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II: Blood pressure rhythms and salt

Germaine CORNELISSEN (*a*), Terukazu KAWASAKI (*b*), Keiko UEZONO (*b*), Catherine DELEA (*c*) and Franz HALBERG (*a*)

(a) Chronobiology Laboratories, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA
(b) 2nd Department of Internal Medicine, Kyushu University, Fukuoka, Japan
(c) Research Section, Audie L. Murphy Memorial VAMC, San Antonio, TX, USA

Summary. - Chronobiologic monitoring, among other uses in clinical practice as well as research, ascertains three kinds of blood pressure change associated with a modification of dietary sodium intake in patients suspected of having an elevated blood pressure: a direct change (increased blood pressure with increased sodium intake), no detectable change, and an inverse change (decreased blood pressure with increased sodium intake).
Key words: blood pressure, chronobiology, circadian rhythm, hypertension, salt.

Riassunto *(Ritmi della pressione arteriosa e apporto di sodio).* - Il monitoraggio cronobiologico nell'ambito delle sue applicazioni nella pratica clinica e nella ricerca consente di accertare tre tipi di risposte associate con le modifiche dell'apporto alimentare di sodio nei pazienti sospettati di avere una pressione arteriosa elevata, e cioè una variazione pressoria in aumento con l'aumento dell'apporto di sodio, nessuna variazione, una variazione in decremento.
Parole chiave: pressione arteriosa, cronobiologia, ritmi circadiani, ipertensione, sale.

Introduction

Since an elevated blood pressure (BP) is a risk factor for developing several cardiovascular diseases, a dietary endeavor toward the prevention and treatment of high BP is warranted [1, 2]. In this context, the role of sodium, potassium, and calcium ions continues to attract much effort from basic [3] and applied [4, 5] viewpoints. Possibilities for prevention have also been explored, of course, by other means, e.g., through reduced calorie intake and increased calorie output [6].
elective breeding in experimental animals [7] and clinical tests in patients with «idiopathic hypertension» [8] have revealed direct or no BP changes in association with changes in amount of dietary sodium intake, i.e., a reduction or no reduction in BP with a reduction in sodium intake. An inverse BP change, i.e., an increase in BP with a decrease in sodium intake, has also been noted in human beings [9, 10]. The three kinds of BP variation in relation to the manipulation of salt intake are here reconsidered on a personalized basis, using inferential statistical tools for the assessment of BP excess with respect to time-specified reference standards [11, 12], rather than by relying on one, two or a few time-unspecified measurements [5, 13-15]. Results from 2 studies, reviewed against the background of prior publications, are reported below. For each, informed consent was obtained after the nature of the study protocol had been fully explained.

Study A: manipulation of sodium intake in Minnesota

With chronobiologic methods, this study, briefly described in a conference proceedings [16], was carried out on individuals diagnosed on the basis of conventional time-unspecified BP measurements as having borderline hypertension. In this study, 13 adult, otherwise apparently clinically healthy men 40 to 60 years of age had casual SBP (in mm Hg) between 125 and 160 and DBP (in mm Hg) between 80 and 95 or $140 \leq SBP \leq 160$ and $DBP < 80$, or $SBP < 125$ and $90 \leq DBP \leq 95$. Their BP was monitored automatically at about 10-min intervals for 24 h at the end of each of three stages, each lasting 2 months. During stage I, aimed at obtaining a reference for the circadian BP rhythm, the subjects followed their regular way of living. During stage II, the subjects were asked to reduce their sodium intake as compared to Stage I by at least 30 mEq Na/day on the average, without reducing caloric intake. In stage III, they were asked to maintain the low Na intake of Stage II and to restrict their caloric intake to induce at least a 2-kg body weight loss.

Study B: manipulation of sodium intake in Maryland

Another investigation, study B, was carried out at the National Institutes of Health in Bethesda, MD, USA, where one of us (FH) had served as a

consultant. Data from this study, published by the original investigators ([8]; cfr. also [10]), are here analyzed with newer methodology, as a complement to study A and other work discussed in a companion paper [17]. Study B was carried out on patients with «idiopathic hypertension» in whom known causes of BP elevation had been ruled out.

In study B, 16 patients were examined, again in 3 stages: I, a moderately reduced (intermediate)-sodium diet; II, a very low-sodium diet; and III, a high sodium diet. More specifically, the basic diet taken by the patients contained 9 mEq of sodium and 70 mEq of potassium per day. Patients were studied for one week on this diet with 100 mEq of sodium chloride added each day (intermediate or moderately reduced sodium diet), then for one week on this diet alone (very low sodium diet) and finally for one week on this diet with 240 mEq of sodium chloride added each day (high sodium diet). The diet consisting of 109 mEq of sodium/day is referred to as intermediate or moderately reduced sodium diet, as compared to the subjects' usual sodium intake, since 11 of the 16 subjects who had self-measured BP for an entire week showed a progressive decrease in their SBP and DBP MESOR on this diet (discussed further below). For the last 2 days on each diet, BP was measured automatically every 30 min.

Circadian rhythm characteristics of subjects investigated

Not all of the subjects participating in these studies actually had an elevated BP; some of them were MESOR-normotensive (they were originally selected on the basis of casual BP measurements). In study A, 7 of the 12 men contributing data during the reference stage («usual» sodium intake) had circadian MESORs of both SBP and DBP inside the corresponding reference intervals for a clinically healthy peer group. None of them had an elevated circadian amplitude of BP. In study B, 3 of the 15 men contributing data during the first study stage had circadian MESORs of both SBP and DBP below the upper 90% prediction limits derived for a clinically healthy peer group. None had an elevated circadian BP amplitude.

Table 1. – Extent (mean, SE and median) and incidence (n of subjects) of direct or inverse change in blood pressure with sodium restriction or sodium loading (*a*)

	Prior study		Study A		Study B			
	1st to 2nd profile		Usual to low Na		Intermediate to very low Na		Very low to high Na	
Change (*b*)	"Direct"	"Inverse"	Direct	Inverse	Direct	Inverse	Direct	Inverse
SBP								
Mean	− 7.5	+ 6.6⁺	− 7.8	+ 6.6⁺	− 15.6	+ 2.7*	+ 15.8	− 4.3
SE	1.3	2.1	2.7	1.6	3.4	1.4	3.2	<.1
n	25	15	5	7	12	3	14	2
Median	− 4.7	+ 4.9	− 5.7	+ 7.3	− 10.5	+ 3.2	+ 13.4	− 4.3
DBP								
Mean	− 6.1	+ 3.9	− 5.6	+ 4.9⁺	− 8.5	+ 1.3**	+ 5.9	− 3.3
SE	1.1	0.9	1.7	2.1	1.8	0.3	1.6	0.9
n	21	19	7	5	11	4	11	5
Median	− 5.4	+ 2.4	− 6.3	+ 3.7	− 8.4	+ 1.4	+ 5.4	− 2.5

(*a*) These group statistics introduce the following individualized assessment:
Direct change: BP decrease with reduced sodium intake and/or increase with sodium loading;
Inverse change: BP increase with reduced sodium intake and/or decrease with sodium loading: change here classified as direct or inverse irrespective of statistical significance of BP change.
SBP = systolic blood pressure; BDP = diastolic blood pressure.

Prior study [12, 17]: 40 presumably clinically healthy men, providing two 24-h BP profiles about 1 month apart, in the absence of any voluntary dietary manipulation; «direct» and «inverse» change here refer to a decrease or increase in BP MESOR in second as compared to first profile.

Study A [16]: 13 men with BP originally believed to be elevated; 3 stages, each lasting 2 months; usual Na diet, reduced-sodium diet targetted to reduce salt by at least 30 mEq Na/day, and reduced calorie diet (effect not tabulated herein; see text).

Study B [8]: 16 men with BP originally believed to be elevated; 3 stages, each lasting one week: intermediate (109 mEq Na/day), very low (9 mEq Na/day), and high (249 mEq Na/day) sodium diet (with 70 mEq K/day on each study stage).

(*b*) n = number of changes of a given kind; SE = standard error. Mean, SE and Median expressed in mm Hg.

(*) $p < .10$; (**) $p < .05$; (⁺) $p > .95$ for comparison of extent (absolute change) of inverse *vs* corresponding direct changes (Student's t-test).

Individually assessed change in sodium intake and BP

Data averaged over consecutive 1.7-h spans (1.7-h is a prominent ultradian period; Study A; [16] or 1-h spans (study B; [8] were tested for the equality of MESOR between consecutive study stages. (The difference in averaging span is not likely to influence the results presented here). Indices of BP excess, computed on the basis of the original data, were also compared in consecutive study stages.

MESOR tests

The incidence and extent of direct and inverse change in BP are nearly comparable, Table 1. As in the absence of dietary change [12, 17], BP can decrease, not change or increase with statistical significance following sodium restriction in Study A [16], Table 2a. The last stage of Study A, involving caloric restriction for two months is characterized primarily by a decrease of SBP and DBP, Table 2a.

Three different kinds of BP change with modifications in salt intake-direct, inverse, and no change-are again observed in Study B [8], in our analyses comparing the BP MESOR between the intermediate and the very low sodium diets and between the very low and high sodium diets, Table 3a. Although, in this study, the average extent of inverse change is smaller than the extent of direct change, Table 1, in some cases, a decrease in sodium intake is associated with a statistically significant increase in BP and an increase in sodium intake with a decrease in BP.

Sodium restriction may be more likely associated with a reduced BP in subjects who had a relatively high BP-MESOR in the reference stage. To test this possibility, and taking the contribution of a regression to the mean into consideration, the sum of the MESORs before and after sodium restriction was correlated to their difference. A negative correlation is indeed observed for both SBP ($r = -0.60$; $p < .005$) and DBP ($r = -0.55$; $p < .005$).

Tests of BP excess

In order to account for both the MESOR and circadian amplitude in assessing any BP change in relation to sodium restriction or loading, indices of blood pressure excess (hypertensive index, HTI; [17] are computed. This index represents the area (integrated over 24 h) delineated by the upper time-specified 95% prediction limit of SBP and DBP derived from data on healthy peer-groups and the BP curve of the subject when it exceeds the reference limit. Such indices, expressed in mm Hg × h, were computed for each subject in each stage of study A, as shown in Table 2a. Differences in these indices of BP excess associated with salt restriction (transition from stage I to stage II) and with calorie reduction (transition from stage II to stage III) are shown in Table 2b.

Table 2a. – MESOR and 24-h hypertensive index (HTI) of blood pressure data above peer-group chronodesmic limits (90% time-specified prediction limits) (*a*)

Stage: Subject ID (age)	MESOR (mm Hg)						HTI (mm Hg x h during 24 h)					
	SBP			DBP			SBP			DBP		
	I	II	III	I	II	III	I	II	III	I	II	III
01 (53)	143.2	129.5*↓	121.1*↓	92.3	83.4*↓	79.6	180	10	11	105	7	10
02 (49)	157.4	143.2*↓	NA	104.0	91.0*↓	NA	414	164	NA	260	74	NA
03 (55)	134.7	139.9*↑	118.6*↓	85.4	84.7	77.7*↓	NA	59	0	NA	21	2
04 (53)	141.8	136.1*↓	119.6*↓	91.4	91.5	83.8*↓	113	35	< 1	65	53	8
05 (50)	108.0	118.3*↑	110.0*↓	80.9	82.0	78.1*↓	2	< 1	1	7	8	< 1
06 (58)	122.6	122.2	121.0	84.2	77.9*↓	78.2	13	2	5	18	1	4
07 (40)	132.4	140.1*↑	119.8*↓	89.1	99.9*↑	86.7*↓	50	113	1	56	182	40
08 (42)	128.3	129.2	121.2*↓	81.3	80.3	74.4*↓	9	17	< 1	7	6	0
09 (44)	124.1	136.8*↑	117.5*↓	80.1	88.9*↑	76.9*↓	9	42	0	4	30	1
10 (50)	130.6	132.0	121.2*↓	80.4	78.0	76.8	21	64	7	< 1	2	2
11 (56)	129.9	124.8*↓	113.6*↓	86.4	79.3*↓	71.0*↓	20	9	5	60	3	< 1
12 (60)	NA	NA	NA	NA	NA	NA	44	NA	NA	12	NA	NA
13 (52)	110.2	117.5*↑	94.3*↓	69.1	72.8	63.7*↓	0	2	0	0	4	0

(*) $p < 0.05$ for a test of equality of MESOR; under II for comparison between stages I and II; under III for a comparison between stages II and III; ↑ indicates a statistically significant increase and ↓ a statistically significant decrease between the two profiles. See Table 2b for changes in HTI between consecutive study stages.

(*a*) Data from Study A [16]: I = reference stage; II = low salt intake; III = caloric reduction stage; NA = not available. Chronodesmic limits determined on the basis of data from 39 presumably healthy men, 20-60 years of age, monitored for 24 h at 7.5 min intervals on 2 occasions [12,17].

Table 2b. – Change in BP excess after salt restriction and calorie reduction (a)

Subject ID	SBP				DBP			
	HTI (II) – HTI (I)		HTI (III) – HTI (II)		HTI (II) – HTI (I)		HTI (III) – HTI (II)	
01	−170	**	+ 1	NS	−98	**	+ 3	NS
02	−250	**	NA		−186	**	NA	
03	NA		−59	NS	NA		−19	NS
04	−78	*	−35	NS	−12	NS	−45	NS
05	−2	NS	+ 1	NS	+ 1	NS	−8	NS
06	−10	NS	+ 3	NS	−16	NS	+ 2	NS
07	+ 63	*	−112	**	+127	**	−143	**
08	+ 8	NS	−17	NS	−1	NS	−6	NS
09	+ 33	NS	−42	NS	+ 26	NS	−29	NS
10	+ 43	NS	−57	+	+ 2	NS	−1	NS
11	−11	NS	−4	NS	−56	+	−3	NS
12	NA		NA		NA		NA	
13	+ 2	NS	−2	NS	+ 4	NS	−4	NS

(a) Data from Study A [16]: Differences calculated from HTI values originally obtained with 2 decimals: discrepancies between results in Table 2b and differences from values in Table 2a due to rounding.

(**) $p \leq 0.01$; (*) $p \leq 0.05$; (+) $0.05 < p < 0.10$; NS $p > 0.10$.

In study A [16], only one 24-h profile/subject/stage is available. Hence, in order to test individual responses, it is necessary to independently estimate the HTI variance. A prediction interval for the 24-h HTI is obtained by means of the average mean square from replicate estimations of this index in 2 studies, one involving 40 clinically healthy subjects on their «usual» routine of living, each providing two 24-h profiles [12], the other involving 16 subjects each providing two 24-h profiles on each of different diets (Study B, [8]). When computing the 24-h HTI with respect to time-specified peer-group limits, the 90%, 95%, and 99% prediction intervals are 51.3, 61.3, and 81.0 mm Hg × h, respectively. Changes in 24-h HTI values exceeding these limits are then considered to be statistically significant at the .10, .05 or .01 probability level, respectively.

Results again suggest that modifications in salt intake can be associated with three kinds of BP change. Moreover, the two subjects with the higher HTI at the outset are also the two subjects who have the largest decrease in HTI after reducing sodium intake. The subjects showing an inverse change (an increase in HTI) with sodium restriction are more responsive to further calorie restriction as compared to the other subjects, Table 2. This observation should be qualified by the choice of the study design wherein the calorie reduction stage always follows the sodium restriction stage. Some subjects had already lost weight ($\geq$ 2 kg) in association with only sodium restriction.

In study B [8], the 24-h HTI, on the average, is lower on the very low sodium diet and higher on the high sodium diet ($p < .01$). The HTI from 15 patients, each providing two HTI estimates on each diet, in relation to peer-group limits (upper 95% time-specified prediction limits), expressed in mm Hg × h, averages ($\pm$ SE) 259 ± 46, 87 ± 17, and 289 ± 51 for SBP and 167 ± 29, 77 ± 13, and 132 ± 21 for DBP, on the intermediate, very low and high sodium diets, respectively. (One of the 16 patients does not provide data on the intermediate sodium diet). Whereas, on the average, a very low sodium diet lowers excess pressure and a high-sodium diet raises excess pressure, individual BP changes differ widely, Tables 3 a,b. Some individuals may decrease their HTI in association with a high-sodium intake. Since BP is monitored for 48 h on each diet in study B, it is possible to obtain replicates for the HTI on each diet. Any change in HTI on sodium restriction or on sodium loading can thus be tested by Student's t-test, at least tentatively. Table 3 shows that the extent of inverse change is relatively small and only of borderline if any statistical significance. Any inverse change in BP associated with sodium restriction (it is not necessarily a response to dietary change) is more characteristic of MESOR-normotension than of MESOR-hypertension.

Rate of BP change following dietary manipulation

In study B [8], 11 of the 16 subjects self-measured their BP, mostly during waking, on the five days preceding the automatically monitored 48-h BP profile at the end of each weekly study stage. It is

Table 3a. – MESOR and hypertensive index (HTI) of blood pressure data above peer-group chronodesmic limits (90% time-specified prediction limits) (*a*)

Stage: Subject ID	MESOR (mm Hg)						HTI (mm Hg x h during 24-h)					
	SBP			DBP			SBP			DBP		
	I	II	III	I	II	III	I	II	III	I	II	III
01	169.5	134.8*↓	168.2*↑	93.8	82.7*↓	88.6*↑	690	46	681	83	6	47
02	172.4	143.9*↓	159.1*↑	109.2	97.9*↓	98.3	751	150	459	390	141	163
03	133.0	123.9*↓	137.6*↑	96.6	89.0*↓	92.2*↑	42	26	109	129	52	88
04	NA	151.6	153.7	NA	100.1	103.5	NA	284	335	NA	181	253
05	144.2	138.9*↓	146.0*↑	83.2	84.6	82.1	137	95	173	3	28	25
06	144.4	142.4	154.4*↑	96.7	94.4	99.8*↑	149	111	344	123	74	177
07	138.9	130.3*↓	141.9*↑	81.7	82.3	80.9	121	22	149	10	0	10
08	108.2	113.2*↑	126.2*↑	81.6	83.3	89.1*↑	6	0	40	2	8	79
09	136.7	125.7*↓	121.3*↓	100.9	92.0*↓	87.1*↓	89	22	1	200	84	21
10	156.1	135.0*↓	152.5*↑	109.9	96.9*↓	104.8*↑	399	72	304	396	150	286
11	129.8	121.1*↓	123.5	83.8	85.3	79.3*↓	43	10	8	16	46	16
12	148.2	148.3	143.9*↓	103.0	100.4*↓	98.5	238	238	186	243	190	172
13	154.7	118.1*↓	149.9*↑	111.7	89.3*↓	108.8*↑	364	3	263	449	54	376
14	154.5	144.0*↓	185.7*↑	99.7	95.0*↓	104.0*↑	374	154	1077	186	139	281
15	121.8	125.0	139.0*↑	85.8	84.6	88.2*↑	9	20	131	23	8	50
16	159.6	149.1*↓	155.3*↑	104.7	96.2*↓	97.3	469	240	388	289	126	135

(*) $p < 0.05$ for a test of equality of MESOR; under II for comparison between stages I and II; under III for a comparison between stages II and III; ↑ indicates a statistically significant increase and ↓ a statistically significant decrease between the two profiles. See Table 3b for changes in HTI between consecutive study stages.

(*a*) Data from Study B [8]: I = moderately reduced sodium intake (109 mEq Na/day); II = low sodium intake (9 mEq Na/day); III = high sodium intake (249 mEq Na/day); NA = not available. Chronodesmic limits determined on the basis of data from 39 presumably healthy men, 20-60 years of age, monitored for 24 h at 7.5 min intervals on 2 occasions [12, 17].

Table 3b. – Change in BP excess after sodium reduction and loading (*a*)

Subject ID	SBP				DBP			
	HTI (II) – HTI (I)		HTI (III) – HTI (II)		HTI (II) – HTI (I)		HTI (III) – HTI (II)	
01	−644	**	636	*	−77	*	41	NS
02	−601	**	309	*	−249	*	22	NS
03	−17	NS	83	*	−77	NS	36	NS
04	NA		51	NS	NA		72	NS
05	−42	NS	78	NS	+ 25	NS	−3	NS
06	−39	NS	233	**	−49	NS	104	NS
07	−100	+	127	*	−9	*	9	NS
08	−6	NS	40	NS	+ 6	NS	72	*
09	−67	NS	−21	NS	−117	NS	−63	+
10	−327	*	232	*	−247	*	137	+
11	−33	NS	−1	NS	+ 30	NS	−30	NS
12	+ 1	NS	−52	NS	−53	NS	−17	NS
13	−362	*	260	*	−395	**	321	**
14	−221	NS	924	**	−47	NS	142	NS
15	+ 11	NS	111	*	−15	NS	42	NS
16	−229	NS	148	NS	−163	NS	9	NS

(*a*) Data from Study B [8]: Differences calculated from HTI values originally obtained with 2 decimals: discrepancies between results in Table 3b and differences from values in Table 3a due to rounding.

(**) $p \leq 0.01$; (*) $p \leq 0.05$; (+) $0.05 < p < 0.10$; NS $p > 0.10$ (from Student's t-test).

thus possible to determine how fast these subjects change their BP following a change in sodium intake, information that could assist in the cost-effective future planning of the duration of stages differing in terms of sodium intake. Any bias from self-measurements of BP by subjects expecting changes in BP following dietary manipulation is not apparent in the light of complementary data from 48-h automatic monitoring at the end of each study stage.

On a group basis, the MESOR for SBP and DBP decreases linearly with time ($p < .01$) under sodium restriction, while it increases with time ($p < .05$) under sodium loading. Student's t-tests applied daily for testing departure of the BP-MESOR from the initial MESOR (equated to 100% at the start of each study stage for each subject) indicate that the BP change is gradual rather than immediate: statistical significance is achieved only after 5 to 6 days of sodium restriction; under sodium loading, BP changes statistically significantly after 4 days for SBP but not (yet) after 7 days for DBP; this result may be accounted for in part by an initial decrease in DBP MESOR on day 2, followed by a steady increase starting on day 3, Fig. 1.

A decrease in BP-MESOR during the first study stage is also apparent for SBP ($r = .41$; $p < .01$) but not for DBP ($r = -.19$; $p > .10$). Student's t-tests on data from consecutive days show a statistically significant decrease of BP-MESOR after 5 days for both SBP and DBP. Most subjects' usual diet probably contained more than 109 mEq/day. In this context, the assumption that some persons may decrease their BP upon hospitalization is not critical since BP (monitored automatically around the clock) during a week of hospitalization may increase, decrease, or remain unaltered, just as it does at home [18]. A better controlled study in the hospital need not precede but may follow a less-standardized study at home, which would be more realistic and closer to ordinary, everyday conditions.

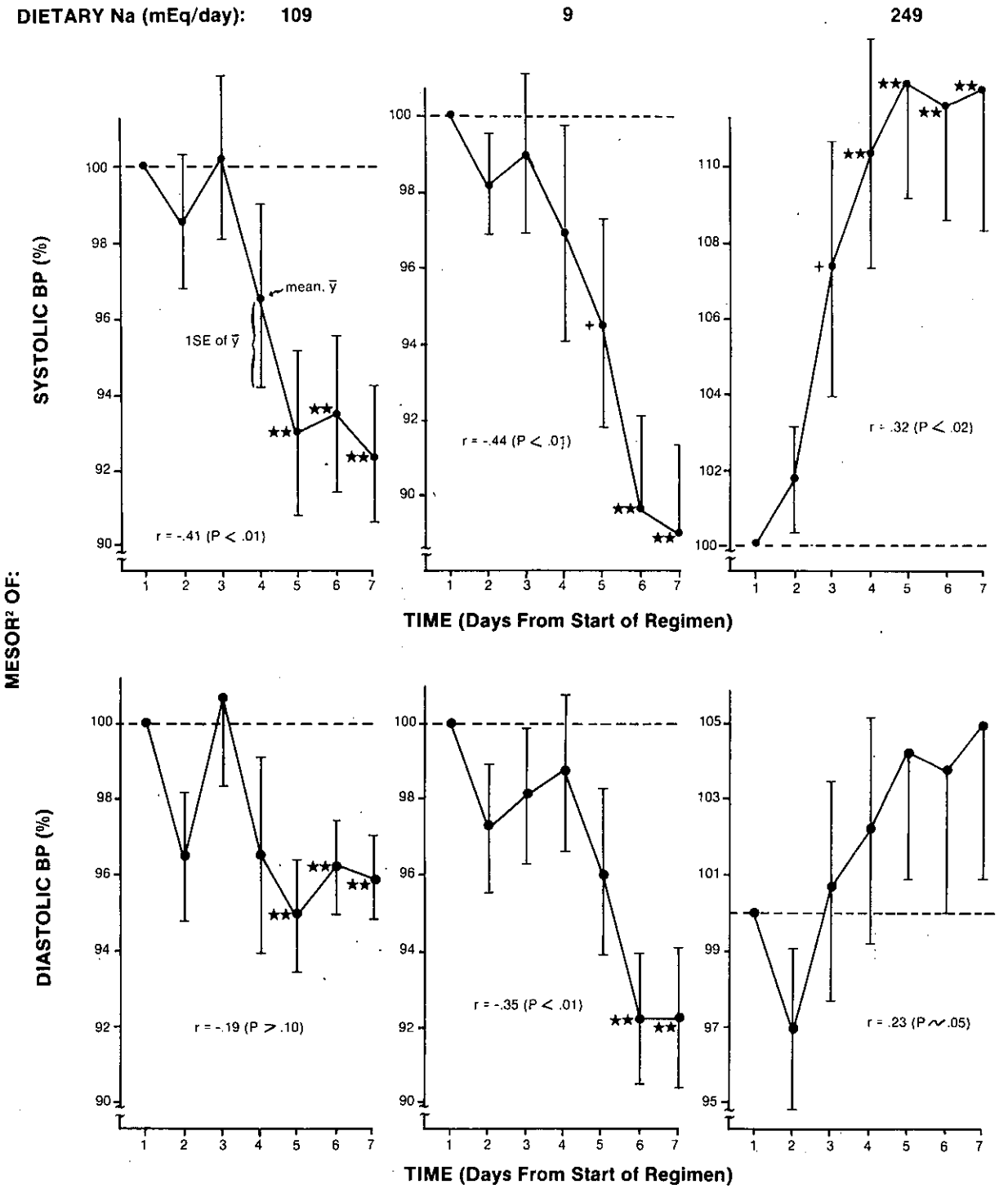
Other hints of 3 kinds of BP change after modification of sodium intake

That certain individuals increase their BP after a moderate restriction of dietary sodium content or supplementation of potassium intake is also reported (without rhythmometry or assessment of the statistical significance of changes in the individual) on the basis of 12 patients with mild essential hypertension studied on three different diets (a control, a sodium-restricted, and a potassium-supplemented diet), each taken for at least 4 weeks [19]. The sequence of regimens is randomized. Under standardized conditions, at the end of each regimen, intra-arterial pressure is recorded continuously and vasoactive hormones are measured hourly for 24 h. Following sodium restriction, mean DBP decreases in 7 patients and increases in 5 patients. In data taken off the published graphs, the decrease ranges from 2 to 20 mm Hg (mean $\pm$ SE: 9.4 ± 2.7 mm Hg) and the increase from 4 to 9 mm Hg (mean $\pm$ SE: 5.9 ± 0.9 mm Hg). In association with potassium supplementation, the mean DBP decreases in 6 patients (6.7 ± 1.6 mm Hg) and increases in 6 other patients (4.3 ± 1.6 mm Hg). The authors note a correlation of individual differences in mean DBP between the control and sodium-restricted diets with concomitant differences in plasma renin activity, concluding that the pressure-reducing effects of sodium restriction may possibly be limited if not overcome by stimulation of renin release.

Dietary effects *vs* day-to-day variability?

Three kinds of BP change are also observed in healthy subjects in the absence of dietary manipulation [12, 17]. This finding prompts the question as to whether changes in BP following a modification of the dietary sodium intake reflect the effect of a change in sodium intake *per se* or merely the day-to-day or infradian variation (rhythms with a frequency lower than circadian) of BP [18, 20]. To answer this question, several additional tests are applied. In the absence of randomized concomitant controls and of the use of a placebo in Studies A and B, reliance can only be placed here on a data base derived from clinically healthy men who monitored their BP automatically for 24 h on two occasions [12, 17].

A first examination reveals that in subjects of Study B [8], as compared to healthy men, an inverse change in MESOR occurs less often ($p < 0.05$ by χ^2 test) and is of lesser extent ($p < 0.05$ by Student's t-test), while the extent of direct change is more pronounced after modification of sodium intake ($p < 0.05$). A larger incidence of no BP change gauged by the HTI is also observed for clinically healthy subjects as compared to subjects investigated in either Study A or Study B ($p < .05$). (It may be noted that even the subjects found to be normotensive in Study A by around-the-clock monitoring *may*, but need not, have some reactive characteristics that prompted their selection in the first place and that may or may not render them different from the population at large). Moreover, the effect of a modification in sodium intake, as gauged by linear regression for those subjects who self-measured their BP during the whole week in each stage, is in good agreement with results from the MESOR test and the HTI comparison. An inverse change in DBP associated with sodium loading is validated with statistical significance by all 3 approaches (MESOR test, HTI comparison and linear regression) for one of the 11 subjects who carried out self-measurements in Study B. Moreover, the analysis by linear regression, an approach considering BP data over a



1) Data from 11 subjects in study B: r and P from linear regression: ★★ P < .01; ★ P < .05; + P < .10 from Student t-test (in testing equality of mean mesor to 100%, with mesor at start of study regimen equated to 100%).

2) 24-h rhythm-adjusted mean (MESOR) expressed relative to mesor of day 1 in each stage of study.

Fig. 1. – Change in BP-MESOR in each of three stages, each lasting one week (Study B; [8]). Results from 11 subjects who self-measured their BP before the 48-h profile monitored automatically; BP values expressed as a percentage of the MESOR of the first day in each stage.

longer span, suggests an inverse DBP change for another of the 11 subjects, while the 2 other approaches suggest no BP change.

A correlation between the sum and the difference of the MESORs in the reference stage and following sodium restriction is statistically significant ($p < 0.05$) in subjects with actual or suspected high BP, whereas it is not statistically significant ($p > .10$) between two 24-h profiles, less than or about 1 month apart, in clinically normotensive men. This result supports the increase in extent of direct change in BP following manipulation of sodium intake. The larger incidence and extent of BP change, observed after manipulation of sodium intake, as compared to the expected day-to-day variation, indicates the need to rely on more than one approach - on the HTI, if not on a linear regression, rather than only the MESOR - to establish any change in BP of a given patient following a change, e.g., in non-drug or drug treatment. Moreover, in view of the importance of a clinical decision which should minimize false positives and false negatives, a 24-h profile should be replaced by at least a 48-h or preferably a 1-week or longer profile, to avoid too large an instability of the MESOR (or other) estimate. Long-term profiles can rely in part on self-measurements. Alternatively, automatic 48-h profiles may be repeated on several occasions. Sampling of BP on more than one day, as recommended by Rosner [21] and Rosner and Polk [22], should be complemented by the assessment of circadian BP variability as a minimum.

In view of the day-to-day variation in BP, it also seems highly desirable, if not mandatory, to use a placebo for diagnostic purposes in everyday practice. The lack of a placebo in the studies here reported prompted the extensive work with a reference data base. Inferences drawn in relation to such a data base hold for the population, but are only a complement and not a substitute for the placebo-drug comparison. The latter is needed whenever intervention is considered for a given individual concerning treatment that may be taken for a lifetime.

Discussion

Laragh *et al.* [14, 23] consider, without chronobiologic considerations, that hypertensives with low concentrations of circulating renin are most likely to show BP elevation when adding salt to their diet, while high-renin hypertensives do not respond to salt. Plasma renin, however, is a circadian rhythmic function [24, 25]; reference to both BP and renin is best made chronobiologically. With this reservation, one also confronts a report that hypertensives with a low renin concentration, having abnormally low concentrations of calcium in their blood, are likely to be helped by calcium supplements [14, 23]. Chronobiologic methods are needed to clarify whether people with mild hypertension, as diagnosed on the basis of their BP-MESOR, also exhibit a low renin-MESOR and whether this circumstance contributes to a reportedly lesser consumption of calcium, among other nutritional factors, in hypertensives as compared to normotensives [5].

Gordon *et al.* [24], apart from first demonstrating the circadian bioperiodicity of plasma renin activity, also note an increase in the concentration of this variable as a result of sodium deprivation. In an international comparative study of clinically healthy women, the MESOR of plasma renin activity, determined every 4 h for 24 h, is higher in Kyushu, Japan, than in Minnesota, USA [25]. Epidemiologic studies associate a higher incidence of hypertension in countries such as Japan with larger salt consumption. The incidence of a high BP-MESOR may also be related, at least in part, to a lower plasma renin activity MESOR, which would render the individuals highly sensitive to salt intake. A progressive stimulation of the renin-angiotensin system is reportedly a potential limiting factor to the anti-hypertensive action of diuretics [26]; if so, the anti-hypertensive effect of dietary salt restriction may be similarly limited.

Weinberger [27] also reported increases in BP following sodium restriction and postulates that genetically-mediated differences in the renin-angiotensin-aldosterone system may play a major role in the heterogeneity of physiologic responses-sensitivity or resistance-to sodium. For instance, Weinberger found that black subjects (reportedly at a higher risk of developing high blood pressure) excrete sodium less efficiently than whites of the same age and that plasma renin activity was significantly lower in black subjects than in white subjects, even after volume depletion. From these findings and results on twins, Weinberger anticipated but did not find an inverse correlation between BP and plasma renin activity and plasma aldosterone. The opposite relation was observed. Normotensive first-degree relatives of patients with documented essential hypertension were also found to have higher BP and plasma renin activity in the reference stage than did race-, age- and sex-matched controls with no family history of hypertension. Moreover, they were also found to have a diminished ability to excrete a sodium load. Progressive increases in sodium intake revealed that changes in BP were mirrored by decreases in the activity of the renin-angiotensin-aldosterone system and circulating catecholamines, and associated with a marked increase in glomerular filtration rate and cardiac output. But not all subjects showed an increase in BP, suggesting the presence of a compensatory mechanism (possibly involving potassium), enabling them to oppose the rise in BP with volume expansion. On the basis of these observations, Weinberger concludes that sodium restriction cannot be considered a universal treatment or prophylaxis for hypertension, since in sodium-resistant individuals, such dietary manipulation may actually increase BP.

Kawasaki *et al.* [28] also report that approximately 20% of 89 patients with essential hypertension showed increments in BP on a low salt diet and/or a decrement on a high salt diet. These authors further note that plasma renin activity had a tendency to be higher among these patients, and that none of them was treated with diuretics alone, results that seem to corroborate Laragh's vasoconstriction-volume hypothesis [29]. Similar results have been reported by Longworth *et al.* [30]. In untreated patients with essential hypertension, daily sodium intake was reduced for 10 days from 197 to 70 mEq/day in 82 outpatients and from 124 to 14 mEq/day in 25 inpatients. A decrease in BP of 10 mm Hg or more was observed in only 14 outpatients and in 10 inpatients, mostly classified as having low-renin hypertension. An increase in BP of at least 5 mm Hg was observed in as many as 14 outpatients and in 7 inpatients. Such increases were found to be most common in the group with high-renin hypertension. All these studies suggest that dietary salt deprivation may not be effective for all patients with an elevated BP, and that it may even be counterproductive in some.

Precursors of coronary artery and primary hipertensive diseases were investigated in childhood and contrasted in blacks *vs.* whites [31]. Reportedly, black children had a lower urinary K^+ excretion and demonstrated natriuresis when K^+ was administered orally. A special issue of the American Heart Journal focusing on coronary heart disease in black populations [32] pays relatively little attention to differences in nutrition, and in particular to differences between the two populations in the dietary intake of Na^+ and K^+ . The MRFIT study reported that in a reference stage, blacks had higher mean BP values and a higher prevalence of high BP than whites, were more often smokers but smoked fewer cigarettes per day, and had a higher prevalence of ECG abnormalities. Dietary lipid composition was reportedly similar for black and white men, as were weight and body mass index, plasma total cholesterol and low-density lipoprotein cholesterol concentrations, whereas high-density lipoprotein cholesterol was reportedly higher and triglyceride concentrations lower for blacks than whites [33]. A needed chronobiologic approach to ethnic aspects of BP is overdue.

Another question awaiting clinical investigation is the human circadian stage-dependence of any BP change with salt loading. This line of study provides clues to underlying mechanisms. BP elevation develops more readily in rats ingesting salt loads while at rest (9/10) than in those ingesting salt during their active circadian stage (6/10) [34]. There are many other chronobiologic aspects to any approach involving BP [35, 36]. Further studies on dietary or drug manipulation for reducing BP may benefit from the tools presented elsewhere [35, 36] and herein, notably in relation to the personalized assessment of BP excess, expressed in mm Hg × h rather than in mm Hg and evaluated against chronobiologic limits established for healthy individuals rather than based on limits from mortality statistics by insurance companies. Software and hardware are available today to exploit circadian BP variation for personalized preventive screening, as well as for diagnosis and treatment. In health, we may well pass the salt shaker at certain times without doing any harm, while we may do harm in inviting everybody to pass on the salt [36]. Lifetime studies on this matter are now warranted to track the extent of reproducibility of a change in BP associated with a change in sodium intake in health as well as in individuals developing MESOR-hypertension. Such studies and any other approach to human BP may exploit not only modern instrumentation, but also chronobiologic concepts and methods, thereby also extending critical data bases for the establishment of reference ranges for single values and rhythm parameters. Questions as to whether other computerized analyses [37] also provide clinically useful information require further study.

The cumulative effect of a high BP represents one of the main factors underlying incapacitating diseases of our civilization; the prevention of the associated suffering and expense is perhaps the major health problem of our age. Nursing care after a stroke or heart attack is rather costly, as is a coronary bypass operation or a transplant; dialysis amounts to a substantial cost each year. By using a rhythm-assessing approach, we may, for an individual at a given time, clarify not only whether or not to pass the salt shaker or to pass *on* it, but more generally we may decide whom to treat, when and how. Although automatic instrumentation is still expensive, it is useful and convenient as well as cost-effective when it provides a data base from which minimal sampling requirements can be derived to guide recommendations for self-measurements [9, 12].

Conclusions

Whether self-measured or automatically measured, whether interpreted by the chronobiologically literate lay person or physician, the chronobiology of BP involves statistical considerations, including a P-value, heretofore used mostly for group comparisons. The important P-values advocated herein in a medical context help tell the likelihood that a given increase or decrease in BP-MESOR, occurring spontaneously or induced, e.g., by manipulating dietary sodium intake, is a matter of chance and, if not, whether it is a concern in health care. The P-values *help* consider whether a given drug or non-drug treatment such as a modification of dietary sodium intake has an effect upon the BP-MESOR of a given individual at a given time.

Addendum

The importance of assessing, on an individual basis, BP responses to changes in sodium intake is reflected by the fact that a comparison of two populations with differing salt consumption may not show any difference in BP [38]. The fact that factors other than sodium intake need to be considered is illustrated by a recent study of a Nepalese population characterized by a low BP despite its high salt consumption [39]. Among these factors, social ones are suggested by a comparison of BP variation in apparently healthy subjects living in a rural *vs* a metropolitan area: not only was the BP MESOR higher, but the circadian amplitude was also larger in the subjects living in the metropolitan area than in those residing in a rural area [40].

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