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Cugini, Pietro
Institute of II Medical Clinics University of Rome

Kawasaki, Terukazu
Institute of Health Science, Kyushu University

Di Palma, Loredana
Institute of II Medical Clinics University of Rome

Otsuka, Kuniaki
Department of Internal Medicine, Tokyo Women's Medical College

他

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Innovative Criteria for Diagnosing Arterial Hypertension via Blood Pressure Monitoring: The Chronodiagnosis

Pietro CUGINI*, Terukazu KAWASAKI, Loredana DI PALMA*,
Kuniaki OTSUKA** and Keiko UEZONO

Summary

There is an increasing use of ambulatory blood pressure(BP) monitoring for the clinical diagnosis of arterial hypertension. The BP monitoring is still analyzed with reference to fixed limits. This diagnostic method is highly improved by the use of temporal criteria according to a methodology which is called "chronodiagnosis" of arterial hypertension. The chronodiagnostic procedure is structured in three levels, each one providing a specific assessment of BP 24-h pattern. Level 1 analyses the discrete variability of BP raw values. Level 2 estimates the periodic component of BP 24-h pattern which is physiologically arranged to fluctuate with a circadian rhythm. Level 3 computes measures on the BP 24-h pattern as a "whole" in order to estimate the Baric Impact produced by the circadian oscillation. According to the chronodiagnostic procedure arterial hypertension can be qualified in its excess and temporal duration. The chronobiometric approach to BP monitoring provides, thus, 1. a more accurate diagnosis; 2. a clinical estimate of the tensiogenic regimen, 3. a clinical classification of arterial hypertension into definite chronopathologic types.

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PRINCIPLES OF CHRONODIAGNOSIS

The XIXth International Conference for Chronobiology held in Washington D.C. in 1989 has been a milestone for the intelligence of blood pressure (BP) monitoring in clinical diagnosis of arterial hypertension (AH). In that setting, it has been rebated that the use of fixed standards invariably generates false diagnoses when dealing with a time-dependent variable (Fig.1). Furthermore, it has been stressed that BP is not simply a time-varying function, as already demonstrated by many hypertensinologists[17),18),21–23)], but also and principally a periodic variable showing a well-constituted circadian rhythm, as documented by several chronobiologic studies[2),4),10),13)].

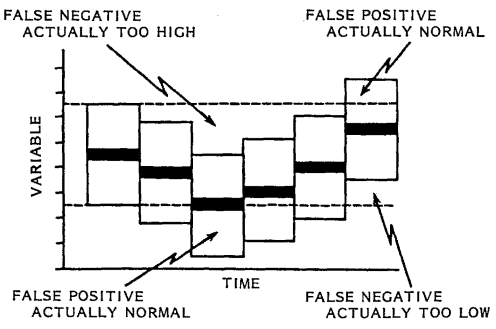

Fig.1 Genesis of false diagnoses by using fixed reference limits for a time-dependent biological variable.

Institute of Health Science, Kyushu University, Kasuga 816, Japan.
*Institute of II Medical Clinics, University of Rome, 00161 Rome, Italy.
**Department of Internal Medicine, Tokyo Women's Medical College, Tokyo 116, Japan.

Two fundamental principles were established. First, the diagnosis of AH is more accurate if performed via BP monitoring rather than via "casual" sphygmomanometric measurements. Second, the diagnos is of AH is more reliable if the BP monitoring is gauged in its discrete and periodic variability. Accordingly, it has been suggested that the diagnosis of AH should be based on temporal rules, becoming an ordinary process of chronodiagnosis.

INDISPENSABLE ELEMENTS FOR CHRONODIAGNOSIS

According to the chronodiagnostic principles, the individual BP monitoring has to be conveniently expressed in its discrete variability and periodic fluctuation.

The discrete variability is represented by "chronograms" derived by the plot of systolic and diastolic raw values as a function of time on a cartesian diagram (Fig.2).

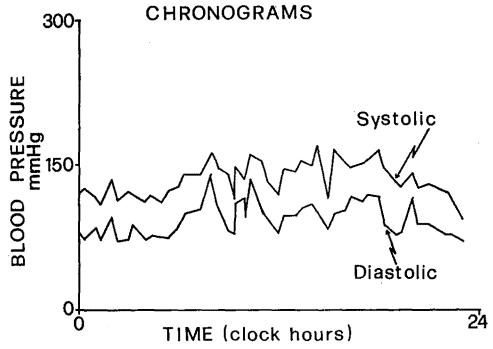

Fig.2 Representation of systolic and diastolic blood pressure 24-h pattern via time-qualified raw values interpolated by an interrupted line, the so-called "Chronograms".

The periodic variability is represented, in turn, by "cosinorgrams" provided by the bidimensional plot of the optimal sine wave which fits the time-qualified raw values of systolic(SBP) and diastolic BP(DBP) (Fig.3).

The best fitting waveform profiles are derived by means of Single Cosinor Analysis (12), a procedure of periodic regression using the cosine function $Yt = M + A \times \cos(2\pi/TAU \times t + \phi)$ for the interpolation by means of the method of least squares (Fig.4). The cosinor analysis enables us to estimate the parameters of the sinusoidal oscillation in terms of mean level of fluctuation, i.e., Mesor (M, acronym of Midline Estimating Statistic Of Rhythm); extent of oscillation, i.e., Amplitude (A); timing of oscillatory phase,i.e., Acrophase (ϕ); by adopting as period (TAU), the length of 24-h corresponding to a day-night cycle. Additionally, the periodic variability of BP 24-h pattern is represented as "aesorgrams" given by the diagramatic representation of the area underlying the cosine curve of systolic and diastolic circadian rhythm (Fig.5).

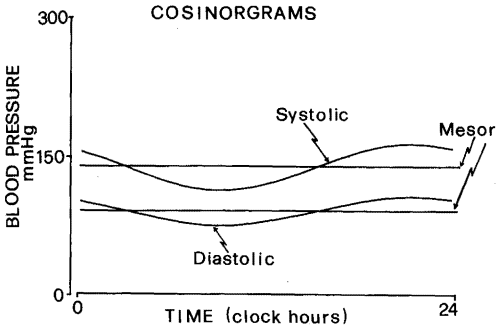

Fig.3 Representation of systolic and diastolic blood pressure 24-h pattern via the best fitting of sine curve of time-qualified raw values, the so-called "Cosinorgrams".

The aesorgrams are quantified by the area covered by the circadian oscillation(Fig.6). Such an area is measured by means of a periodic integration method(Single cosint analysis) using the formula $Yt = \int_{t_1}^{t_{24}} [M + A \times \cos(2\pi/TAU \times t + \phi)] dt$[5]. The estimated corresponds to the parameter AESOR (acronym of Area Estimating Statistic Of Rhythm). As far as the BP 24-h pattern is concerned, the AESOR represents the mmHg that were effective because of the circadian oscillation. This product overtime is called Baric Impact (BI).

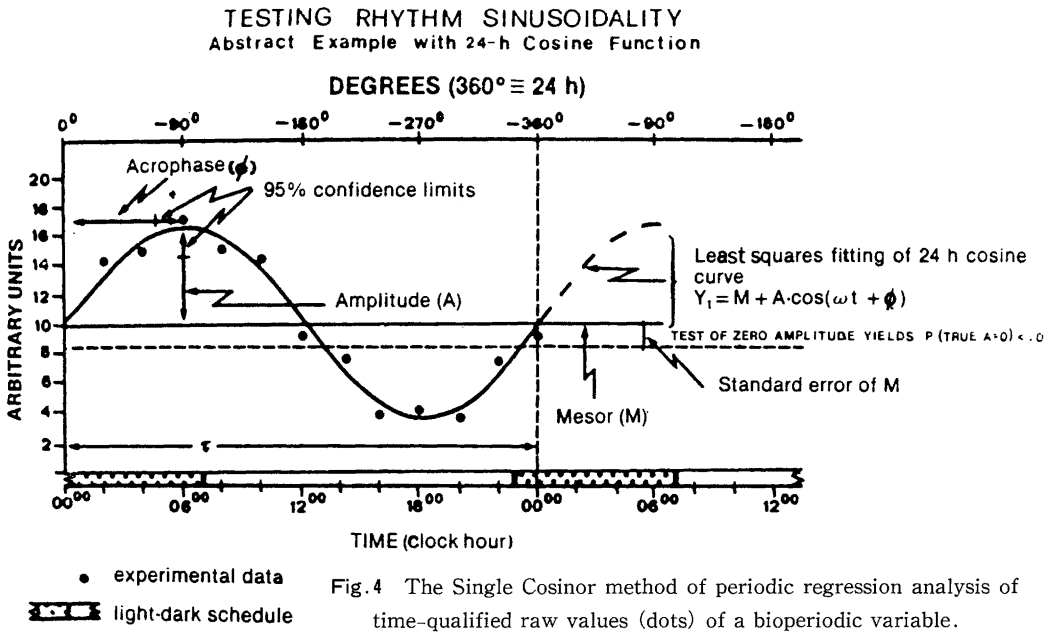

Fig.4 The Single Cosinor method of periodic regression analysis of time-qualified raw values (dots) of a bioperiodic variable.

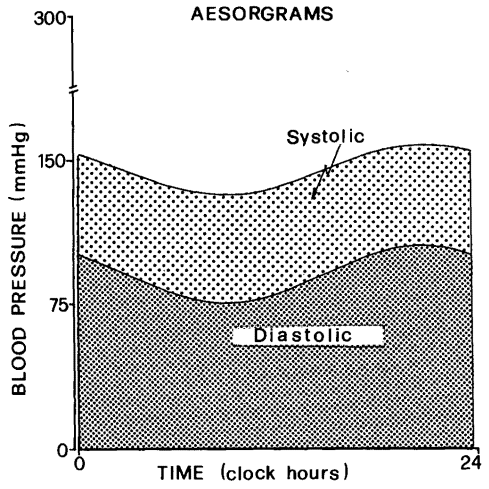

Fig.5 Representation of systolic and diastolic blood pressure 24-h pattern via the area covered by the best fitting sinusoidal curve of time-qualified raw values, the so-called "Aesorgrams".

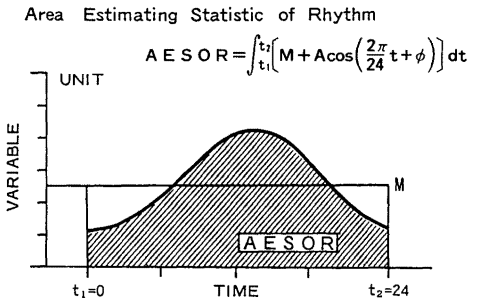

Fig.6 Determination of Aesor by single cosint analysis as the periodic integral of the area covered by the optimal sine wave fitting the circadian oscillation of a biorhythmic variable.

TIME-QUALIFIED REFERENCE LIMITS FOR CHRONODIAGNOSIS

Importantly, for the chronodiagnosis of AH it is essential that the reference standards(desms) are appropriate to represent temporally both the discrete and periodic variability of BP 24-h pattern. Therefore, the time-qualified standards in use are respectively the chronodesms(Fig.7), cosinordesms(Fig.8) and aesordesms(Fig.9). They are used for comparing the individual systolic and diastolic chronograms, cosinorgrams and aesorgrams, respectively.

How to construct these temporal indices of reference is largely described elsewhere[3)8)19)20)].

What is important to stress is that the temporal

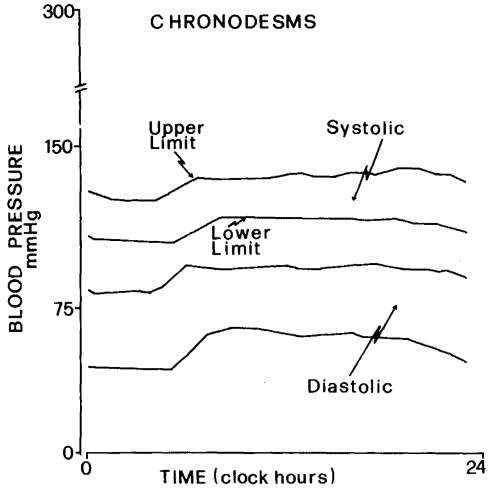

Fig.7 Representation of reference limits for time-qualified values of systolic and diastolic blood pressure as an interrupted band which includes in each time point 90% of distribution with 90% of probability, the so called "Chronodesms".

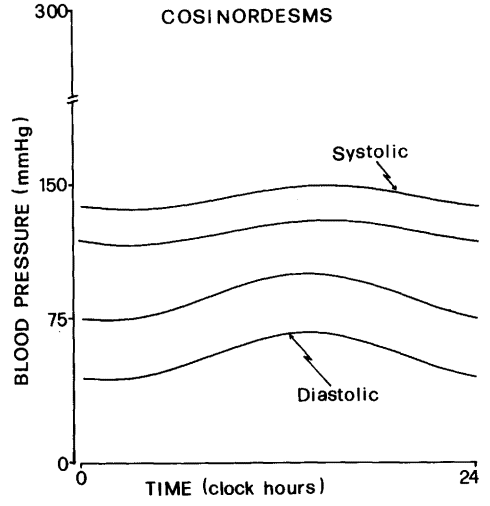

Fig.8 Representation of reference limits for circadian oscillation of systolic and diastolic blood pressure as a sinusoidal band which includes 90% of oscillatory distribution with 90% of probability, the so-called "Cosinordesms".

indices of reference ordinarily represent the variability in a proportion which includes 90% of distri-

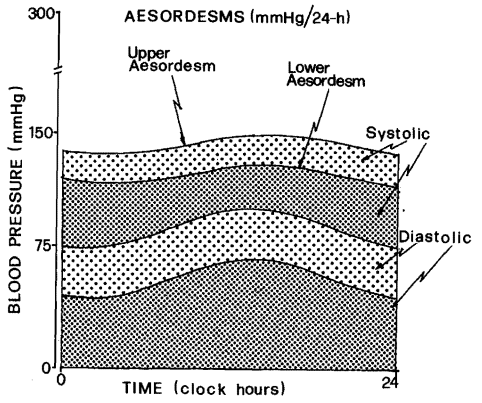

Fig.9 Representation of reference limits for the area covered by the circadian oscillation of systolic and diastolic blood pressure as a sinusoidal band whose surface includes 90% of oscillotory areas with 90% of probability, the so-called "Aesordesms".

bution with 90% of probability. Statistically, these standards can be defined 90% Tolerance Limits or 90% Prediction Limits[11)16)24)25)].

CHRONODIAGNOSTIC PROCEDURE

In the chronodiagnostic process, three comparisons have to be performed in order to decipher whether or not an individual BP monitoring is deviant from normotension. The procedure is, thus, ordered by levels.

1) Level 1. Comparison of individual BP chronograms to chronodesms

In this first step, the individual chronograms for systolic and diastolic BP are confronted with the relative chronodesms (Fig.10). The aim is to detect how many BP values exceed the upper limit of their time-qualified reference standards. The diagnosis of AH will be stipulated whether there is evidence of supranormal values.

Statisticians recommend to consider that any series of measurements, including the temporal one, is subject to the influence of noise or random disturbance. Because of this stochastic variability, which is erratic within the series, any BP monitoring, even the most accurate, may contain

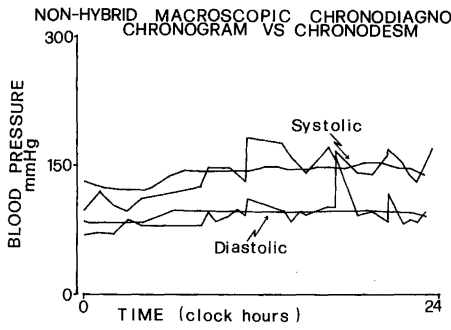

Fig.10 Level 1 of chronodiagnosis of arterial hypertension: Comparison of the individual systolic and diastolic chronograms to the corresponding chronodesms.

values expected by chance. This aleatory component causes the Error Type 1 (alpha error) which can be committed by analyzing the chronograms versus the chronodesms. The question is how to eliminate such a source of erroneity in the Level 1 of chronodiagnosis. Statisticians again suggest to adopt a filter, that is to say a level of probability beyond which the abnormal values may not be considered an effect of putative noise. The alpha level of probability, worldwidely accepted, is $p<0.05$, which means that at least 1 BP value over 20 measurements may be expected as an effect of ramdomness. This implies that the chronodiagnosis of AH is made on the assumption that of least 5% of total measurements are supranormal. It is important to stress that the probabilistic correction of chronodiagnosis is fundamental in order to avoid the incidence of false positives.

In ordinary conditions, the BP monitoring is programmed to take readings at 15-30 min intervals. This means that the collection of a time series is constituted by 48-96 date points. The stochastic filter assumes that the deviant measures to remove range from 3 to 6. The question is which values are to be removed from those which constitute to the supranormal component. The other question is whether or not the deviant values to be removed are truly abnormal.

In attempting to avoid error Type 1, one can commit Error Type 2 (beta error) which consists in considering stochastic a measure whose abnormality is not the effect of randomness. In other words, and with respect to BP, there could be a few values which are truly elevated because of a labile AH without being due to random variability. In order to avoid errors Type 1 and 2, it is fundamental to consider that BP follows in its intra-individual and inter-individual variability the so-called "normal" distribution[7].

This means that one can consider to be stochastic only those values which fall within the 95th and 100th percentile. Therefore, AH will be diagnosed if the individual BP chronograms includes; 1. more than 5% of values within the 95th and 100th percentile; 2. any value above the 100th percentile, as compared to the pertaining chronodesms. Obviously, any artifactitious measurement has to be preventively removed from the series, the artifacts merely depend on technical biases, constituting detectable errors of incorrectness.

In concrete situations, the comparison of BP 24-h values with the coincident time points of the chronodesmic band has to be made with a certain flexibility. It must be pointed out that the chronodesmic limit is made by an interrupted interpolation of discrete standard limits computed by 15-30 min intervals. If a raw value in BP monitoring falls in between, its estimate has to be referred to the nearest time-qualified reference limit, unless the intermediate standard is calculated by interpolation techniques, e.g, the Newton's interpolation method.

2) Level 2. Comparison of individual BP cosinorgrams to cosinordesms

Statisticians suggest that a way to remove the effect of randomness may be the use of analytical functions which express the mean trend if the series is directional. Any time series is per se a directional sequence. Therefore, the time series may be conveniently explored by analytical functions. The question is how to choose the model which is optimal for that a given time series.

Chronobiologists have largely demonstrated that

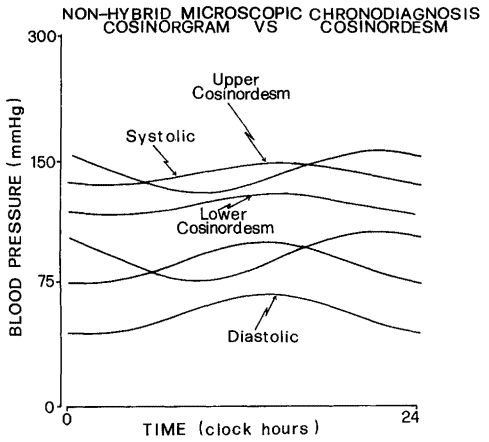

Fig.11 Level 2 of chronodiagnosis of arterial hypertension: Comparison of the individual systolic and diastolic cosinorgrams with the corresponding cosinordesms.

BP is a periodic function over 24-h span[2)4)10)13)]. Geometrically, the optimal model for analytically exploring oscillating phenomena is the periodic regression analysis. According to the periodic regression, the BP 24-h pattern can be, thus, explored in the systematic component of their cyclic structure. Therefore, the above-mentioned cosinor analysis is fundamental for discovering whether or not that a given BP monitoring is in some way affected by distortions. In that case, the abnormality may be related to the intrinsic structure of the BP 24-h pattern. This means that the diagnosis of AH, made via cosinorgrams, reflects the occurrence of hypertensive values which are not dependent on a casual disorder in BP 24-h pattern. In other words, the Level 2 of chronodiagnosis allows us to inequivocably define whether or not BP monitoring is truly hypertensive.

Practically, the second step is performed by comparing the individual systolic and diastolic cosinorgrams to the parent cosinordesms (Fig. 11).

If the cosinorgrams exceed the 90% upper limits of reference cosinordesms, there is an evidence in favor of a non-erroneous diagnosis of AH.

It must be furtherly rebated that the BP cosinorgrams are analytical curves which are depured by the biological noise of random values. Their disproportionate overlapping to 90% upper cosinordesms is, thus, a probatory that the BP 24-h pattern is systematically altered in its elevation. The cosinorgrams may be, thus, used for better understanding the mechanisms for which AH formally develops.

The clinical experience with the comparison of cosinorgrams to the pertaining cosinordesms has demonstrated that several mechanisms may cause the BP 24-h pattern to deviate from normotension. These choronopathologic disturbances may relate to phase, amplitude and/or mesor of BP circadian rhythm.

For instance, a phase-shift can be the mechanism which causes the systolic and diastolic cosinorgrams to exceed the upper 90% cosinordesms(Fig.12) in a limited part of the day, usually night-time, giving rise to the so-called "Phase-hypertension" [6].

An amplitude increase may itself cause the systolic and diastolic cosinorgrams to be redundant with limitation to a portion of the day, either diurnal or nocturnal(Fig.13). This kind of mechanism promotes the so-called "Amplitude-hypertension" [14),15)].

A mesor elevation may be a third mechanism (Fig.14). In this case, the AH takes the name of "Mesor-hypertension" [14),15)].

Interestingly, both "Amplitude-hypertension" and "Mesor-hypertension" may be associated with a phase rotation which causes the BP circadian rhythm to be reversed[9)]. Because of this combination, there are two further chrono-pathologic types of AH, namely "Reverse amplitude-hypertension" (Fig.15), and "Reverse mesor-hypertension" (Fig.16).

Lastly, the mechanism of alteration may reside in a mesor increase associated with the abrogation of BP circadian rhythm[9)]. In such a circumstance, the AH will take the appellative of "Aperiodic-hypertension" (Fig.17).

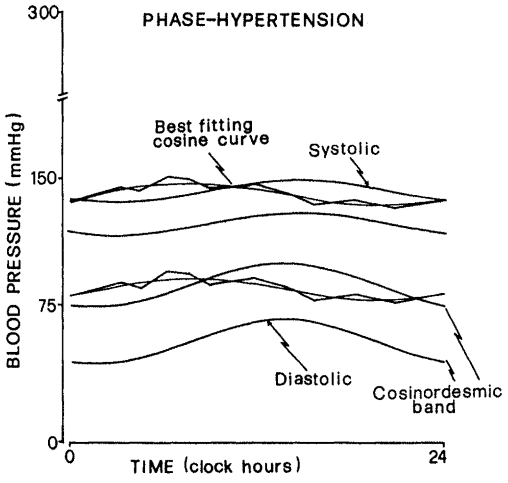

Fig. 12 Illustrative example of "Phase-hypertension" due to an abnormal shift of the ordinary timing of oscillation in circadian rhythm of blood pressure causing the individual systolic and diastolic cosinorgrams to partially exceed the corresponding chronodesms.

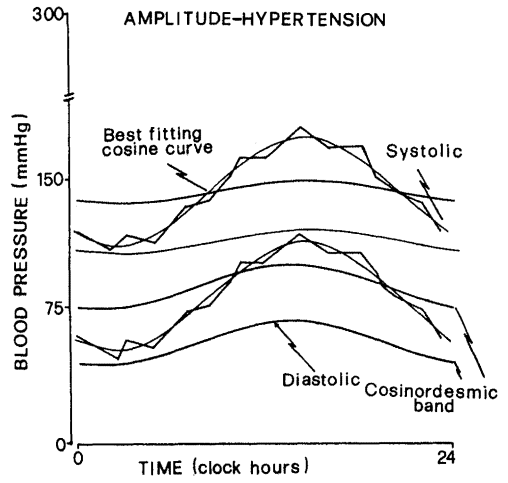

Fig. 13 Illustrative example of "Amplitude-hypertension" due to abnormal increase of the ordinary amplitude of oscillation in circadian rhythm of blood pressure, causing the individual systolic and diastolic cosinorgrams to exceed the corresponding cosinordesms.

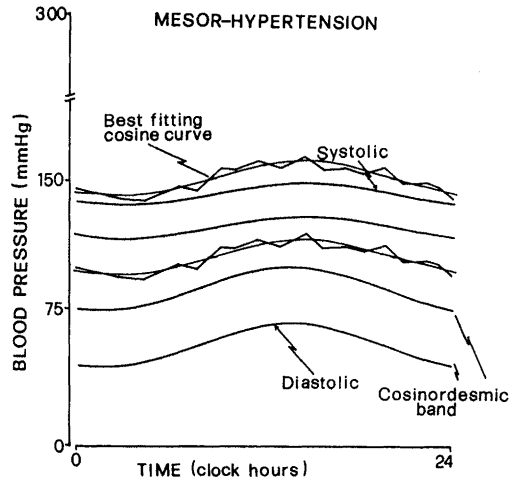

Fig. 14 Illustrative example of "Mesor-hypertension" due to an abnormal increase of the ordinary mean level of oscillation incircadian rhythm of blood pressure, causing the individual systolic and diastolic cosinorgrams to totally exceed the corresponding cosinordesms.

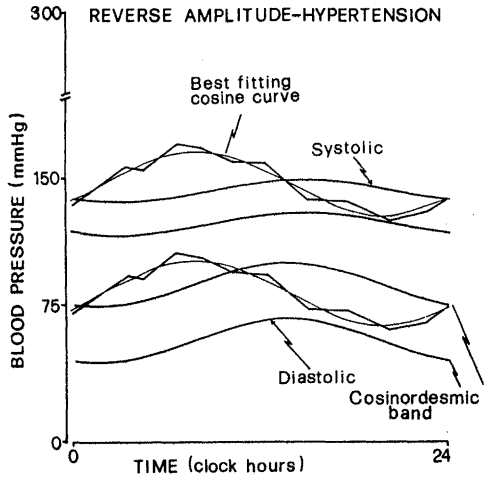

Fig.15 Illustrative example of "Reverse amplitude-hypertension" due to an abnormal increase of the ordinary amplitude, and shift in the ordinary phase of oscillation in circadian rhythm of blood pressure, causing the individual systolic and diastolic cosinorgrams to exceed the corresponding cosinordesms.

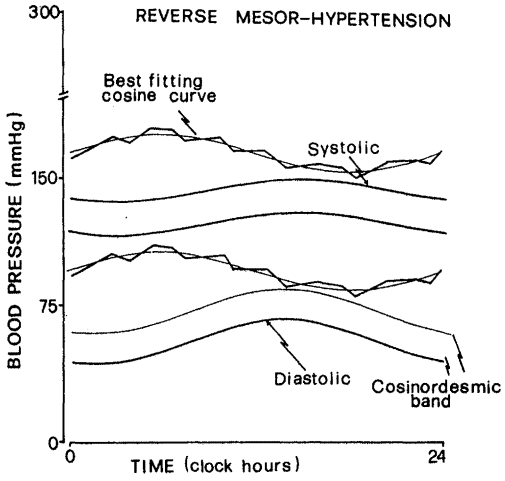

Fig.16 Illustrative example of "Reverse mesor-hypertension" due to an abnormal increase of ordinary mean level and a shift in the ordinary phase of oscillation, causing the individual systolic and diastolic cosinorgrams to exceed the corresponding cosinordesms.

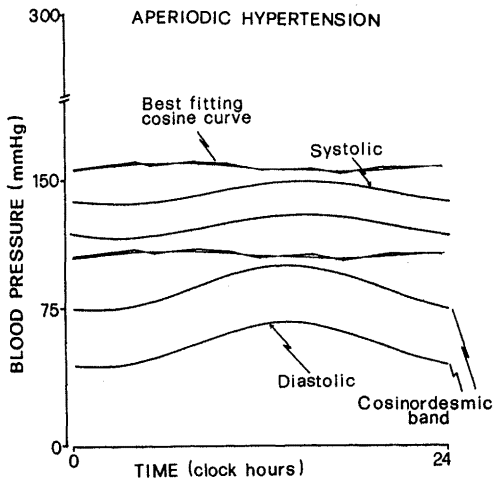

Fig.17 Illustrative example of "Aperiodic hypertension" due to an abnormal increase of the ordinary mean level and the lack of the ordinary oscillation in circadian rhythm of blood pressure, causing the individual systolic and diastolic cosinorgrams to exceed the corresponding cosinordesms.

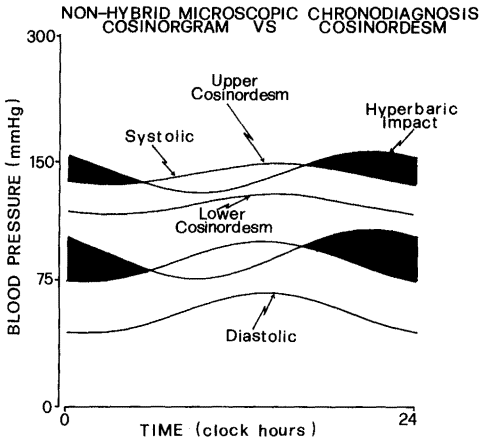

Fig.18 Illustrative example of Hyperbaric Impact due to an abnormal phase shift and/or an increase in the ordinary amplitude and or mean level of oscillation in blood pressure circadian rhythm, causing the individual systolic and diastolic cosinorgrams to exceed the corresponding cosinordesms.

Importantly, whatever the mechanism may be, there will be invariably an area of BP excess resulting from the disproportion of the individual systolic and diastolic cosinorgrams versus the relative cosionordesms (Fig.18). Such an area can be measured as the product of BP excess by the time of its duration[14),15)]. This estimate is called "Hyperbaric Impact" (HI), and its duration is named "Duration of Excess" (DE).

It is evident that BP monitoring may have an unlimited number of features. Nevertheless, its deviant shape will invariably be represented by at least one of the chronopathologic models of AH. This implies that AH is always accompanied by an area of HI. The DE may be lower than 12-h, as in the case of phase-hypertension, amplitude-hypertension, and reverse amplitude-hypertension, or higher than 12-h, as in the presence of mesor-hypertension, reverse mesor-hypertension and aperiodic hypertension.

It must be stressed that the HI quantifies the BP excess in its global entity. Therefore, in the near future, the HI should replace the present criteria for grading AH, which are still based on the fixed limits given by World Health Organization[1)]. The reasons of this prediction will be clarified in the last chapter of this article.

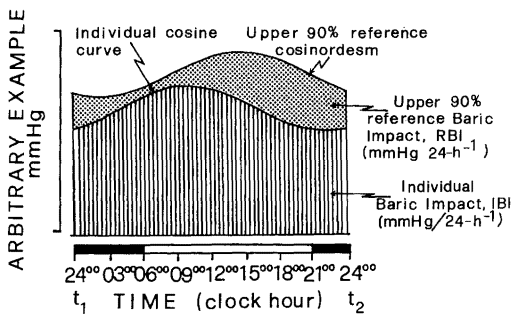

Fig.19 Level 3 of chronodiagnosis of arterial hypertension: Comparison of individual Baric Impact to the reference Baric Impact to detect the Baric Excess.

3) Level 3. Comparison of individual BP aesorgrams to aesordesms

The third step in chronodiagnostic process is the comparison of the Aesorgrams for SBP and DBP with the parent 90% upper aesordesms. As already mentioned, the AESOR, computed by cosint analysis, is a parameter which estimates the circadian oscillation of BP in its entire excursion. This means that a given BP monitoring may be assessed as a global phenomenon. The comparison of the individual BI(IBI) to the reference BI (RBI) may be, thus, important to detect whether or not a given AH is tensiogenetically active (Fig. 19). For instance, phase-hypertension is characterized by a BI which is almost normal despite the HI (Fig.20). By contrast, the other chronopathologic types of AH all show an abnormal increase in BI along with an area of HI. As the HI may be disjoined by a concomitant increment in BI, one can argue that there are "tensiogenetically-active" and "non-tensiogenetically-active" forms of AH. The condition of being or

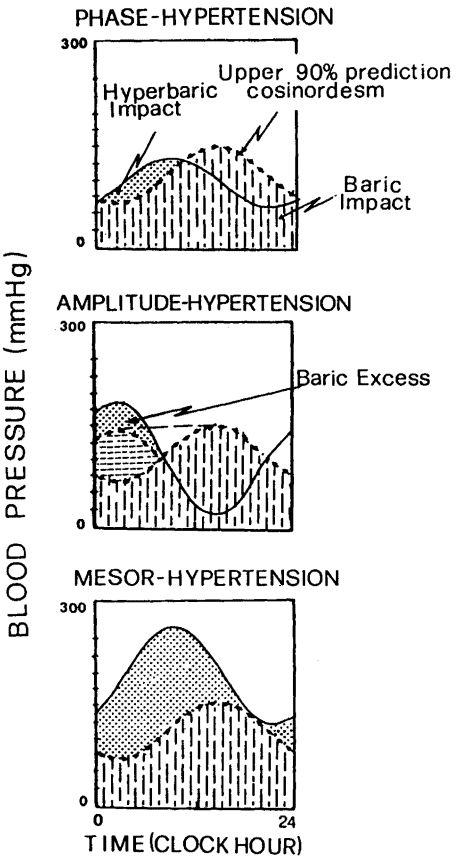

Fig.20 The presence of a Baric Excess is not obliged in cosinorgrams which exceed the upper cosinordesms, causing a Hyperbaric Impact.

not tensiogenetically-active may be clinically defined at the Level 3 of choronodiagnosis by calculating the Baric Excess (BE) as the subtraction of IBI to RBI (BE = IBI-RBI).

Tensiogenetically-active will be that AH which is characterized not only by a HI but also by a BE. Conceptually, the hypertensive damage of target organs could be related to BE more than to HI as the occurrence of a BE is an inequivocable feature that the periodic variability of BP 24-h pattern is increased in its amplitude or in its mean level on oscillation.

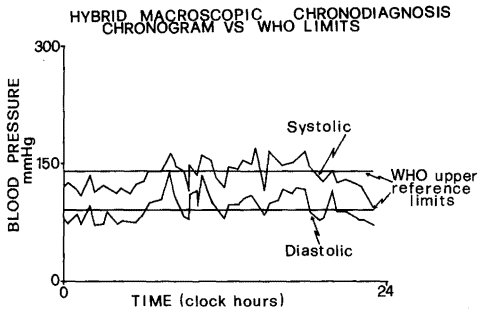

Fig.21 Hybrid chronodiagnosis of arterial hypertension by comparing the individual systolic and diastolic chronograms to the fixed reference limits given by World Health Organization (WHO).

INNOVATIVE CONCEPTS OF CHRONODIAGNOSIS

Those who use the BP monitoring for clinical purposes can testify that the diagnosis of AH is presently still formulated with reference to WHO's limits [1]. This article has already remarked that this approach is conceptually erroneous due to the within-day variability of BP. Statistically, the reference to fixed standards is only apparently a temporal biometry (Fig.21). In reality, it is just a mathematical count of supranormal values, which is performed independently of any temporal location of data within their temporal band of variability. If the temporal biometry is bound by time, BP values are really compared to the cut-off limit which is associated with that a given time point.

In final analysis, the methods of comparing time-qualified measures with fixed standards are in a hybrid procedure which can be rejected also under the terms of mere statistical correctness. This is in conclusion the conceptual message of Level 1 of chronodiagnosis.

The conceptual innovations of Level 2 are even more pregnant. The diagnosis of AH is made by an inferential method of analysis which removes any stochastic component from the BP monitoring. The BP 24-h pattern is, thus, analyzed in its intrinsic structure which is physiologically arranged to be periodic over the 24-h span. This

approach, thus, explores the true essence of the BP 24-h pattern, letting us to attribute any deviation to a model of derangement. Such a possibility is of great importance for clinicians. The diagnosis is biostatistically accurate, and AH may be defined in its formal mechanism of constitution, and classified in its chronopathologic type. Therefore, AH may be easily recognized simply by the appellative of its classification.

In conclusion, through the Level 2 of chronodiagnosis, the BP monitoring is explored to in its intimate mechanism of disturbance to make a reliable diagnosis and to classify the hypertensive disorder. The advantages for clinical medicine are, thus, evident.

The Level 3 of chronodiagnosis offers a further tool for medical practice. Physiologically, BP results beat to beat by the product of heart contractility and arterial tone. The real expression of BP is neither its 24-h mean level nor its amplitude of variation. What operates inside the vascular walls as a function of time is the algebraic sum of tensions that really take place in relation with the within-day variability of BP. Therefore, the tensiogenic load in arterial vessels is the integral BP values over time. Such a tensiogenic load is correctly measured by the Baric Impact. By the Level 3 of chronodiagnosis, there is, thus, the possibility of quantifying the BP 24-h pattern as a "whole" for a better understanding of the relationships which exist between the circadian pressure regimen and the organs directly or indirectly compromised by AH. In other words, the clinicians may be enabled by the BI to detect whether or not the AH is more or less tensiogenically dangerous for the function of target organs.

As a final comment, it must be remarked that AH is presently classified in its on the basis of raw values. Usually, the grading is made on the value which is the highest inside the BP monitoring. As a deviant BP monitoring may show high values in a sporadic or permanent fashion, the severity of AH may appear to be the same, despite the different number of higher BP values. Therefore, it is tremendously reductive and conservative grading AH by the most representative value, which is just one of the overall measures which compose the BP 24-h pattern.

In order not to declassify the clinical importance of BP time-qualified values, it is absolutely indispensable to exploit the HI for grading AH. High BP is in this way quantified in its excess and temporal duration, as the sum of all abnormal values.

The closing remarks of this article want to stress that modern medicine is now in the position of revisiting more accurately the clinical field of AH. The criteria of chronodiagnosis can open the frontiers for a more precise diagnosis and quantification of what the consistency of AH may be.

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