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# I: Rhythms and blood pressure

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**Summary.** - The time (*chronos*) structure of life (*bios*) is the topic of a computer-implemented science (*logos*), chronobiology. Chronobiologic methods for resolving physiologic time structure provide a more reliable mean, the MESOR, and other parametric dynamic measures of blood pressure variability. The amplitude is a measure of predictable extent of change and the acrophase a measure of timing of overall high values within each cycle of the rhythmic function. Such chronobiologic endpoints are often more sensitive than the mean for separating groups at different risk of developing high blood pressure. About 24-h (circadian) rhythms account for a sizeable part of predictable variability in blood pressure. Methodology to assess the characteristics of circadian blood pressure rhythms also provides time-varying reference limits for the interpretation of single measurements. Deviant blood pressures can be quantified by reference to such circadian-stage-dependent limits, derived from the automatically monitored blood pressure profiles of healthy peer groups. Excess or deficit in blood pressure can also be assessed as a hypertensive or hypotensive index integrated over 24 h. Chronobiologic monitoring has wide uses in practice as well as research, whether it is carried out by self-or automatic measurements, once the data are analyzed by appropriate computer methods that are now readily available.

*Key words*: blood pressure, chronobiology, circadian rhythms, hypertension.

**Riassunto** *(Ritmi circadiani e pressione arteriosa)*. - La struttura temporale (*cronos*) della vita (*bios*) è il campo di una scienza (*logos*) ottimizzata dal computer, la cronobiologia. I metodi cronobiologici per risolvere la struttura temporale-fisiologica forniscono una media più affidabile, il MESOR, ed altre misure parametriche dinamiche della variabilità della pressione arteriosa. L'ampiezza oscillatoria è una misura dell'entità predicibile di variazione e l'acrofase è una misura dell'orario dei valori più elevati in assoluto nell'ambito di ciascun ciclo di una funzione ritmica. Questi elementi cronobiologici sono spesso più sensibili della media per separare gruppi con differenti rischi di sviluppare l'ipertensione. I ritmi di circa 24 ore (circadiani) valgono per una parte misurabile del ritmo circadiano della pressione arteriosa. La metodologia di riunire le caratteristiche del ritmo circadiano della pressione arteriosa è anche in grado di provvedere i limiti di riferimento tempo-qualificati per l'interpretazione delle singole misure. Pressioni arteriose devianti possono essere quantificate con riferimento a grandi limiti dipentenli dallo stato circardiano, derivati dai profili della pressione arteriosa monitorata automaticamente in gruppi di soggetti sani. Un accesso o un deficit nella pressione arteriosa possono essere anche valutati come indici ipertensivi o ipotensivi integrati nelle 24 ore. Il monitoraggio cronobiologico ha un ampio uso nella pratica e nella ricerca, se esso è fatto tramite misure sia personali che automatiche, una volta che i dati sono analizzati da opportuni metodi computerizzati che ora sono facilmente disponibili.

*Parole chiave*: pressione arteriosa, cronobiologia, ritmi circadiani, ipertensione.

## Introduction

Concern for an elevated blood pressure (BP) is warranted, since high BP is a risk factor for developing several cardiovascular diseases. Moreover, once a high BP is properly diagnosed, something can be done about it. With important exceptions [1, 2], reports indicate that, on a population basis, the higher either the systolic (S) or the diastolic (D) BP, the higher the mortality rate, notably from certain degenerative cardio-, cerebro-, reno- and retinovascular diseases. Mortality rate rises progressively with a rise in pressures still within the so-called adult "normal" range [3-6]. Even at mean values below 110 (SBP) and 70 (DBP) mm Hg, the MESOR (acronym for midline-estimating statistic of rhythm) separates clinically healthy adult women at high versus low familial risk of developing high BP, when they are monitored for 24 h, mostly in recumbency [2, 7].

Dynamic indices of BP variability that is predictable, in the sense that it is rhythmic, Table 1, provide early clues of a heightened risk [8-12], even when a mean fails to do so. Already at birth, the about (*circa*)-daily (*dies* = day) (circadian) [2, 8-10], about-weekly (circaseptan) [2, 10-12] and about-yearly (circannual) [2] amplitudes of BP differentiate neonates with a negative or a positive family history of high BP. These indices derive from the study (*logos*) of the time (*chronos*) structure of life (*bios*), the fledgling new science of chronobiology [13].

Chronobiologic methods rely on dense systematic serial BP measurements around the clock, analyzed by special software [2, 14-16] complemented, if need be, by time-specified sparse measurements, rather than merely on 24-h monitoring ([17]; for reviews

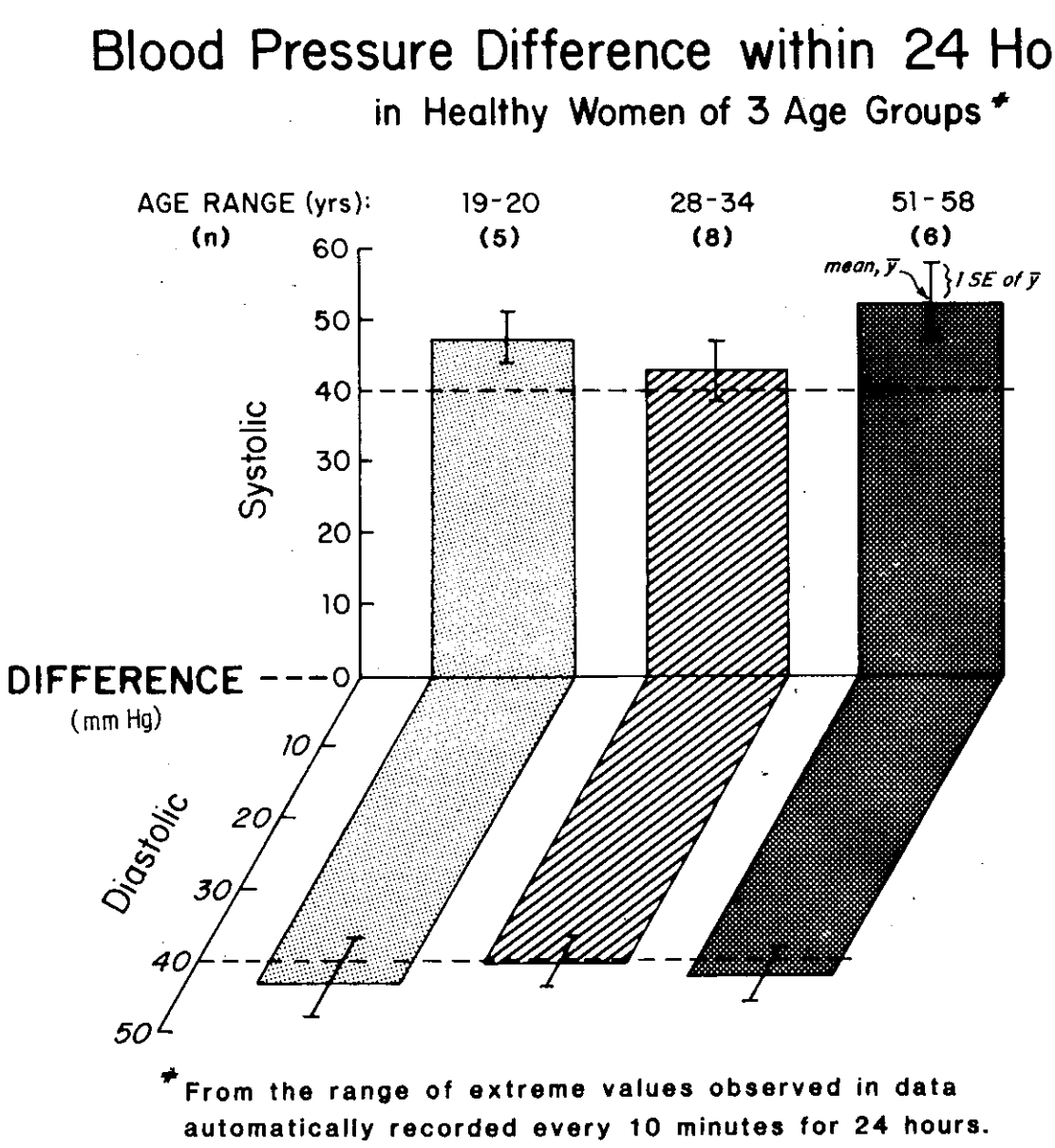



**Fig. 1.** - Intra-individual variability in blood pressure and heart rate of clinically healthy women during recumbency.

see [2] and [18]), that as yet fails to exploit chronobiologic analyses. To the extent that chronobiologic methods are cost-effective, they are a useful substitute for traditional (casual) single BP measurements taken at arbitrarily picked times, a custom now current in epidemiology and in clinical practice. The concept of a BP excess or deficit [2, 15, 16], expressed in mm Hg x h, measured as the integral (area) of BPs above or below time-varying critical limits, respectively, during a given time span (such as 24 h, in view of the prominent circadian rhythm characterizing BP), may also prove to be useful and has to be developed further. This chronobiologic approach allows *statistical* inferences to be drawn with an estimate of their uncertainty not only for groups, but also for the *individual*.

**Single time-unspecified *vs* serial BP measurements**

Discussions of any relation of some dietary constituent [19] or other factor to the development of an elevated BP have relied mainly on one, two or a few time-unspecified measurements [19-22]. Even when based on a mean of several replicated casual measurements rather than on systematic measurements taken around the clock, a BP found to be "high" or "low" in association with a change in treatment is often unreliable. The unreliability of single BP measurements stems from two sources, predictable biological rhythms and (as yet) unpredictable residual variability. The latter is contributed in part by the measurement error and amounts to about 7 mm Hg [23]. Biological

**Table 1.** – Chronobiologic endpoints, e.g. of human blood pressure

| | | |
|---|---|---|
| 1. | **MESOR, M:** | midline, estimating, statistic of rhythm, based on systematic sampling, taking dynamics into account; replaces mean of casual measurements at arbitrary times |
| 2. | **Range, R:** | total<br>partial, e.g., 90%, 50%, circadian range (e.g., of hourly mean values) |
| 3. | **Standard deviation, SD** | |
| 4. | **Trends:** | Intercept and slope of linear trend; coefficients of higher-order (e.g., quadratic or cubic) polynomials |
| 5. | **Periodicities:** | Rhythm characteristics, e.g.:<br>circadian amplitude, A<br>circadian acrophase, Ø<br>circadian waveform, (A, Ø) of harmonics |
| 6. | **Non-periodic, non-trend components** | Parameters describing shape of spectrum, e.g., high frequency dominant over low frequency or *vice versa* |

*All of the above endpoints may or may not be deviant. Other endpoints, related to cumulative deviation, are:*

| | | |
|---|---|---|
| 7. | **Excess:** | short-term: extent: hyperbaric index duration & timing of elevation<br>long-term projection; e.g., 10-year excess |
| 8. | **Deficit:** | short-term: extent: hypobaric index duration & timing of deficit<br>long-term projection; e.g., 10-year deficit |

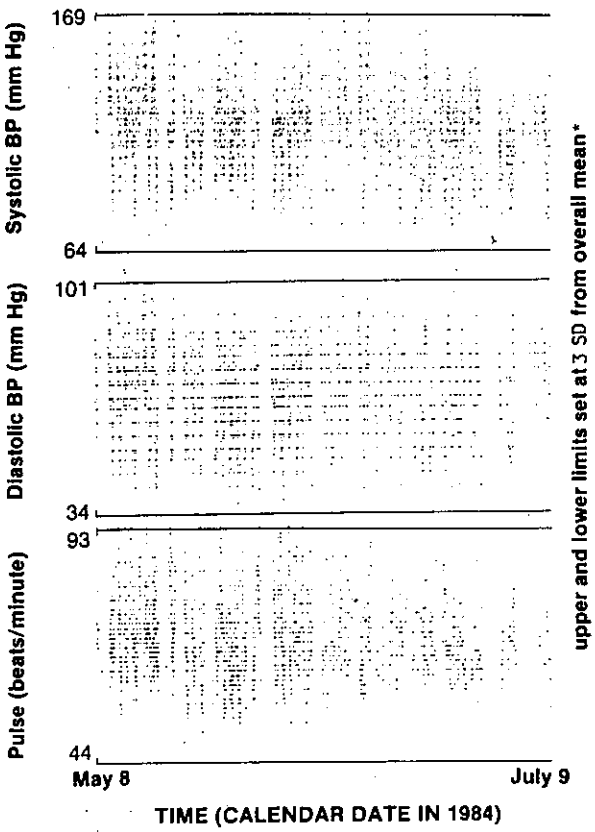



**Fig. 2.** - Fully ambulatory automatic monitoring of a clinically apparently healthy woman (EH, age 64 years) reveals a wide range of cardiovascular variability. Questions about *the* blood pressure (BP) of a patient are indeed rhetorical. The assessment of variation that can be cost-effectively recorded and interpreted, is mandatory. *Dots outside limits indicate outliers; SD = standard deviation.

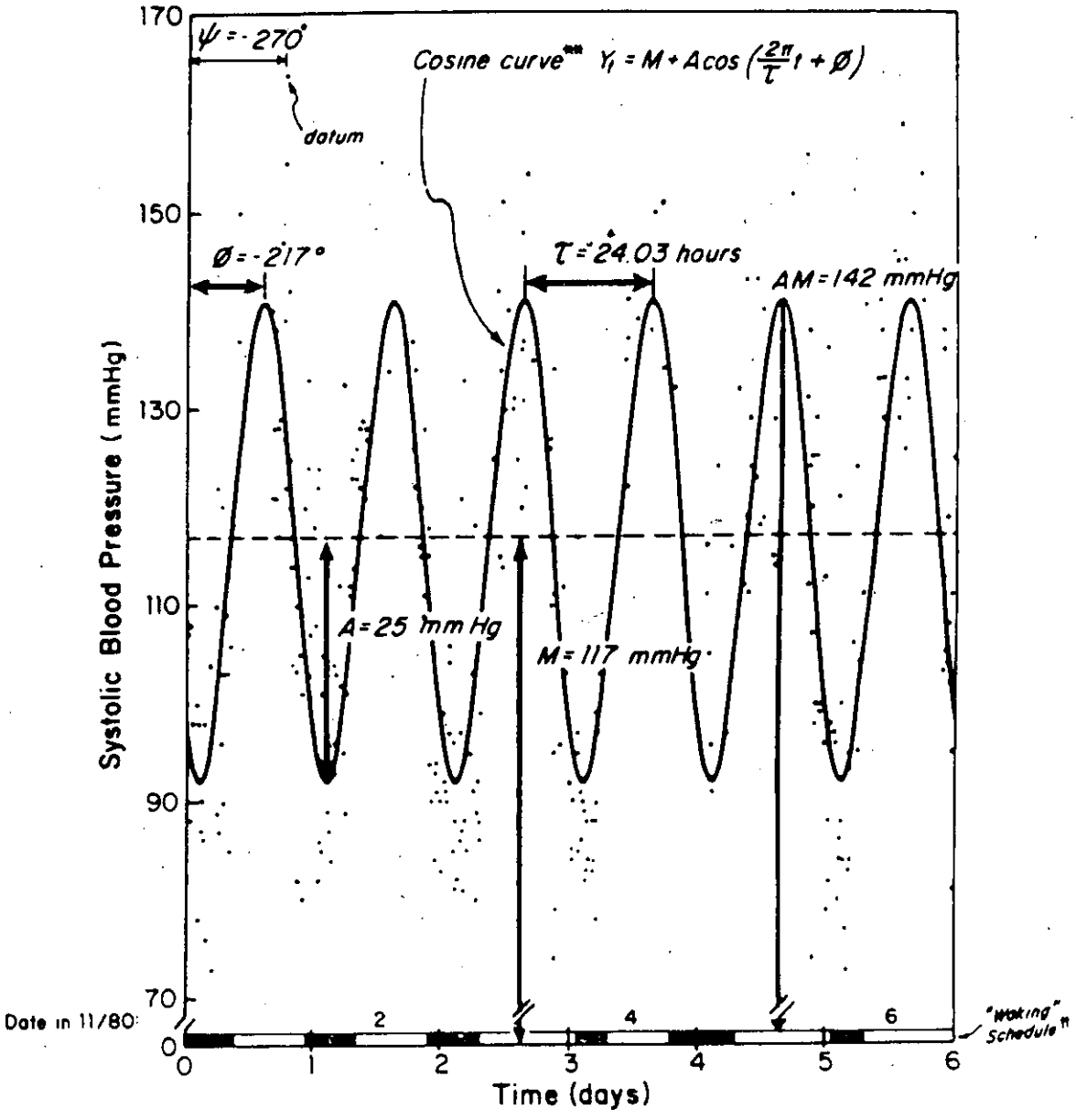
rhythms, notably circadian rhythms, are prominent [2, 16, 23-31] and account for a sizeable portion of the total variability of BP. Both predictable (since rhythmic) and residual variability in BP may lead to unusually high or low values that may occur only at certain times not covered by casual sampling [7, 28]. With automatic instrumentation for indirect non-invasive room-restricted or ambulatory measurement of BP, it becomes possible to follow the time course of individual BP variation around the clock in all members of large groups [2].

## Circadian rhythm in blood pressure

Around-the-clock monitoring documents the large intra-individual variability in SBP, DBP and heart rate (HR), Figs 1 and 2. It also documents the prominence of circadian rhythms, with a period of about 24 h, apparent from the least-squares fit of a single 24 h cosine curve to the data, Fig. 3, which also provides measures of uncertainty for each rhythm characteristic, Fig. 4 and Table 1.

Hourly averages of BP data measured over 26 days by a post-menopausal woman in apparent clinical health [30] show a range of 80 mm Hg for SBP and of 40 mm Hg for DBP, with an overlap of 18 mm Hg between the two distributions, Fig. 5. The mean pulse pressure is about 47 mm Hg. These statistics indicate that the range of change within a day of both SBP and DBP can be actually larger than the average pulse pressure (the difference between SBP and DBP). In the vast majority of individuals, the highest DBP measured at one time within 24 h exceeds the lowest SBP measured at another time within the same 24 h [14,16]. This is the case for 74 out of 80 BP series from 40 men, 20 to 60 years of age, monitored on 2 occasions at 7.5 min intervals for 24 h, the average difference between the highest DBP and lowest SBP being as much as $16.7 \pm 1.4$ (SE) mm Hg [16-27]. Neglect of circadian stage then is no more warranted than the failure to distinguish SBP from DBP.

# Parameters of Circadian Rhythm in Systolic Blood Pressure Estimated by Non-Linear Least Squares Procedure*




*Applied to automatically recorded data from healthy woman 60 years of age

**Fitted to data by non-linear least squares, with $Y_t$ = value of curve at time t, M = MESOR = average value of curve over integral number of cycles; A = amplitude = half of difference between highest and lowest value of curve; AM = acrometron = highest predicted value, τ = period = duration of one complete cycle; Ø = acrophase = timing of highest value in curve (here in relation to 00[00] on first day of data collection), with 360° ± τ ψ = macrophase = timing of highest value. Procedure also provides confidence interval for parameters (M, A, τ, and Ø)

"From automatic actometry; rest-span shaded

**Fig. 3.** - By fitting, as a first approximation, a 24-h cosine curve through the data, rhythm parameters can be estimated.

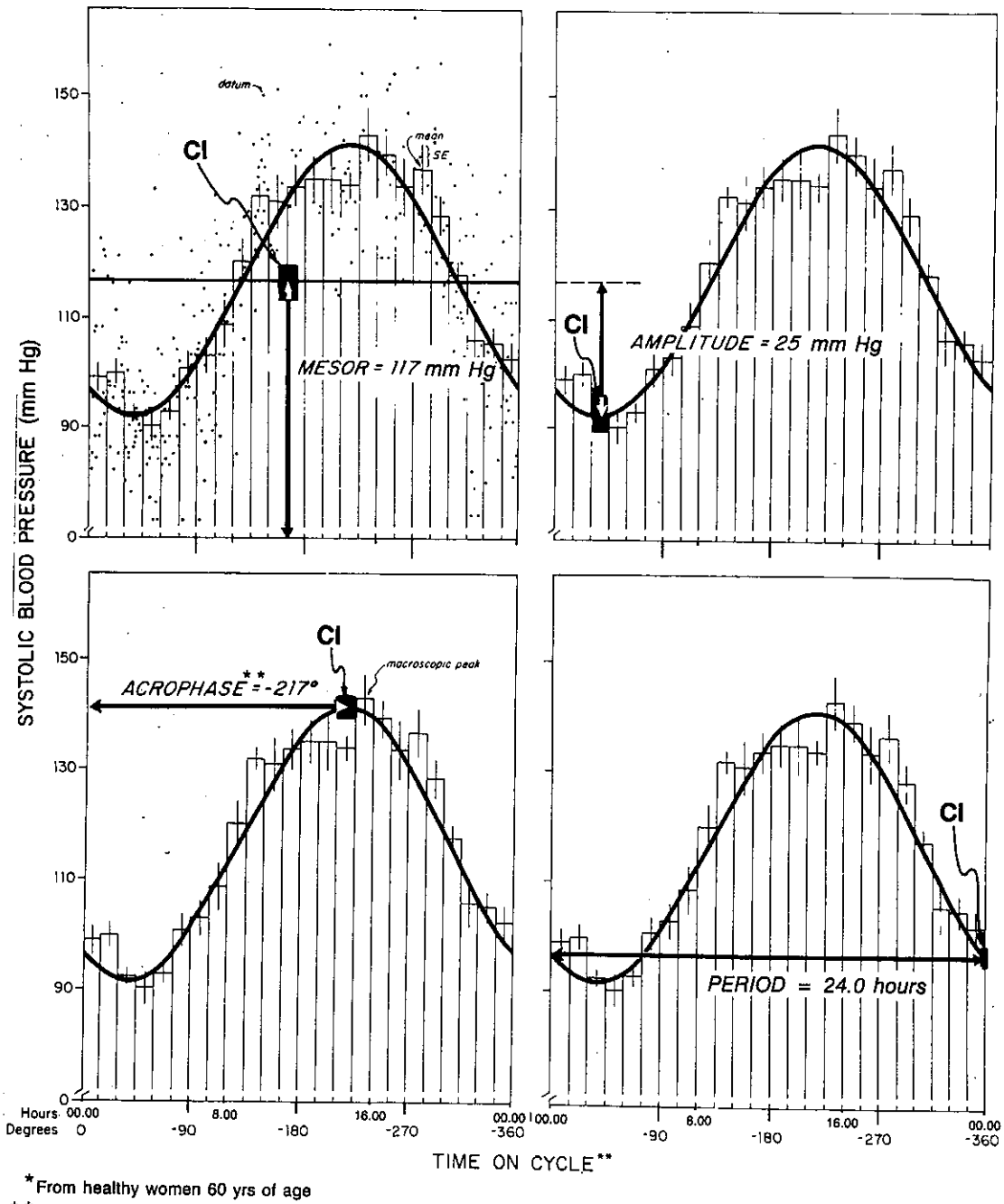
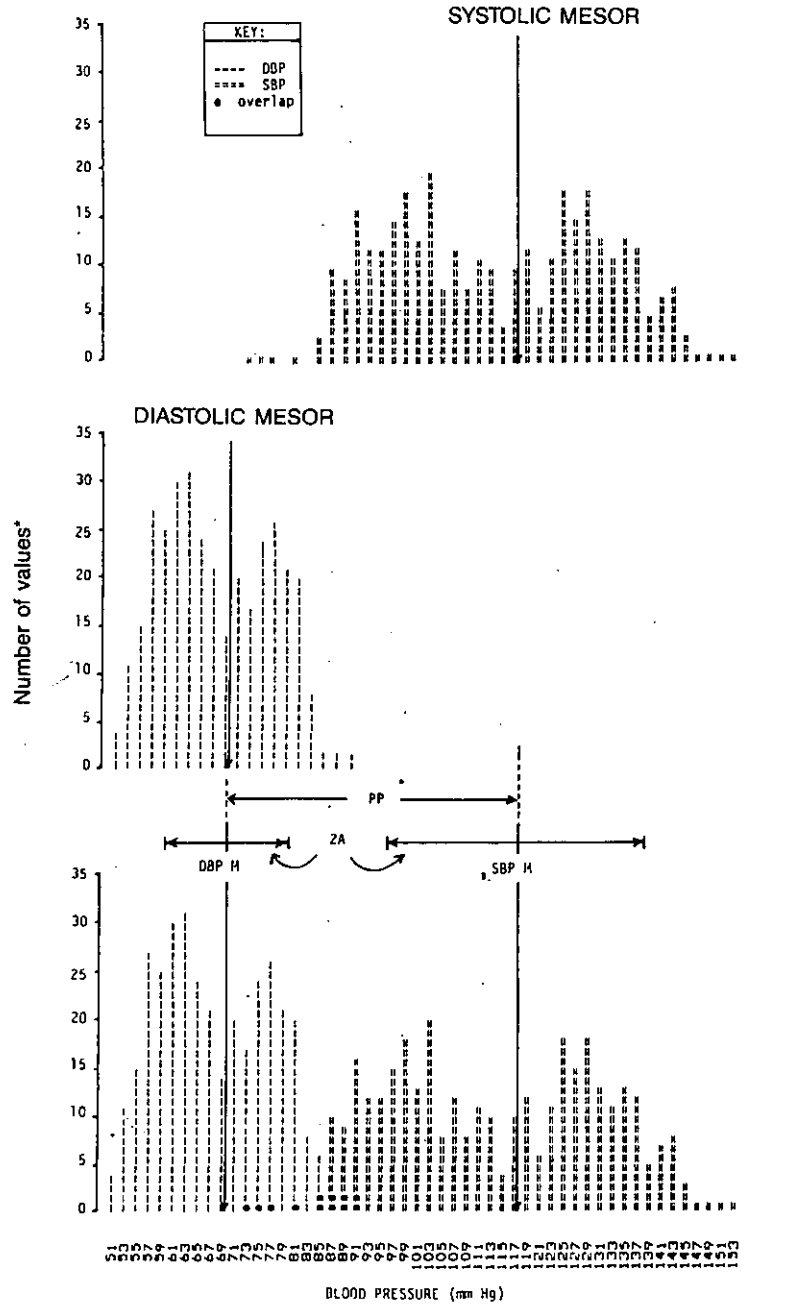



**Fig. 4.** - The computer-yielded so-called microscopic estimates of rhythm characteristics such as MESOR, amplitude, acrophase and period can each be given with their uncertainties, shown as small vertical bars for MESOR and amplitude, and as horizontal uncertainties for acrophase and period.

# OVERLAPPING SYSTOLIC AND DIASTOLIC BLOOD PRESSURE MEASUREMENTS ON A POST-MENOPAUSAL CLINICALLY HEALTHY WOMAN




*Hourly averages of data mostly at ~10 min. intervals, with interruptions, for 26 days; M = MESOR; A = circadian Amplitude; SBP = Systolic Blood Pressure; DBP = Diastolic BP; PP = Average Pulse Pressure (PP = SBP M - DBP M).
Overlap of original data would be even greater.

**Fig. 5.** - Circadian change can exceed the pressure difference between systole and diastole and hence is best assessed. The wide variability of systolic (S) and diastolic (D) blood pressure (BP) in a clinically apparently healthy woman is revealed in a histogram, a plot of the frequency of BPs in different BP classes. Many DBPs are higher than the low SBPs at other times. There is an overlap of 18 mm Hg between the two distributions (the highest DBP is 91 and the lowest SBP 73 mm Hg). It is a major mistake to ignore the difference between SBP and DBP. By the same token, a difference as the result of circadian variation, that can be just as large or larger, is best exploited rather than ignored.

**Table 2.** – Frequency ranges for terms describing components in a spectrum of biologic rhythms with emphasis on the circulation, notably blood pressure (BP) and heart rate (HR)(*a*)

| Domain region | Frequency (f) range ($f=1/\tau$; cicle in $\tau$; $\tau$=period) | Illustrative example | Validated free-running from reference period (literature) |
|---|---|---|---|
| Ultradian | $\tau < 20$ h | | |
| circacentuminutan | $\tau = 1.7 \pm 1$ h | BP, particularly at night [33, 34] | |
| circasemidian | $\tau = 12 \pm 2$ h | 12 h component contributes markedly to circadian BP waveform [35] | |
| Circadian | $\tau = 24 \pm 4$ h | Human BP & HR [35] | Yes [36] |
| dian | $\tau = 24 \pm 0.2$ h | Human BP & HR under synchronized social routine [37, 38] | |
| Infradian | $\tau > 28$ h | | |
| circadidian | $\tau = 2 \pm 0.5$ d | Body weight, urine volume and core temperature of C3H mice on alternate-day feeding schedules [39] | |
| circasemiseptan | $\tau = 3.5 \pm 1$ d | Sudden human death [40]<br>ECG pathology [41] | |
| circaseptan | $\tau = 7 \pm 1.5$ d | Rejection of human heart transplants [42, 43]<br>Circaseptan features as a response to birth [44, 45]<br>Human 17-ketosteroid excretion [46] | Yes [46] |
| circadiseptan | $\tau = 14 \pm 3$ d | » » » » | |
| circavigintan | $\tau = 21 \pm 3$ d | » » » » | |
| circatrigintan | $\tau = 30 \pm 5$ d | » » » [46, 47] | |
| circannual | $\tau = 1$ y $\pm 2$ m | Human blood pressure [48-50]<br>Correlation of cardiovascular disease risk with circannual amplitude of aldosterone [49] | Yes [51, 52] |
| circaseptennian | $\tau = 7$ y $\pm 1$ y | Gonadal index of marine invertebrates [53] | |
| circaduodecennian | $\tau = 12$ y $\pm 2$ y | Human blood pressure [50] | Yes (*b*) |

(*a*) Rhythms with different frequencies (or reciprocals of frequency, i.e., periods) usually characterize the same variable, such as blood pressure, if it is measured with sufficient density and for a long span. $\tau$ = period; h = hour; d = day; m = month; y = year. Terms coined in relation to frequency, by analogy to usage in physics, where frequencies higher than those audible or visible are called **ultra**sonic and **ultra**violet, frequencies higher than one cycle per 20 h are designated as **ultra**dian. By the same token, as frequencies lower than audible or visible are called **infra**sonic or **infra**red, rhythms with a frequency lower than one cycle per 28 h are designated as **infra**dian. *Circacentuminutan* is preferred to *circacentiminutan* in order to distinguish a multiplication, as in *centuplicate*, from a division, as in *centimeter*. The suffix-*ennian* instead of-*annual* for periods longer than 1 year serves to avoid the connotation of "annual" as a suffix after numbers larger than 1 to denote events that repeat themselves within the year, as in *biannual* or *triannual*, meaning twice or thrice a year. The change from *duo-* (used earlier in *circaduodian) to di-* is prompted by the desire for consistency (e.g., with *circadiseptan*) and by the need to use an infix that denotes a doubling (rather than the addition of two, as done advisedly in *circaduodecennian*). A term such as *circasemidian* (and, perhaps, others if left unqualified) describes only a spectral component, without any implication as to whether the component represents a rhythm in its own right, rather than merely the waveform of a rhythm with a different (e.g., lower) frequency. Physiologic tests are required to distinguish these possibilities. A single human variable such as blood pressure or heart rate exhibits most if not all of the periods listed. William MacDonald, Michael V. Molitor and, for the past decade, Robert P. Sonkowsky, all at one time professors in the Classics Department, University of Minnesota, kindly participated in the coining and/or updating of these terms. Originally proposed as adjectives, their use as nouns, for brevity, also seems acceptable.

(*b*) Free-running with respect to sunspot cycle; tentative and awaiting analysis of as-yet unavailable longer physiologic series.

### Extent of change

In a population of clinically healthy men, the range of change within a day averages $68.9 \pm 15.7$ (SD) and $56.2 \pm 14.9$ mm Hg for SBP and DBP, respectively. For comparison, their average pulse pressure is smaller ($43.0 \pm 10.4$ mm Hg). Circadian rhythms, when they are underestimated by the fit of a single cosine curve (rather than evaluated by a set of harmonics), account for a change per day of 24 mm Hg in SBP and 18 mm Hg in DBP [16]; i.e., on the average, a change with a predictable timing of 24 (SBP) and of 18 (DBP) mm Hg can be expected to occur within 24 h in any given, healthy individual as part of the much larger total variation. Infradian rhythms with a lower-than-circadian frequency and ultradian rhythms (for review, see [32]) (or harmonics accounting for the circadian waveform) with a higher-than-circadian frequency also contribute part of the variability in BP, Table 2. Under the sampling conditions of studies reported herein [33-53], these changes with a frequency other than circadian remain part of the residual term.

In view of both rhythmic and residual variability, the necessary BP sampling designs exceed the scope of those currently used. Tools meeting the need of proper designs are another requisite to be considered. Even with relatively dense measurements collected for 24 h on different days, the 24 h BP mean differs in a majority of cases, with statistical significance from day to day, Fig. 6. Such differences reflect in part the phenomenon of a regression toward the mean [54-56] and in part the operation of rhythms with a frequency lower than circadian [2, 7, 30]. Such evidence points to the need for measuring BP for spans longer than 24 h. Recent studies on sampling requirements reveal that a proper screening for diagnostic purposes and the assessment of the effect of non-drug or drug treatment on BP should be based on around-the-clock monitoring for 48 h at a time as a minimum, that such profiles should be repeated under different conditions of life, in the case of deviant values, e.g., during workdays by comparison to weekends, and that in the case of intervention, such profiles should be complemented with self-measurements over longer spans [2, 23, 29].

### Endpoints of rhythmic time structure. The sphygmochron

The MESOR is usually more reliable than the arithmetic mean, notably when data are collected at unequal intervals over a non-integral number of cycles, Figs 7-9 [2, 29]. The circadian amplitude, a measure of the predictable extent of change within 24 h, provides valuable information, as in the case of an individual with a MESOR of 142/91 mm Hg for systolic/diastolic BP before intervention. An increase in amplitude was seen to accompany a decrease in MESOR following a non-drug intervention, dietary sodium restriction [57]. Because of the relatively large amplitude in the stage associated with sodium restriction, the highest systolic BPs reached within a circadian cycle were almost as high as the highest values observed during the reference stage. There is also evidence from the spontaneously hypertensive rat that an elevation of the circadian amplitude may precede an elevation of the MESOR [58]. The circadian acrophase yields information regarding the timing of BP elevation, useful for timing treatment [2, 14]. It may also be a factor in predicting a patient's risk of developing future cardiovascular complications [59], notably during pregnancy [2]. The waveform of a rhythm, which usually deviates from a cosine curve, can be described by the fit of harmonics of the fundamental (circadian) component. These harmonics contribute with statistical significance to the variability on hand [2, 16, 23, 60].

Automatic monitoring of BP, yielding dense data around the clock, provides information that needs to be interpreted differently from single measurements. First, since many measurements are taken, it becomes much more likely to find at least one or a few values above the currently arbitrarily used limits, such as 140/90 mm Hg for single or "protracted" measurements [6, 61]. The question of whether the BP is above or below a given threshold can be replaced by questions such as "to what extent does the BP exceed the threshold at a given time?" and "how long does BP remain above the threshold?" Second, although any single measurement may be associated with an error of about 7 mm Hg, the error characterizing the 24-h mean is much smaller. A relatively small elevation of the MESOR, even if it is only of a few mm Hg, cannot be indiscriminately disregarded as negligible if it is statistically significant, since even without progression, in the absence of regression, this excess is likely to accumulate day after day for a lifetime, which thereby may be shortened. Moreover, when data are collected automatically, evenly around the clock, the error associated with the estimation of the MESOR is usually smaller than that associated with the estimation of the mean, Table 3.

Indices to reflect harm from an elevated (or lowered) BP should consider, with the MESOR, the extent, duration and timing of BP elevation (or lowering), with the likelihood that harm increases with both the magnitude and duration of BP elevation (or lowering) and that the harm brought about by deviations may be circadian stage-dependent. As one of several possible approximations, the integral over 24 h of BPs above (or below) specified critical limits quantifies such harm [2, 15, 16, 62-65]. As a first approximation only [64], the integral has the units of mm Hg $\times$ h, representing an impulse per unit area, and is denoted the 24-h hypertensive index, HTI (or as a hypotensive index, in the case of deficit) (Fig. 10) [2, 62, 63]. The non parametric indices of excess and/or deficit (both can occur with an increase in circadian amplitude,

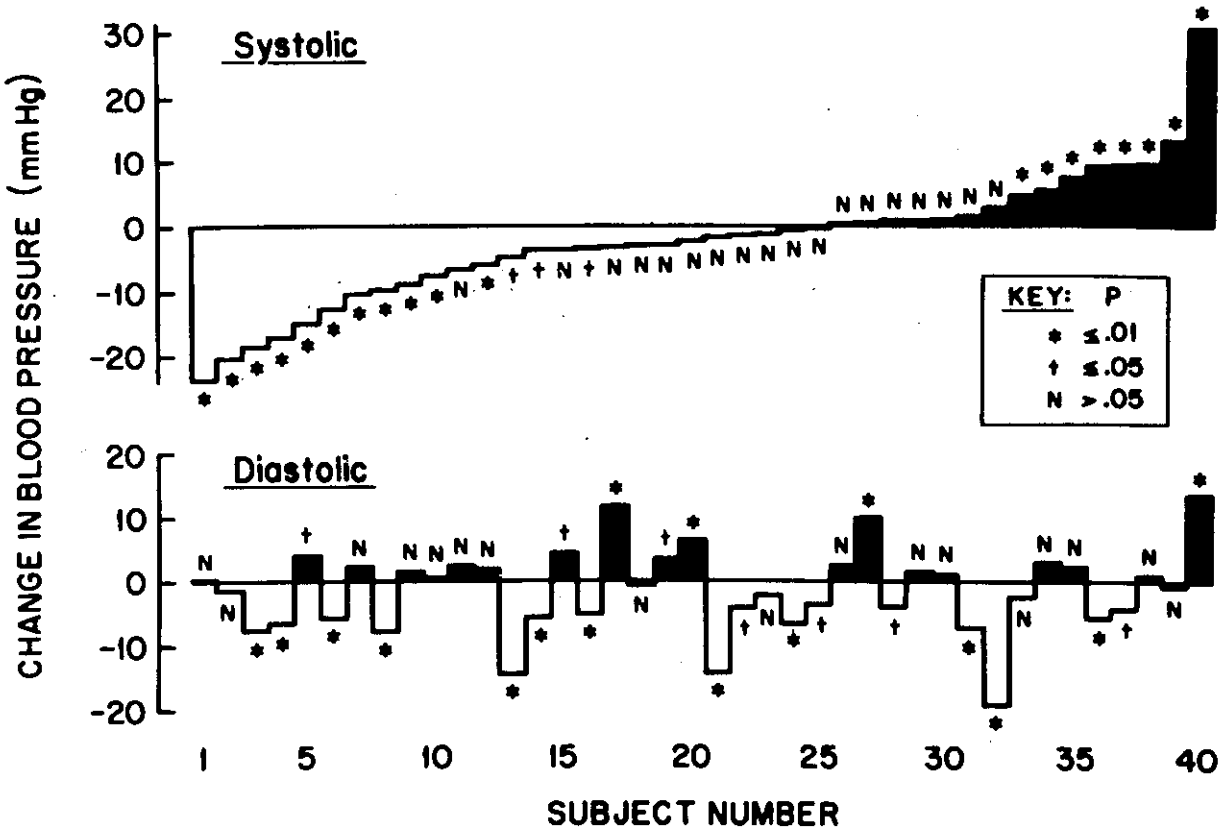



**Fig. 6.** - Statistically significant difference (decrease in 14 cases, increase in 8 cases) in rhythm-adjusted mean (MESOR) of human blood pressure between two profiles obtained at 7.5-min intervals, - 1 month apart, by automatic monitor on presumably healthy men 20-60 years of age.

**Table 3.** – Summary of reduction in SE of the MESOR as compared to the arithmetic mean (*)

| Variable (**) | Percent reduction in SE | |
|---|---|---|
| | Original data | Hourly averages |
| SBP | 24.1% | 34.6% |
| DBP | 21.5% | 32.1% |
| HR | 25.5% | 21.8% |

(*) Data from 40 clinically healthy men 20-60 years of age, monitored every 7.5 minutes for 24 h on two occasions, less than 3 weeks apart.

(**) SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

in the absence of a concomitant increase in circadian MESOR) can be incorporated into summaries of BP and HR profiles over time involving a computer comparison with peers. Such summaries, dubbed sphygmochrons, are shown in Fig. 11 and 12. One (Fig. 11) is rather simple and addresses the general practitioner or even the person interested in self-help for health care. The other (Fig. 12) is more complete and addresses the specialist.

The use of these indices of excess and deficit requires the establishment of critical limits above which a BP may be considered to be harmful. Our information about anatomic and physiological effects of BP, the detailed nature of any dependence of cardiovascular risk upon the characteristics of variability in BP, and the extent of reversibility of lesions, reviewed elsewhere [2, 64, 65], is limited. Hence, one recourse is to rely on reference limits derived from BP series obtained from apparently healthy individuals. Since BP undergoes a prominent circadian variation, critical limits that are fixed should be substituted, whenever pertinent data are available, by limits that vary as a function of the circadian rhythm stage, as a first approximation. Time-specified (e.g., 90%) prediction limits (chronodesms) [2, 14, 16, 66, 67] are such limits, computed from an age - and sex - matched reference population. Some of these limits [2, 16, 66] accommodate changes in variance and in mean for moving intervals over which data are pooled, assuming, as a first approximation, that during these intervals no appreciable changes in population characteristics take place. Based on the variabilities encountered, both within a given subject and among subjects, reference limits can be calculated for each interval [2, 66]. Eventually, the HTI will also have to account for any mitigation of harm, derived from the extent to and the duration for which BPs are below the

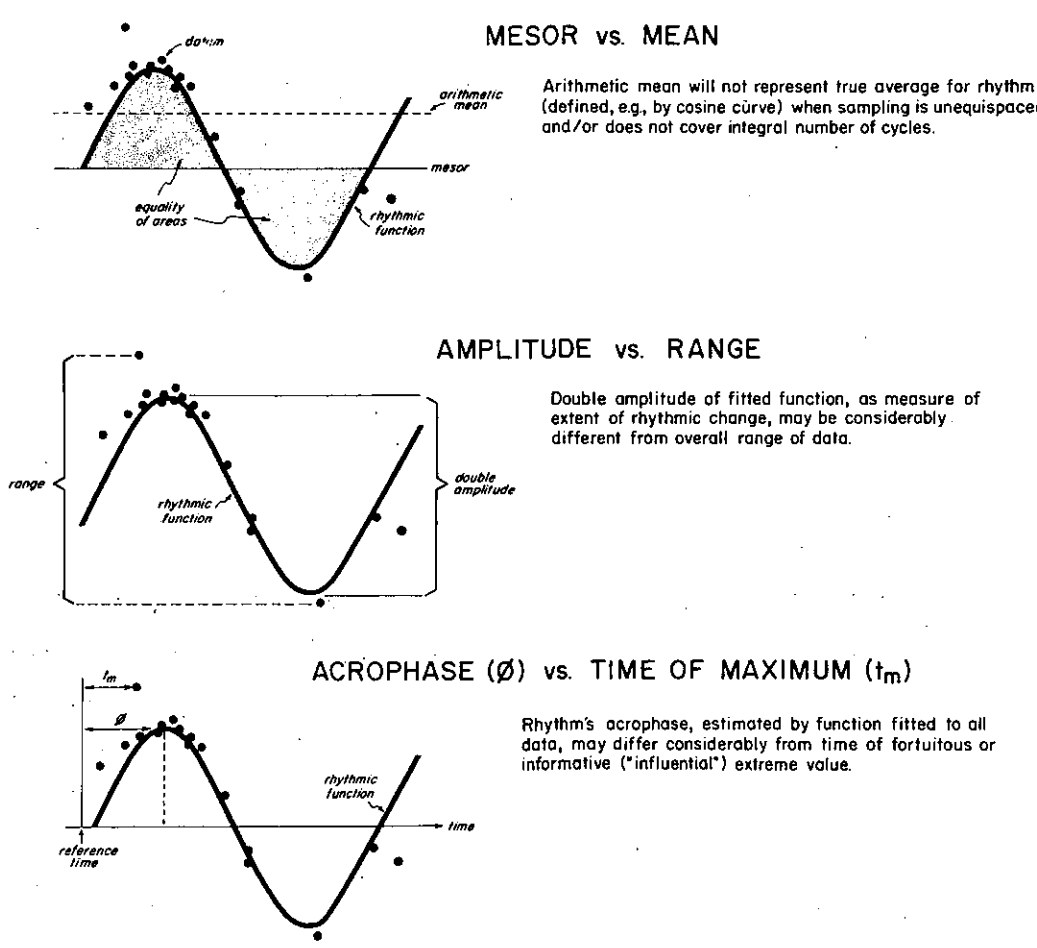
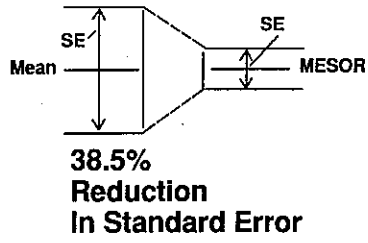



**Fig. 7.** - When data are collected at irregular time intervals, the MESOR usually differs from the arithmetic mean. When sampling is not uniform, the MESOR usually provides a more accurate estimate of location. Similarly, the amplitude differs from the range and the acrophase from the time of maximum.

* When data characterized by rhythms are equidistant and dense (available at intervals, $\Delta <$ period, $\tau$ ) and cover an integral number of $\tau$s, the M (though identical to the Arithmetic Mean) has a smaller Standard Error (SE).




Reason:

How large the SE of the mean is depends on the total variability in the data. But if a large portion of this variability can be ascribed to the rhythmic time structure in the data, fitting an approximating cosine curve can considerably reduce the residual variance, which in turn determines how large (or rather how small) the SEs on the MESOR and on the other parameters of the fitted model are. Thus, the better the cosine model fits the data, the greater the reduction in SE on the (rhythm-adjusted) mean.

**Fig. 8.** - Another advantage of the MESOR is that it is usually associated with a smaller SE.

time-varying limit, for any nonlinearities in the effect of excess or deficit and, in particular, for the dependence of the effect upon the rhythm stage in which it occurs [64].

### Day-to-day variability of BP MESOR in health

When data are collected around the clock on two or more occasions, it is possible to carry out a MESOR-test among the different profiles [68, 69] to test the equality of their MESOR. Changes in daily BP MESOR are thus observed between separate 24-h BP profiles. This is the case for 40 clinically healthy adult men sampled every 7.5 min for 24 h on 2 occasions, about one month apart [16]. Averages over 1 h spans reduce the serial correlation of residuals in such data [70]. No statistically significant difference in MESOR in found in 18 cases for SBP and in 17 cases for DBP. As compared to the first

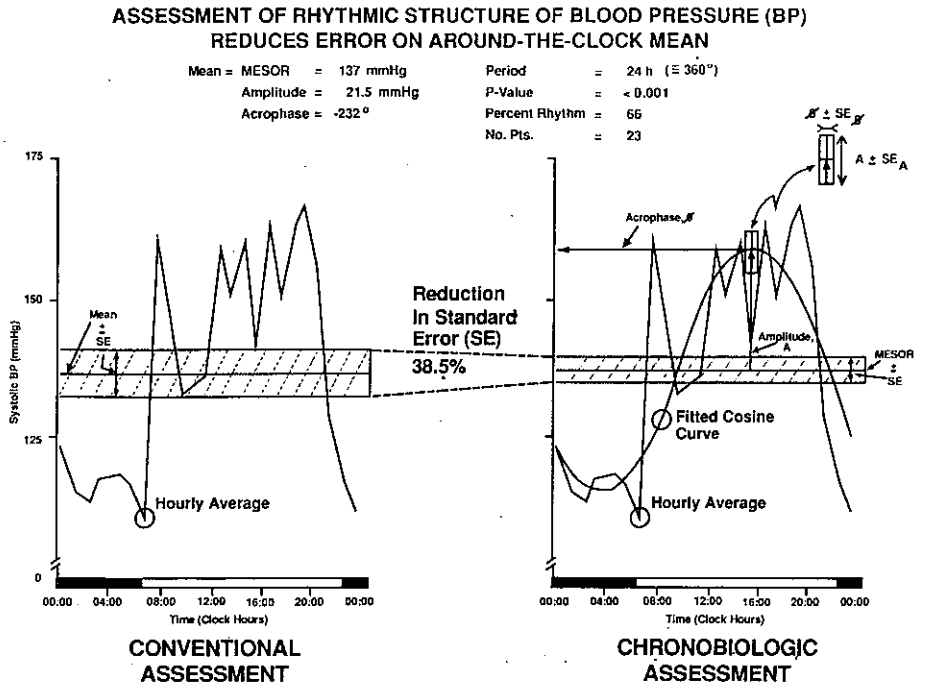



**Fig. 9.** - The reduction in SE of the MESOR versus the mean can be attributed to the fact that a large portion of the variability in the data around the mean is not random but predictable, and can be accounted for by rhythms such as the circadian or about 24-h rhythms.

**Table 4.** – Day-to-day variability of MESOR in clinically healthy men, 20-60 years of age (*a*) *MESOR (mm Hg)* (*b*)

| Sub. | SBP First profile | SBP Second profile | SBP Difference | | DBP First profile | DBP Second profile | DBP Difference | | Sub. | SBP First profile | SBP Second profile | SBP Difference | | DBP First profile | DBP Second profile | DBP Difference | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 120.5 | 130.1 | + 9.6 | ** | 75.1 | 70.9 | − 4.2 | * | 21 | 117.0 | 126.3 | + 9.3 | ** | 85.5 | 80.0 | − 5.5 | ** |
| 2 | 128.7 | 116.1 | −12.6 | ** | 68.8 | 63.3 | − 5.5 | ** | 22 | 132.8 | 122.7 | −10.1 | ** | 71.4 | 73.7 | + 2.3 | NS |
| 3 | 115.6 | 110.9 | − 4.7 | * | 80.1 | 65.7 | −14.4 | ** | 23 | 123.6 | 121.8 | − 1.8 | NS | 83.8 | 69.2 | −14.6 | ** |
| 4 | 115.8 | 109.8 | − 6.0 | ** | 83.8 | 85.8 | + 2.0 | NS | 24 | 103.5 | 104.6 | + 1.1 | NS | 67.0 | 68.0 | + 1.0 | NS |
| 5 | 123.7 | 103.6 | −20.1 | ** | 64.2 | 62.9 | − 1.3 | NS | 25 | 118.6 | 115.6 | − 3.0 | NS | 72.9 | 72.3 | − 0.6 | NS |
| 6 | 126.4 | 119.0 | − 7.4 | ** | 83.8 | 84.4 | + 0.6 | NS | 26 | 119.4 | 115.8 | − 3.6 | NS | 70.9 | 75.3 | + 4.4 | * |
| 7 | 110.8 | 107.7 | − 3.1 | NS | 58.5 | 70.4 | +11.9 | ** | 27 | 116.2 | 117.1 | + 0.9 | NS | 74.9 | 76.3 | + 1.4 | NS |
| 8 | 125.9 | 126.1 | + 0.2 | NS | 66.9 | 69.3 | + 2.4 | NS | 28 | 115.2 | 115.5 | + 0.3 | NS | 67.9 | 77.9 | +10.0 | ** |
| 9 | 125.8 | 125.4 | − 0.4 | NS | 75.5 | 68.7 | − 6.8 | ** | 29 | 121.9 | 129.3 | + 7.4 | ** | 75.0 | 77.1 | + 2.1 | NS |
| 10 | 127.2 | 158.1 | +30.9 | ** | 85.9 | 99.5 | +13.6 | ** | 30 | 107.1 | 105.7 | − 1.4 | NS | 70.0 | 65.9 | − 4.1 | * |
| 11 | 114.9 | 111.3 | − 3.6 | * | 77.0 | 71.6 | − 5.4 | ** | 31 | 111.5 | 117.0 | + 5.5 | ** | 66.4 | 69.4 | + 3.0 | NS |
| 12 | 105.0 | 103.8 | − 1.2 | NS | 65.6 | 63.5 | − 2.1 | NS | 32 | 111.1 | 112.8 | + 1.7 | NS | 69.5 | 62.4 | − 7.1 | ** |
| 13 | 95.9 | 100.8 | + 4.9 | ** | 70.4 | 68.1 | − 2.3 | NS | 33 | 102.1 | 103.0 | + 0.9 | NS | 76.0 | 72.0 | − 4.0 | * |
| 14 | 104.5 | 101.2 | − 3.3 | * | 68.5 | 63.4 | − 5.1 | ** | 34 | 119.2 | 118.9 | − 0.3 | NS | 75.7 | 72.3 | − 3.4 | * |
| 15 | 129.7 | 120.9 | − 8.8 | ** | 79.2 | 80.9 | + 1.7 | NS | 35 | 127.2 | 103.5 | −23.7 | ** | 81.4 | 81.7 | + 0.3 | NS |
| 16 | 115.0 | 124.7 | + 9.7 | ** | 73.0 | 73.9 | + 0.9 | NS | 36 | 111.2 | 108.2 | − 3.0 | NS | 70.7 | 74.2 | + 3.5 | * |
| 17 | 116.2 | 97.9 | −18.3 | ** | 79.0 | 71.7 | − 7.3 | ** | 37 | 104.9 | 107.8 | + 2.9 | NS | 69.0 | 49.6 | −19.4 | ** |
| 18 | 118.3 | 108.6 | − 9.7 | ** | 89.5 | 81.6 | − 7.9 | ** | 38 | 117.6 | 131.2 | +13.6 | ** | 81.1 | 80.6 | − 0.5 | NS |
| 19 | 118.9 | 116.7 | − 2.2 | NS | 77.5 | 84.0 | + 6.5 | ** | 39 | 130.0 | 123.6 | − 6.4 | NS | 81.3 | 83.9 | + 2.6 | NS |
| 20 | 119.4 | 104.5 | −14.9 | ** | 74.4 | 78.4 | + 4.0 | * | 40 | 147.6 | 130.6 | −17.0 | ** | 70.8 | 64.4 | − 6.4 | ** |

(*a*) Data collected automatically every 7.5 min for 24 h, averaged hourly in 2 profiles obtained about 1 month apart [19]. SBP = Systolic Blood Pressure; DBP = Diastolic BP. **$p < .01$; *$p < .05$; NS $p > .05$ for test of equality of MESOR between the 2 profiles.

(*b*) MESOR = rhythm-adjusted 24-h mean.

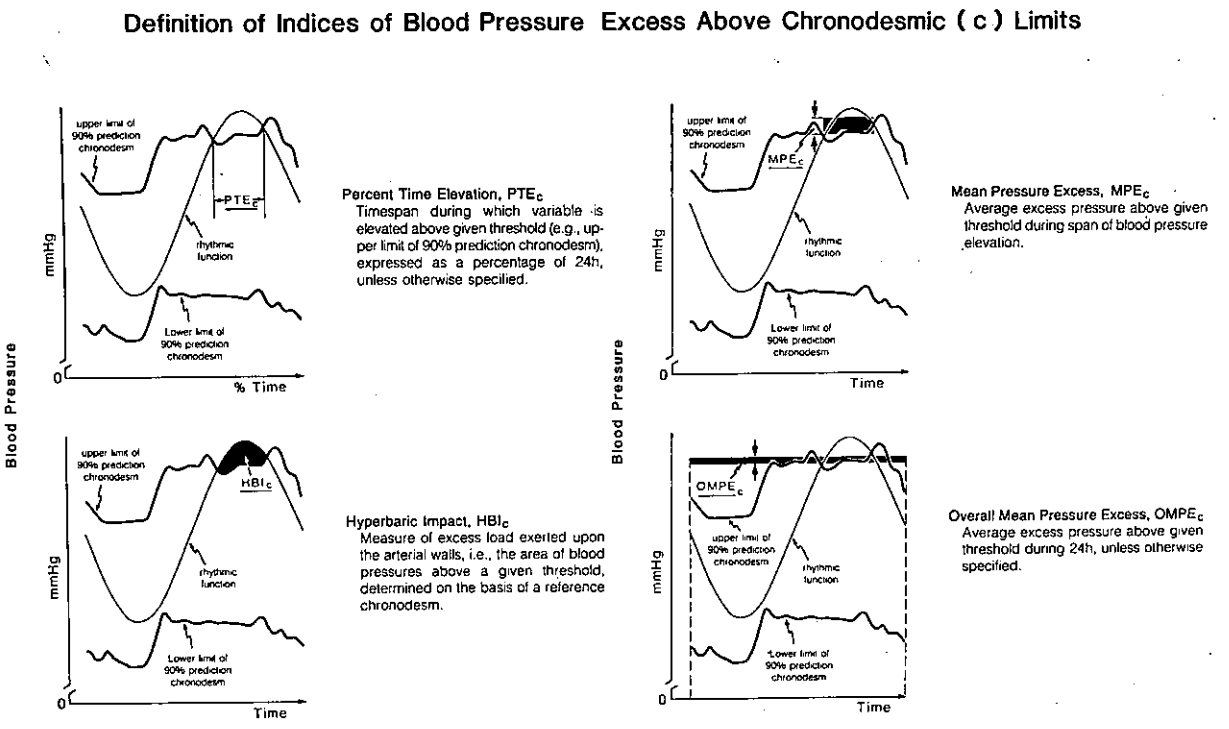



**Fig. 10.** - Definitions of indices of blood pressure excess, notably of hypertensive index. HTI (also called the hyperbaric impact, HBI). There may or may not be a cumulative excess (or deficit) in blood pressure. If there is such a deviation from the acceptable, the (deficit or) excess can recur only during part of each day or be present day and night. These questions can be answered by computing chronobiologic endopoints. The graphs present 90% prediction limits as a reference for assessing excess, as a blackened area, difined as the integral of blood pressures above the upper prediction limit during one cycle of the rhythm (e.g. 24 h). This excess can be computed directly in mm Hg × h. At least in principle, the concept of blood pressure excess is similar to that of pack-years of cigarettes or of person-years of exposure to asbestos. Measures of mean pressure excess and overall mean pressure excess can also be provided. Moreover, when automatic instrumentation is not available, and one must rely on self-measurements at intervals longer than the 7.5-15 min (that are easily implemented only with automatic instruments), a cosine curve can be fitted to the sparser data and endpoints of excess, including the hypertensive index, can be computed on this basis, as shown in the abstract graph. On groups, the hypertensive indices, computed from the cosine curve fit, correlate well with those obtained on the basis of actual dense measurements.

profile, the second has a lower MESOR ("direct change") in 14 instances for SBP and in 16 instances for DBP; the second profile has a higher MESOR ("inverse change") in 8 cases for SBP and in 7 cases for DBP, Fig. 6. The average absolute change in MESOR between the 2 profiles in clinically healthy men is less than 10 mm Hg, Table 4. Such a difference is reached or exceeded by 9 of 40 individuals for SBP and 6 of 40 individuals for DBP. Statistically significant differences in BP MESOR between consecutive days are also observed in individuals who monitor their BP automatically during a week or longer [7, 71].

In order to investigate any relation between the SBP MESOR during the first 24-h profile and the change in MESOR between the two profiles, a tendency toward the mean occurring naturally in the absence of any intervention has to be accounted for. The correlation is thus computed between the sum of the 2 MESORs and their difference ($r = .202$; $P = .208$). Since BP MESORs change from day to day, BP monitoring for more than a single 24-h span should estimate BP parameters and their changes in the abssence as well as the presence of dietary or other manipulation. Furthermore, since individual differences in BP change following such manipulations are found [14, 72], it is important to design experiments wherein, in addition to untreated control spans and, if possible, control groups, each subject undergoes all or at least most treatments, the sequence of treatments being randomized. Whenever possible, any change in BP should be assessed individually. In order to avoid any bias, primarily when subjects measure and record their own BP, a placebo should be usesd, not only in research projects but also in everyday pratice.

## Conclusions

In medical and scientific practice, the dictum to treat the individual and not the condition, i.e., the patient and not the disease, remains wishful

# SPHYGMOCHRON™-S (short form)

**MONITORING PROFILE OVER TIME; COMPUTER COMPARISON WITH PEER GROUP LIMITS**

## BLOOD PRESSURE (BP) AND RELATED CARDIOVASCULAR SUMMARY.

(Circadian Sphygmochron: from *sphygmo-*, of or relating to the circulation, notably blood pressure, as well as pulse and *chronos*, time)

Name _____ Patient # ESch 8610 No. of Profiles: 1

Age 63 Sex (M) [F] Monitoring From October 8 To October 24, 1986

TIME OF AWAKENING (A) 06 30 (Day of Profile) ( 06 30 (Habitually) ) FALLING ASLEEP (S) 23 00 (Day of Profile) ( 23 00 (Habitually) )

Rx: Dyazide 1 p.o., qA & q 15 30; Hydralazine 75 mg p.o. qA & q 15 30; Aldomet 260 mg p.o., q 15 30; Proventil 2mg p.o., qA, q 15 30 & qS; Theo-Dur 300 mg p.o., qA, q 15 30 & qS.

COMMENTS[1,2] _____

### CHRONOBIOLOGIC CHARACTERISTICS

| | SYSTOLIC BP (mmHg) | | DIASTOLIC BP (mmHg) | | HEART RATE (bpm) | |
|---|---|---|---|---|---|---|
| | PATIENT VALUE | PEER GROUP REFERENCE LIMITS | PATIENT VALUE | PEER GROUP REFERENCE LIMITS | PATIENT VALUE | PEER GROUP REFERENCE LIMITS |
| ADJUSTED 24-h MEAN (MESOR) | 145.0 | 98.4 – 135.1 RANGE | 88.3 | 60.3 – 87.2 RANGE | 83.7 | 56.4 – 91.2 RANGE |
| PREDICTABLE CHANGE (DOUBLE AMPLITUDE) | 19.48 | 6.40 – 39.40 RANGE | 19.77 | 4.84 – 29.80 RANGE | 6.32 | 5.26 – 36.20 RANGE |
| TIMING OF OVERALL HIGH VALUES (ACROPHASE) (hr:min) | 17:00 | 11:48 – 17:40 RANGE | 16:32 | 11:08 – 16:48 RANGE | 16:56 | 11:44 – 17:20 RANGE |
| PERCENT TIME OF ELEVATION | 64.5 % | | 23.5 % | | 4.3 % | |
| TIMING OF EXCESS | 22:43 (hr:min) | | 17:04 (hr:min) | | 02:18 (hr:min) | |
| EXTENT OF EXCESS DURING 24 HOURS | 132 (mmHg x hour) | | 32 (mmHg x hour) | | < 1 (bpm x hour) | |
| 10-YEAR CUMULATIVE EXCESS | 48.3 (mmHg x hour) (in 1,000's units) | | 11.8 (mmHg x hour) (in 1,000's units) | | < 0.1 (bpm x hour) (in 1,000's units) | |

**INTERVENTION NEEDED**

- [ ] No
- [x] Yes [x] Drug [ ] Non-Drug

**MORE MONITORING NEEDED**

- [ ] Annually
- [x] As soon as possible
- [ ] Other specify _____

PREPARED BY _____ DATE 86 / 10 / 2[illegible]

1. Unusually long standing or lying-down during waking; unusual activity, such as exercise, emotional loads, or schedule changes, e.g., shiftwork, etc. 2) Salt, calories, kind and amount, other, etc.

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For questions, call F. Halberg or G. Cornelissen at 612-624-6976

**Fig. 11.** - Computer-prepared blood pressure summary, the sphygmochron: short form.

Illustrative sphygmochron of patient to whom further monitoring is recommended.

SPHYGMOCHRON™-L

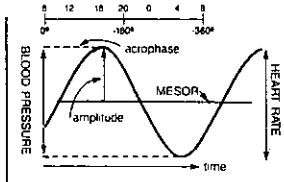
**BLOOD PRESSURE AND RELATED CARDIOVASCULAR MONITORING SUMMARY OVER TIME*** (Circadian Sphygmochron; from *sphygmo-*, of or relating to the circulating pulse, notably blood pressure, and *chronos*, time)

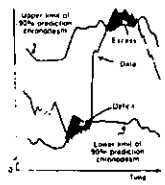
DMar 8605

Name 57 Age | (M) F Sex | From May 15 day, hour, min | To 16 day, hour, min | 19 86

TIMES OF

| Awakening | Activity[1] | Diet[2,3] |
|---|---|---|
| ~ 06 30 | Usual | Usual |
| Going to Sleep | | |
| ~ 23 30 | | |
| Drugs[3] | | |
| None | | |



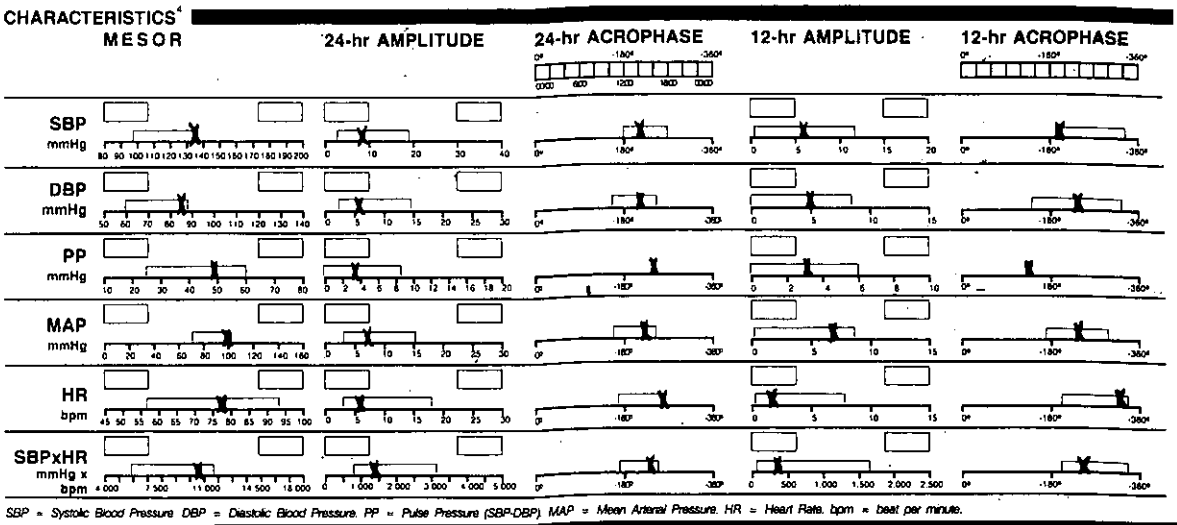



MESOR, (M) rhythm-adjusted mean (midline-estimating statistic of rhythm), defined as average value of rhythmic function (e.g., cosine curve) fitted to data; expressed in same units as original data. Note that MESOR will differ from arithmetic mean if data are unequidistant (e.g., concentrated near crest of rhythm) and/or cover non-integral number of cycles.

AMPLITUDE, (A) half of total predictable change in rhythm, defined by rhythmic function fitted to data; expressed in original or "relative" units, e.g., as percentage of series mean or MESOR.

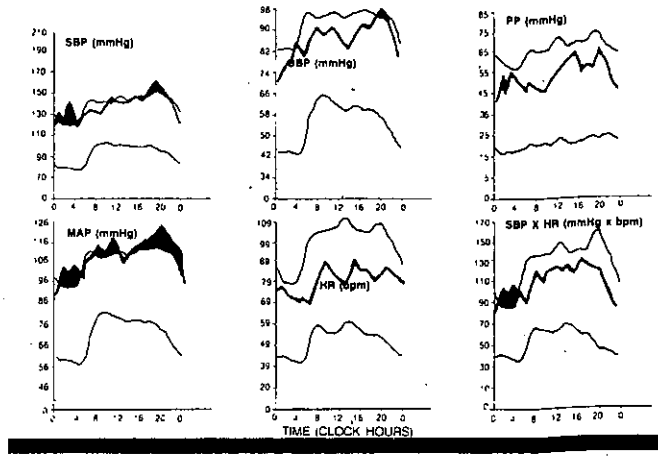
ACROPHASE, (Φ) lag from reference time of rhythm's crest-time, defined by rhythmic function fitted to data; usually expressed in (negative) degrees, with 360° = period, 0° = reference time; customary time units (e.g., clock-hours and minutes, days, weeks, months or years); physiologic units (e.g., number of heart beats, respiratory or menstrual cycles) also appropriate for rhythm synchronized with corresponding period.

**CHARACTERISTICS[4]**



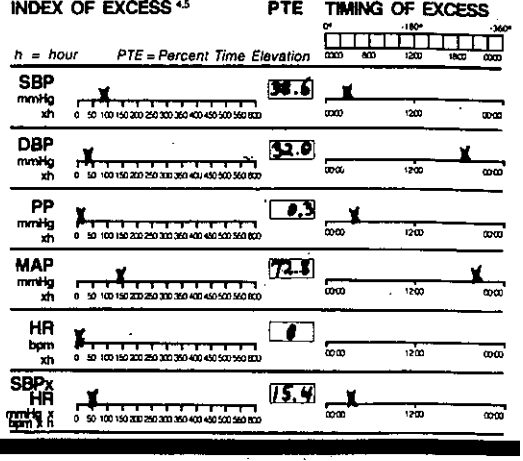

*SBP = Systolic Blood Pressure. DBP = Diastolic Blood Pressure. PP = Pulse Pressure (SBP-DBP). MAP = Mean Arterial Pressure. HR = Heart Rate. bpm = beat per minute.*

**INDICES OF DEVIATION**




**INDEX OF EXCESS[4,5]** | **PTE** | **TIMING OF EXCESS**

*h = hour* *PTE = Percent Time Elevation*




**INTERVENTION NEEDED** ☐ Yes ☐ Drug ☐ Non-Drug ☑ No

**MORE MONITORING NEEDED** ☐ No ☑ Yes

PREPARED BY

86 05 17
DATE (YR, MO, DAY)

1) Unusually long standing or lying-down during waking; unusual activity, such as exercise, etc.; 2) Salt, calories, other, etc.; 3) Kind and amount, if any; 4) Rectangles on baselines indicate acceptable range; other rectangles serve for values off-scale; 5) Values calculated with respect to □ chronodesmic limits (time-specified 90% prediction limits) or with respect to ▭ fixed limits, determined on the basis of the median acrometron (MESOR + amplitude, i.e., highest predictable value) of a peer group: check this box ☐ if index of deficit rather than excess.

* Crosses on form indicate results from your individualized cardiovascular monitoring profile; if numbers (instead of crosses) are used, they refer to several stages of your monitoring, along with results of tests for any change in circadian parameters. (See comments on reverse side, that may also refer to rhythms other than circadian and/or trends.)

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**Fig. 12.** - Computer-prepared blood pressure summary, the sphygmochron: long form.

thinking until the inferential statistical approach, with P-values for a given effect in the given individual, routinely complements the P-values now restricted mostly to the interpretation of results from group comparisons. In a given case, P-values are useful only to the extent that they apply to the individual considered; hence a personalized P-value is the goal of any medical interpretation of observations on a given patient. With this critical qualification, we agree with Rosner [73] that it is "... desirable to screen a large population for hypertensives rather than wait for the hypertensives to seek medical attention".

Another need for scientific medicine is to assess the acceptability or lack of acceptability of a BP (or other rhythmic variable) [13, 74] against (living) peer group reference standards rather than against an arbitrary traditional normal limit. Such peer-group norms can be complemented with individualized norms. These norms can be obtained cost-effectively for the next generation in late primary and secondary education [7, 8, 75]. Characteristics of rhythms can then also be used as gauges of health and their alterations as gauges of a heightened risk of developing a high BP [2, 7]. As the costs of health care increase, chronobiologic literacy as part of self-help to achieve the foregoing goals has no cost-effective alternative [75, 76]. Moreover, the chronobiologic approach illustrated for BP also applies to the meaningful, cost-effective appraisal of endocrine factors coordinating BP [2, 77]. In manipulating the endocrines, with an individualized (rather than population) approach, during pregnancy or at least starting at birth [9], a path may be found toward the prevention of major incapacitating and terminating diseases of our day. Chronobiology implies both timely and early intervention, on the basis of sensitive methods that replace the single measurement snapshots of a roller coaster.

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