

CIRCADIAN URINARY GLUCOCORTICOID AND RHYTHMIC BLOOD PRESSURE COORDINATION

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A b s t r a c t

Circadian variations in urinary 17-hydroxycorticosteroids (17-OHCS) and blood pressure were examined in patients (n=42) with MESOR-hypotension, MESOR-normotension and MESOR-hypertension with no known endocrine disorder. Relations were sought between adrenocortical function and blood pressure. All data were evaluated using the Halberg cosinor analysis. In this study, in a separate group of patients (n=21), life expectancy was also examined as a function of the circadian blood pressure amplitude.

Key words

Circadian rhythm, Urinary glucocorticoid, Blood pressure

INTRODUCTION

While it is textbook knowledge that glucocorticoids are in excess in Cushing's syndrome and deficient in Addison's disease, in association with high and low blood pressures, respectively, the question whether corticoids contribute more generally to the coordination of blood pressure in the normal range appears to be unanswered, as is the question whether corticoids are involved in essential hypotension or essential hypertension. Against this background, we compared three groups of patients in relatively good health, one with hypertension, another with hypotension of unknown etiology and the third group with normotension. Further research is indicated to see whether substitution treatment with physiologic doses of a glucocorticoid may be considered in patients with Addison's disease with essential "hypotension."

MATERIALS AND METHODS

Using a mercury column sphygmomanometer, systolic (S) and diastolic (D) blood pressure (BP) was manually measured 2–3 times at night and 6–7 times during the waking period, on each of 2 days, in 42 men, 20–55 years of age, between 26 August and 3 September 1967 in Germany. Diastolic blood pressure was recorded when the Korotkoff sound faded (DBP₄) and then when it disappeared (DBP₅). Of the 42 men, 12 were MESOR-hypotensive, 13 were MESOR-normotensive, and 17 were MESOR-hypertensive. Urine samples were collected around the clock (5 samples daily, 2 days) for the determination of 17-hydroxycorticosteroid (17-OHCS), creatinine and electrolyte (Na⁺ and K⁺) levels. Each data series was analysed by cosinor (1–3). The MESOR values for SBP, DBP4 and DBP5 were further correlated with the value for MESOR of 17-OHCS. In a separate group of subjects (n=21), life expectancy was analysed in the light of blood pressure rhythm parameters, as reported elsewhere (4, 5).

RESULTS

The circadian rhythm was validated for all variables on a group basis by the Halberg cosinor analysis (Table 1). A consistent positive association between the MESOR (circadian rhythm-adjusted mean) values of urinary 17-OHCS and blood pressure MESOR values was found in the subgroup of 12 hypotensive subjects (Table 2). There was no apparent relation between BP and 17-OHCS in MESOR-hypertension. In MESOR-normotension, the correlation was negative but not significant (Table 2).

The longitudinal data obtained on the follow-up group (n=21) showed that 10 patients were still alive and 11 died (Table 3). As anticipated, those who died within 28 years were older. They had higher blood pressure MESORs in 1967. This table further reveals, however, that the circadian double amplitude (2A) of systolic (P=0.007) and diastolic (P=0.024) blood pressure also relates to life expectancy.

DISCUSSION

In Cushing's syndrome, glucocorticoid excess has been associated with hypertension, as well as with an altered circadian variation of BP but not of heart rate (6). However, in a recent review it has been concluded that: „how cortisol elevates blood pressure is unclear“ (7). Whether or not cortisol contributes to hypertension has been examined by *Shamim et al.* (8). An elevated glucocorticoid excretion profile was found by these investigators in a cohort of recently diagnosed young hypertensive patients, but there was no statistically significant difference between middle-aged hypertensive patients and normotensive controls. *Scheuer and Bechthold* (9) report that „glucocorticoids potentiate central actions of angiotensin to increase arterial pressure“ in instrumented Sprague-Dawley rats.

In this study, a consistent positive association between the MESOR (circadian rhythm-adjusted mean) values of urinary 17-OHCS and blood pressure MESOR values was found in the subgroup of 12 hypotensive subjects. There was no apparent relation between BP and 17-OHCS in MESOR-hypertension. In MESOR-normotension, the correlation was negative but not significant. Our data

Table 1

Circadian characteristics of variables investigated

Variable	PR	P	MESOR \pm SE	Double amplitude (95% CI)
SBP	27	<0.001	128.3 \pm 3.0	8.4 (5.6; 11.3)
DBP ₄	18	0.023	87.9 \pm 2.5	3.3 (0.6; 6.1)
DBP ₅	19	0.037	82.9 \pm 2.3	1.8 (0.4; 3.2)
Volume	23	0.025	99.3 \pm 11.3	60.7 (19.5; 102.0)
Na ⁺	38	<0.001	8.75 \pm 0.29	3.98 (2.78; 5.18)
K ⁺	47	<0.001	2.85 \pm 0.07	1.93 (1.59; 2.28)
Creatinine	54	<0.001	82.1 \pm 1.9	28.1 (18.6; 37.6)
17-OHCS	54	<0.001*	0.39 \pm 0.01	0.26 (0.22; 0.30)

PR, percentage rhythm (proportion of circadian variance accounted for by the fitted model); P, *P*-value from the zero-amplitude test; SE, standard error; CI, confidence interval; *, equal statistical significance for each of the 3 subgroups considered separately.

Table 2

Correlation between blood pressure and 17-hydroxycorticosteroid levels

Subgroup	N	SBP		DBP ₄		DBP ₅	
		r	P	r	P	r	P
MESOR-hypotensive	12	0.528	0.078	0.653	0.021	0.588	0.044
MESOR-normotensive	13	-0.294	0.329	-0.371	0.212	-0.538	0.058
MESOR-hypertensive	17	0.096	0.715	0.027	0.918	-0.058	0.826
All patients	42	0.318	0.040	0.272	0.081	0.195	0.215

N, number of patients; SBP, systolic blood pressure; DBP₄, diastolic blood pressure at the point where the Korotkoff sound fades but is still audible; DBP₅, diastolic blood pressure at the point where the Korotkoff sound disappears; r, Pearson's product-moment correlation; P, *P*-value from the test of H₀: r=0.

Table 3

The 1996 follow-up of 21 men who had a manually measured blood pressure profile in 1967

Subject	Age (years) In 1967	SBP		DBP ₄ †		DBP ₅ ‡	
		M	2A	M	2A	M	2A
<i>Alive (10)</i>							
S08	44	133.2	18.8	98.6	5.7	86.4	5.3
S09	36	115.6	11.4	74.6	11.0	71.6	12.4
S11	41	112.7	10.7	76.0	7.1	69.9	3.3
S16	37	103.7	6.7	68.4	7.6	65.0	6.8
S17	40	94.8	9.2	68.3	6.1	67.1	3.2
S21	35	106.5	6.9	73.7	6.4	69.8	5.3
S30	41	134.7	2.8	94.7	3.6	91.1	6.4
S34	56	143.1	22.4	96.6	10.2	93.5	4.9
S37	34	126.1	6.8	87.8	9.6	87.4	14.5
S74	34	111.1	3.5	79.1	3.7	79.1	3.7
mean (9)	40.6	118.9	10.6	82.1	7.5	78.0	6.9
mean (10)	39.8	118.2	9.9	81.8	7.1	78.1	6.6
<i>Died (11)</i>							
S31	53	182.2	6.3	97.3	12.7	91.9	19.1
S33	47	180.8	11.3	105.7	5.4	116.5	2.8
S35	30	143.0	10.2	84.5	32.0	73.7	13.7
S36	52	165.4	20.5	109.6	8.9	110.0	9.6
S38	52	152.7	12.7	92.6	8.5	89.0	14.8
S39	42	189.3	22.8	110.8	2.4	106.8	7.5
S40	48	148.7	6.7	100.6	4.0	100.0	8.4
S41	56	158.1	38.5	93.1	20.0	89.8	16.5
S43	52	161.0	37.0	103.9	13.7	100.3	7.6
S44	53	149.8	33.5	86.3	12.3	82.1	8.6
S77	40	110.2	8.7	71.3	5.1	68.0	7.6
mean (10)	48.5	163.1	19.9	98.4	12.0	96.0	5.4
mean (11)	47.7	158.3	18.9	96.0	11.4	93.5	10.6
<i>Comparison (19)</i>							
t	2.406	5.965	2.079	3.242	1.561	3.199	1.937
P (1-tail)	0.028	<0.001	0.029	0.003	0.075	0.003	0.035
<i>Comparison (21)</i>							
t	2.542	4.867	2.128	2.747	1.572	2.706	2.109
P (1-tail)	0.010	<0.001	0.025	0.006	0.071	0.007	0.024

SBP, systolic blood pressure; DBP₄, diastolic blood pressure at the point where the Korotkoff sound fades but is still audible; DBP₅, diastolic blood pressure at the point where the Korotkoff sound disappears; M, MESOR (midline-estimating statistic of rhythm); 2A, double amplitude.

Circadian amplitudes in boldface exceed upper 95% prediction limits of 9.4/7.5 mm Hg (SBP/DBP) for self-measurement series from men of similar ages.

support the previous findings that the rules within and outside the physiological range can be opposite to each other.

This is also the case for circulating aldosterone (10). Concentrations of circulating aldosterone show rhythmical circadian and seasonal changes and are higher in patients at low vascular disease risk, as compared to those at high risk. In patients who have no Addison's disease and no signs of adrenal insufficiency from other conditions (11, 12), the finding of MESOR hypotension constitutes a particular challenge for areas of the world where the treatment of MESOR-hypotension is in focus.

The fact that life expectancy is related, among other things, to the circadian amplitude of blood pressure (13, 14) is even more interesting since new evidence suggests that, by reducing the circadian blood pressure amplitude, the number of morbid events can also be reduced (15).

A c k n o w l e d g e m e n t

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CIRKADIÁNNÍ RYTMUS GLUKOKORTIKOIDŮ V MOČI A REGULACE RYTMICITY KREVŇÍHO TLAKU

S o u h r n

Cirkadiánní variabilita 17-hydroxykortikosteroidů v moči a krevního tlaku byla vyšetřována u pacientů bez endokrinologických poruch, kteří měli hypotenzi, normotenzi nebo hypertenzi ve veličině MESOR. Předpokládali jsme vztahy mezi adrenokortikální funkcí a krevním tlakem. V této studii, v rozdělených skupinách pacientů, byla prognóza rizika onemocnění také studována jako funkce cirkadiánní amplitudy krevního tlaku.

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