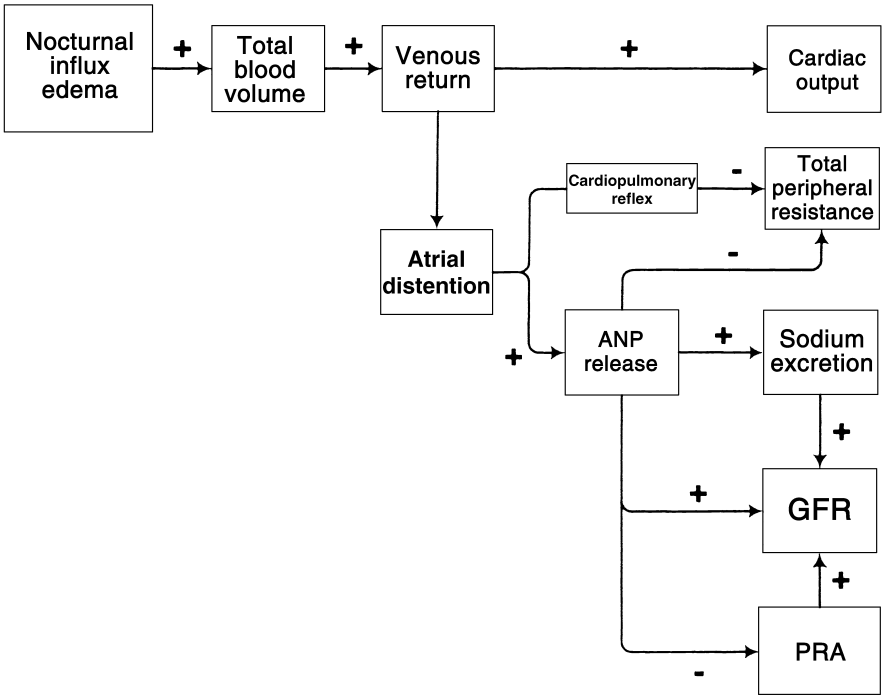

Fig. 2. Schematic presentation of events as an explanation for the observed differences in circadian variation of systemic hemodynamics, sodium excretion, and GFR in patients with nephrotic syndrome (atrial natriuretic peptide and plasma renin activity).

(179 to 678 mL/min), respectively. The FF was higher than in the controls: 20% (18 to 22%). The circadian variability—in absolute values—was less pronounced in this group. When expressed relative to the 24-hour average (A/M), it was comparable to the healthy subjects: 34% (17 to 41%) for GFR and 27% (16 to 41%) for ERPF. In three patients, the orthophase of the circadian rhythms of both GFR and ERPF occurred during the night, and in four, it happened during the day.

Systemic hemodynamics

All Portapres registrations were of good quality, and the percentage of rejected data was less than 5% in all subjects. Figure 1 shows the circadian profiles of systemic hemodynamics in the patients and controls. The average level and the percentage day/night change of SBP and DBP were similar in the two groups. Both in the healthy subjects and the patients, BP was lowest during sleep. The average change of MAP during the night, expressed as a percentage of daytime level, was −9% (range −12 to −6%) in the control group and −9% (−17 to −5%) in the patients. The 24-hour median HR of the patients was significantly greater than in the controls; 78 bpm (67 to 100 bpm) versus 62 bpm (48 to 68 bpm, $P < 0.05$).

A difference was observed in the mechanism underlying the circadian BP variation. In the control subjects, the nightly decrease of BP was caused by a reduction in CO of −14% (−24 to −6%), through a decrease in both HR and SV: −5% (−9 to 3%) and −6% (−8 to −2%), respectively. No significant day/night variation in TPR was observed in this group: The median day-to-night change was 1% (−11 to 13%). As described previously in this article, in the patient group, an identical percentage day/night reduction of BP was present compared with the healthy subjects. However, this was associated with a nocturnal reduction of TPR in six of the seven patients, who had a median reduction of −8% (−20 to 10%, $P = 0.05$). This occurred in the absence of a significant day/night variation in HR, SV, and CO: median changes 0% (−10 to 11%), 1% (−9 to 5%) and 0% (−21 to 3%), respectively.

Influence of systemic hemodynamics

As expected, a significant correlation existed between the circadian variations of ERPF and GFR, both in the controls ($r^2 = 0.11$, $P = 0.01$) and patients ($r^2 = 0.10$, $P = 0.03$). In this analysis, none of the measured hemodynamic parameters contributed significantly to the observed variation of GFR. With regard to ERPF, only CO contributed significantly to the variation in the control group ($r^2 = 0.06$, $P = 0.03$), resulting in an explained variation of 6% in this group. CO was also correlated to the FF ($r^2 = 0.07$, $P = 0.02$) and RBF ($r^2 = 0.06$, $P = 0.03$). These correlations were not found in the patients.

Vasoactive compounds

As expected, the 24-hour averaged levels of PRA and ANP tended to be higher in the patients than in the controls (0.56 ± 0.3 μgAI/L/h, and 44.9 ± 8.4 vs. 1.57 ± 0.2 and 62.5 ± 12.4 ng/L, respectively). In the control

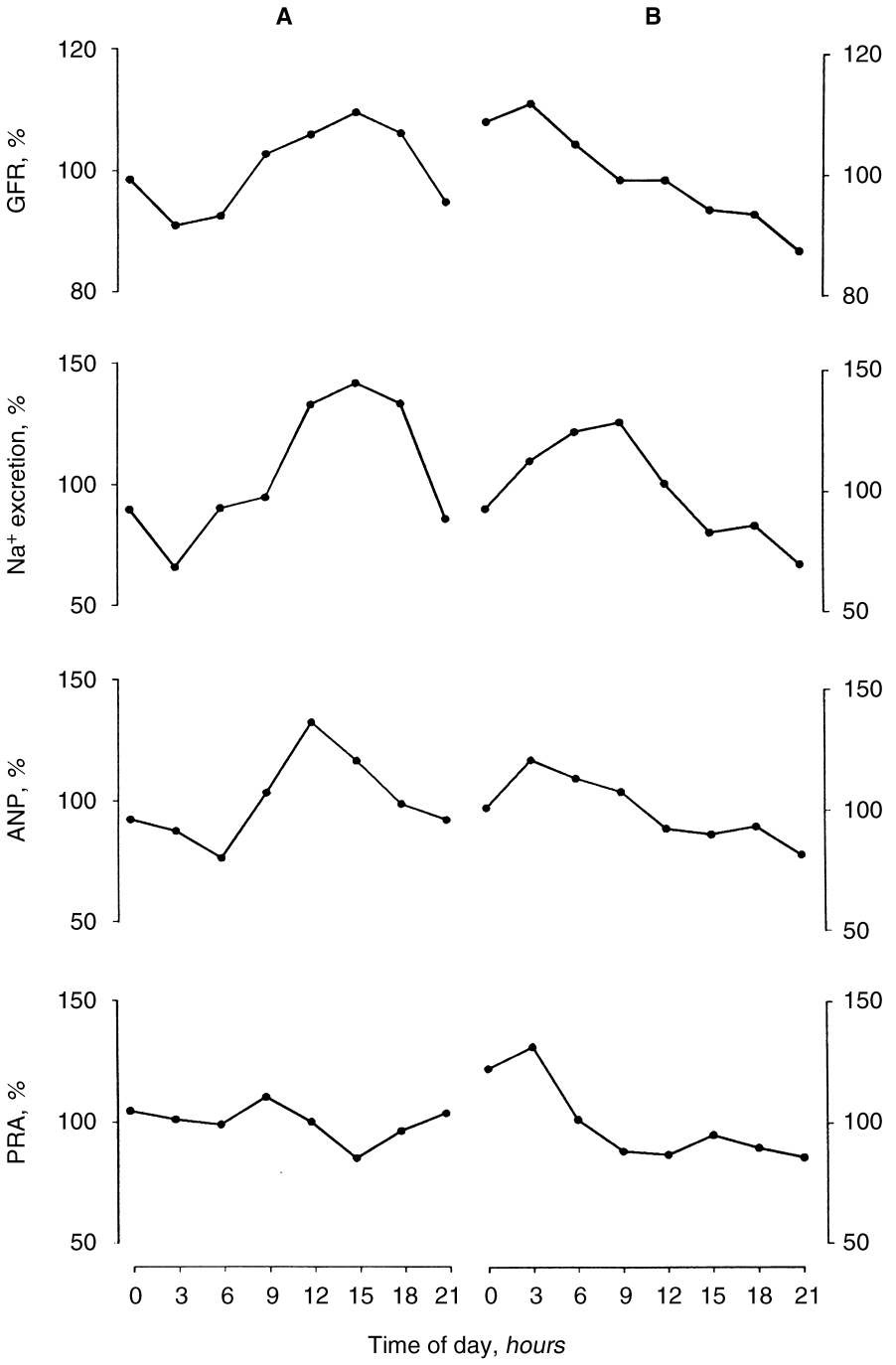

Fig. 3. Circadian variations of GFR, Na^+ excretion, ANP, and PRA, separated for the four patients with nephrotic syndrome exhibiting a normal GFR rhythm (orthophase in daytime, group A) and the three patients with an reversed GFR rhythm (orthophase in nighttime, group B).

subjects, univariate analysis showed that none of the tested vasoactive compounds significantly contributed to the variation of GFR or ERPF. PGE_2 and Tx were correlated to variations of the FF, but not of GFR or ERPF in the control group ($r^2 = 0.05$, $P < 0.01$, and $r^2 = 0.04$, $P = 0.02$, respectively). In the patient group, ANP and PRA were both significantly correlated to the variation of GFR ($r^2 = 0.10$, $P = 0.04$, and $r^2 = 0.20$, $P < 0.01$). Together, ANP and PRA resulted in a 36% explained variation.

DISCUSSION

In our study, the multivariate analysis showed that only 6% of the variation in ERPF was explained by changes in CO in the healthy subjects. Apart from this observation, no significant relationship existed between the day-to-night variations in systemic hemodynamics and GFR in both groups.

The circadian rhythm of arterial BP mainly depends on external factors [22–24]. In shift workers, a change

in activity pattern has been shown to invert promptly the circadian BP rhythm [25]. In contrast, the circadian GFR rhythm seems to be more endogenously determined. Buijsen et al's study in renal transplant patients suggests that the rhythm of GFR occurs independently of autonomic regulation [26]. There are scarce data on the interrelationship between circadian rhythms in the systemic circulation and renal function [27]. A persistent GFR rhythm was found during continuous bed rest, a condition that is associated with an attenuated circadian BP variation [1–5]. Studies in transgenic hypertensive rats support the concept that a direct relationship between the circadian rhythms of GFR and systemic hemodynamics is absent. In this model, an unaffected circadian variation of renal function was observed despite an inverted rhythm of BP [28, 29]. In the present study, three patients had an inverted GFR rhythm with an orthophase during the night, while all had a normally-phased BP rhythm with a clear maximum in daytime. It should also be mentioned that no relationship was present between the amplitudes of the BP and the GFR rhythms.

Although the circadian BP rhythms between the patients and the healthy subjects were comparable, different patterns in the underlying hemodynamics were present. In the controls, the nightly decreases in BP and heart rate were associated with a lower SV and CO, while peripheral resistance remained unchanged. This corresponds with earlier observations from our group [30]. In the patients with nephrotic syndrome, the nightly decreases in SV and CO were less pronounced or even absent. The total peripheral resistance, however, was lowest during the night.

There is no ready explanation for the previously mentioned observation. As mentioned earlier, all patients had severe edema caused by a newly diagnosed nephrotic syndrome with heavy proteinuria, and none had been previously treated with diuretics. We assume that entry of edema at night plays a crucial role in the pathophysiological mechanism explaining both the hemodynamic and renal alterations in the patient group (Fig. 2). First, the redistribution of fluid prevents the drop in CO normally found during the night. The increased venous return might have led to stimulation of atrial stretch receptors, which causes a direct reduction of sympathetic outflow [31] and also triggers the release of ANP [32, 33]. The multivariate analysis showed that more than one third of the circadian variation in GFR was explained by variations in ANP and PRA. These factors are known to influence GFR either directly or indirectly. As shown in Figure 3, three patients had an inverted GFR rhythm, and four patients had a normally phased rhythm. In both subgroups, the circadian rhythms of ANP and sodium excretion were in phase with the GFR rhythm. Although the number of patients is too small for any statistical comparison, these observations support a relationship between the circadian rhythms of GFR, urinary sodium excretion, and plasma ANP concentration. ANP is well known to induce a lower peripheral resistance by a direct vasodilatory action [34, 35]. Also, ANP is known to cause an increase in GFR [35]. Therefore, we hypothesized that the differences in hemodynamic patterns and GFR rhythms between the patients and healthy subjects are both related to changes in ANP and PRA. Again, our data did not indicate a direct relationship between hemodynamic parameters and circadian changes in GFR.

In summary, the present study shows that circadian changes in GFR in healthy subjects are not directly related to fluctuations in systemic BP and CO. It is suggested that in patients with nephrotic syndrome, the entrance of edema fluid into the vascular bed may affect the GFR rhythm through the action of ANP and perhaps other hormones. Thus, no conclusion can be drawn on the genesis of the GFR rhythm in healthy individuals, but it may be the consequence of an intrinsic renal mechanism.

ACKNOWLEDGMENTS

We are much indebted to Mr. K.J. Hiralall, Department of Clinical Chemistry; to Mr. E. Endert and the technicians of the Department of Endocrinology; to Mrs. C.F. Jonkers for dietary advice; and to the nursing staff of F5NS for skillful support.

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APPENDIX

Abbreviations used in this article are: A/M, relative amplitude; ANP, atrial natriuretic peptide; BP, blood pressure; CO, cardiac output; DBP, diastolic blood pressure; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; HR, heart rate; MAP, mean arterial pressure; PAH, paraaminohippuride; PG, prostaglandin; PRA, plasma renin activity; RBF, renal blood flow; RIA, radioimmunoassay; SBP, systolic blood pressure; SV, stroke volume; TPR, total peripheral resistance; TX, thromboxane; U, urinary concentration; V, urine volume.

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