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Mini Review

Chaos, resistant and pseudoresistant hypertension "Thousands of butterflies in the BP control system"

Juan Carlos Yugar-Toledo[1], Nelson Dinamarco[2], Bruno Rodrigues[3] and Heitor Moreno[3]*

[1]MD, PhD, Rio Preto, Faculty of Medicine (FAMERP), SP, Brazil

[2]MD, PhD, Santa Cruz, State University (UESC), BA, Brazil

[3]MD, PhD, State University of Campinas (UNICAMP), SP, Brazil

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***Corresponding author:** Heitor Moreno, MD, PhD, State University of Campinas (UNICAMP), Rua Jasmin, 850, apto 850, Bairro Primavera, Campinas, State of São Paulo (SP), ZIP CODE 13087-460, SP, Brazil, Email: hmoreno@uol.com.br

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Abstract

In Cardiology, we classify hypertensive patients as resistant to treatment, pseudo-resistant, or hyperreactivity subjects, including the WCH (white-coat or masked hypertension). Compliance is another cause of failure in antihypertensive therapy. Hypertension is a complex clinical syndrome and many variables that interfere in BP depend on "The Theory of Chaos" and are not considered. We do not know how many variations the Chaos on BP levels can be. Still, as we have around 30% of "uncontrolled" patients, the Chaos and effects on BP regulation as taking part in this high rates of "uncontrolled" subjects. Chaos is a complicated issue to study, but multi-professional efforts must keep the attention to this relevant "cause" of hypertension. Finally, Chaos theory is well known and accepted in Maths, Economy, Philosophy, Meteorology, Ecology, and other areas of knowledge, but not in the Health area. Crescent attention to Chaos may help better understand some mechanisms and clinical expression of Chaos in pseudo-resistant hypertension and correlated hypertensive syndromes.

Out-of-controlled blood pressure

The brachial technique of Blood Pressure (BP) measurement overestimates the prevalence of uncontrolled Resistant Hypertension (RHTN) in approximately 33% of patients, reinforcing the need of obtaining accurate BP measurements [1]. The most recent AHA/ESC statements on RHTN [2,3] require the exclusion of both the white-coat effect and masked hypertension [4], and nonadherence [5] from the RHTN definition.

BP levels oscillation could lead to false diagnoses such as pseudo-resistance including white-coat [6,7] and masked [8-10] hypertension. Revising some major concepts on General Systems [11,12] and BP regulation [13,14] have to be addressed in this syndrome [15-17].

Pseudo-resistance – prevalence

Despite advances in diagnosis and management strategies, uncontrolled HTN remains a challenging problem and a primary cause of death for 7.5 million people each year globally. Ten years ago, De la Sierra, et al. observed the prevalence of RHTN at 12.2% of treated hypertensive patients included in The Spanish Ambulatory Blood Pressure Monitoring Registry [18]. In 2011, Sim, et al. reported the prevalence of RHTN as 12.8% of all hypertensive patients and 15.3% of hypertensive patients receiving treatment within the Kaiser Permanent Southern California healthcare system BP technique overestimates the 'prevalence of uncontrolled RHTN in approximately 33% of the patients emphasizing the importance of obtaining accurate BP measurements [19]. To understand the occasional increases in BP, some definitions of General Systems and Chaos theories are needed:

Homeostasis: self-regulation processes to maintain stability while adjusting to a dynamic equilibrium by continuous changes;

Allostatic: state of internal and physiological equilibrium maintained by an organism in response to actual or perceived environmental stressors;

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Stochastic: property of a random probability distribution;

Chaos: apparently random or unpredictable behaviors in complex systems governed by deterministic laws. Deterministic chaos suggests a paradox connecting randomness/unpredictability and deterministic processes.

The general system theory and chaos

In 1925, Ludwig von Bertalanffy [20], not satisfied with the physical and deterministic approaches to Biology, proposed an organismic conception (Organismic Biology) emphasizing the organism as a group or system. Biological systems may be cells, organisms, or populations with the common characteristic of being composed of other systems in interaction. These mechanisms were termed *cum plicate (Greek: complicated)* systems [21]. Fundamentally, these hard-to-understand subsystems work jointly to produce coherent behaviors (constancy or *equilibrium*). This initial concept led to a great number of articles, books, and conferences on General System Theory. According to this logic, the human organism is a system of much smaller subsystems with common characteristics [20]. Actually, this most insight concerning real-life *"cum -plicate"* systems dates to Heraclitus (about 540 B.C.) and Claude Bernard (1813-1878) with the concept of Homeostasis. This term was perfected and coined later by Cannon [22]. Homeostasis results from the response to a system perturbation and occur as *feedback mechanisms*, nowadays classified as *positive or negative* [23]. The concepts above gained space in many other areas of knowledge as a new paradigm, called "General Systemic Thought" [20]. A nonlinear or chaotic system behavior of many biological systems, including BP control, has grown since the 1960s. The complex nonlinear systems obey the Chaos Theory, which studies the foresight and order of the complex (chaotic) systems, although apparently random [14]. The antique Determinism and complete Predictability do not exist in the chaotic theory because of its nonlinear expression [14,24]. Chaotic systems and outcomes were subsequently included in the Chaos theory [25,26]. For five decades, theoretical arguments were presented that considered the human body to be a nonlinear dynamic deterministic system and, therefore, dependent on the laws of Chaos [24,27,28]. Accepting such ideas without the restrictions of the traditional, linear, perfect, and immutable Determinism in all Sciences seemed closer to human thought and the universe. Thus, a partial fusion of both classical Determinism and Entropic Chaos has occurred, but homeostasis, general systems, allostasis, *milieu interne,* and equilibrium still have space in human physiology and medicine [27,28]. Finally, the Chaos and the random determinism regulation of such general physiological mechanisms modulate biological systems (including BP) from cell to population levels [27,29].

Blood pressure as a nonlinear variable

Nonlinear behavior is present in almost the totality of the existing systems, including biological ones [14,27,28,30-32]. In this scenario, blood pressure (BP) is a major complex variable, ranging between randomness linearity, and health-disease, by means of the heart rate variability (HRV), using techniques of the chaotic domain [14,33-36].

Some authors use non-linear behavior to calculate a deterministic critical value to the concept of risk, superior to the habitually limited to time and frequency domains [32,36]. Chaotic, discontinuous and uncertainty of Nature, always an enigma to the researchers, has been integrated into Biological and Health Sciences.

The main pathological mechanisms of this syndrome and cardiovascular consequences (target organ damage) are summarized in this figure. However, a static pattern, not representative of the nonlinear chaotic changes. Hypervolemia and autonomic nervous system imbalance are the most relevant factors for HRTN (Resistant) and RfHTN (Refractory) Hypertension, respectively. Obesity, endothelial dysfunction, hyperaldosteronism, sleep apnea, arterial stiffness, and inflammation are also involved in this complex syndrome.

Chaos premises and BP variable behavior

However, these efforts may not be enough to reduce the BP in truly RHTN subjects, or "false out-of-/control" levels can occur in the white-coat effect and masked hypertension. These later patients are usually normotensives by 24h-ABPM or home blood pressure monitoring (HBPM), but the BP increase (office or night) may be concomitant with chaotic variations. [25,35]. The main premises of Chaos are [14,37]: Aperiodicity, finally determined by onset, predictable (polynomial), tendency to go back to the beginning, and cyclicity.

Finally, reviewing some pivotal contents on General Systems and deterministic nonlinear processes is critical to the better comprehension of outlier and unstable BP values in these hard-to-control patients.

Blood pressure (BP) and chaos

BP is a nonlinear dependent variable (y) related to many other influences and factors that aim at cardiovascular homeostasis in a chaotic (complex) general system. Office BP is the gold standard for the screening, diagnosis, and management of hypertension. However, optimal diagnosis and successful management of hypertension cannot exclusively be obtained by a handful of conventionally acquired BP readings. BP and blood flow patterns in humans are quite variable, allowing energy-efficient responses to diverse stimuli from outside (environmental) and inside (diurnal, postural, metabolic, emotional) of the individual [38]. Pressure–flow regulation is a significant component of virtually all integrated physiologic responses and can be systemic or organ-selective [38]. Usually, the most crucial factor in BP regulation is the level of outflow of the sympathetic nervous system (SNS), which affects immediate (seconds, minutes) and long-term (weeks to months) cardiovascular and BP responses [38]. BP variation is the result of normal and abnormal discharges from CNS centers (e.g., posterior hypothalamus), but abnormalities of feedback mechanisms (parasympathetic reflexes) lead to clinical abnormalities [39]. Besides all these participants in BP control, many other components in the blood/plasma/

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serum, cellular and subcellular levels, and other extrinsic interferences integrate the fine-tuned adjustments to get stable and optimal pressor values [1,40]. However, some "small shifts and mistakes" may probably happen in this well-tuned equilibrium and, analogously, turn a calm, silent and blue sky into an unstable, dark, and noisy tempest [41].

As stated in the Chaos theory, small changes in the initial condition (BP) likely determine the duration, strength, and ultimate damage (Hypertensive Disease) to the General System. Indeed, this "storm" in the BP system is not predictable by usual mathematical modeling, probabilistic calculus, or well-established statistical methods [15,42-44]. The key to previewing BP values over time is a nonlinear autoregressive integrated (NLARI) process that applies Newton's second law to stochastic self-restoring systems [14,15,37,44,45]. Even though these mathematical *complicated or complex* equations, just the short-time course can approach biological systems using a chaotic me767thod. As in Meteorology, where weather forecasts have accuracy only for the next 5-7 days, predicting BP levels is a hard issue because of the high number of variables involved in a multiple-order polynomial function [46]. On the other hand, the overall peculiarities in the physiopathology of RHTN syndrome superpose the BP allostatic modulation: (1) small shifts leading to unstable, dramatic, and outlier BP patterns; (2) apparent aperiodicity of BP occurrences (not circadian); (3) hard to predict the evolution and medium-long term clinical outcomes; (4) diversity of BP responses (even none) to external stimuli including therapeutics.

Analytical techniques derived from chaos theory can help characterize the stability and complexity of blood pressure control, which may provide essential measures for predicting cardiovascular risk. Chaos is located in EEG data, R-R intervals from electrocardiograms, and cellular levels, but only a few studies deal with chaos in sustained Hypertension [32,37].

Final consequences

This critical review approaches some crucial topics on Resistant Hypertension and chaotic or complex blood pressure (BP) systems [11,14,32]: 1- Human organism works as a complex nonlinear function. Emergency crises can happen anytime and from any of these modalities.

This review firstly has given a short clinical overview of Resistant Hypertension (RHTN) and its morbidity in these modalities of extreme phenotype individuals. Recently, the RHTN definition has been updated, excluding the white-coat, masked hypertension, medical inertia, and lack of adherence bias. Then, we presented another form of interpreting the blood pressure (BP) levels in uncontrolled hypertensive subjects as a chaotic, partially deterministic, but unpredictable BP levels syndrome using concepts derived from the field of nonlinear dynamics math: The Chaos Theory [47,48]. Besides pseudo-hypertension, lack of adherence, circadian variations, and other conditions of increasing BP (white-coat, masked, early morning effects, or hypertension), chaotic changes should be reminded "as thousands of butterflies in the BP Control System" (E. Lorenz) (figure 1) and co-responsible for out-of-control hypertension. The professionals when measuring BP levels should have considered these concepts.

Both homeostasis and allostasis in a BP stochastic system

There are two main paradigms (homeostasis and allostasis) with different implications for diagnosis and intervention for RHTN. Finally, occasional and circumstantial BP measurements taken and rated in pseudo and true RHTN can avoid both under- and over- diagnoses in out-to-control subjects.

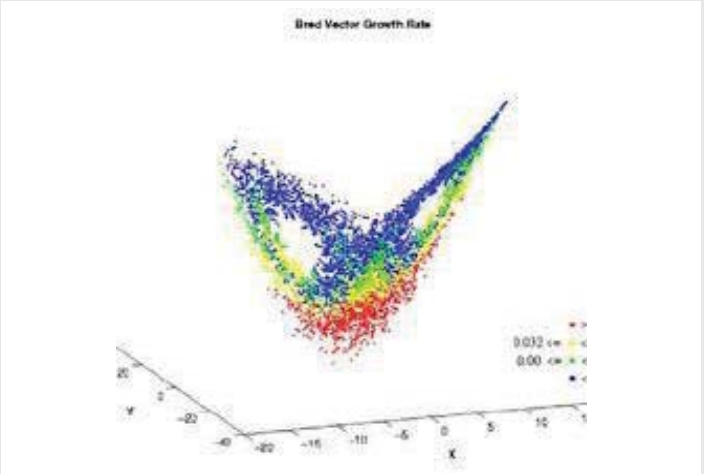

Figure 1: Lorenz´s Butterfly.
The main premises of Chaos are Aperiodicity, finally determined by onset, predictable (polynomial), tendency to go back to the beginning, and cyclicity. (https://www.researchgate.net/figure/The-Lorenz-butterfly-attractor-with-bred-vector-growth-over-8-steps-The-table-indicates_fig2_228931051)

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