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PLASMA RENIN ACTIVITY CIRCADIAN RHYTHM IN HYPERTENSIVE SUBJECTS

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Summary

In 12 outpatients, we documented a statistically significant circadian rhythm in plasma renin activity using the cosinor method. These data were reconfirmed in the chronograms of three hospitalized patients, more rigidly chronobiologically synchronized. Circadian rhythm and meso-reninaemia should be taken into account in renin profiling.

Introduction

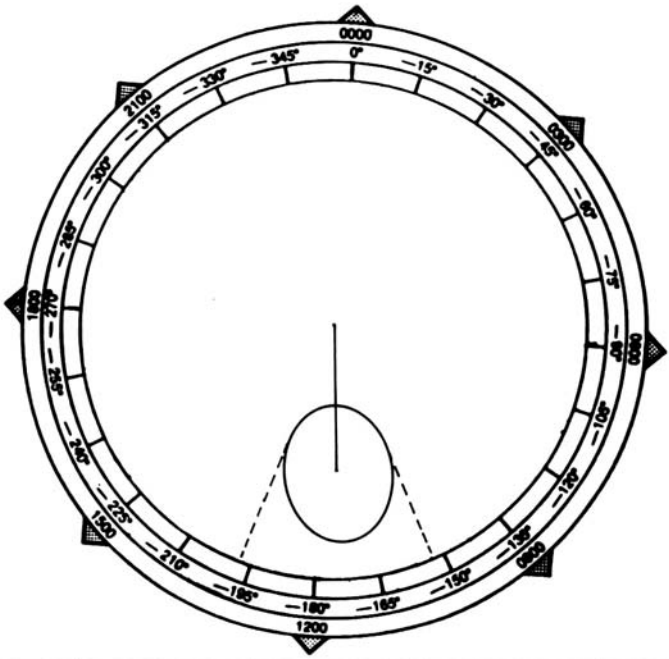
From a pathophysiological point of view it is universally accepted that the renin angiotensin system plays a fundamental role in sustaining the blood pressure of most hypertensive patients, but there still exists considerable disagreement among various authors about the clinical evaluation of the renin system, particularly because of the wide inter-individual variability and the wide circadian oscillations of peripheral plasma renin activity in the same subject. The first important contribution to this problem has been furnished by the Laragh group who maintained that renin secretion normally fluctuates according to the state of sodium balance which varies considerably from day to day. The renin-sodium profile concept was therefore introduced [1,2], increasing thereby the clinical significance of plasma renin activity. There is still much controversy in the clinical interpretation of the great differences in plasma renin activity values, recorded in the same subject during the same day. Recently the field of chronobiology has much progressed, inducing many authors to consider whether this daily variability, considered confusing in clinical evaluations of the renin profile, could in effect be disguising a biorhythm which must necessarily be accounted for in the production of this hormone. In the recent literature much has been published which confirms the existence of a plasma renin activity circadian rhythm [3–6].

What remains to be ascertained is the importance and implications that such

results have on clinical practice. In fact most of these studies were performed on hospitalized patients rigidly synchronized chronobiologically so that normal living conditions would not be reflected. The main aim of our research was to demonstrate the existence of a renin circadian rhythm in hypertensive patients during outpatient blood sampling. These subjects were synchronized only as far as sleep/awakeness and meal-timing schedules are concerned.

Patients and methods

Our study was performed on 12 volunteer patients (6 males and 6 females, aged 42.00±17.87 years) affected by hypertension, defined as a blood pressure persistently above 140/95mmHg while receiving no drug therapy. All patients were first hospitalized in our Institute of Nephrology of the University of Chieti and subjected to a complete work-up. The blood pressure (BP) and heart rate were checked four times per day using an automatic instrument (Dinamap Applied Medical Research) with the patients in erect and supine positions. The initial evaluation included peripheral plasma renin activity with renin-sodium profiling. The plasma renin activity was determined using a radioimmunoassay method (Lepetit RIA renin Kit; normal values: supine plasma renin activity 0.16–0.66ng/ml/hr; erect plasma renin activity 0.73 2.13ng/ml/hr). When the clinical indications were present, we associated selective catheterization of renal veins for plasma renin activity determination to digital subtraction angiography. The diagnosis at the end of the work up was: essential hypertension, 10 cases; renovascular hypertension, 2 cases. After being discharged, all the patients were asked to return one week later to our outpatients department for evaluation of the circadian rhythm of plasma renin activity. The patients were asked to sleep in hospital, eat at home at fixed times (11.00 and 18.00), carry out their normal routine and work and be back in our unit at a fixed time for blood sampling. Blood was drawn at four hourly intervals (at 04.00, 08.00, 12.00, 16.00, 20.00 and 00.00). For each patient we calculated the mean plasma renin activity value at all six points (mesor-reninaemia). The relative changes from the individual mean at each time point (expressed as percentages) were then evaluated by the cosinor method. To establish the possibility of interference caused by movement and meal times, we decided also to evaluate the circadian rhythm of plasma renin activity in three hospitalized patients, two of which were affected by reno vascular hypertension and one by essential hypertension. The study proceeded for two consecutive days, samples were drawn at four hourly intervals (at 04.00, 08.00, 12.00, 16.00, 20.00 and 00.00); all patients were placed in a recumbent position for at least one hour before blood drawing. After a week the above study was repeated on the same patients changing only the times at which they ate their meals (13.00 and 20.00) and the hours at which the blood samples were taken (at 02.00, 06.00, 10.00, 14.00, 18.00, 22.00). For this small number of observations it was not possible to perform the cosinor evaluation. So a mean chronogram was computed for the relative changes from the individual mean (expressed as percentages). This computation makes it possible to observe the occurrence of mean values, which after the addition or the subtraction of two standard errors, still fall respectively under or over 100.



no. obs.	mesor	amplitude	acrophase	95% C.L.
12	100	64.66% ± 10.06	hr 11.38	hr 10.15-13.09

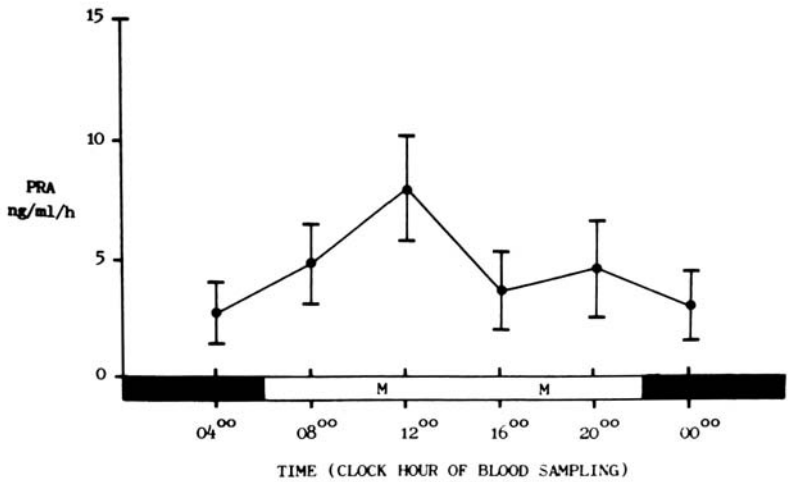


Figure 1. Above: Cosinor display for relative values of plasma renin activity in 12 hypertensive patients. Below: mean (± SE) for absolute values of plasma renin activity (ng/ml/hr) in 12 hypertensive patients. (M=meals)

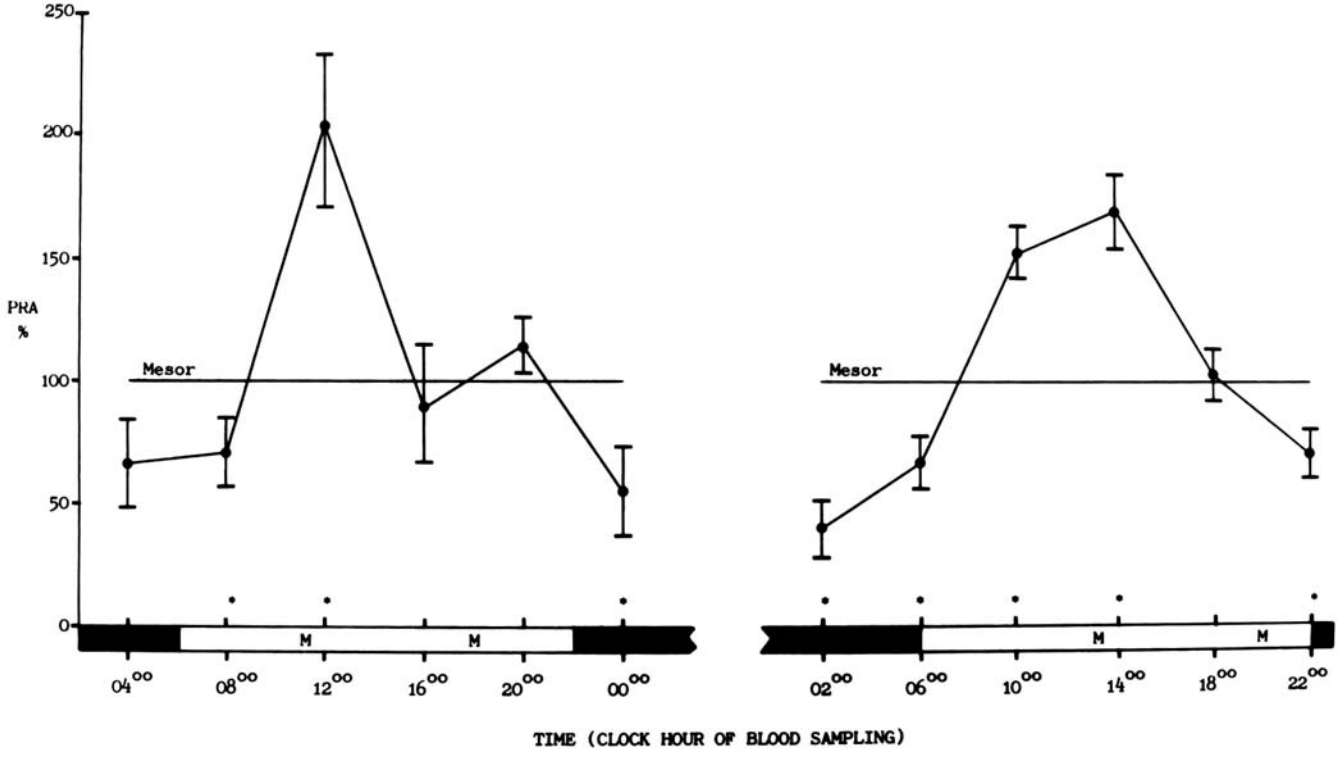


Figure 2. Mean (± SE) values of plasma renin activity relative changes from the individual mean (expressed as percentages) in three hypertensive patients. The asterisks indicate the mean values, which after the addition or subtraction of 2SE, still fall respectively under or over 100. (M=meals)

TABLE I. Mesor-reninaemia evaluation

Number	Name	Date	Hours												Mesor-reninaemia Mean±SE
			02	04	06	08	10	12	14	16	18	20	22	00	
1	ZF	03/02/85		3.48		2.90		6.64		3.45		4.26		4.92	4.28±0.56
2	ZF	04/02/85		3.77		2.80		5.92		3.48		5.26		2.66	3.98±0.54
3	ZF	11/02/85	1.80		3.10		4.71		5.43		3.01		2.28		3.37±0.58
4	ZF	12/02/85	1.40		2.73		6.11		4.93		3.81		2.87		3.62±0.69
5	DQR	16/03/85		2.04		3.63		21.55		9.87		9.16		3.89	8.36±2.94
6	DQR	17/03/85		1.87		3.39		14.37		12.07		11.30		3.26	7.71±2.23
7	DQR	22/03/85	0.98		2.93		11.6		13.81		6.44		6.30		7.00±2.01
8	DQR	23/03/85	1.74		2.78		9.01		16.40		11.61		6.85		8.04±2.26
9	AS	15/01/85		0.49		0.57		1.23		0.05		0.42		0.02	0.46±0.18
10	AS	22/01/85	0.48		0.60		1.13		0.96		0.54		0.20		0.65±0.14

Results

According to the 24 hour urinary excretion of sodium, we found in the first 12 patients different renin-sodium profiles with normal, low or high peripheral plasma renin activity values at the eighth hour.

In all patients we documented a significant circadian plasma renin activity rhythm with acrophase at 11.38hr, 95 per cent confidence limits between 10.15hr and 13.09hr, amplitude of 64.66±10.06 per cent (Figure 1).

Of two patients affected by reno-vascular hypertension, in whom renal vein renin activity showed lateralization of renin secretion to the ischaemic kidney with controlateral suppression, only one presented elevated peripheral plasma renin activity values. It is interesting, however, to observe that both patients affected by reno-vascular hypertension showed an elevated mesor-reninaemia. A circadian profile with maximal value at 12.00hr (Figure 2), was found by mean chronogram in the three hospitalized patients – two affected by reno-vascular hypertension and one affected by essential hypertension – on whom we performed the plasma renin activity circadian rhythm for two consecutive days. In these same patients on whom we repeated the test after a week, changing the meal times and blood sampling times, the mean chronogram showed a maximal peak at 14.00hr (Figure 2). In these patients, it is interesting to note that even though we recorded a wide variability of plasma renin activity values within the same day or on the following day in the same subject, the mesor-reninaemia values still remain similar (Table I).

Discussion

Our as yet preliminary data obtained on too small a number of subjects do not allow us to draw definite conclusions, but do confirm the presence of a plasma renin activity circadian rhythm in outpatients leading as normal a life as possible. The occurrence of a circadian rhythm with maximal values at approximately the same time of day, both in the 12 outpatients and three subjects, observing one hour of supine position before the blood sampling and with different meal-timing seems to demonstrate that the plasma renin activity circadian rhythm is quite strong and must be accounted for when clinically evaluating the renin-angiotensin system. The greater reproducibility of the mesor-reninaemia when compared to a single morning value of peripheral plasma renin activity is extremely important, even though needing further confirmation. In those patients in whom the circadian rhythm was repeated for two days, the mesor-reninaemia values appear similar in spite of the occurrence of wide circadian variations. Therefore such data could suggest that an estimation of mesor-reninaemia (obtained on six equidistant points) could represent a more precise parameter of the renin profile of a hypertensive subject. Further studies are in progress to confirm the usefulness of mesor-reninaemia in diagnosing secondary hypertensive forms and in selecting an adequate primary hypertension therapy.

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