Salt Sensitivity in Essential Hypertension as Determined by the Cosinor Method

CHARLES C. BITTLE, JR., DAVID J. MOLINA, AND FREDERIC C. BARTTER

SUMMARY A method of data reduction for the statistical examination of mean arterial pressure in essential hypertensive subjects to determine salt sensitivity was examined. A computerized method was used to estimate the best-fitting cosine curve for data collected every 30 minutes for 24 hours. The effect of sodium loading on the cosinor parameters (mesor, amplitude, and acrophase) in 45 subjects with essential hypertension and five normotensive control subjects was assessed. Twenty-five percent of the essential hypertensive subjects in the study were found to be salt-sensitive with a statistically significant increase in their mesors with sodium loading (p < 0.05). The non-salt-sensitive group was found to contain a subpopulation with a statistically significant decrease in their mesor with sodium loading (p < 0.05). Sodium loading appears to affect the lability of mean arterial pressure independently of mesor changes. (Hypertension 7: 989-994, 1985)

KEY WORDS • cosinor • blood pressure • hypertension • salt sensitivity • circadian

ALTHOUGH 20% of the American population is said to be hypertensive, there is no well-accepted definition for this condition. A scientific analysis of the hypertensive state and the parameters involved in hypertension is at the onset plagued by the inadequacy of its definition. "Whereas it is generally believed that a blood pressure measurement above 140 mm Hg systolic and 90 mm Hg diastolic is necessary for diagnosis in adults, there is no consensus whatsoever as to how long each day the systolic and diastolic pressures must be above these conventional limits to constitute the criteria for the label 'hypertension.'" Virtually all normotensive subjects will have arterial blood pressures above these conventional limits on occasion, and virtually all subjects with fixed hypertension will have pressures below these values during a 24-hour span.

It is firmly established that blood pressure is a rhythmic function.2-8 Within the course of 1 day, there may be a range of 30 mm Hg systolic and 20 mm Hg diastolic. There have been only a few papers in the literature in which the blood pressure was recorded throughout a 24-hour span.1, 2, 6, 9, 10 Many investigators may have measured blood pressure frequently throughout the day, but the data may not have been reported because of inefficient methods of data reduction.

In this article we offer a method capable of reducing a large body of data to a few numbers that can be examined statistically. A computerized method, adapted from Cornelissen et al.,11 is used to construct a cosine curve from data collected every 30 minutes for 24 hours. The resulting parameters — mesor, amplitude, and acrophase — are compared in patients with essential hypertension to determine their sensitivity to sodium loading.

Subjects and Methods

Fifty subjects (45 men and 5 women) with idiopathic hypertension, defined by obtaining three diastolic blood pressures over 90 mm Hg in the clinic, were admitted to the Clinical Research Units of the Clinical Center, National Institutes of Health, Bethesda, Maryland, and the Audie L. Murphy Memorial Veterans' Hospital, San Antonio, Texas, for diagnostic workup and study. Their ages ranged from 35 to 65 years. Casual (morning) clinic blood pressure ranged from 150 to 180 mm Hg systolic and 90 to 120 mm Hg diastolic. Patients with secondary causes of hypertension and extensive end-organ damage were excluded on the basis of a complete history, a physical examination, a urinalysis, plasma potassium and creatinine levels, plasma renin activity, and plasma aldosterone, cortisol, and norepinephrine concentrations.
Five patients who initially were seen with elevated blood pressure in the clinic had blood pressures in the normal range when hospitalized. These subjects were studied using the same protocol as for the hypertensive patients but were considered normotensive for the study. All subjects gave informed consent.

The protocol was approved by Institutional Review Boards of the National Heart, Lung, and Blood Institute and of the University of Texas Health Science Center at San Antonio and by the Research and Development Committee of the Audie L. Murphy Memorial Veterans’ Hospital.

All subjects had discontinued antihypertensive medications at least 1 week before admission and received no medications during the course of the study. They were in the hospital at least 7 days before the study began, during which time they were adjusting to their diets. All subjects maintained a constant activity pattern and adhered to a constant metabolic diet containing 9 mEq of sodium per day and 50 to 70 mEq of potassium per day. Patients were studied for 7 days on the low sodium diet (9 mEq) followed by 7 days on the high sodium diet (249 mEq in Bethesda, 309 in San Antonio; the average daily intake of sodium for that geographic location). The high sodium diet was accomplished by adding 240 or 300 mEq of sodium chloride, given as 10 mEq tablets, to the basic 9 mEq sodium diet. On the first day of the low sodium diet, furosemide (40 mg 3 times a day) was given orally.

Body weight was measured each morning after the patient had voided. Blood pressure, pulse, and temperature were measured every 4 hours after the patient had been supine for 5 minutes or longer. On the last day of the low and high sodium diets, blood pressure was measured every 30 minutes with the automatic Arteriosonde (Model II, Roche Labs, Nutley, NJ, USA) with the patient in the supine position. These 48 measurements were used to fit a cosine curve. Patients whose average mean blood pressure (calculated as diastolic pressure plus one-third of pulse pressure) on Day 7 of the high salt regimen exceeded that on the low salt regimen by 10% or more were considered salt-sensitive; those whose average mean blood pressure did not increase by approximately 10% or fell were considered non-salt-sensitive.

The cosine function is as follows \[ f(t) = M + A \cos(\omega t + \phi) + e(t), \] where \( M, \beta, \) and \( \gamma \) are estimated by the linear least-squares method from which \( A \) and \( \phi \) can be derived. (An outline of the method and computer programs may be obtained by writing to the first author [C.C.B., Jr.].)

### Results

The effect of acclimatization in a subject with essential hypertension is expressed in Figure 1, where the cosinor parameters for 17 days of hospitalization have been obtained by two different methods. In Figure 1, one can see a rise in amplitude in the first 5 days of hospitalization with cosinor parameters computed separately for each day.

Each patient in this study had cosinor parameters estimated while receiving a low salt diet and a high salt diet. These parameters were compared to examine the pharmacological effect of sodium chloride in the diet on the mean arterial pressure of patients with essential hypertension. The mean arterial pressures and cosinor parameters for a representative salt-sensitive patient are illustrated in Figure 2 and for a non-salt-sensitive patient in Figure 3.

![Figure 1. The daily amplitude and mesor of blood pressure plotted for 17 days in a 52-year-old man.](image1)

![Figure 2. Mean arterial pressure (MAP) plotted every 30 minutes while the patient was receiving a low sodium intake and a high sodium intake for 24 hours. The cosine curve plotted with the cosinor parameters for each intake is superimposed on the data. The subject had salt-sensitive hypertension.](image2)
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In Figure 2, the subject's mean arterial pressure for each time of day is plotted. The cosinor curve has been constructed for each set of data (high sodium and low sodium) by plotting the mesors, amplitudes, and acrophases. Since this subject had salt-sensitive hypertension, the mesor on the high sodium diet was higher than that on the low sodium diet. The amplitudes and acrophases for both curves were similar.

In Figure 3, the subject's mean arterial pressure for each time of day is plotted and the cosinor curves are constructed. It is evident from the close association of the mesors that this subject had non-salt-sensitive hypertension. In this patient, the amplitudes of the two curves were not of the same magnitude and the acrophases were out of synchrony.

The cosinor parameters for the subjects in this study are listed in Table 1 (see p. 992). The first 13 patients were considered salt-sensitive because they met the criterion of having a rise of approximately 10% or more in the relative change of their mesor. Although the division of salt sensitivity from non-salt sensitivity was arbitrarily decided on at a 10% relative change in mesor, Kawasaki et al.9 found that those who had a rise of approximately 10% or more in their mean arterial pressure also showed a greater retention of urinary sodium, which lasted for 5 days, while the group whose blood pressure rose less than 10% retained less sodium, which had escaped by Day 3. This division was later confirmed when Fujita et al.10 found, in a separate group of patients, the same rise in blood pressure, the same pattern of sodium retention, and in addition, a rise in cardiac output in the salt-sensitive group.

The remaining 32 subjects (Patients 14–45) were considered non-salt-sensitive. The non-salt-sensitive group was subdivided into those subjects (Patients 14–35) with an elevation of their mesors (but less than approximately 10%) in changing from a low to a high sodium diet (type I) and those subjects (Patients 36–45) with a depression of their mesors in changing from a low to a high sodium diet (type II). With this method of grouping the study population of 45 hypertensive subjects into salt-sensitive, non-salt-sensitive type I, and non-salt-sensitive type II, approximately 25% had salt-sensitive hypertension, 50% had non-salt-sensitive type I hypertension, and 25% had non-salt-sensitive type II hypertension (Figure 4). For the normotensive subjects studied, one was salt-sensitive, three were non-salt-sensitive type I, and one was non-salt-sensitive type II.

The mesor and amplitude-acrophase tests of Nelson et al.12 provide a means for testing significant change of the cosine parameters of each subject. Figures 4 and 5 show the results of these tests. The relative change of mesor with sodium loading for the study population is diagrammed in Figure 4. The mesor test was performed on each hypertensive subject, and 39 of the 45 had a significant change in mesor with sodium loading.

In Figure 4, the response of mean arterial pressure to sodium loading in 45 subjects with essential hypertension. The data are plotted as percent change of mesor, the difference of the low sodium from high sodium diet mesors divided by the low sodium diet mesor multiplied by 100%. At the right are those subjects with a significant change in mesor determined by the mesor test.

Figure 5. Amplitude changes with sodium loading for 45 subjects with essential hypertension are plotted as the change (in mm Hg) from low sodium to high sodium diets. At the right are those subjects with a significant change by the amplitude-acrophase test.
at the 90% confidence level ($p < 0.10$). The 11 hypertensive subjects with no significant change in mesor were all in the non-salt-sensitive groups. The amplitude-acrophase test was performed (Figure 5), and only 18 of the 45 hypertensive subjects showed a significant change in this test at the 90% confidence level ($p < 0.10$); those with no significant change in amplitude-acrophase were evenly distributed across the groups.

Discussion

With any major change in a person's external environment, one can be reasonably confident that a physiological adjustment of the internal environment will ensue. This physiological adjustment has been called acclimatization\textsuperscript{15} and has been recognized as a major variable in the experimental design of a protocol that involves removing subjects from their natural environment for investigation. This effect has also been noted by Weber et al.,\textsuperscript{16} who found a greater correlation of the second and third whole day blood pressure pattern in six patients with essential hypertension. The effect of acclimatization, as illustrated in Figure 1, is shown by a rise in daily amplitude during the first 5 days of hospitalization and a stabilization thereafter. Amplitude changes appear to be a more sensitive indicator of changes in the external environment and may reflect the sensitive, but transient, effects of the sympathetic nervous system to changes of the external environment.

The anecdotal clinical observation that blood pressure will fall with bed rest in a hospital setting has been discussed in the treatment of essential hypertension for many years. The so-called hospital effect is also illustrated by the mesor, appears to be an index...
of the internal changes seen with an environmental change and appears to be independent of the rapid fluctuations seen with acclimatization.

There is controversy in the literature concerning the effect of physical activity on mean arterial pressure. Rowlands et al.\textsuperscript{15} have stated that the circadian variations in blood pressures can be explained chiefly by the fluctuations of the intensity of a person’s physical actions during the day. Raferty et al.\textsuperscript{17} and Reinberg et al.\textsuperscript{18} have stated that an intrinsic circadian rhythm exists in hypertension, which is independent of any effect that physical activity may have, and that physical activity plays no role in the circadian variation of arterial pressures. This issue was not addressed in the design of this study’s protocol; however, we did acknowledge the fact that physical activity may be a confounding variable, which must be controlled, and thus restricted our subjects to bed rest with bathroom privileges during the days of data collection.

The mean arterial pressure was computed from each of the diastolic and systolic pressures. The mean arterial pressure is the integration of the systolic and diastolic pressures over time for each ventricular contraction-relaxation cycle and may be calculated as one-third the pulse pressure added to the diastolic pressure. The cosinor parameters represent the plot of a subject’s mean arterial pressure.

### Table 1 (continued)

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<th>Patient no.</th>
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<th>Normotensive</th>
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The calculations are based on the supposition that one may fit a cosine function to the data, which may show a statistically significant better fit than a zero-amplitude cosine curve, the straight horizontal line, at a desired level of confidence. Rejection of a nonzero amplitude may dictate the use of other methods of analysis such as analysis of variance. This does not imply that the true physiological phenomenon follows a cosine curve, as is frequently assumed.\textsuperscript{1} A zero-slope mesor...
was presupposed in this study based on the daily measurements of arterial pressures taken every 6 hours before the day in which data were collected every 30 minutes. In a long-term study of multicyle data one cannot assume a zero slope as one may in a 24-hour study. In the comparison of chronobiological data among subjects, methods have been used that assume acrophase synchronism, such as averaging of arterial pressures of many subjects at timed intervals before analysis. Acrophase synchronism between subjects has not been found to occur in this study, since acrophases occurred at any time of the day (see Table 1). There was, however, a cluster in the distribution of acrophases between −1500 and −2100 hours.

One aim of this study was to examine the effects of sodium chloride on subjects with essential hypertension so that one may separate the salt-sensitive hypertensive subjects from the non-salt-sensitive hypertensive subjects to facilitate an appropriate treatment of their hypertension with salt-restricted diets.19, 20 The results of the mesor test provide quantitative statistical evidence of the existence of two types of subjects in relation to their response to sodium chloride: the salt-sensitive, who had a significant increase in mesor greater than 10%, and the non-salt-sensitive types I and II, who had a less than 10% increase or significant decrease in mesor, respectively. Of considerable interest are the six subjects who had a significant decrease in mesor with sodium loading (p < 0.10). They represent 13% of the study population and are classified as type II non-salt-sensitive. This group’s blood pressure was improved by a regular daily diet of 240 mEq of sodium. Salt restriction in this group may prove to be of little benefit to this group.

Three possibilities may occur with sodium loading: significant decreases in the amplitude and acrophase parameters, significant changes in the amplitude-acrophase test with sodium loading were not directly correlated with significant changes in the mesor test. Thus, salt sensitivity by mesor criteria was not necessarily correlated directly with amplitude-acrophase changes. This finding indicates that the lability of mean arterial pressure may be exacerbated by sodium loading.

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