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Chronobiology approach to human hypertension

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Summary. - The present article is aimed to make the status of the art on the diagnosis of hypertension using the non-invasive automated devices for measuring blood pressure (BP) over the 24 h span. The diagnostic procedure is based on specific criteria eminently devoted to the temporal evaluation of the BP 24 h pattern in its variability, either discrete or periodic. The procedure, called "chronodiagnosis of hypertension", is articulated in three procedural levels, each corresponding to a particular chronobiometry of the BP 24 h pattern. The chronodiagnostic procedure is detailed step by step.
Key words: blood pressure, chronobiology, circadian rhythms, hypertension, monitoring.

Riassunto *(L'approccio cronobiologico all'ipertensione umana)*. - Il presente articolo è volto a fare lo stato dell'arte nella diagnosi di ipertensione tramite strumenti automatici non invasivi per la misura della pressione arteriosa (PA) nelle 24 ore. La procedura diagnostica è basata su criteri specifici basati eminentemente sulla valutazione temporale del comportamento pressorio di 24 ore nella sua variabilità, sia discreta che periodica. La procedura, chiamata «cronodiagnosi della ipertensione» è articolata in tre fasi, ciascuna corrispondente ad una particolare cronobiometria della pressione arteriosa di 24 ore. La procedura cronodiagnostica è dettagliata passo per passo.
Parole chiave: pressione arteriosa, cronobiologia, ritmi circadiani, ipertensione, monitoraggio.

Introduction

The advances in technology and computer science provided a renewed interest in the diagnosis of arterial hypertension by combining the non-invasive automated monitoring of blood pressure (BP) with the chronobiological procedures.

The diagnostic approach to hypertension is now totally changed in virtue of three fundamental considerations. First, repeated measures over the 24 h span better explore the eventual elevation of BP values. Second, the dependency of the BP 24 h pattern on circadian time [1-4] suggests the use of temporal criteria of diagnosis. Third, the periodic properties of the BP 24 h pattern [5-8] suggest the diagnostic adoption of chronobiological methods in clinical practice.

This report is, thus, a presentation of what is the status of the art for diagnosing hypertension via BP non-invasive ambulatory monitoring combined with chronobiological criteria. Such a process is called "chronodiagnosis of hypertension" *.

Chronodiagnosis of hypertension

The chronodiagnostic technique is articulated in three levels.

Level 1. Comparison of individual chronograms with chronodesms

The initial part of the chronodiagnostic procedure is aimed to compare the raw values of the individual systolic and diastolic BP curves, i.e., the chronograms (Fig. 1) versus the corresponding time-qualified reference limits, i.e., the chronodesms (Fig. 2).

The chronogram is given directly by time-qualified values of BP monitoring. The chronodesms for systolic and diastolic BP can be constructed

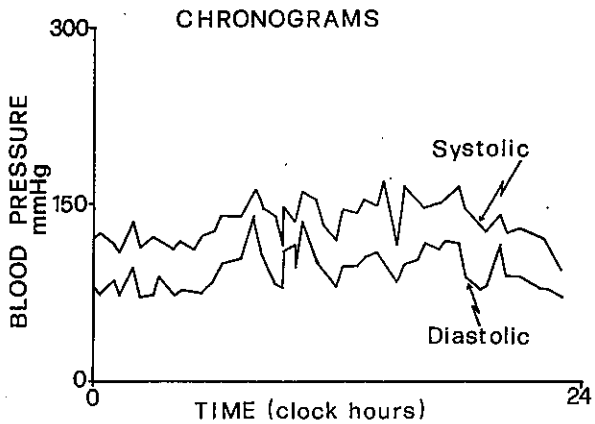


Fig. 1. - Discrete time-qualified values of systolic and diastolic blood pressure represented as interpolated curves, i.e., the chronograms.

* "Chronodiagnosis" is a term opposite to "monodiagnosis" with which it is intended the comparison of isolated or monitored BP values to the fixed limits given by WHO.

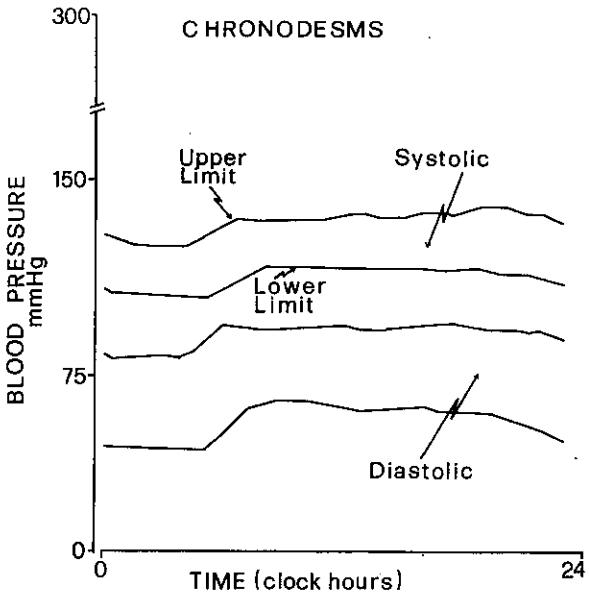


Fig. 2. - Reference limits for discrete time-qualified values of systolic and diastolic blood pressure represented as interpolated bands, i.e., the chronodesms.

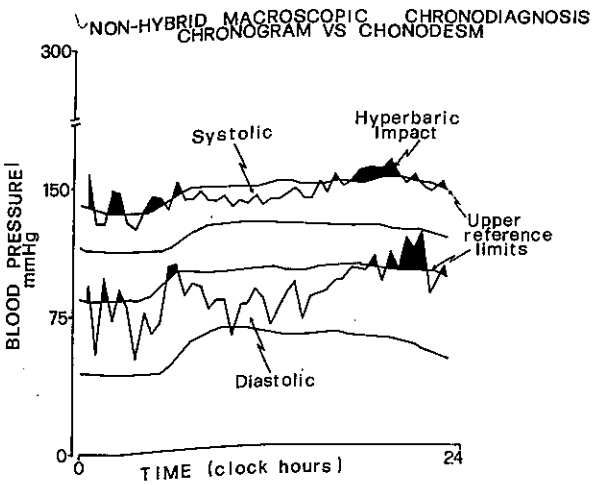


Fig. 4. - The measurement of discrete hyperbaric Impact is performed by summing the integrated areas which result from the excess of systolic and/or diastolic chronograms with the pertaining chronodesms.

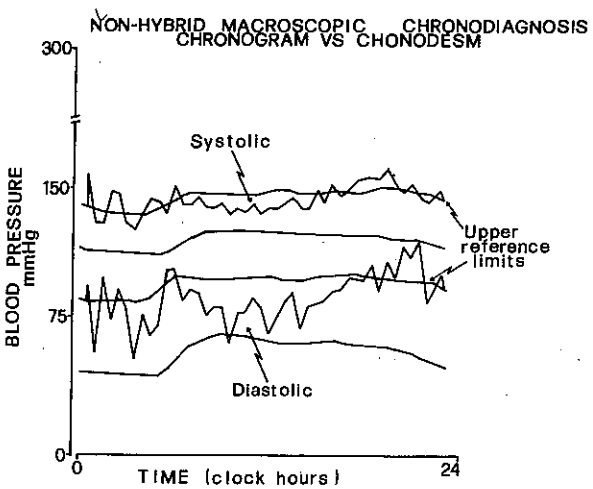


Fig. 3. - Level 1 of chronodiagnosis: comparison of systolic and diastolic chronograms with the pertaining chronodesms.

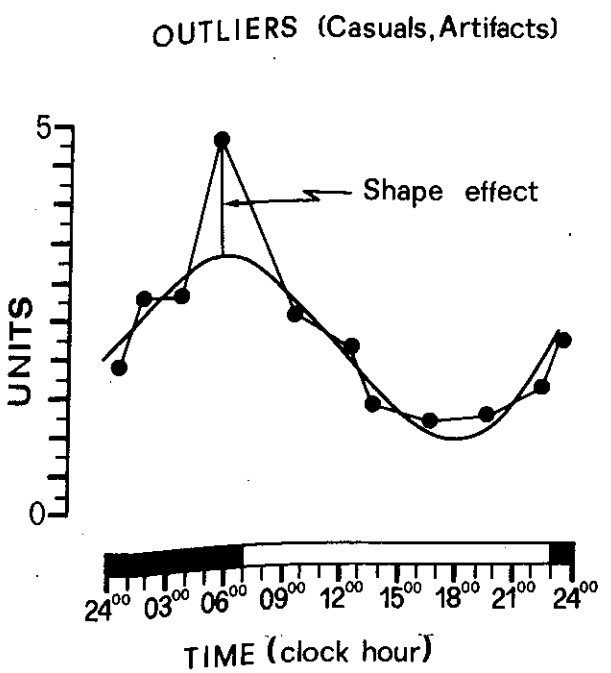


Fig. 5. - Any series of experimental measurements is probabilistically affected by erroneous values caused by random variability.

using the formula for 90% Prediction Limits (90%PL).

The aim of the Level 1 is double. The comparison is firstly made for determining whether or not there is a number of BP values which exceed the corresponding temporal upper limits (Fig. 3).

The second contrast tends to estimate the discrete Hyperbaric Impact (dHI) as an integrated area determined by BP values exceeding their time-qualified limit. This area quantifies hypertension as the product of abnormal tensions for the duration of their excess (Fig. 4).

It must be realized that the comparative technique of raw values is affected by a certain degree of imprecision. The counting of supranormal values is influenced by the random variability (biological noise) which is unavoidably present in each temporal series of discrete data (Fig. 5). The estimation of dHI may be, thus, erroneous depending also on the sampling interval which conditions the window of the integrated area (Fig. 6).

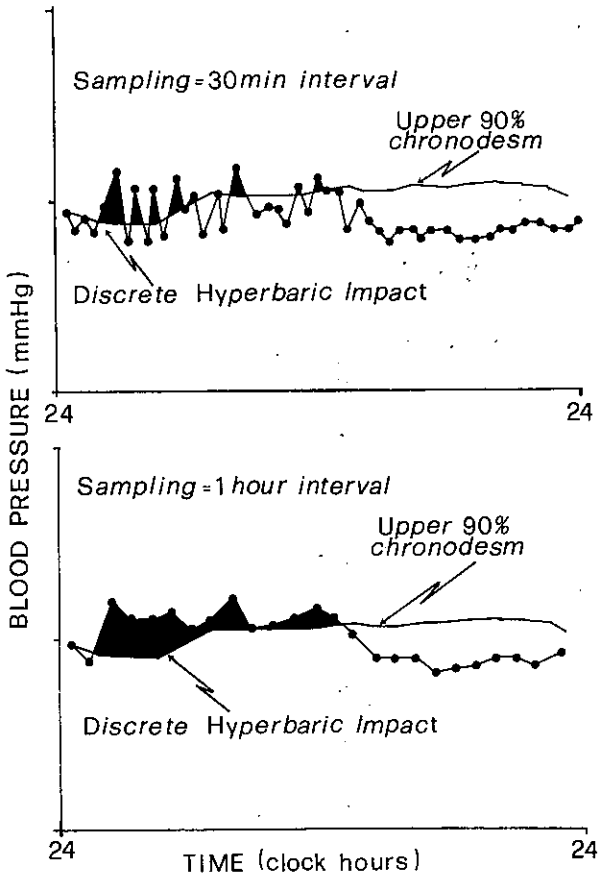


Fig. 6. - The measurement of discrete hyperbaric Impact is dependent on the sampling interval.

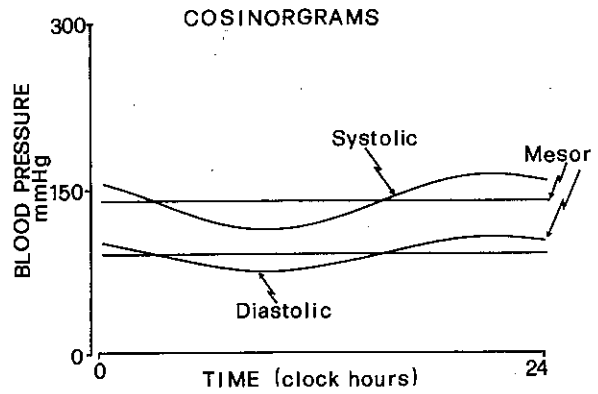


Fig. 7. - Continuous time-qualified values of systolic and diastolic blood pressure represented as sinusoidal curves of the best fitting waveform profiles, i.e., the cosinorgrams.

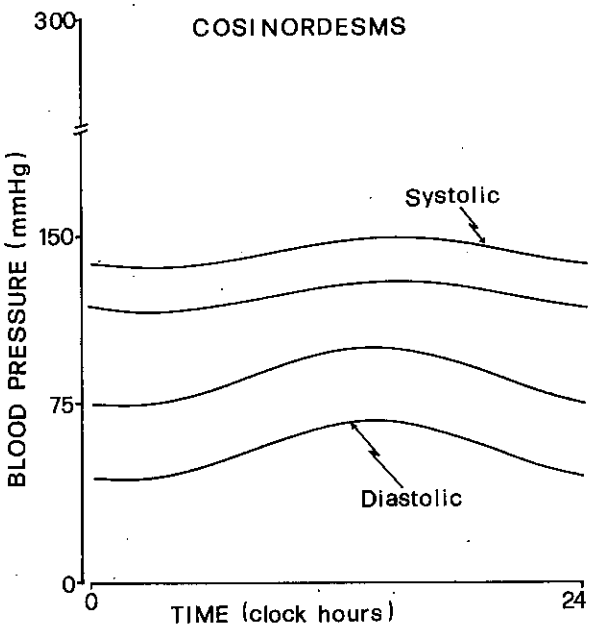


Fig. 8. - Reference limits for continuous time-qualified values of systolic and diastolic blood pressure represented as sinusoidal bands of the best fitting waveform profiles, i.e., the cosinordesms.

The obvious consequence of the random variability is the occurrence of falsely positive diagnoses. This implies the use of a probabilistic filter above which the supranormal values can be regarded not to be dependent on the randomness. The adoption of a time base is mandatory in order to avoid uncorrectness in the calculation of dHI.

The filter to Error Type 1 is ordinarily posed at a P level of probability less than 5%, and the time base for sampling may be fixed at least 30 min interval. With this emendation, the BP monitoring will be constituted by no less than 48 measurements over the 24 h span which means that two to three abnormally high values may be regarded as erroneous and non-predictable for hypertension.

Therefore, the chronodiagnosis at the Level 1 of its procedure assumes that in a given subject hypertension may be diagnosed whether there is evidence that the 24 h values of systolic and/or diastolic BP exceed the time-qualified reference limits in a proportion higher than 5% of the total readings. In this situation the dHI can be measured.

It is very important to stress that the accuracy of the diagnosis via the comparison of the individual chronograms with the chronodesms is disputable even though the raw data are filtered in order to avoid false positive cases of hypertension. There is no possibility to know *a priori* which values are to be removed. Additionally, it may be possible that the supranormal values are not due to the random variability, being, by contrary, a true expression of a deviant excess. In this case, filtering of raw data will cause a false negative diagnosis of hypertension, generating the so called Error Type 2 or Beta Error. For this reason the chronodiagnosis of hypertension has to be complemented by the Level 2 of the procedure which is aimed to remove the random variability from BP 24 h pattern by using inferential methods of chronobiometry.

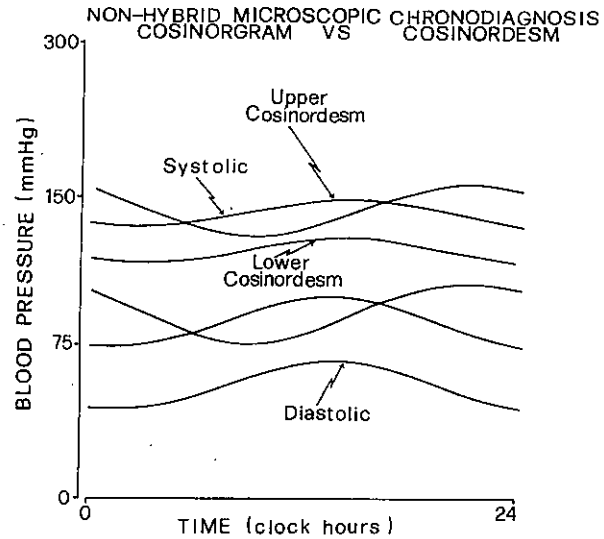


Fig. 9. - Level 2 of chronodiagnosis: comparison of systolic and diastolic cosinorgrams with the pertaining cosinordesms.

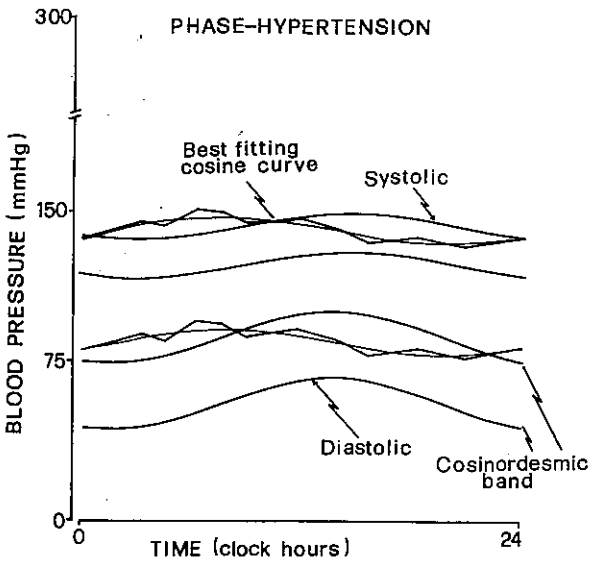


Fig. 10. - An isolated rotation of phase in the circadian rhythm of blood pressure causes the systolic and/or diastolic cosinorgrams to exceed the pertaining cosinordesms, giving rise to a systematic hypertension called "phase-hypertension".

Level 2. Comparison of individual cosinorgrams with cosinordesms

The second part of the chronodiagnostic procedure is aimed to compare the calculated values of the optimal sine wave which fits the individual systolic and diastolic BP curves, i.e., the cosinorgrams (Fig. 7) versus the corresponding cosinordesms (Fig. 8).

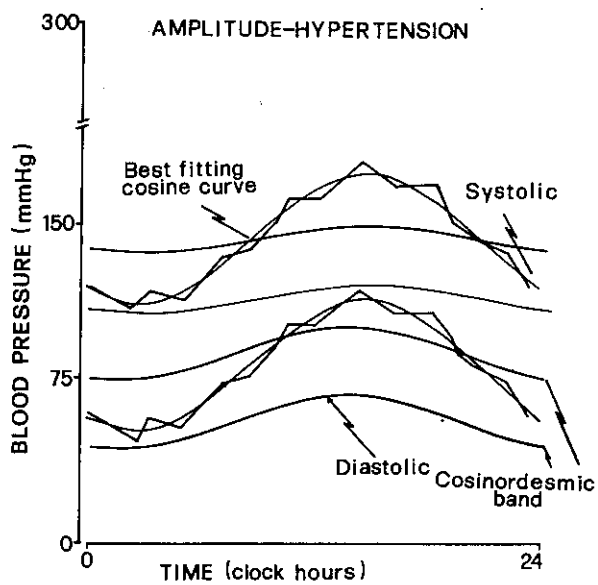


Fig. 11. - An isolated magnification of oscillatory amplitude in the circadian rhythm of blood pressure causes the systolic and/or diastolic cosinorgrams to exceed the pertaining cosinordesms, giving rise to a systematic hypertension called "amplitude-hypertension".

The best fitting waveform profile is found by means of the Single Cosinor method [9] according to the formula

$$Yt = M + A * \cos(2\pi/24*t + \varnothing) \quad (1)$$

where M is the mesor, A is the amplitude, and $\varnothing$ is the acrophase.

The cosinordesms for systolic and diastolic BP can be calculated as the 90%PL of the rhythmometric parameters, M, A and $\varnothing$.

The scope of the Level 2 is bivalent. The first comparison is made for estimating whether or not the M, A and/or $\varnothing$ exceed their corresponding limits (Fig. 9).

It is important to stress that the optimal sine wave represents the oscillatory structure of the BP 24 h pattern in its systematic component. The calculated values of the sinuoidal wave are, thus, noise-free. This implies that the individual cosinorgram which exceeds its cosinordesm is consistently probatory for a systematic elevation of BP values which is not expected by chance. Accordingly, the comparison of cosinorgrams with cosinordesms allows us to pose with sufficient accuracy the diagnosis of "systematic hypertension" which makes "pendant" to the "casual hypertension" being diagnosed at the Level 1 but not confirmed at the Level 2.

It must be reemphasized that the Level 2 of the chronodiagnostic procedure consists in estimating whether or not the oscillatory properties of the BP 24 h pattern are normal or exceed the upper limit of their sinusoidal variability. Furthermore, the procedure serves to ascertain whether or not the BP 24 h pattern changes in a periodic fashion according

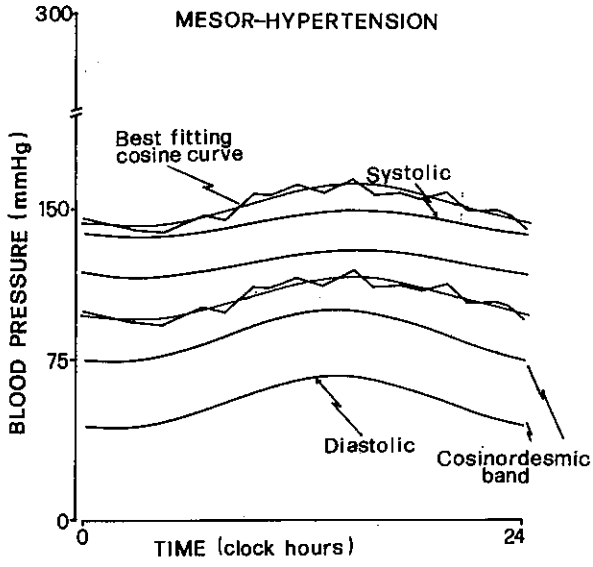


Fig. 12. - An isolated increase of oscillatory meal level in the circadian rhythm of blood pressure causes the systolic and/or diastolic cosinorgrams to exceed the pertaining cosinordesms, giving rise to a systematic hypertension called "mesor-hypertension".

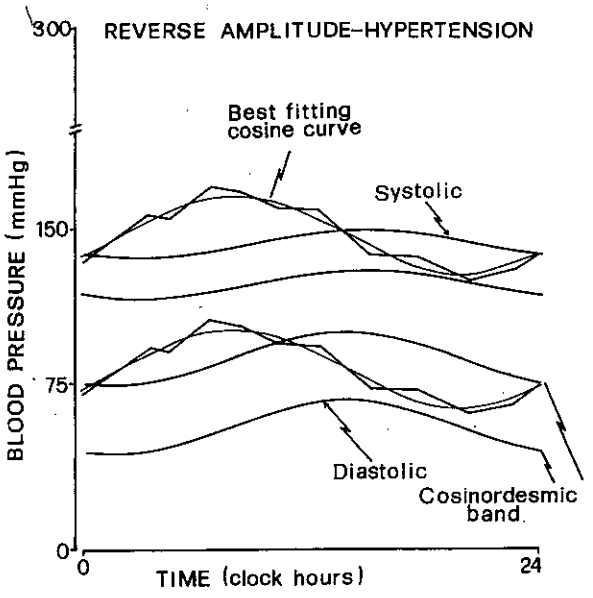


Fig. 13. - A combined rotation of phase and magnification of oscillatory amplitude in the circadian rhythm of blood pressure cause the systolic and/or diastolic cosinorgrams to exceed the pertaining cosinordesms, giving rise to a systematic hypertension called "amplitude allo-hypertension".

to a significant circadian rhythm. All of this makes it possible to qualify the "systematic" hypertension by means of the rhythmometric deviation which causes the cosinorgram to exceed the cosinordesm. In line with this concept, six cosinortypes of systematic hypertension can be identified.

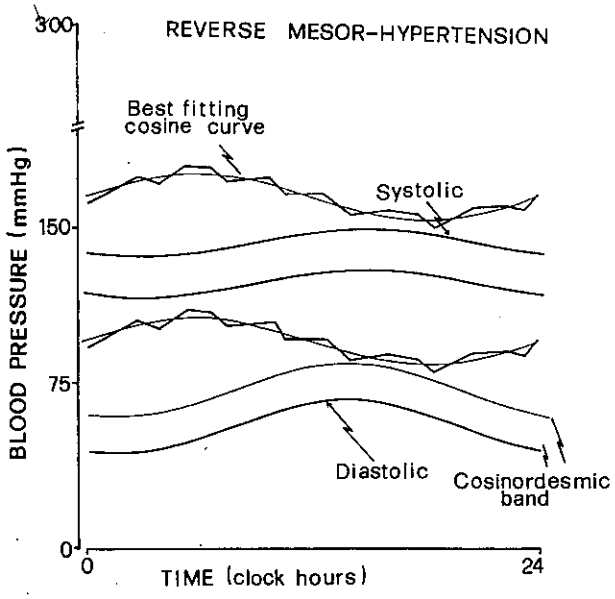


Fig. 14. - A combined rotation of phase and increase of oscillatory mean level in the circadian rhythm of blood pressure cause the systolic and/or diastolic cosinorgrams to exceed the pertaining cosinordesms, giving rise to a systematic hypertension called "mesor allo-hypertension".

If the deviation from its normal limits refers to the acrophase (Fig. 10) there will be the cosinortype of high BP called "phase-hypertension" [10].

Halberg *et al.* [11, 12] have already described the cosinortypes called "amplitude-hypertension" (Fig. 11) and "mesor-hypertension" (Fig. 12) with reference to an abnormal increase, respectively, in the extent or in the mean level of the rhythmic oscillation.

If the elevation of amplitude or mesor is combined with an abnormal location of acrophase, there will be two other cosinortypes of high BP, respectively termed by us [10] "reverse amplitude-hypertension" or "amplitude allohypertension" (Fig. 13), and "reverse mesor-hypertension" or "mesor allohypertension" (Fig. 14).

Finally, there will be the possibility that the BP is elevated because of an abnormal increase in mesor without an appropriate oscillation due to the lack of the circadian rhythm. This cosinortype of high BP was phrased by us [10] "aperiodic mesor-hypertension" or, simply, "aperiodic hypertension" (Fig. 15).

The cosinortypes of hypertension have the advantage of formally identifying, by means of a well-defined morphology, the potentially infinite features which can be shown by a BP monitoring when deviating from its normal pattern. This typology makes the deviant BP monitoring to be comparable by means of its cosinortype and the rhythmometric attributes which characterize its abnormality.

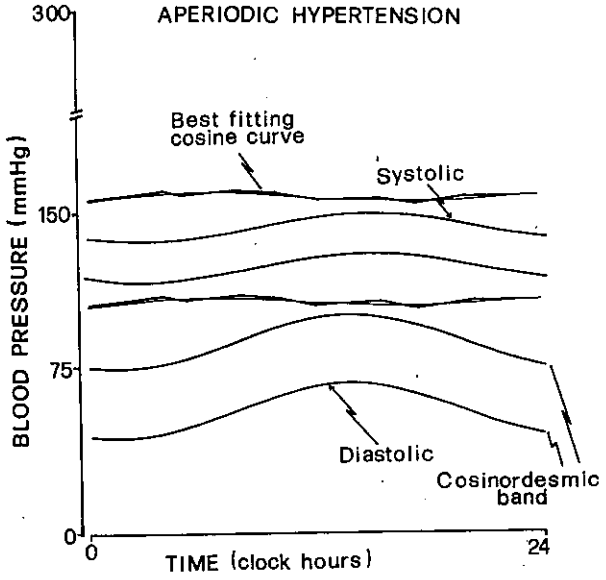


Fig. 15. - The disappearance for the circadian rhythm of blood pressure may cause the systolic and/or diastolic cosinorgrams to exceed the pertaining cosinordesms, giving rise to a systematic hypertension called "aperiodic hypertension".

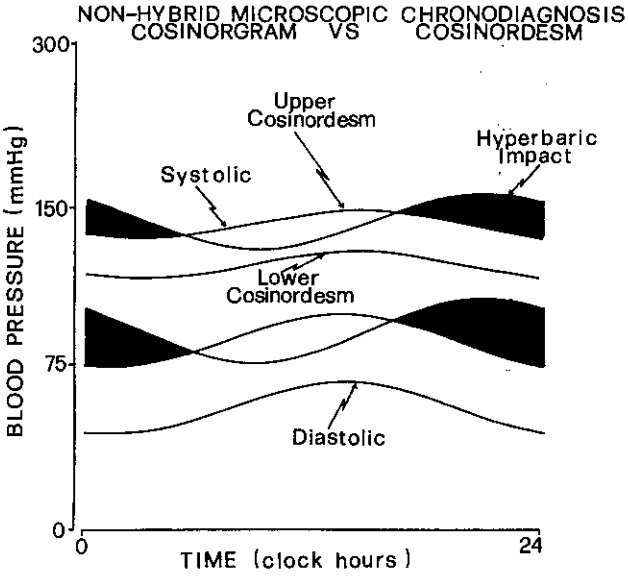
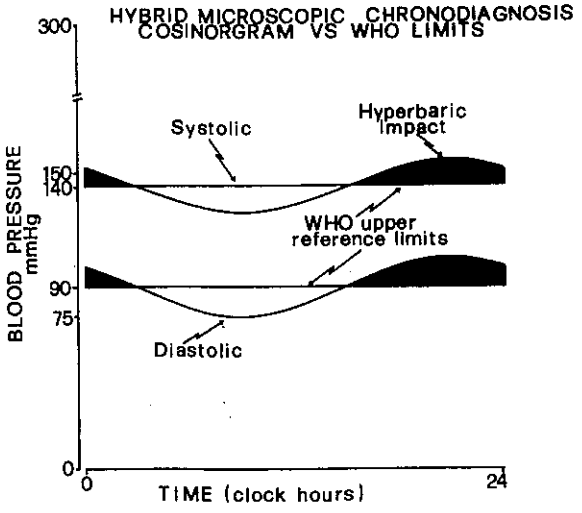


Fig. 16. - The measurement of inferential hyperbaric impact is performed by summing the integrated areas which result from the excess of systolic and/or diastolic cosinorgrams with the pertaining cosinordesms.

The second step of the chronodiagnostic procedure at the Level 2 is performed with the intention of calculating the inferential Hyperbaric Impact (iHI), as an integrated area which quantifies hypertension as the product of the "calculated" supranormal tensions over the time of their excess (Fig. 16).



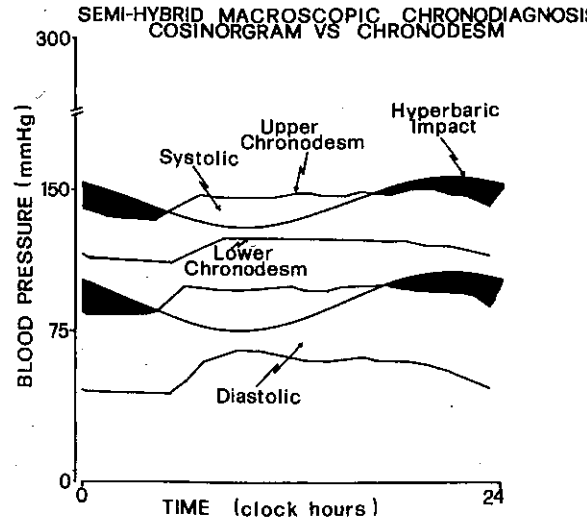


Fig. 17. - Hybrid anf semi-hybrid techniques for estimating the hyperbaric impact by comparing systolic and diastolic cosinorgrams with the fixed reference limits given respectively by World Health Organization (WHO) or the chronodesms.

Such an estimate is made by a technique [13] which differs from that originally proposed by Halberg *et al.* [11, 12]. The area of excess results by definition from the comparison of two analytical and, thus, non-discrete curves. Due to its characteristics, the iHI may be regarded as the most appropriate quantifier of the "systematic hypertension" when compared with other hybrid techniques (Fig. 17).

This is a crucial concept which, although discussed in the following chapter, requires a brief comment. It must be realized that mathematically speaking the sinusoidalization is a process of transformation which causes a discrete series to be represented by a continuous pattern. This effect is

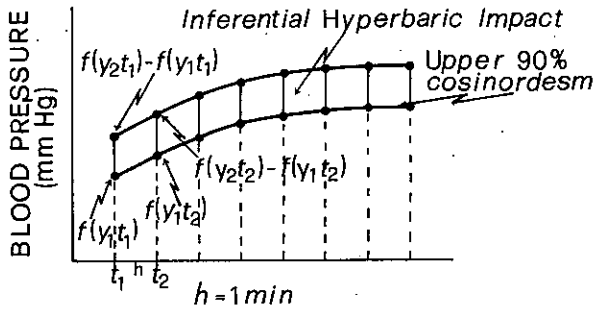


Fig. 18. - Each integrated area of inferential hyperbaric impact is measured as the sum of trapezoids with which the whole surface can be partitioned taking as an unitary division the distance h, spatially equal to one minute.

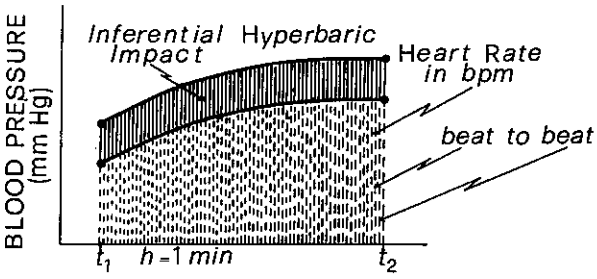


Fig. 19. - The unitary subarea includes the beat-to-beat heart rate per min. Its estimate multiplied by the heart beats per min (bpm) determines the blood pressure excess related to pulsatory activity in one min, i.e., the baric load in mmHg per min.

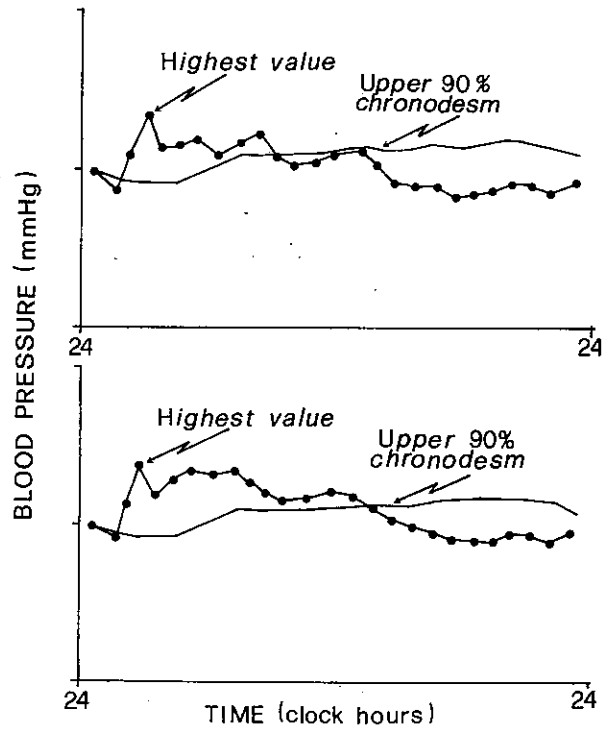


Fig. 20. - The present system for grading hypertension in its severity is based on the magnitude of the highest value which constitutes the temporal series of blood pressure measurements regardless of how many values are higher than normal over the 24 h span.

of relevant importance when considering that the non-invasive automated monitoring is intrinsically an intermittent recording of BP values. The sinusoidalization of the BP chronogram may be, thus, seen as a mathematical operation which returns a continuous monitoring from a discontinuous recording of sphygmomanometric measures. In virtue of this, the iHI may be intended as the estimate which quantifies the BP excess as it were measured by a beat to beat monitoring. This assumption is, however, true provided that the area of excess is integrated at 1 min interval (Fig. 18), and the integrated value is multiplied by the beats per minute (bpm) corresponding to the heart rate (HR) that was effective over that time of high BP (Fig. 19). By simplicity, the HR may correspond to its mean value over the 24 h span, i.e., to its mesor.

The iHI is estimated by the integral equation

$$iHI = \int_{t1}^{t2} (Y_1 t - Y_2 t)dt \qquad (2)$$

where t is equal to 0.0166 corresponding to the period of 24 h, divided by 1440 min, Y_1 is the cosine function of the individual BP monitoring (equation 4), and Y_2 corresponds to the cosine function of the upper 90% cosinordesm for the BP 24 h pattern (equation 5). Its value is expressed in mmHg/dt/1 min. Its product by the HR mesor corresponds to the parameter inferential Hyperbaric Load (iHL) measured in mmH/dt.

Therefore,

$$iHL = iHB * HR\ mesor \qquad (3)$$

What is the position of the iHI and iHL in the chronodiagnostic process? In our opinion they serve not only to diagnose the abnormally high BP but principally to grade the severity of hypertension.

Presently, the classification of the benign hypertension includes the following grades, i.e., borderline, mild, moderate and severe forms. It must be stressed that this graduation is performed on the assumption that the severity is given by the BP value which was found to be the highest in absolute. This criterion of classification is acceptable when dealing with the "casual" values of BP. Its validity is, on the contrary, highly questionable when considering high BP in a temporal context. It may be possible that a given BP monitoring shows only a few isolated values which stand above their chronodesm (Fig. 20). Alternatively, it may happen that the BP monitoring shows several values which exceed their reference limits over an extended portion of the day (Fig. 20). It is obvious that the severity of high BP may be falsely estimated assuming as a classifier the

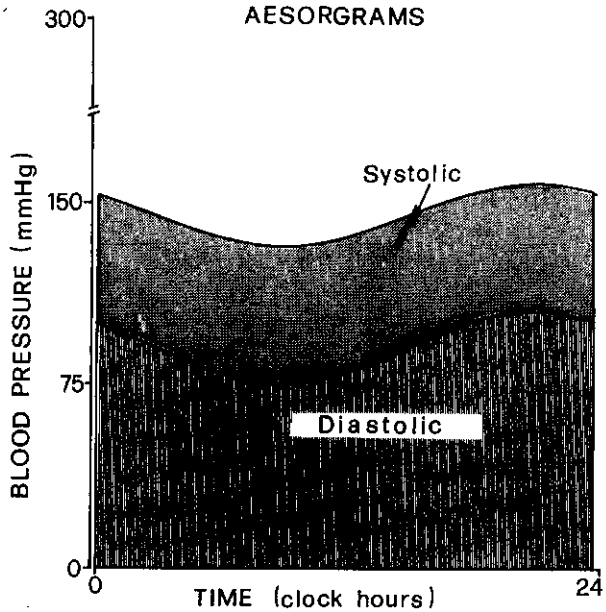


Fig. 21. - Integrated measurements of continuous time-qualified values of systolic and diastolic blood pressure represented as sinusoidal areas covered by the pertaining cosinorgrams, i.e., the aesorgrams.

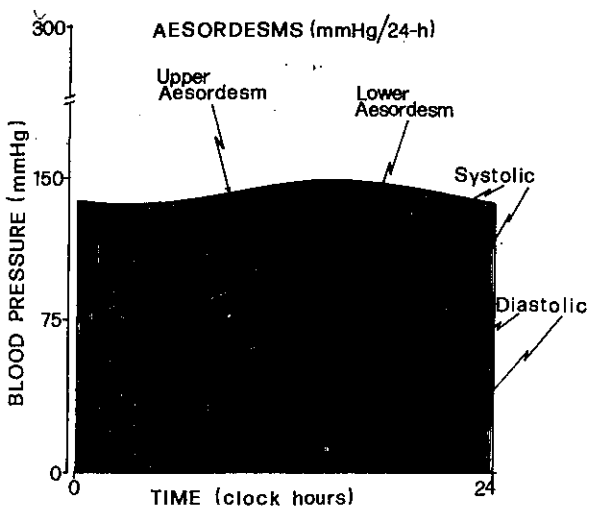


Fig. 22. - Reference limits for the integrated measurements of continuous time-qualified values of systolic and diastolic blood pressure represented as sinusoidal bands, i.e., the aesordesms.

highest detected value. It is quite obvious that the severity of a pathological condition may not prescind from the temporal duration over which its deviant status persists. This means that the severity of hypertension is more conveniently expressed by integrating high BP values (HBPV) by the temporal duration their excess (DE). Therefore, the product HBPV * DE is the appropriate classifier for the severity of hypertension, its values expressing both

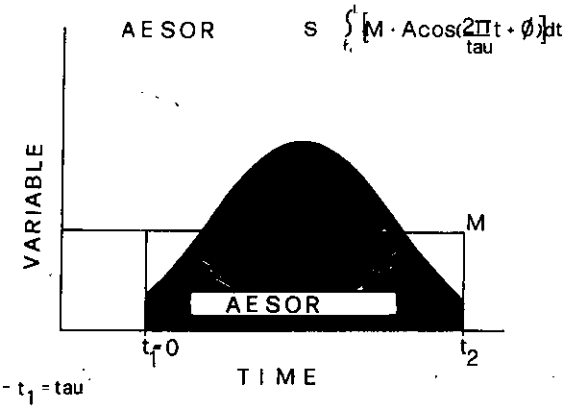


Fig. 23. - The estimate of the sinusoidal area covered by circadian oscillation of blood pressure is a parameter called "aesor", acronym of area estimating statistic of rhythm.

the quantitative and temporal characteristics of the deviant status. It must be taken into account that the iHI is just the product of the BP excess by its duration. This quality explains why in our mind iHI is regarded as a powerful parameter for grading hypertension in its severity [13]. This concept will be more extensively described in the following pages.

Level 3. Comparison of individual aesorgrams with aesordesms

The third approach in the chronodiagnostic procedure is aimed to compare the entire area covered by the optimal sine wave of the individual systolic and diastolic BP curves, i.e., the aesorgrams (Fig. 21) with the aesordesms (Fig. 22).

The aesorgram is developed by means of the cosint analysis [14] via the parameter aesor (acronym of Area Estimating Statistic of Rhythm). The cosint analysis is a method of periodic integration which estimates the aesor via the formula

$$\text{Aesor} = \int_{t0}^{t24} (M + A * \cos(2\pi/24 * t + \varnothing))dt \qquad (4)$$

as shown in Fig. 23.

The aesordesms correspond to the reference areas covered respectively by the upper and lower 90% cosinordesms.

The approach at the Level 3 has two main purposes. First, the BP 24 h pattern is quantified as a global phenomenon which causes by its circadian fluctuation a given tensive load. As already pointed out in the previous chapter, the cosine curve factually operates the transformation of the intermittent monitoring into a continuous pattern. Therefore, the Aesor of the individual cosine curve allows us to estimate the individual Baric Impact (iBI) by integrating the "calculated" values of the oscillation at 1 min interval (Fig. 24). The product of the iBI, ordinarily expressed in mmHg/24 h/1min, by HR mesor in bpm (Fig. 25), gives an

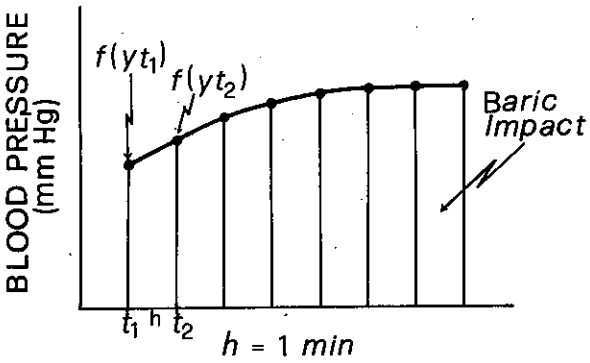


Fig. 24. - The aesor is calculated by the sum of trapezoids resulting from the division of the 24 h oscillation into unitary interval h, each corresponding to the spatial distance of one minute.

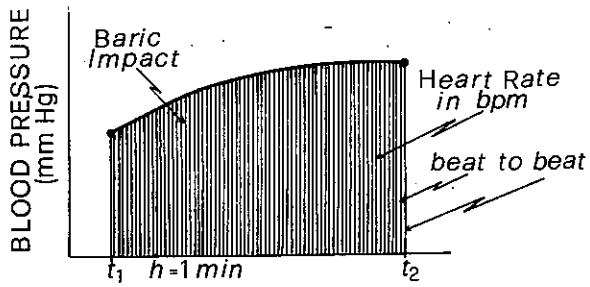


Fig. 25. - Each unitary subarea includes the beat-to-beat heart rate per min. Its estimate multiplied by heart beats per min (bpm) computes the Baric Load in mmHg per min produced by pulsatory activity.

estimate of the individual Baric Load (iBL) in mmHg/24 h which is associated with that a given BP monitoring.

$$iBL = iBI * HR\ mesor \quad (5)$$

Taking this conceptualization into account, it is obvious that the aesordesms may be regarded as the limits for the reference BI (rBI).

Importantly, the iBI and iBL have a proper role within the context of the chronodiagnostic process. In our opinion, their position is fundamental for correlating the effects of the BP regimen on the target organs. Presently, the relationships of hypertension with the cardiovascular damage is faced in various ways.

Regardless of the "casual" measurements, the correlation is usually made by using the BP 24 h mean or its standard deviation [15, 16] or its iHI [17, 18]. It must be strongly emphasized that the tensive effect (TE) of BP regimen depends not only on its BP values but also on how many times these values take place. Really, the TE on the target organ is expressed by the following formula

$$TE = \sum_{i-1}^{n} BPi \quad (6)$$

where i corresponds to the first measurement and n is the total number of the beat to beat BP values. Considering that the n values in a beat to beat monitoring take place during a cycle time of 24 h, the formula 13 can be rewritten as the discrete integral of the BP values over time

$$TE = \int_{t0}^{t24} (BP)dt \quad (7)$$

It is important to remember that the BP 24 h pattern is physiologically the expression of a circadian rhythm. Therefore, the formula 14 can be modified as follows

$$TE = \int_{t0}^{t24} (M + A * \cos(2\pi/24 * t + \varnothing))dt \quad (8)$$

using the cosine function which ordinarily is applied for describing the circadian rhythmicity of bioperiodic phenomena.

Surprisingly, this formula is perfectly identical to the equation 9 which is used for estimating the Aesor. Therefore, the assumption that the iBI and iBL may be the optimal estimators for correlating the BP regimen to the cardiovascular damage has received a non-empirical but mathematical evidence.

The second purpose of the chronodiagnosis at the Level 3 is that of comparing the iBI with the rBI in order to know how tensiogenetically aggressive is the diagnosed hypertension.

This information can be obtained by the parameter individual Baric Excess (iBE) which results from the formula

$$iBE = iBI - rBI \quad (9)$$

As already mentioned, hypertension is inequivocably associated with a positive measure of the iHI. However, if high BP merely depends on a phase-shift as in "phase-hypertension", the iBI is not exceeding the rBI, indicating that hypertension is not associated with iBE. This implies that high BP may coexist with two forms, i.e., "BE negative hypertension" and "BE positive hypertension". Obviously, the "BE negative hypertension" means that its iBI and iBL is not abnormal. Therefore, the TE may be regarded to be physiological. The opposite can be said for the "BE positive hypertension".

For this reason, the iBE may be regarded as an estimator of the tensiogenic aggressivity that high BP may exert via its BI and BL. By translation, the "BE negative hypertension" and the "BE positive hypertension" may be respectively called "innocent hypertension" and "aggressive hypertension".

Reliability of monodiagnosis versus chronodiagnosis

Having defined the curves and criteria with which the chronodiagnosis can be carried out, it was mandatory to perform a reevaluation of a sample in which the subjects were *a priori* classified as nor-

Table 1. – *A posteriori* chronodiagnostic reclassification of cases *a priori* diagnosed as normotensive or hypertensive by casual sphygmomanometry (based on diastolic blood pressure pattern)

A posteriori chronodiagnosis	*A priori* monodiagnosis	
	Normotension	Hypertension
True	79%	86%
False	21% (*)	14% (**)

Monodiagnosis: casual blood pressure measurement *versus* WHO refererence limits.
Chronodiagnosis: blood pressure monitoring versus chronodesms.
(*) Actually hypertensive; (**) actually normotensive.

Table 2. – *A posteriori* chronodiagnostic reclassification of cases *a priori* erroneously diagnosed as normotensive (false negatives) by casual sphygmomanometry (based on diastolic blood pressure pattern)

A posteriori chronodiagnosis	*A priori* monodiagnosis
Hypertension	Normotension
Borderline	67%
Mild	19%
Moderate	10%
Severe	4%

Monodiagnosis: casual blood pressure measurement *versus* WHO refererence limits.
Chronodiagnosis: blood pressure monitoring versus chronodesms.

Table 3. – *A posteriori* chronodiagnostic reclassification of cases *a priori* erroneously diagnosed as hypertensive (false positives) by casual sphygmomanometry (based on diastolic blood pressure pattern)

A posteriori chronodiagnosis	*A priori* monodiagnosis			
	Hypertension			
	Borderline	Mild	Moderate	Severe
Normotension	54%	34%	12%	0%

Monodiagnosis: casual blood pressure measurement *versus* WHO refererence limits.
Chronodiagnosis: blood pressure monitoring versus chronodesms.

motensive or hypertensive by the monodiagnosis. The *a posteriori* validation was performed with the intension of estimating the performance accuracy of the presently used monodiagnostic procedure.

Table 1 shows the percentage of true and false cases either normotensive or hypertensive resulting from the chronodiagnostic reclassification. It appears evident that about one case on five normotensive subjects is erroneously classified by the monodiagnosis as affected by hypertension. On the other hand, one hypertensive patient on nine hypertensives is erroneously diagnosed as a normotensive subject.

Table 2 displays the diagnostic verdict concerning the cases falsely classified as normotensive by the monodiagnosis. It is clear that the false normotensive subjects were more frequently recognized as affected by borderline hypertension.

Table 3 depicts the diagnosis of cases falsely classified as borderline, mild, moderate or severe hypertensives. It is evident that the false hypertensives were more frequently diagnosed as affected by borderline hypertension.

All of this means that the monodiagnosis is critical in making an unambiguous boundary between normotension and hypertension.

Table 4 shows the accuracy of the monodiagnosis as results from the revalidation versus the chronodiagnosis. It is evident that the monodiagnostic procedure is poorly sensitive and even less specific. According to its predictive value, it can be said that the monodiagnosis provides an erroneous verdict in about one case every five subjects.

A posteriori versus a priori time-qualified reference limits

The revalidation of the monodiagnosis provided an *a posteriori* sample of true normotensive subjects, including the false positive case of hypertension. This sample was used to recalculate the time-qualified reference limits (post-test reference limits).

Fig. 26 shows the post-test chronodesms, cosinordesms and aesordesms as compared to the corresponding pre-test desms.

The profound difference should convince us that it is profoundly erroneous to construct the time-qualified reference standards for normotension by using a sample of subjects classified by the monodiagnosis as normotensive. The sample has to be purified by using the chronodiagnostic procedure to remove false negatives and to include true negatives and false positives.

Table 4. – Accuracy of monodiagnosis in detecting normotension and hypertension as tested by chronodiagnosis (based on diastolic blood pressure pattern)

Estimator	Estimate
Sensitivity	83%
Specificity	71%
Predictive value	79%

Monodiagnosis: casual blood pressure measurement *versus* WHO refererence limits.
Chronodiagnosis: blood pressure monitoring versus chronodesms.

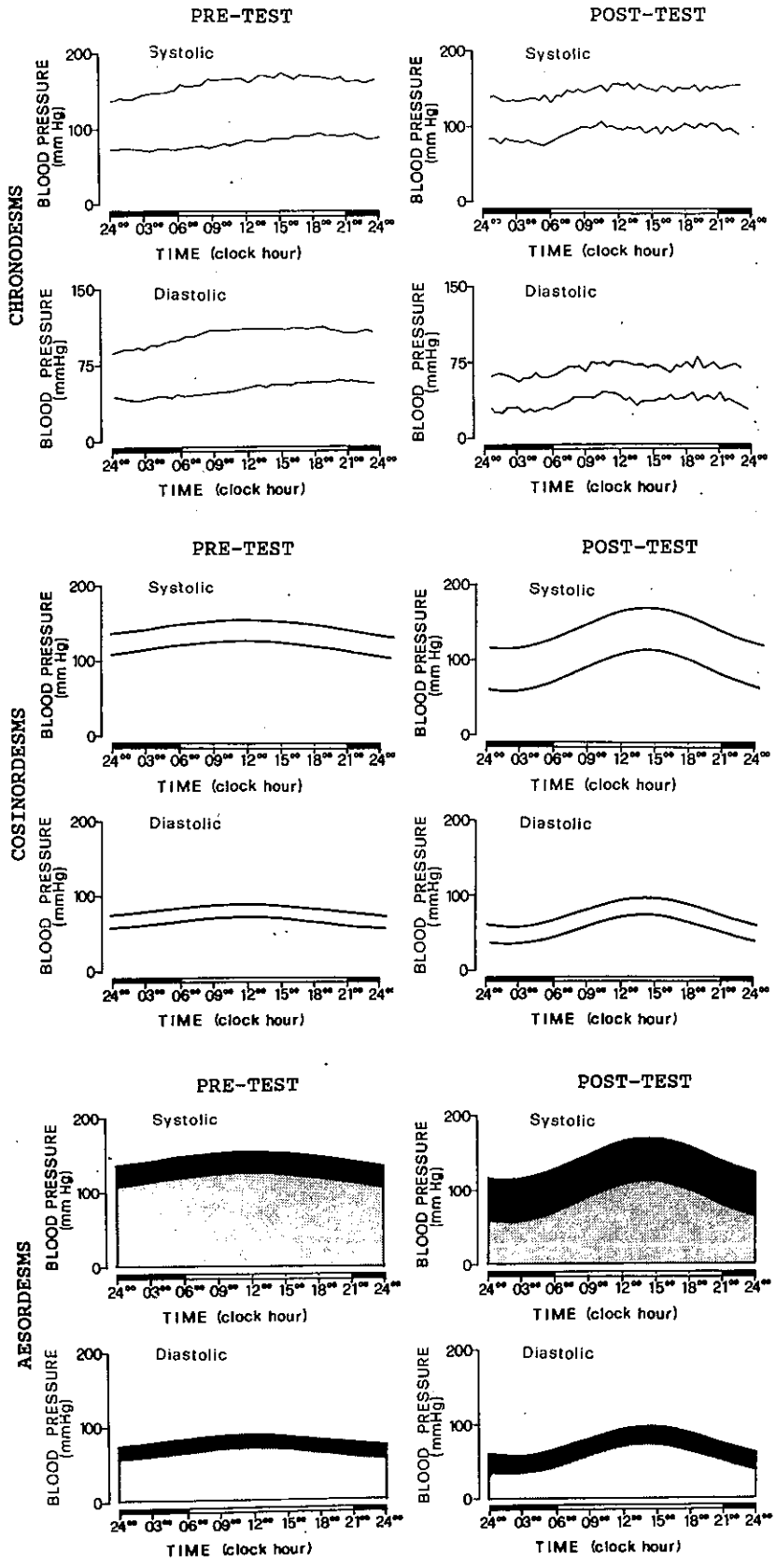


Fig. 26. - Dramatic differences in time-qualified reference limits for blood pressure depending on the diagnostic criteria with which the sample of normotensive subjects was constituted. Left panels show the reference limits based on the monodiagnosis. Right panels display the reference limits based on the chronodiagnosis.

Table 5. – *A posteriori* chronodiagnostic reclassification of cases *a priori* erroneously diagnosed as hypertensive by casual sphygmomanometry and stratified according to severity (based on diastolic blood pressure pattern)

A posteriori chronodiagnosis	*A priori* monodiagnosis			
	Hypertension			
	Borderline	Mild	Moderate	Severe
True	60%	73%	63%	33%
False	40%	27%	37%	67%

Monodiagnosis: casual blood pressure measurement *versus* WHO refererence limits.
Chronodiagnosis: blood pressure monitoring versus chronodesms.

Table 6. – *A posteriori* chronodiagnostic redistribution of cases *a priori* correctly diagnosed as hypertensive (true positives) by casual sphygmomanometry (based on diastolic blood pressure pattern)

A posteriori chronodiagnosis	*A priori* monodiagnosis			
	Hypertension			
Hypertension	Borderline	Mild	Moderate	Severe
Borderline	60%	19,5%	4.7%	0%
Mild	30%	33,5%	29%	0%
Moderate	10%	47%	29%	10%
Severe	0%	0%	33.7%	90%

Monodiagnosis: casual blood pressure measurement *versus* WHO refererence limits.
Chronodiagnosis: blood pressure monitoring versus chronodesms.

Monodiagnosis *versus* chronodiagnosis in grading hypertension

The reevaluation was extended to validate the accuracy of the monodiagnosis in grading hypertension.

Table 5 shows the percentage of cases confirmed to be true or false for the diagnosis of borderline, mild, moderate or severe hypertension. It is evident that the percentage of misclassification is very wide. Most of the errors are however committed in recognizing borderline or severe forms of hypertension. In other words, the monodiagnosis appears to overstimate the extreme grades of severity for high BP.

Table 6 displays the redistribution of cases erroneously classified in the severity of their hypertension. It is evident that a proportion of cases classified as borderline, mild, moderate, severe hypertensives really belong to antecedent or subsequent grades of hypertension. Therefore, the borderline hypertensives are affected by mild or moderate hypertension in a proportion of respectively 30% and 10%. The mild hypertensives are bearer of a borderline or moderate hypertension with frequency of about 20% and 50%. The moderate hypertensives are classifiable as borderline, mild or severe hypertensives in a rate of about 5%, 29% and 40%, respectively. The severe hypertensives are affected by moderate hypertension in a percentage of 40%.

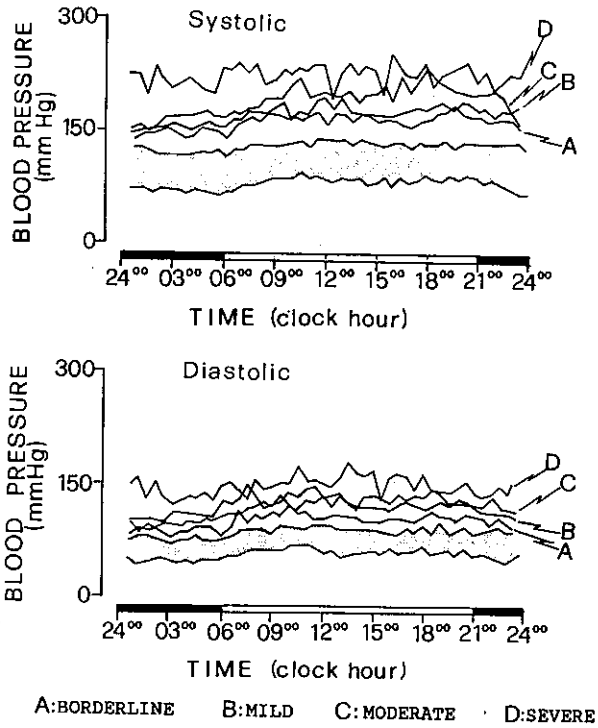
Table 7. – Accuracy of monodiagnosis in grading hypertension in its borderline, mild, moderate and severe forms as tested by chronodiagnosis (based on diastolic blood pressure pattern)

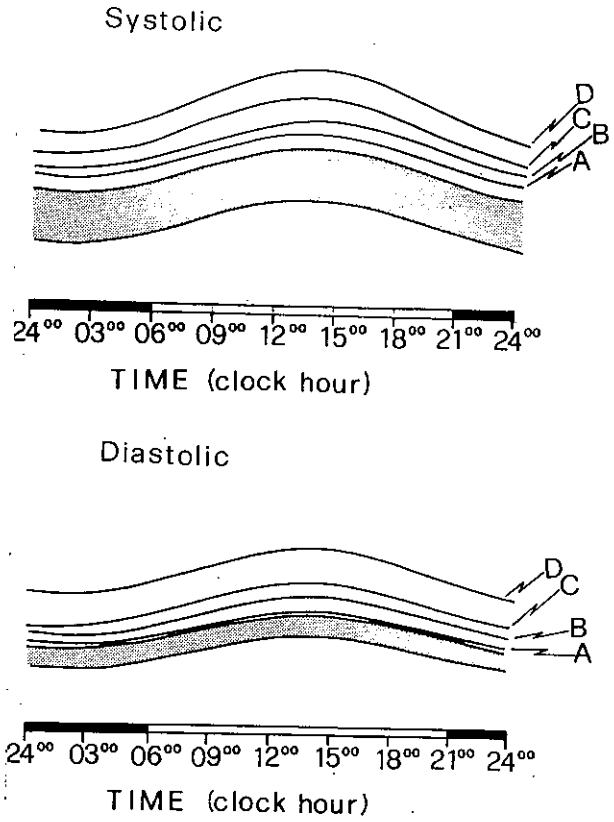
Estimator	Estimate			
	Hypertension			
	Borderline	Mild	Moderate	Severe
Sensitivity	64%	91%	93%	88%
Specificity	71%	71%	71%	71%
Predictive value	68%	80%	78%	73%

Monodiagnosis: casual blood pressure measurement *versus* WHO refererence limits.
Chronodiagnosis: blood pressure monitoring versus chronodesms.

Table 8. – Cut off limits for diagnosing and grading hypertension via chronodiagnosis of individual non invasive ambulatory monitoring

Diagnosis	24 h mean level (mmHg)		Oscillatory amplitude (mmHg)		Baric load (mmHg/24 h)		Hyperbaric impact (mmHg/24 h)		Baric excess (mmHg/24 h)	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Normotension	126	74	20	14	181.718	106.707	0	0	0	0
Borderline hypertension	138	77	20	14	199.038	11.060	11.157	4.631	17.319	4.330
Mild hypertension	140	90	21	17	201.922	129.779	19.163	19.090	20.204	23.072
Moderate hypertension	155	96	26	19	223.503	138.417	29.712	24.079	41.785	31.709
Severe hypertension	181	118	30	23	261.020	170.139	64.391	50.016	79.302	63.431
Malignant hypertension	> 181	> 118	> 30	> 23	> 261.020	> 170.139	> 64.391	> 50.016	> 79.302	> 63.431





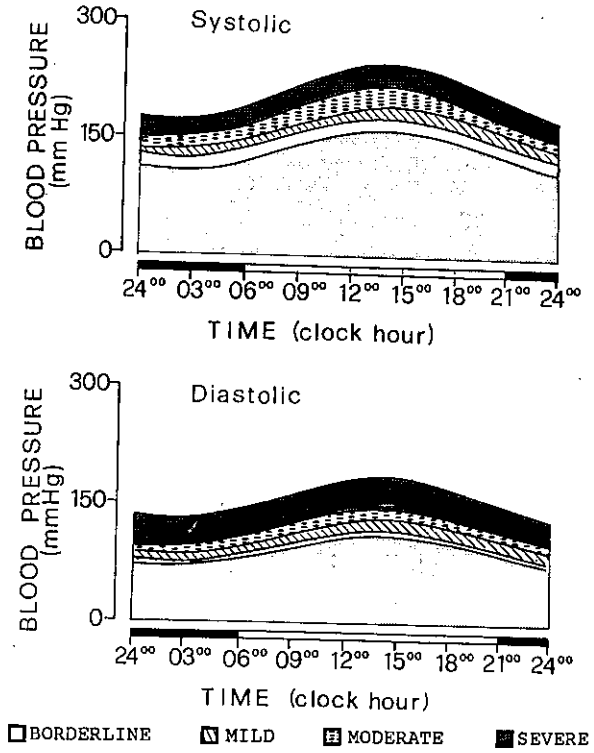


Fig. 27. - Time-qualified limits for unambiguously diagnosing and grading hypertension using the chronodiagnostic procedure.

Table 7 shows the sensitivity, specificity and predictive value of the monodiagnosis in recognizing borderline, mild, moderate and severe cases of hypertension. It is evident that the accuracy is higher for the intermediate grades of hypertension. In detail, the monodiagnosis fails about 4, 2, 2 and 3 times every ten in appropriately classifying respectively the borderline, mild, moderate and severe cases of hypertension.

Grading hypertension via chronodiagnosis

The reevaluation of hypertensive cases gave origin to an *a posteriori* sample of true borderline, mild, moderate and severe hypertension. These cases were used for quantifying the limits to be used for grading the chronodiagnosis of hypertension.

Fig. 27 shows the limits in terms of chronograms, cosinorgrams and aesorgrams for the systolic and diastolic BP 24 h pattern with reference to the borderline, mild, moderate and severe forms of hypertension. Details on these limits can be obtained in Table 8.

Conclusions

The technological development in biomedical instrumentation has made possible the automated measure of BP out of any human intervention. The automated monitoring implies a view of BP as a

function which is inherently variable over the 24 h span. Because of this, the monodiagnosis appears to be no more responding to its clinical scope. Its limits are biometrically demonstrated in this study. The suitable approach is the chronodiagnosis. In addiction to BP monitors, physicians now possess the numerical curves, the mathematical criteria and the biostatistical standards for applying the chronodiagnosis of hypertension in clinical practice. In our opinion, the time of an erroneous approach to BP 24 h pattern in humans is terminated.

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