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Abstract

The science-based study of the heart has allowed us to know its structure and function deeply, through the fragmentation and analysis of its parts, following the guidelines that so many achievements have given to us. However, at the time of re-assembling those analyzed fragments, we realize that something is missing; the simply sum of the parts is not equal to everything. Thus, for decades, numerous scientists have studied novel strategies that allow us understanding, every natural phenomena from a more inclusive, open and integrative models, which closely address to interactions rather than components. In this way, we can observe how, the behavior of many variables usually transgress the conventional plane and moves towards non-linearity and fractality, making a complex tissue that will maintain its structure while thermodynamically viable. Thus, this document shows the way how, the non-linear study of complex cardiovascular dynamics, begins to give us answers to many questions that the clinical cardiologist poses every day.

Key words: Complexity. Heart. Entropy. Fractal. Heart failure. Myocardial infarct. Non-linear.

Resumen

El estudio científico del corazón nos ha permitido conocer su estructura y función profundamente, mediante la fragmentación y el análisis de sus partes, atendiendo a las pautas del método que tantos logros nos ha dado. Sin embargo, al momento de volver a ensamblar esos fragmentos analizados nos percatamos de que algo falta; simplemente la suma de las partes no hace al todo. Es así que, desde hace décadas, numerosos científicos han estudiado estrategias novedosas que permitan entender los fenómenos naturales desde modelos más incluyentes, abiertos e integradores, que atiendan con cercanía a las interacciones más que a los componentes. De esta manera, observamos que muchas variables suelen transgredir el plano convencional y parten hacia la no linealidad y la fractalidad, formando un tejido complejo que mantendrá su estructura mientras termodinámicamente sea viable. Así, en este documento se muestra la manera en que el estudio no lineal de la dinámica compleja cardiovascular comienza a darnos luz en muchas de las preguntas que a diario se plantea el cardiólogo clínico.

Palabras clave: Complejidad. Corazón. Entropía. Fractal. Infarto del miocardio. Insuficiencia cardíaca. No lineal.

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Date of reception: 05-02-2020

Date of acceptance: 18-07-2020

DOI: 10.24875/ACME.M21000224

Available online: 20-10-2021

Arch Cardiol Mex (Eng). 2021;91(3):294-302

www.archivoscardiologia.com

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“Medicine does not escape the *sign of the times*; therefore, based on the knowledge of them, it is possible to conceive living organisms as systems that are complex par excellence, which forces for an epistemic review of the principles that govern it to be carried out.”

Human being's nature has driven him to the deepest introspection for understanding that mysterious intersection between his body and his spirit: the heart. Currently, science concretely states that our heart is that “organ of muscular nature, common to all vertebrates and many invertebrates, which acts as a driver of blood and which in the human being is located in the thoracic cavity”². However, common sense tells us that, actually, we are dealing with a much more complex phenomenon, which could be studied even from the perspective of disciplines as dissimilar as psychology, esotericism and religion³.

Cardiovascular structure and function is often addressed from a linear perspective and with highly controlled (closed) models, in the search for the development of equations that predict its behavior. Cardiac structure can be characterized from the macroscopic to the subatomic plane, in a process of fragmentation and description that we use to call “analysis”. Thus, each element of this pumping organ is separated and investigated in detail in an isolated, reductionist manner. Once the expert in the subject has exhausted his elements of observation and analysis, he is usually convinced of knowing the phenomenon in depth. Now it only remains to put all parts back together, amalgamating the obtained information hoping to understand the functioning of the heart as a whole, an undertaking that becomes, to say the least, a truly interesting challenge. At the conclusion of this first stage, only the role of the heart within the body, society and the universe would remain to be progressively understood, since we are inevitably part of an open system, in permanent and forced connection with our environment.

The structure and function of the heart are mainly expressed as changes in the matter-energy duality. Thus, the light we see, the sounds we hear, the pressure or heat we feel, are sensory translations of nature, which are expressed in forms as whimsical as the electromagnetic spectrum, sound or thermodynamics, among others. It is technology that has allowed us to broaden our perceptual capacity beyond our physiology and gain access to this language.

Through the structured knowledge offered by the scientific method, the study of the human body reached its maximum splendor, and it were personalities such as Descartes and Newton, among others, who entered

the scene for the first time. It is here that the association between two variables was recorded in a Cartesian plane and analyzed by means of geometry, a mathematical process that gives science a highly predictive character, by having faith that nature has a linear behavior.

Over the last 500 years, the macroscopic structure of human being has been described in detail by personalities such as Renaissance polymath Leonardo da Vinci, followed by a large group of anatomists such as Andreas Vesalius (*De humani corporis fabrica*) or Jean Léo Testut (*Traité d'anatomie humaine*). With the advent of the microscope (Zacharias Janssen, 1590), structural description deepened to a more elementary, but no less intricate plane. Brand-new “cell theory” would explain the way organs and body systems are made up, in turn, of small organelles (*organelli*), thanks to the studies of scientists such as Marcello Malpighi, Rudolf Virchow, Camillo Golgi and Santiago Ramón y Cajal. However, the issue would not stop there, since in the 19th and 20th centuries, personalities such as John Dalton, Ernest Rutherford, Niels Bohr, Arnold Sommerfeld and Erwin Schrödinger developed a model that could explain the composition of matter at levels so small that they escaped the microscope slide. These structures were recognized thanks to indirect manifestations, i.e., their interactions with other elements or phenomena, and thus was the “atomic model” born, a container of countless structures. In the end, and in theory, our heart could be “disassembled” even into subatomic particles.

In an almost parallel manner, cardiovascular function has been studied. The role of the heart as a pump was probably observed from time immemorial. In Europe, Galen explained the process of health and disease through *pneumas* (natural, vital and animal), and blood was believed to be mixed in the ventricles and “aerated” by a structure called “tracheartery”, to subsequently go to the brain and, from there, to the nerves. Already in the 17th century, William Harvey would describe blood circulation as we know it today (*Exercitatio anatomica de motu cordis et sanguinis in animalibus*), based on the works by René Descartes and Michel Servet, among others.

On the other side of the ocean, the extraction of the living and beating organ, as part of the Mexica rituals, surely gave rise to its Nahuatl name, *Yóllotl*, a term that means heart and circle at the same time. This oscillatory behavior that initiates, has a development and returns to the beginning is similar to the functioning of a pendulum. For decades, the study of cardiac function

has been based on the so-called “cardiac cycle”. This functional unit has multiple expressions determined by the observation method, ranging from the “lub dub” heard when bringing the ear close to somebody’s chest to the more complex methods of cardiac dynamics nonlinear analysis⁴.

One of the great advances in the understanding of cardiovascular function is the simultaneous grouping of the various manifestations of the cardiac cycle using Wiggers-Lewis diagram. Here, the graphs obtained by traditional methods, such as electrocardiogram (electromagnetic expression of ion exchange through the myocyte membrane), phonomechanocardiogram (acoustic expression of secondary vibrations at the valves closure and opening), hemodynamic polygraph (expression of changes in blood pressure and volume within the cardiac chambers) and systemic arterial tensiometry (expression of changes in blood vessel tension in relation to blood pressure and arterial traveling wave) overlap in the timeline. It should be mentioned that all these graphs are the “visual translation” of original physical phenomena. This is how we can associate electrical changes (cellular excitation) with intracavitary volume and pressure changes (cellular contraction) and blood flow (valvular function and fluid dynamics), in something that would appear to be a perpetual and perfectly periodic cycle. The mathematical linearity of this diagram confers highly predictive properties to it, if we rely on Descartes mechanistic physiology. The pump function of the heart would seem to culminate with the appearance of blood flow, determined by pressure gradients, volume changes and blood intrinsic properties.

On the other hand, from a thermodynamic point of view, the emergence of biochemistry and sophisticated methods of *in vitro* and *in vivo* testing has shown us that the organism, and in particular the heart, can use energy in an almost inexhaustible way in order to be able to vigorously contract itself an average of one hundred thousand times a day, with the least amount of heat production, including the functioning of other organs and systems such as the digestive and endocrine systems.

One of the fundamental principles of cell theory lies in homeostasis, a concept initially described by Claude Bernard and later refined by Walter Cannon and Arturo Rosenblueth. In general, homeostasis maintains cell structures and functions intact, “beyond equilibrium”, through the generation of various sorts of gradients by complex adaptive phenomena, many of them based on feedback mechanisms. Thus, the system seeks to

maintain this imbalance, at least for a time that we call “existence” (De Pomposo)⁵.

Technological advances and cardiac pumping function apparent simplicity have enthused different groups of researchers for developing a device that completely replaces the vital organ: the artificial heart. However, this is where problems begin.

The pacemaker, for example, has been enormously successful since the middle of the 20th century, when it began to keep patients alive with very slow rhythms (sinus node dysfunction or complete atrioventricular block). Currently, thousands of devices are implanted every day, and in the market we can find a great diversity of models with different programs and therapies, even with sophisticated defibrillation protocols.

On the other hand, in an attempt to replace the pump function of the heart, John Gibbon designed the first cardiovascular mechanical support system, then known as “heart-lung device”, which could keep a patient alive for a couple of hours, sufficient to perform intra-cardiac surgery. Shortly after, this extracorporeal circulation pump was optimized and its functioning could be increased from hours to days⁶. The first implantation of a total artificial heart was carried out by Denton Cooley (1969), which would keep the patient alive for 64 hours before being brought to heart transplant surgery. Currently, modern devices, such as the Syn-Cardia or Soft Total Artificial Heart from ETH in Zurich (Fig. 1), have cardiac chambers armed with a pulsatile flow pump, four disc valves and an external pneumatic generator. The functioning record of this type of devices is 1,374 days, and patient survival during the first year is 60%. Total artificial heart has been used in patients with cardiac graft rejection, intractable arrhythmias, complex congenital heart disease or ventricular rupture. This type of device is still aimed at fulfilling the role of “bridge” between cardiogenic shock and heart transplantation, with a success rate that ranges from 60% to 80%.

Everything was going relatively well, until we started noticing that these high-tech solutions are not as effective as we had predicted. Regarding pacemakers, we can see that there are still problems to be solved, such as battery limited lifetime, generator externalization, placement site infection, electrodes colonization or fracture, electromagnetic interference, pathological myocardial remodeling secondary to artificial stimulation and, especially, “rigid” and uncoordinated stimulation with regard to patient real life, despite the development of sophisticated body activity sensors⁷. On the other hand, despite the innovations made to

Figure 1. Total artificial heart. Since the 1960s, various models of artificial heart have been designed, with the purpose to be able to replace cardiac pumping function, which has been achieved for a restricted time and with variable results. This is a “soft” artificial heart model, developed in Zurich, which has the characteristic of looking more like the natural human heart than its predecessors.

artificial heart, innumerable complications attributed to the implant and medium and long-term maintenance, and lack of reintegration of patients to a “normal life”, prevent for it to be considered as a destination therapy in these cases^{8,9}.

Why has an artificial heart failed to replace the native organ if its physiology simply depends on a couple of variables and its behavior is predictably cyclic? What are we overlooking? Is the Aristotelian principle of cause and effect an adequate strategy to explain the cardiovascular phenomenon?

Analogously, weather is a phenomenon with similar characteristics, determined by few variables of cyclical behavior. A heavy snowfall or warm weather depend on two situations: air temperature and the altitude where the measurement was made. Thus, the different combinations of cold air above and hot air below, or vice versa, will generate specific atmospheric changes. Edward Norton Lorenz, a mathematician and meteorologist, developed an equation whereby he could accurately predict the weather, confident that it was a simple and theoretically linear phenomenon. Thus, he observed that, if he ran the same mathematical model twice on his rudimentary computing equipment, the occurrence of minimal changes in baseline conditions were associated with a drastically different and,

Figure 2. Lorenz attractor. In this graph, we can observe something very similar to what Lorenz achieved in the search for a linear model that would allow weather changes to be predicted.

therefore, unpredictable, end result. However, when the data were carefully analyzed, although they did not form a perfect straight line, they did generate a graph with a certain morphology, recognized as the Lorenz attractor (Fig. 2), poorly predictable, but not random at all.

On the other hand, mathematician Mitchell Jay Feigenbaum used a logistic equation, known as Feigenbaum’s function, in which a value was initially assigned to x and the resulting number would be assigned again to x when running the formula again:

$$g(x) = -g\left(g\left(\frac{1}{\infty}x\right)\right)$$

This way, the equation would be continuously fed back, and the final graph would be a series of points originated by itself. First, a line was generated that, subsequently, would show a “bifurcation”, and as the graph continued to develop, more bifurcations would appear on it, to a point where a spectacular pattern that no one could have predicted is observed (Fig. 3). In addition, when the equation is run again, the end result is the same. Thus, something that should behave like a perfectly predictable line generates a completely different graph, but with a certain structure. Somehow, this graph is the result of emergent properties that gradually appear and that we did not know.

If this happens with sciences as hard as physics or even mathematical language, what can we expect from cardiovascular system behavior? Thus, the first lesson learned is that, even with few variables, a phenomenon can have a “non-linear” behavior.

Edgar Morin explains that variables existing in nature intertwine and form an intricate network of connections. In this true *plexus* of interactions, if each variable was a thread, pulling one would elicit a series of local and

Figure 3. Feigenbaum bifurcation diagram. This graph shows how a mathematical equation can independently have emergent properties such as bifurcations, fractality and, sometimes, zones of chaos, periodicity and noise⁴⁹.

distant reactions, resulting from the interactions of this with other threads, of the other threads with others and many of them with each other. This *tissue* structure facilitates the emergence of new properties of the system, sometimes with their own behavioral laws, such as the resonance or self-organization phenomenon can be. *Complexus* means that which is woven together; indeed, there is “complexity when the different elements that constitute a whole are inseparable and there is an interdependent, interactive and inter-retroactive weave between the object of knowledge and its context, the parts and the whole, the whole and the parts, the parts between each other. Consequently, complexity is a merger between unity and multiplicity”¹⁰. Thus, that which is “complex” arises from the series of interactions of interwoven variables, unlike that which is “complicated”, which has its origin in our inability to understand the nature of a phenomenon (De Pomposo).

Therefore, it is almost inevitable feeling that complexity surrounds us, being part of countless systems that openly coexist, where their particular nonlinear dynamics goes from periodic to quasi-periodic behavior and chaos; most of the time maintaining its structure against the action of fluctuations or disturbances and, especially, resisting the entropic dissipation that will inevitably make for it to fall into a final thermodynamic equilibrium. Through the analysis of complex systems we will be

able to observe multiple emergent properties, where the whole is more than the sum of its parts; the attractors and self-organization that emanate from it.

Cardiovascular anatomy

One of the morphological characteristics of the cardiovascular system that has been more widely studied from a complexity point of view is the vascular tree. Blood vessels spatial distribution has an interesting geometry, since like other branched structures it has a fractionated dimension, i.e., not two-dimensional (2.0), but also not entirely three-dimensional (3.0). The shape of the vascular tree is scale-independent, and in the great vessels, it is very similar to that of the smaller caliber vessels, with this distribution following the power law. “A fractal is a rough or fragmented geometric shape that can be split into parts, each of which is (at least approximately) a reduced-size copy of the whole”¹¹. Branching of the vascular tree confers different levels of organization to it, which affects blood flow characteristics (Fig. 4). The arterial tree has been calculated to have an average fractal dimension of 2.7, similar to that of broccoli or chromatin. The fractal dimension varies from 2.33 in the great vessels, where flow is more turbulent, up to very close to 3 in the capillaries¹¹⁻¹³. There are several methods to measure

Figure 4. Vascular tree fractality. In this diagram, arterial tree-dimensional characteristic is observed, which varies depending on the vessels size, always with a fractional component. In the image on the right, vessel distribution is observed to be very similar, regardless of the scale.

fractality of a structure, but the fractal dimension (FD) is the most accurate¹⁴. Knowledge about fractality is highly useful for researchers who are designing artificial blood vessels, for the detection of heart failure or atrial fibrillation and angiogenesis evaluation^{15,16}.

Heart rate

One of the phenomena that have been studied with greater interest is heart rate behavior, which has a non-linear and also complex behavior. The start of the cardiac cycle can be marked with sinus node activation, which is an event determined by the interaction of variables such as spontaneous diastolic depolarization slope, autonomic nervous system flow (sympathetic-parasympathetic), blood pressure on the atrial wall, body temperature, etc.

The electrocardiogram can provide us with important information about heart rate dynamics and autonomic nervous system influence, which we know as heart rate variability, which shows various patterns in time, frequency or both domains when studied with nonlinear analysis methods. These include phase space reconstruction analysis, the Lyapunov exponent, correlation dimension, detrended fluctuation analysis, recurrence map, the Poincaré map, approximate entropy and sample entropy, among others^{17,18}.

On one hand, Baillie et al.¹⁹ state that heart rate dynamics of a healthy heart is non-linear, has no low dimensional chaos and is multifractal, which makes for heart rate not to return to the same stationary

equilibrium state after being affected by some disturbance. In contrast, more recent studies maintain that heart rate has a chaotic behavior that is closely related to autonomic nervous system control²⁰.

Various studies show that the cardiac cycle under physiological conditions is not a perfectly periodic oscillator, with correlation dimensions (D_2) that range from 3.6 to 5.2²¹. The origin of a heartbeat can depend on the previous beat or on the interaction of previous beats, adopting a periodic, quasi-periodic, chaotic or frankly random behavior (noise)²².

When talking about stimulus conduction and propagation, we should remember that the myocardium is a group of cells with excitable and conductive properties that make up a syncytium, interconnected by cell bonds with high mechanical resilience and low electrical resistance. However, depolarization of a cell may or may not be transmitted to neighboring cells, as long as the conditions for its propagation are met; a phenomenon similar to fish schools or bird flocks self-organization, and analogous to mechanical resonance, where a body starts vibrating when subjected to the action of an oscillatory force that has the same vibration period as that body²³. On the other hand, the energy whereby the electrical and mechanical impulse is transmitted in the myocardium will reach the rest of the tissue if the magnitude is appropriate and, especially, if thermodynamic entropy is adequate. Entropy is a magnitude that, somehow, measures the degree of organization of a system in which, the higher the randomness, the higher the entropy. This is a status function that is extensive

and that that grows naturally, describing the “thermodynamic irreversibility of the system”. The cardiovascular system is thermodynamically dissipative and provides a large amount of information, although, in general, it has dynamics with low entropy. Cardiac dynamics, assessed using “entropy proportions”, can help the doctor identify various types of diseases, in particular when evaluating phenomena of “self-organization”, a characteristic of complex phenomena that is important in the regulation of the cardiovascular system, from electrical activation of the heart to blood pressure control.

Myocardial electrical and contractile activity spatio-temporal propagation follows various patterns; flat, oscillatory, circular, spiral and even ellipsoidal wave fronts are observed. These patterns are closely related to various variables, such as myocardial fibers geometry and spatial arrangement, myocyte sub-structures arrangement, and intracellular Ca^{++} and acetylcholine concentrations, among others. These propagation patterns are observed even in isolated myocytes, where different cellular organelles can generate true micro-reentries^{24,25}.

Due to the difficulties for conducting myocardial conduction studies in vivo, in silico models have been developed, such as the Ten Tusscher-Noble-Noble-Panfilov (TNNP) model, which allows to reproduce myocardial initial excitable conditions and see the effect on wave front propagation, even on a three-dimensional plane (Fig. 5)²⁶. Among other findings, ventricular tachycardia has been observed to be associated with the formation of a spiral wave front that propagates through the myocardium, while, in ventricular fibrillation, these patterns have a much more turbulent behavior, associated with heterogeneity in muscle fiber shape and ion concentrations²⁷⁻³¹.

Heart rate dynamics variability also shows that the cardiovascular system, in addition to being complex, is open. Thus, several researchers have demonstrated that stress or mental overload induction can change heart rate nonlinear dynamics^{32,33}.

Muscle contraction and hemodynamics

Cardiac contraction is a mechanical phenomenon that has, on one hand, a hierarchical chain of events that start with sinus node diastolic depolarization, which triggers changes in ion concentration, especially Ca^{++} , which in turn depolarizes the cell, neighboring cells and the entire heart. However, on the other hand, various studies have shown that contractile proteins (actin and

Figure 5. In this in silico model, presented by Cherry and Fenton²⁷, the internet user can change electrolyte concentration characteristics or send a series of extra stimuli, which will generate various types of propagation wave fronts in the virtual myocardium. This model in particular corresponds to the classic spiral observed during ventricular tachycardia.

myosin) are not only influenced by the sinus node, but have autonomous oscillatory properties, thus becoming a true “molecular motor”³⁴.

Traditionally, blood flow has been studied based on Newtonian fluid dynamics, using stable flow models such as Poiseuille equation, Bernoulli equation, Casson equation and Reynolds number; these involve the behavior of blood and vascular structures. However, we should remember that blood is not a simple fluid, but a tissue; it is composed of water, electrolytes, cells and other elements, each one with characteristics of its own and individual behavior³⁵. Moreover, blood flow is not uniform throughout the cardiovascular system, since it shows important differences in terms of size, shape and vessel arrangement and blood composition. Particularly in small-caliber vessels, such as arterioles and capillaries, the size of blood-forming elements, changes in viscosity and low parietal shear rate make for it to behave as a non-Newtonian fluid. On the other hand, the heart, heart valves and blood vessels are not a mere pump and piping system either; the vascular tree and cardiac structures have a fractal structure that clearly determines flow characteristics³⁶. In addition, hemodynamics is determined in part by wall tension and shear stress, which are properties that have a nonlinear behavior (Casson equation) that can affect blood cells

integrity. Nonlinear models already exist for assessing the degree of hemolysis associated with medical devices' contact with blood³⁷.

On the other hand, the resistance offered by the vessel surface or a heart chamber determines the degree of blood displacement; if resistance was absent, flow would not exist. Blood flow behavior in small-caliber circulation can be more accurately studied with the "dissipative particle dynamics" model³⁸.

When blood flow is studied, attention should be paid to other characteristics that are often excluded, such as its oscillatory behavior, high speed transmission of ventricular contraction by vascular walls (traveling wave), vascular tree fractal distribution or interface between the blood column and vessel wall pulsatile movement. To this end, new models have been developed, such as the "air reservoir" (Windkessel) theory, Womersley and Bessel equations, or Karniadakis "coarse-graining molecular dynamics" model, intended to include the behavior of subatomic particles as well^{39,40}.

Thus, cardiovascular rhythm is the result of the interaction of several oscillators observed in cardiac pulse, the traveling wave, blood flow, autonomic nervous system flow and even intracellular ionic oscillators. These oscillators can have a periodic, quasi-periodic, chaotic or noisy behavior, a situation that favors physiological or pathological state, as the case may be⁴¹⁻⁴³.

According to Wiggers-Lewis diagram, blood flow is closely related to different variables, such as heart valves opening and closing. Zheng and Guo⁴⁴ proposed a nonlinear method for heart sounds behavior analysis as an effective means for chronic heart failure identification.

Cardiopulmonary coupling

Ventilation and circulation are two closely-related processes, and both heart rate and respiratory rate are physiologically coupled, which has been demonstrated by heart rate variability conventional analysis and by the potency spectrum in the frequency domain^{45,46}. Studies in individuals under assisted mechanical ventilation have shown that, by varying the ventilation mode from assisted-controlled to spontaneous ventilation with pressure support or without support, changes in heart rate behavior are observed that range from linear patterns to a complex, nonlinear dynamics, which tends to be of the chaotic type. This behavior has become evident with the study of nonlinear dynamics complexity through

phase space specialized analyses, which include the Lyapunov exponent, approximate entropy, fractal dimension, correlation dimension and Hurst exponent, among others⁴⁷. In addition, cardiopulmonary coupling nonlinear analysis allows to identify pathologies such as obstructive sleep apnea-hypopnea syndrome⁴⁸.

The phenomenon of atherothrombosis, which leads to vascular occlusion and target tissue injury (tissue infarction), appears to have a distribution governed by the power law, where countless, very small thrombi are dissolved by the fibrinolytic system, while only very few thrombi reach sufficient size to cause vascular catastrophe. This presentation is similar to that observed with telluric movements⁴⁹.

Conclusion

In summary, throughout his existence, the human being has used different strategies to understand his environment, with the scientific method, usually reductionist and linear, currently being the most widely used; however, even so, many phenomenological aspects clearly escape our sight. Day by day, a growing group of researchers delves into this relatively novel study approach, in which nature is seen as a complex, open and non-linear system; the perspective is different, and so is the language and its methods. Accessing this new world is not easy, but the reward is well worth the effort.

Acknowledgements

To Javier Rosado, Alexandre de Pomposo, Ady Castillo, Lilia Rodríguez, Aquiles Ilarraza, Rafael Chávez Domínguez and all those who study complexity in our country.

Conflict of interests

None.

Funding

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments have been performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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