Blood Pressure Monitoring: a Chronobiological Approach to Hypertension Diagnosis

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Automatic devices for noninvasive blood pressure (BP) monitoring have been developed in the 80s. Improved accuracy in the diagnosis of elevated BP has become possible due to objective detection of BP fluctuations over a 24-hour period. The obvious advantages of such a method of outpatient BP measurements are: repeated readings, the possibility of taking the blood pressure or in the workplace, the possibility of night measurements, individualized therapeutic schemes, identification of "incidental hypertension hour", the possibility of comparing the data with the results of other monitorings, minimization of negative psychological effects, and the possibility of using the resultant 24-hour curves in image recognition procedures.

The results of 24-hour chronobiological studies have helped detect the presence or absence of a 24-hour BP rhythm. Such studies permit a comparison of the results with the variable standard BP range instead of a fixed range and thus help minimize the number of diagnostic errors. It has been found possible to improve diagnostic accuracy by eliminating the source of regular diagnostic errors which lead to "false-positive" or "false-negative" diagnoses (Fig. 1). At the same time, a number of complicated problems arise: 1) how to analyze the results of monitoring using statistical tests? 2) how to calculate the time limits of normal BP? 3) how to compare the results of a certain monitoring with the standard range of values?

BP monitoring can be regarded as an effective approach to the evaluation of the total time organization. The diagnosis of hypertension by BP monitoring and the use of time criteria can be termed chronodiagnosis. In the present study three chronodiagnostic methods are discussed: 1) statistical analysis of BP monitoring results; 2) statistical evaluation of chronodesm limits; 3) detection of BP excesses (surges) during individual monitoring.

1. Statistical analysis of individual BP monitoring

The initial step in a chronodiagnostic procedure is to evaluate the biometric characteristics of BP monitoring in a person. An individual BP curve in this paper is processed by so-called macroscopic and microscopic analysis. Such a dual approach had to be resorted to because a 24-hour curve obtained as a result of 24-hour monitoring can be used in both discrete and periodic variability.

1.1 Macroscopic analysis

The noninferential (macroscopic) method is used for discrete determination of variability during 24-hour monitoring. It is realized with the aid of traditional mathematical statistical methods and consists in the use of nontransformed discrete initial data and the deriving, on their basis, of parameters of the central position and variance (Fig. 2). A description of the parameters used is presented in Table 1.

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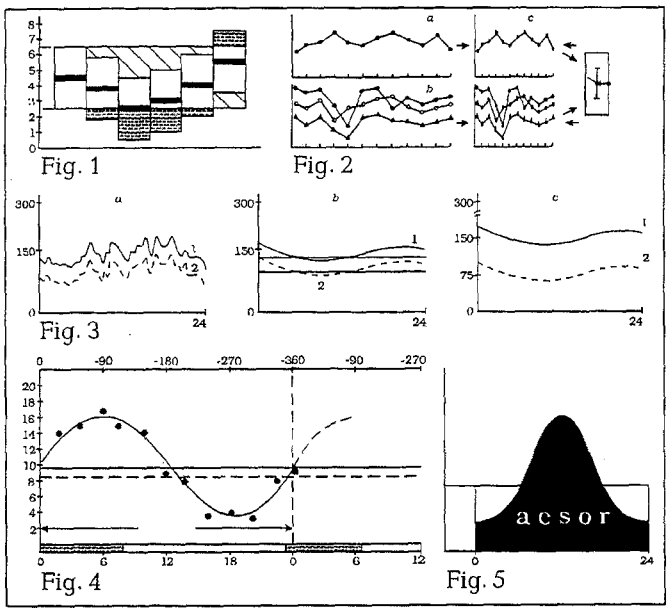

Fig. 1. Types of erroneous diagnosis of hypertension (without consideration for blood pressure chronomonitoring). Oblique dashed line shows false–positive and false–negative diagnosis of arterial hypertension. Black shading: mean arterial pressure level. Here and in Figs. 2–8: time in h laid as the abscissa.

Fig. 2. Individual and group macroscopic description of chrono–medical information. Ordinate: AP level (mm Hg). *a* – chronogram of a patient; *b* – chronogram of a group of patients; *c* – the same, in the jist form.

Fig. 3. Graphic methods of representing chronobiologic data. *a* – chronogram. 1 – systolic AP upper curve; 2 – diastolic AP lower curve. *b* – cosinorgram. 1 – systolic AP; 2 – diastolic AP; straight lines – systolic and diastolic AP mesors. *c* – aesorgram. Zone between 1 and 2 – systolic AP fluctuation limits; below 2 – diastolic AP.

Fig. 4. Cosinusoidal approximation of experimental data. Oblique dashed line – sleeping period; straight line – mesor, zone between unbroken and broken straight lines – mesor standard error. Curve – cosinusoid, upper horizontal straight line – grades. Laid off as ordinate: conditional units.

Fig. 5. Azor square under individual cosinor analysis curve. M – mesor. Laid off as ordinate: AP value.

The discrete variability of systolic and diastolic arterial pressure (SAP and DAP, respectively) is shown in the chronogram (Fig. 3, *a*).

1.2 Microscopic analysis

Inferential (microscopic) analysis of individual BP monitoring implies the use of two methods. In the first, the microscopic procedure serves for evaluation of the periodic variability. This approach is realized with a special chronobiological method called simple (individual) cosinor analysis [6,7], based on approximation to the initial data of the cosinusoidal curve by the least squares method and calculation of its rhythmometric parameters (Table 2).

The approximation curve is defined as a curve of the type

$$Yt = M + A \cdot cos(2\pi / 24 \cdot t + \varphi),$$

providing the best approximation to the initial data by the least squares method (Fig. 4).

SAP and DAP periodic variabilities are shown on the cosinorgram (Fig. 3, *b*).

The second microscopic approach [2,3] makes use of estimation of the area under the cosinusoidal curve obtained by individual cosinor analysis (Fig. 5). The suggested designation of this area, calculated as a cosinusoidal function integral resulting from individual cosinor analysis, is "aesor". This parameter (Table 3) expresses the total sum of pressure which is effective within 24 h and is calculated according to the formula

$$\int_{t=0}^{t=24} (M + \cos(2\pi / 24 \cdot t - \varphi))dt.$$

The integral periodicity of SAP and DAP is shown on the aesorgram (Fig. 3, *c*).

2. Chronodesm evaluation procedure

The data influencing the diagnosis of hypertension formally make up the individual chronogram, cosinorgram, and aesorgram. Therefore, it is advisable for diagnostic comparison to evaluate some of the reference standards calculated from the data obtained in examinations of normal subjects. Before describing different versions of such standards [1,8,10,11], we should like to emphasize that the standard range is determined according to a common rule [4,11,12], which consists in the calculation of 90% of the tolerance limits (TL). We shall designate the mentioned limits as 90% TL.

We can calculate 90% TL from the results of 24-hour monitoring, provided two conditions are observed: first, it is assumed that the experimental data are characterized by a normal distribution, and second, that random selection is used and the results of measurements of the studied parameter in at least 30 normal subjects are used. These conditions permit the application of statistical evaluations on the basis of the Student distribution.

TABLE 1. Noninferential (Macroscopic) Evaluation Parameters Obtained on the Basis of Standard Statistical Procedures Applied to BP Values in Discrete Time Sections

Parameter	Chronodiagnostic value	Measurement unit
24–hour mean value	Arithmetic mean of 24–hour BP values	mm Hg
Standard deviation	68% confidence interval of mean value	mm Hg
Peak	Highest BP	mm Hg
Minimal value	Lowest BP	mm Hg
Variability coefficient	Degree of variability of BP values in relation to mean	%

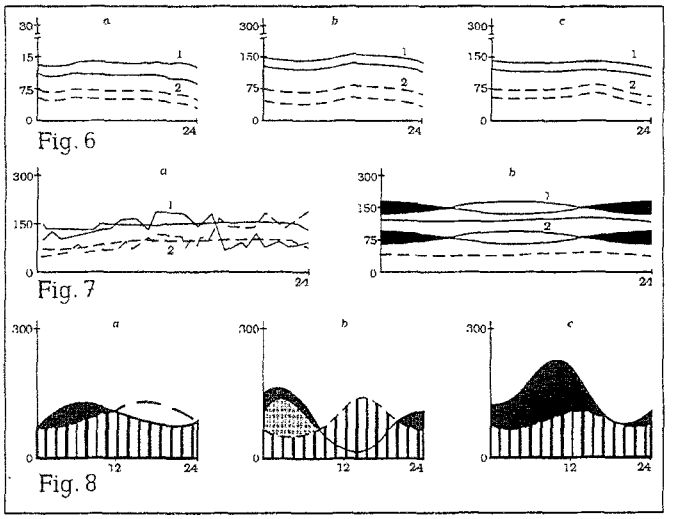

Fig. 6. Various desm types. *a* – chronodesms. 1 – zone between upper unbroken lines: systolic AP chronodesm; zone between dashed lines – diastolic AP chronodesm. *b* – aesordesms. 1 – systolic AP aesordesm; 2 – diastolic AP aesordesm.

Fig. 7. Variants of relative disposition of chronogram and cosinorgram in relation to respective desms. *a* – chronogram in relation to chronodesm. 1 – systolic AP; 2 – diastolic AP. Relatively straight lines: chronodesm borders. *b* – cosinorgram in relation to cosinordesm. 1, 2 – same as in *a*. Black shade: hyperbaric increase.

Fig. 8. Hypertension varieties. *a* – phase hypertension. Broken curve – upper cosinordesm. Dotted zone – hyperbaric increase. Vertical shading – pressure increase. Laid off as ordinate: AP. *b* – amplitude hypertension, *c* – mesor hypertension.

Taking the aforesaid into account, we adduce that 90% TL is calculated by the formula:

$$90\%TL = M \pm SD \cdot t(p = 0.1, n-1),$$

where M is the mean, SD is the standard deviation, $t(p=0.1, n-1)$ is the 90% percentile of the Student t distribution with $n-1$ degree of freedom, n being more than 30.

The standard region for comparison of the individual chronograms is a result of application of the above formulas to each time point, i.e.

$$M(t) \pm SD(t) \cdot t(0.1, n-1).$$

Calculating 90% TL for SAP and DAP in such a way, we derive standard time values which are called chronodesms [6]. Hence, chronodesms may be defined as arbitrary time standards including 90% BP values in each time section with a 90% probability.

To compare individual cosinorgrams, it is necessary to have the standards characterized by periodic variability. It seems advisable to use formulas similar to the aforementioned, not to the initial (discrete) data, but to a function of the type

$$M + A \cdot \cos(2\pi / 24 \cdot t - \varphi),$$

that is,

$$(Mm \pm SDm \cdot t(0.1, n-1)) + M_A \pm$$
$$\pm SD_A \cdot t(0.1, n-1)) \cos(2\pi / 24 \cdot t - \varphi).$$

The above formulas help obtain time standards called cosinordesms [10]. Cosinordesms can therefore be defined as a sinusoidal band containing 90% of cosinorgrams with a 90% probability.

An individual aesorgram should correlate with a corresponding standard, which in this case can be obtained by the formulas:

$$\int_{t=0}^{t=24} (M(m) \pm SD(m) \cdot t(p = 0.1, n-1)) +$$
$$+ (M_A \pm SD_A \cdot t(p = 0.1, n-1)) \times$$
$$\times \cos(2\pi / 24 \cdot t + \varphi) dt.$$

The highest and lowest 90% TL for SAP and DAP aesor from time standards which are called aesordesms [3]; they are shown in Fig. 6, *c*.

3. Determination of BP excesses during individual monitoring

The previous steps provided all the elements for the final chronodiagnostic procedure. Hypertension can be diagnosed just by comparing individual BP monitoring chronograms, cosinorgrams, and aesorgrams with the corresponding standards. Comparison of SAP and DAP chronograms with chronodesms permits a "macroscopic diagnosis of hypertension," while the procedure of comparing SAP and DAP cosinorgrams and aesorgrams with the corresponding cosinordesms and aesordesms allows for a "microscopic diagnosis of hypertension."

3.1 Macroscopic diagnosis of hypertension

The purpose of this is to calculate the percent of BP values surpassing the upper threshold of the normal range to the total count of time sections and to qualify BP values in time, as is shown in Fig. 7, *a*.

We would emphasize that any time data series is "hindered" in a certain way during measurements or surrounding incidental effects [3]. A stochastic component causing "white noise" can provoke an erroneous diagnosis of hypertension if the data are not

TABLE 2. Parameters of Rhythm Obtained by Cosinor Analysis

Parameter	Chronodiagnostic value	Measurement unit
Mesor	Mean level of 24-hour sinusoid best approximating initial data	mm Hg
Amplitude	Maximum deviation of 24-hour sinusoid from mesor	mm Hg
Acrophase	Time of peak of 24-hour sinusoid	hour, min

TABLE 3. Macroscopic Evaluation of Area under Sinusoidal Curve Obtained by Cosinor Analysis

Parameter	Chronodiagnostic value	Measurement unit
Aesor (area under curve statistically evaluating rhythm)	Total pressure over 24 h as a result of 24-hour BP variability	mm Hg×h

filtered in some way. According to some authors, stochastic distortions during BP monitoring can account for approximately 3% of the whole number of points measured [3]. Hence, hypertension can be diagnosed only by BP monitoring which shows that the higher chronodesm limit is surpassed in more than 3% of points [3].

3.2 Microscopic diagnosis of hypertension

The purpose of a microscopic comparison of cosinorgrams with cosinordesms is to elucidate, on the basis of assessing the degree to which the higher cosinordesm threshold is surpassed by cosinorgrams, whether the mesor and/or amplitude increase caused by periodic SAP and DAP oscillations is abnormal, as shown in Fig. 7, *b*. The set of points on the plane that are enclosed between the part of the cosinorgram surpassing the upper cosinordesm limit and the topmost limit is called the "hyperbaric impact" (HI), the time limits of HI representing the duration of BP increase (excess) [2,5].

HI can be caused by mesor increase ("mesor hypertension" [5]) by an abnormally high fluctuation amplitude ("amplitude hypertension"), and finally, by a shift of the fluctuation phase ("phase hypertension") [2]. Microscopically, hypertension can therefore be represented as a hemodynamic state characterized by an increase of the upper chronodesm limit resulting from circadian BP fluctuations described by a mesor increase and/or a shift in acrophase (Fig. 8). The microscopic approach is supplemented by a comparison of SAP and DAP aesorgrams with the upper 90% aesordesm limit.

Supposing that aesor is the evaluation of pressure surge (PI or BI - basic impact), it can be assteded that aesorgram rise reflects a possible appearance of a pressure excess (PE or BE) which is connected with the difference between the individual (IBI) impact (surge) of pressure (PI) and its higher standard RBI (R - reference) of PI, and BE=IBI-RBI [3]. Hence, the BE value characterizes the degree of pressure surge.

4. Discussion

A question arises: Which of the two methods of chronodiagnosis is more informative? We must mention first of all that the informative value of the macroscopic and microscopic diagnostic elements is not identical. This is due to the fact that a chronogram, as a discrete values curve, is usually "contaminated" by stochastic noise [9]; in contrast, a cosinorgram, being an analytical curve, is free of "noise" and the elevation of its values above the standard values in the form of the cosinordesm is, in our view, more cogent proof that higher BP curve values are truly connected with disturbances of normal BP structure.

Macroscopically diagnosed high BP is therefore a guarantee of correct diagnosis of hypertension. Consequently, microscopic chronodiagnosis of hypertension becomes a necessary tool, supplementing the macroscopic approach. Furthermore, the microscopic approach is the basis for a quantitative evaluation of BP excesses and for specific analysis of HI, PE, and BE values that helps assess the severity and duration of hypertension. This paper has aimed to explain the new method for BP monitoring, permitting the use of time standards for chronodiagnosis of hypertension.

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