Exploiting the ambulatory blood pressure monitoring via chronobiometric and chaosbiometric methods for a more exhaustive diagnostic approach to arterial hypertension

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Abstract

Presently, the ambulatory (A) blood (B) pressure (P) monitoring (M) is mainly used for diagnosing arterial hypertension (AH) in some special clinical conditions in which the causal sphygmomanometry appears not to be enough exhaustive. However, it must be pointed out that the actual approach to ABPM is almost simplistic, only consisting in a biometric analysis of discrete raw temporal values for systolic (S) and diastolic (D) BP and heart rate (HR). It must be stressed that BP and HR are hemodynamic variables characterized by a well-established circadian rhythm (C) in their 24-h physiological values. Therefore, an appropriate chronobiometric approach, via Single Cosinor method, can improve the diagnostic value, its optimal oscillatory curve reducing all the biometric information to three parameters, i.e., MESOR (M, mean level of oscillation), Amplitude (A, extent of oscillation from M) and Acrophase (φ, timing of A with respect to local midnight). Accordingly, one can detect whether the BP CR is still manifest, as it is in essential hypertension (EH), or altered, as it is in secondary hypertension (SH). Therefore, by using the discriminant analysis for the three multivariate parameters, M, A, φ, of the BP cosine curve, one can statistically predict whether a new monitored hypertensive patient has a significant probability to be affected by EH or SH. Interestingly, by applying a further chronobiometric integration analysis, i.e., the Cosint analysis, it is possible to estimate the area under the BP oscillatory curve, for calculating the overall, diurnal, nocturnal, hourly pressure load (Baric Impact, BI) in terms respectively of mm\(^2\)Hg/24-h, mm\(^2\)Hg/16-h, mm\(^2\)Hg/8-h, mm\(^2\)Hg/1-h. By comparing the overall BI of the new monitored hypertensive patient to its upper reference limit, one can estimate how much is the Baric Excess (Hyperbaric Impact, HI) caused by the personal hypertensive regimen. Finally, by using the chaos method of fractal interpolation to BP 24-h values, it is possible to establish whether or not the monitored hypertensive subject is presumably at risk of unpredictable high BP values (presumptive risk of hypertensive crisis).

Key words: ABPM, arterial hypertension, blood pressure, essential hypertension

Casual versus monitored sphygmomanometry for diagnosing arterial hypertension

In ordinary clinical practice, the diagnosis of arterial hypertension (AH) is mainly pointed out by casual sphygmomanometric measurements of systolic (S) and diastolic (D) blood pressure (BP), whose values are compared to the time-unvarying reference limits (1). However, it is well known that the clinic casual sphygmomanometry is per se not so much accurate in discovering borderline, spurious or odd-hour elevations of BP (2), resulting, thus, in a possible source of false negative cases. To skip such a diagnostic limitation, it is proposed to adopt the non-invasive ambulatory blood pressure monitoring (ABPM), feasible via portable automated devices which are programmed to record and store sphygmomanometric measurements of SBP and DBP at given intervals of time over the day-night span, letting the monitored subjects to be free of living their usual style of life (3-10). The monitored temporal series of SBP and DBP values are then, transferred from the monitor to a personal computer to be electronically analyzed via a standardized biometric procedure that can be defined “conventional biometric approach to ABPM”.

Conventional biometric approach to ABPM

Once the SBP and DBP data have been memorized into a magnetic support (hard disk) of a personal computer a dedicated software performs a standardized biometric analysis by conventionally comparing each one of the monitored values to their pertinent diurnal and nocturnal upper reference limits, in consideration that BP shows a nyctohemeral variability in its within-day pattern (11-13). In so doing, the software counts the number of values that are higher than normal, considering that a percentage ≥20% (pressure load) is highly indicative for posing a diagnosis of AH.

In addition, the software performs a biometric estimate of the SBP and DBP daily, diurnal and nocturnal mean, along
with their standard deviation, and calculates the percentage of the diurnal and nocturnal mean difference (DNMD). As a matter of facts, such a percentage lets us to classify the monitored subject, resulted to be affected by AH, as a “dipper” (DNMD ≥10%), a “non-dipper” (DNMD ≥0%-<59%), an “inverter” (DNMD >0%, i.e., negative). Importantly, any hypertensive subject who is not classified as a “dipper” has to be considered at a higher risk for target organ damage (14-17).

Criticism to the limited informative power of the conventional biometric approach to ABPM

What has been so far summarized represents the highest degree of information that the ABPM, via its conventional biometric approach, presently offers to clinicians for a more accurate diagnosis of AH.

But the question is “May the ABPM be more conveniently exploited in order to obtain more exhaustive information for diagnosing AH?”. In other words, “Are there some other mathematical-statistical procedures of biometric analysis that can be used to better exploit the diagnostic power of the BP 24-h data provided by ABPM?”. It is important to say that the answer to these questions is positive. As a arguments and evidences that document the possibility to further analyze the ABPM by taking into consideration the objective characteristics of the BP 24-h pattern, with respect to: 1. the nychtohemeral variability of its values; 2. the unpredictability of each one of its values.

Both these features suggest to further approach the ABPM BP, respectively, via: 1. a chronobiometric analysis of BP intra-diem variability; 2. a chaobiometric analysis of unpredictability in BP within-day single-values.

Approaching the ABPM via a “chronobiometric analysis” of BP time-qualified values

The rationale of a chronobiometric approach to ABPM relies on the preliminary important evidence that the BP within-day variability can be regarded in its nychtohemeral-arity as the physiological expression of a biological rhythm that fluctuates with a period of 24-h, i.e., a circadian rhythm (CR) (18-23).

Being a well established CR, the manifest BP within-day variability represents a structured predictable pattern whose rhythmic parameters are the estimates that indicate the physiology of its cyclic arrangement. This implies that any derangement in the rhythmic properties of BP CR, from its slightest shift to its heaviest loss, has to be considered as a clinical sign of a pathophysiology in hemodynamic pressure regulation. Accordingly, the chronobiological approach to ABPM lets us to have more information about the pathophysiologic mechanisms that characterized the elevation of BP in humans (24-31). This is one of the three main reasons for which it is scientifically recommended to approach the ABPM via a “Descriptive Rhythmic Analysis” (DRA) for validating and quantifying the SBP and DBP CR, as it will be better explained below (see, Subchapter 1).

The second important reason that explains why it is necessary to approach the ABPM via a second type of chronobiometric procedure, namely the “Integrative Rhythmic Analysis” (IRA) lies on the evidence that the BP 24-h values are data that can be used for accurately estimating the pressure regimen, to be intended as “pressure load”, not as a percentage of BP values higher than normal, but as an “integration of pressures over time”. In fact, according to the physical principles, a real pressure load, alias Baric Impact (BI), has to be intended as the “integral estimate of all the pressures that effectively have operated between the initial and final temporal limits of an established period of time” (32-34). Therefore, the second chronobiometric approach to ABPM deals with the IRA addressed to quantify the real pressure load, as it will be better explained below (see, Subchapter 3).

1. Approaching the ABPM via the “Descriptive Rhythmic Analysis” of Single-Cosinor method for validating and quantifying the BP CR

This type of chronobiometric approach to ABPM is aimed at analyzing the SBP and DBP time-qualified values for statistically validating the presence of a CR and biometrically estimating its rhythmic parameters.

The validation and quantification of BP CR, i.e., the DRA, in each individual ABPM can be performed by means of the Single-Cosinor analysis (36), a method that consists in fitting a periodic regressive function, having a 24-h period (τ) as a known constant, to the raw, discrete, temporal data, using the “least squares method” for minimizing the sum of residuals, and finding out the best fitting sinusoidal curve (cosinogram). The cosine regression function is expressed by the following equation:

\[ Y_t = M + A \times \cos \left( \frac{2\pi}{\tau} t + \phi \right) + \varepsilon \]

in which, the symbols M, A and ϕ (phi) represent the computable parameters of CR, having the following informative meaning: M (MESOR, acronym of midline estimating statistic of rhythm, or rhythm-adjusted mean): mean oscillatory level which equals the arithmetic mean when the temporal series is made by equidistant data; A (Amplitude): oscillatory extent from M; ϕ (Acrophase or Phase): timing of a occurrence related to local midnight. The symbol ε (Error) represents the incidence of casual values that occur in any series of collected measurements, including the temporal ones.

Importantly, in order to avoid the Error, due to the randomness of casual data, the Single-Cosinor method is able
to validate the “Rhythm Statistical Significance” by verifying if the F coefficient, given by the ratio between the variance of the regression and the variance of raw discrete temporal data, is high enough to reject the null-hypothesis of zero-amplitude at a statistical P level of probability ≤0.05.

Assuming that the Single-Cosinor analysis primarily establishes whether the BP CR is preserved or abolished, it is very important to emphasize that by comparing the individual rhythmometric parameters M, A and φ (phi) to their upper reference limits (37-40), the clinicians are posed in the diagnostic position of identifying the formal within-day pathophysiological patterns that are associated with the elevation of BP 24-h values, i.e., the formal pathophysiological condition consists in the presence of the chronotype NRAH, the DRA will necessarily give rise to two subchronotypes, respectively the: Eu-Phased or Non-Inverted RAH (better Eu-RAH) and the Allo-phased or Inverted RAH (better Allo-RAH). Both the Eu-RAH and Allo-RAH can be characterized by an increase: 1. in Amplitude, giving respectively rise to the subchronovarians: “Amplitude Eu-RAH” and “Amplitude Allo-RAH”, or 2. In MESOR, giving respectively rise to the subchronovarians: “MESOR Eu-RAH” and “MESOR Allo-RAH”. Finally, in the presence of the chronotype NRAH, the DRA will necessarily demonstrate that both the Amplitude and Acrophase are not significant, the first one being negligible, the second one being erratic, so that the rhythmometric condition consists in the increase in MESOR, giving rise to the subchronovariant “MESOR NRAH”.

2. Approaching the ABPM via the “Integrative Rhythmometric Analysis” of Single-Cosint method for estimating the pressure regimen as a real pressure load, alias Baric Impact

This type of chronobiometric approach to ABPM is aimed at estimating the pressure regimen via a real “pressure load” (PL), alias “Baric Impact” (BI), as the result of the integral of all the monitored BP values over two given limits of time. The quantification of BI from each individual ABPM can be performed by means of the Single-Cosint analysis (42-45), a method that consists in measuring the integrative parameter AESOR (acronym of area estimating statistic of rhythm) as the area subtended by the values, at each time t (Y), of the optimal sinusoidal curve (cosinorgram) between an initial (T1) and a final time (T2) within which the integration has to be performed. The integrative cosine function is expressed by the following equation:

\[ AESOR = \frac{1}{T} \int_{T1}^{T2} f(t)dt = \frac{1}{T} \left[ M + A \cos \left( \frac{2\pi}{TAU} T + \phi \right) \right] dt \]

integrative cosine function of BP 24-h monitored data, depending on the extension of the integration interval between T1 and T2 (dT), returns the daily BI in mm\(^2\)/24-h (dT: from 0-h to 24-h), the diurnal BI in mm\(^2\)/16-h (dT: from 7-h to 23-h), the nocturnal BI in mm\(^2\)/8-h (dT: from 23-h to 7-h) as well as the hourly BI in mm\(^2\)/1-h (dT: from 0h to 1h or from 1-h to 2-h or from 3-h to 4-h, etc.).

Interestingly, by comparing the individual daily, diurnal, nocturnal and/or hourly BI to their respective upper reference limits, the clinicians are posed in the diagnostic position of estimating the “quantum of excess” (QE), alias “baric excess” (BE), alias “baric hyperimpact” (BH), alias “hyperbaric impact” (HI), that characterizes the pressure regimen of a subject defined as hypertensive by the ABPM conventional biometric analysis. These daily, diurnal, nocturnal, hourly HIs are respectively estimated in mm\(^2\)/24-h, mm\(^2\)/16-h, mm\(^2\)/8-h, hourly mm\(^2\)/1-h.

3. Using the rhythmometric parameters of BP CR via a “Multivariate Discriminant Analysis” for probabilistically predicting between primary and secondary AH

With respect to MDA (35), it must be stressed that, statistically speaking, this method is a comparative as well as a classificative procedure that can be very helpful for discriminating between two preselected groups of members by means of some variables and, subsequently, establishing whether a new entry probabilistically belongs to one of these groups. The MDA is able to estimate the mean level of separation (Lo) that can be regarded as a boundary for separating the Gaussian curves that represent the statistical distribution of the overall data in each group under scrutiny. If the two Gaussian curves are separated by the Lo level for less than 5% of their tails, it can be assumed that the two groups can be discriminated at a statistical significant level of probability by the variables under scrutiny.

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**Table 1. Summary of main chronotypes (letters in bold) and subchronotypes (letters in bold and italics), with their chronovarianants (letters in italics) of arterial hypertension (AH) as diagnosed by the “Descriptive Rhythmometric Analysis” of raw, discrete blood pressure 24-h values recorded via ambulatory blood pressure monitoring.**

<table>
<thead>
<tr>
<th>Rhythmic AH (RAH)</th>
<th>Euphased or Non-Inverted RAH (Eu-RAH)</th>
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<tr>
<td></td>
<td>• Amplitude Eu-RAH</td>
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<td>• MESOR Eu-RAH</td>
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<td>• MESOR NRAH</td>
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**Table 2. Summary of main chronotypes (letters in bold) and subchronotypes (letters in bold and italics), with their chronovarianants (letters in italics) of arterial hypertension (AH) as diagnosed by the “Descriptive Rhythmometric Analysis” of raw, discrete blood pressure 24-h values recorded via ambulatory blood pressure monitoring.**

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<tr>
<td>Allophased or Inverted RAH (Allo-RAH)</td>
<td>• Amplitude Allo-RAH</td>
<td>• MESOR Allo-RAH</td>
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<tr>
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Furthermore, in the presence of a significant level of discrimination, a new member can be entered into the MDA by adding the values of each covariate. Running again the analysis, the method will estimate the discriminant level \((L)\) of the new data, whose value will belong to one of the two distributions. Therefore, the new entry can be allocated in one of the two groups under scrutiny with a given significant level of probability.

At this point, it is fundamental to stress what is, statistically speaking, the informative power of the rhythmometric parameters, \(M, A\) and \(\phi\), with respect to the raw, discrete time-qualified values. Basically, the rhythmometric parameters reduce the biometric information of each temporal series of data to only three degree of freedom. This prerequisite is very fundamental in that it is very difficult to biometrically compare any possible type of within-day variability, because of the almost infinite variety of unpredictable patterns, in raw, discrete temporal values. Therefore, an overall simplification to only three descriptive parameters lets us to use the rhythmometric estimates in each method of multivariate statistical analysis.

In order to better understand the relationship between MDA and BP rhythmometric parameters, it is important to stress that the Single-Cosinor method estimates both the \(\text{MESOR}\) and \(\text{Amplitude}\) in mmHg, and the \(\text{Acrophase}\) in sexagesimal degrees \((^\circ)\), rotating clockwise, that are expressed in negative values because of the use of a cosine function. Therefore, \(-360^\circ = 24\text{ h}; -15^\circ = 1\text{ h}; -1^\circ = 4\text{ min}\), so that \(0^\circ = \text{h 0 (initial midnight)}; -90^\circ = \text{h 6}; -180^\circ = \text{h 12 (noon)}; -270^\circ = \text{h 18}; -360^\circ = \text{h 24 of the subsequent midnight}\). Interestingly, the physiological \(\text{Acrophase}\) of BP CR occurs early in the afternoon, its value ranging from \(-180^\circ\) to \(-235^\circ\). Because of this, a BP \(\text{Acrophase}\) shifted respectively to evening or night or morning hours will assume a value from \(-235^\circ\) to \(-345^\circ\); from \(0^\circ\) to \(-105^\circ\); from \(-105^\circ\) to \(-180^\circ\), respectively.

These premises serve to better understand what is the chronopathological meaning of the “dipping”, “inverting” and “non-dipping” phenomena documentable in hypertensives by the conventional biometric approach to ABPM.

In such a circumstance, the DRA will demonstrate that the “dipper hypertensives” are subjects characterized by the chronotype “RAH” in that their BP CR is significant and shows: 1. a normal value in \(\text{Acrophase}\) timing (as per the subchronotype called: “Eu-RAH”), associated respectively with: 2. a significant increase in \(\text{Amplitude}\) value (as per the subchronovariant called: “Amplitude Eu-RAH”), or alternatively; 3. a significant increase in \(\text{MESOR}\) value (as per subchronovariant called: “MESOR Eu-RAH”). In turn, the “inverter hypertensives” are subjects characterized by the chronotype “RAH” in that their BP CR is significant but shows: 1. an abnormal value in \(\text{Acrophase}\) timing (as per the subchronotype called “Allo-RAH”), associated respectively with: 2. a significant increase in \(\text{Amplitude}\) value (as per the subchronovariant called “Amplitude Allo-RAH”); or alternatively, 3. a significant increased \(\text{MESOR}\) value (as per subchronovariant called “MESOR Allo-RAH”). Finally, the “non-dipper hypertensives” are subjects characterized by the chronotype “NRAH”, in that their BP CR is not significant, because of a low value in \(\text{Amplitude}\) and an abnormal value in \(\text{Acrophase}\) timing, and shows a significant increase in \(\text{MESOR}\) value (as per subchronovariant called “MESOR NRAH”).

It must be emphasized that clinical studies demonstrated the “dipper hypertensives” are patients usually affected by essential AH (EAH), while both the “inverter hypertensives” and “non-dipper hypertensives” mainly result to be affected by secondary AH (SAH) (46-55).

The rationale of a chaosbiometric approach to ABPM lies on the preliminary important evidence that the BP within-day variability is made by values which are unequal each other as well as unpredictable in their entity. This means that their occurrence is characterized by a certain degree of “disorder”, say a “biological chaos” or “biochaos”, within the limits of their variability (56-60). For example, such a biochaos can reach its maximum in the circumstance of a hypertensive crisis. However, the fact that the BP 24-h pattern is arranged in a periodic fashion, lets us to derive that, under physiological conditions, the biochaos of the their unpredictable values can cohabit with their predictable periodic structure. This implies that the disorder in BP within-day values cannot be regarded as the sign of an entropic chaos.

### Approaching the ABPM via a “chaosbiometric analysis” of BP time-qualified values

There are patients who show the “dipping phenomenon” are subjects who show the Amplitude Eu-RAH or the MERSOR Eu-RAH, while the secondary hypertensives with the “inverting phenomenon” are patients who show the Amplitude Allo-RAH or the MERSOR Allo-RAH. Finally, secondary hypertensives with the “non-dipping phenomenon” are patients who show the MERSOR NRAH.

Therefore, the dipper hypertensives with essential AH as well as of the inverter or non-dipper hypertensives with secondary AH will be characterized by the changes in values of BP rhythmometric parameters as shown in Table 2.

Because of these consistent differences in rhythmometric values of SBP and DBP CR, the MDA is potentially able to differentiate between essential and secondary hypertensives and to suggest whether a hypertensive subject is probably affected by essential or secondary AH. Such a probabilistic hint can be very important in that the clinician has an objective suggestion to delve into the clinical investigations aimed at discovering the etiology of AH in that a given patient.

<table>
<thead>
<tr>
<th>Table 2. Table of Truth showing the changes in values for the rhythmometric parameters of BP CR in AH.</th>
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<tbody>
<tr>
<td><strong>Rhythmometric parameters</strong></td>
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<tr>
<td><strong>Essential AH showing the “dipping phenomenon”</strong></td>
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<tr>
<td>• Amplitude Eu-RAH</td>
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<tr>
<td>• MERSOR Eu-RAH</td>
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<tr>
<td><strong>Secondary AH showing the “inverting phenomenon”</strong></td>
</tr>
<tr>
<td>• Amplitude Allo-RAH</td>
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<tr>
<td>• MERSOR Allo-RAH</td>
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<tr>
<td><strong>Secondary AH showing the non-dipping phenomenon</strong></td>
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<td>• MERSOR NRAH</td>
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</table>

\(\text{NSD}^\circ = \text{Negative Sexagesimal Degrees}; N = \text{Normal}; H = \text{High}; L = \text{Low}; A = \text{Abnormal}\)
(alias, indeterministic chaos), such as the one that occurs as a dissipative effect of the second law of thermodynamics. The disorder in BP within-day values, coexisting with the structured periodicity of their variability, can be regarded as a syntropic chaos (alias, deterministic chaos) (56-60). This means that the deterministic chaos can be regarded as an intrinsic physiological feature of the BP within-day variability along with the circadian rhythmicity.

According to the “principle of cause-effect”, the implicit presence of a deterministic chaos in a time-qualified series of raw, discrete, unpredictable data can be regarded as the formal mechanism that causes a certain degree of disorder, say “non-linear variability”, in their temporal pattern. Because of this non-linearity, the time-qualified series of raw, discrete (say, intervallary) data can be geometrically seen as a “non-Euclidean temporal profile”, whose values, by principle, could not be interpolated according to a linear model (say, according a Newtonian interpolation) within their equidistant or non-equidistant intervals of time.

Studies of chaos mathematics of non-linear systems have demonstrated that the non-Euclidean shapes usually represent a model of variability that is called “fractal” (61, 62), in that the overall profile of the equidistantly or non-equidistantly sampled discrete data can be detected, in a minimized fashion, in each time interval within two consecutive data. This means that in a time-qualified series of discrete data, each interval of time represents a window in which it is reproduced, in minimized values, the shape of the entire non-Euclidean profile, according to the “principles of similarity and homothety” (identical orientation in space). Because of this, each temporal segment is a non-linear representation of the non-linearity of its whole, i.e., a temporal fractal of its overall fractal. Mutatis mutandis, it can be said that in a temporal fractal the temporal profile of its whole is a magnified shape of the temporal profile of its parts, or, vice versa, that the temporal profile of its parts is a minimized shape of the temporal profile of its whole, so that the part is similar to its whole, and vice versa.

Assuming a fractal model for the time-qualified unpredictable values, it is obvious that their non-linear variability can be conveniently approached by such a descriptive method of chaos mathematics that is known as “Fractal Interpolation Analysis” (FIA) (63).

With respect to FIA, it must be stressed that, mathematically speaking, this method belongs to the “Iterated Function Systems” (IFS) of chaos mathematics that operate by means of Affine Transformations (AT) estimating fractal codes as translation, angle and rotation for the relationships between data. How it has been already explained, the fractal interpolation resamples and reconstructs, by minimization, the overall profile of a time-qualified series of unpredictable data into each time interval between two consecutive discrete values. Each intertime is, thus, a fractal (a part which repeats minimized its image, a facsimile of itself) of the overall fractal that serves as a baseline model of itself. The fractal interpolation can be iterated inside the intertimes of the fractalized series for n times, giving origin to a higher-order fractal interpolation. In each iteration, the fractal interpolation generates unpredictable chaotic values which interpolate the intertime as non-linear entities whose dimension (fractal dimension) can be also a fraction of units. In so doing, the fractal interpolation develops unpredictable chaotic values which can result to be exaggerated entities, figuratively called “singularities” or “catastrophers”, depending on the degree of disorder that characterizes that a time data series under scrutiny.

1. Approaching the ABPM via the “Fractal Interpolation Analysis” of non-linear mathematical methods for exploring the individual risk of unpredictable elevations in BP values, say the presumptive risk of hypertensive crisis

This type of chaobiometric approach lies on the fact, already discussed, that the BP time-qualified values are unpredictable in their entity and sequence, despite the presence of a CR, as per a disorder that is responsible for non-linear within-day variability. Because of this chaotic “temporal fractal” one can suppose that a chaobiometric approach to ABPM via FIA allows us to investigate the BP within-day variability in its deterministic chaos. In addition, when dealing with the BP time-qualified values, the eventual occurrence of chaotic singularities can be interpreted as a proneness of the hypertensive subject to develop unpredictable elevations of BP, revealing, thus, an individual “risk” to develop hypertensive crisis (64, 65).

The chaobiometric approach to ABPM, via FIA, is made, by simplicity, on the time-qualified raw, discrete values of Mean (M) BP. The MBP series is fractalized, the chaotic values, developed inside each time interval, are replotted along with the original ABPM data, that were the prime fractal model to be minimized always self-similar in an n-order fractal reproduction (58). The fractalized MBP values that result to be higher than their third standard deviation are regarded as “outliers”, and considered to be the expression of an episode of singularity. Accordingly, the hypertensive subject whose ABPM provided such a potential risk of singularities is regarded as a person presumptively at risk of hypertensive crisis. The risk is presumable and not probable in that the fractal interpolation, dealing with chaotic data is, by principle, a method not statistically reliable.

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