We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 1

Fractal Analysis of Cardiovascular Signals Empowering the Bioengineering Knowledge

Ricardo L. Armentano, Walter Legnani and
Leandro J. Cymberknop

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67784

Abstract

The cardiovascular system is composed of a complex network of vessels, where highly uniform hierarchical branching structures are regulated by the anatomy and local flow requirements. Arteries bifurcate many times before they become capillaries where the scaling factor of vessel length, diameter and angle between two children branches is established at each level of recurrence. This behaviour can be easily described using a *fractal* scaling principle. Moreover, it was observed that the basic pattern of blood distribution is also fractal, imposed both by the anatomy of the vascular tree and the local regulation of vascular tone. In this chapter, arterial physiology was analysed, where waveform complexity of arterial pressure time series was related to arterial stiffness changes, pulse pressure variations and the presence wave reflection. Fractal dimension was used as a nonlinear measure, giving place to a 'holistic approach of fractal dimension variations throughout the arterial network', both in health and disease.

Keywords: fractal dimension, cardiovascular disease, arterial blood pressure

1. Introduction

1.1. The arterial function

Major arteries play two primary functions: to carry blood (they act as conduits) and to reduce its pulsatility (they act as dampers). Consequently, pathologies and systemic complications related to the myocardium will be mainly mechanical, including ruptures, clogs and pumping failures [1]. Along with the blood transport function, the damping function of arteries is responsible for supplying blood to body organs under a stabilized arterial

INTECH
open science | open minds

© 2017 The Author(s). Licensee InTech. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

pressure regime, under laminar flow conditions. Otherwise, in the course of time, tissues would suffer pulsatility-derived degradation [2]. Thus, the response from the arterial tree in terms of intermittent excitement can be described as a mechanical filtering mechanism (removal of sudden variations) of high frequencies or pulsatile phenomena [3]. Cardiovascular pathologies such as arteriosclerosis and its most common form, atherosclerosis, drastically affect the blood transport and arterial damping functions. Atherosclerosis, in particular, is an example of a disease that affects the conductive aspects of flow, thus contributing to luminal obstruction through the formation of atheromatous plaque. Therefore, certain organs (such as the heart) may be progressively and inevitably unable to receive blood flow under normal conditions (ischemic process). It is evident, then, that atherosclerosis is focal, acting at the level of the tunica intima and in a clearly occlusive form [1]. Alternatively, the damping function is affected by arteriosclerosis, mainly through an increase in arterial stiffening (AS) without affecting the transport function. For this reason, arteriosclerosis acts diffusely at the level of the arterial tunica media and with dilation consequences [1].

Although AS increases irreversibly with age, it is important to differentiate the processes altering or accelerating its normal development [4]. With age, systemic arteries' walls undergo histological changes at the level of the tunica intima and tunica media. The presence of factors such as arterial hypertension (HBP), diabetes mellitus (DM), chronic kidney failure, or dyslipidaemia (alteration in the concentration of lipids) is directly responsible for the anticipated increase in the loss of arterial blood vessel distensibility [5]. This is due to the fact that significant changes in AS are used as early markers of vascular disease clinical signs. In this sense, a biological marker is defined as a characteristic that can be measured and evaluated objectively and that constitutes an indicator of normal biological processes, pathogenic processes or pharmacological responses. Age, gender, blood pressure, cholesterol, and diabetes are considered representative markers of cardiovascular risk (CVR) since they can help to predict the occurrence or development of CVDs [6]. More specifically, arterial biomarkers include AS, central blood pressure (CBP, measured in the aorta, at the output of left ventricle), the pulse wave velocity (PWV), the ankle-brachial index (ABI), endothelial dysfunction (ED), intima-media thickness (IMT) and coronary artery calcium (CAC). Currently, the inclusion of arterial biomarkers in the calculations of CVR prediction statistical models such as Framingham, European SCORE and Reynolds is unquestionable [6].

1.2. Arterial viscoelasticity

If a material experiences a reversible deformation when stress is applied on it (recovering its original shape when excitement ceases), it is assumed that it has a mechanical property called elasticity. The relationship between the applied stress and the experienced deformation (stress-strain curve, SSC) determines the type of elasticity of the material. Elasticity can be linear, where the SSC is represented by a straight line passing through the origin of the coordinates, in which case it is called Hookean. However, biological materials usually exhibit SSCs with convexity, a behaviour described as non-linear. In addition, vascular walls have viscosity (a characteristic of the fluids determined by their opposition

http://dx.doi.org/10.5772/67784

to tangential deformations) and must therefore be considered viscoelastic materials. The presence of viscosity in a material generates a delay in its deformation when a sudden stress is applied [7]. It is well known that the viscoelastic properties of the wall are linked to their constituent elements (elastin, collagen and smooth muscle fibres), and each of these elements is associated with a specific stiffness module [6]. Viscoelasticity can be evaluated by analysing the loop that describes the relation between arterial pressure (AP) and the resulting distension of the arterial diameter (AD). When creating the graph, where the abscissae correspond to AD and the ordinates correspond to AP, a hysteresis loop can be observed (after a cardiac cycle has elapsed). As a result of ventricular ejection, artery dilation describes a trajectory in the graph (systolic phase) which does not repeat during the emptying phase (diastolic phase). This means that the expansion and relaxation trajectories are dissimilar [8]. The elimination of the viscous behaviour would result in a strictly elastic pressure versus diameter relationship where both trajectories would be coincident (**Figure 1**).

1.3. Arterial stiffness assessment: clinical implications

Arterial wall stiffness can be quantified through non-invasive methodologies with direct applicability on human beings. In this sense, indexes accounting for the presence of vascular pathologies, related to AS variations, have been developed. The proper implementation of the analysis methodology as well as its reliability is permanently subjected to global consensus because of the high variability observed in *in vivo* experiments. In

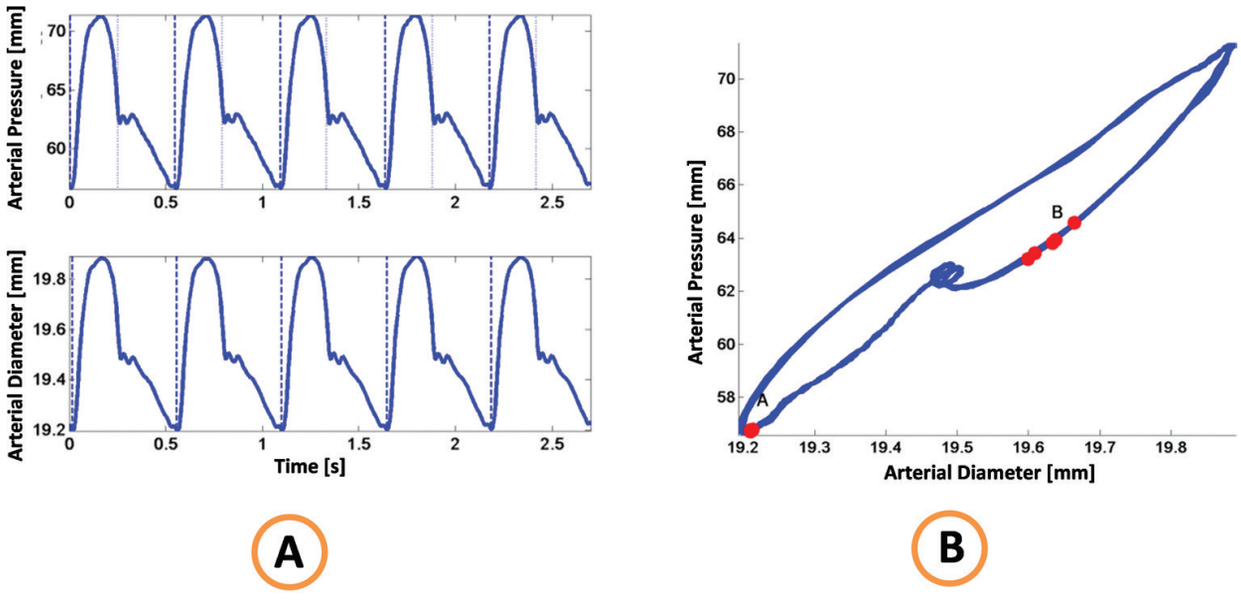

Figure 1. (A) Time series of arterial pressure (top panel) and diameter (bottom panel) obtained for a segment of an aortic conduit. Dashed lines: beginning of systolic phase. Dotted line: beginning of diastolic phase. (B) Hysteresis loop formed by the pressure-diameter relationship. Trajectory AB (clockwise direction) represents the cardiac systole while trajectory BA (same direction) represents the diastole. As can be observed, both trajectories differ because of the presence of viscous phenomena in the wall.

general terms, AS variation can be obtained at a systemic, regional or local level. At the systemic level, it reflects the joint opposition of the major arteries to the pulsatile effects of ventricular ejection [9]. At a regional level, it is often quantified in arterial sites of physiological relevance, such as the aorta (due to the prevalence of the damping function) or specific limbs like the arm. At the local level, it provides information related to the level of arterial wall distensibility [9]. Consequently, it is essential to properly identify the scope and functionality of the indexes used to characterize AS, essentially due to anatomic dependences and excitement conditions, which need to be considered in order to determine it.

There are many elasticity studies where measures are limited to the circumferential effect and to limited regions of the stress-strain curve, which are considered linear. An example is the estimation of the SSC slope, called the deformation modulus or Young's modulus (E), during the interval defined by the diastolic phase, where only elastic behaviours of the arterial walls intervene. This magnitude provides information on structural stiffness, and its determination requires knowing the values of AP, AD, and parietal thickness (h), which are characteristic of the vascular structure under study. However, the evaluation of the functional stiffness is based merely on the change of AD of its diastolic value due to a relative change of AP. This second magnitude, called Peterson modulus (EP), is of greater interest since it provides information on the reserve function of the major arteries [10]. It is used assuming a linear relationship between pressure and deformation, so that its determination is based on the use of systo-diastolic values corresponding to AP and AD, thus providing information at the local level. Pulse pressure (PP) is determined by the difference between the systolic and diastolic values of AP. It is one of the most useful parameters (clinically speaking), representative of AS. This index depends on systolic unloading, AS and the reflections generated in the periphery of the arterial tree. It increases with age (a result of an increase in systolic pressure), and it is influenced by the amplification factor (AF) of the arterial pressure wave (which becomes less pronounced with age). As a result of the above, special attention should be paid when using the PP value obtained through measurements on the brachial artery as a substitute of central PP (aortic and carotid). In this regard, the Framingham study has shown the applicability of PP in the prediction of cardiovascular events in people over 50 years old, rather than individual values of SBP or DBP [11, 12]. It was also mentioned that the SSC is clearly non-linear. An interesting aspect is that it can be adjusted to an exponential curve (through the AP vs. AD relation). As a consequence, the stiffness index can be defined [13]. Likewise, the pressure waves are subjected to amplitude changes along their path as a result of blood viscosity, the distribution of arterial branches and the variations of distensibilities throughout the circulatory system. Modifications in the arterial wall, such as the rupture of the elastic sheet, collagen deposits and calcium deposits, have a direct effect on AS [6]. As a consequence, arterial pulse wave velocity (PWV) is considered the most simple, robust, non-invasive and reproducible method to evaluate AS. The methodology to obtain it consists in measuring the phase difference (temporal displacement) of the AP wave when evaluated in two remote sites of the vascular network (often superficial arteries), whose distance is

known with precision. An example is the circulation line between the carotid artery, which is anatomically located in the neck, and the femoral artery, located in the upper thigh. Finally, changes in wall stiffness can be also estimated assuming that the arterial wall is an isotropic homogeneous elastic material, so that the linear elastic theory is able to be applied considering the first derivative of AP with respect to the strain, giving rise to the 'pressure-strain elastic modulus' (EPS) [8].

1.4. Arterial pressure waveform: morphologic evaluation

In general terms, AP is often defined as an oscillating magnitude that propagates from the cardiac muscle to the peripheral arteries. Like a mechanical wave (such the acoustic wave), it can be reflected and amplified [14]. As such, it has amplitude and frequency and can be analysed both in the temporal domain as well as in terms of its frequency content. It was assumed that variations in AS (dependent upon the anatomic disposition of the vascular conduit), the structural changes shown by the branching process and the eventual presence of obstructions, generate reflections of the mechanical magnitudes that propagate through the arterial network. Consequently, the AP wave increases in amplitude (scaling phenomenon, called amplification factor, AF) together with a level of non-linear deformation because its frequency components are not affected with the same intensity [14].

1.4.1. Augmentation index (AIX): assessment of wave reflection

The augmentation index quantifies the difference between the first and second systolic peaks (referring to PP) providing an indirect measure of the arrival time of the waves reflected from the arterial tree periphery. It is associated with the arterial mechanical properties through PWV because an increase in the latter (produced by a variation in AS) induces an early return of such peripheral reflections. At the aortic level, the reflected AP wave combines with the incident magnitude during systole, an interval in which the left ventricle is still ejecting blood. As a result, an increase in PP is observed called augmentation pressure (AuP), and thus extra work must be performed by the left ventricle to overcome such conditions [5]. In relation to the above, AIX can be determined as AuP divided by PP × 100 to give a percentage [15]. In clinical terms, AIX increases with age and in the presence of HBP, DM and hypercholesterolemia, among other pathologies. It can further be associated with the presence of ED, as a consequence of its close link with AS.

The evaluation of early descriptors or markers of pathologies on time domain signals is based on the analysis of representative parameters of the AP wave because its morphology is determined by the ventricular ejection pattern and the elasticity of the arterial tree [14]. Systolic, diastolic and mean pressures, the time occurrence of the dicrotic notch, PP and AIX provide relevant information on the waveform and suffer alterations with age and the onset of vascular pathologies (**Figure 2**). Likewise, signal morphology associated with vascular mechanics shows a marked irregularity. Unlike sinusoidal waveforms, they cannot be represented analytically through a deterministic function [16].

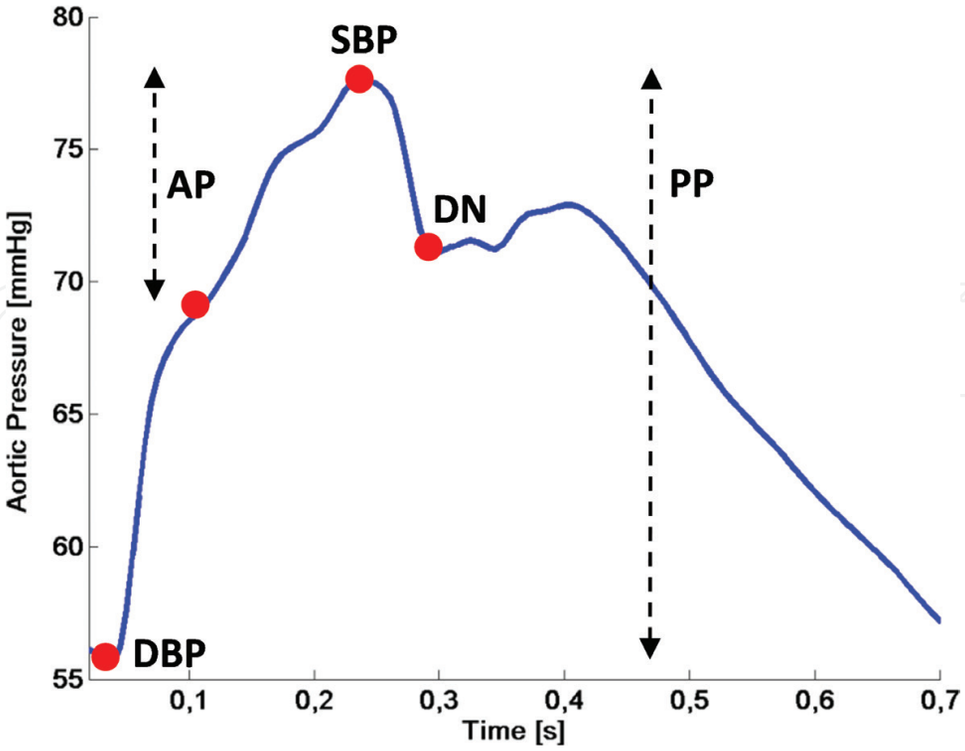

Figure 2. Analysis of a pulse wave for an arterial pressure signal. Diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse pressure (PP), dicrotic notch (DN), augmentation pressure (AP).

2. Fractal analysis

2.1. The concept of 'dimension'

Before defining the concept of fractality, it is indispensable to introduce the concept of *dimension*. Formally speaking, it can be defined as the quantification of space occupied by a set near each of its points [17]. Furthermore, the traditional Euclidian approach argues that a curve is a uni-dimensional object, a surface is a two-dimensional object, and a volume is a tri-dimensional object. In such a statement, the dimension can be quantified in topological terms (TD), using whole numbers. Therefore, the object can be assumed to be embedded in a line (TD = 1), in a plane (TD = 2) or in the space (TD = 3). More precisely, the intuitive notion of dimension associates the space that the object occupies (V_O) with a linear unit of measure (e), using a power law, so that [18]

$$V_O \approx e^D \tag{1}$$

where V_O can be considered a distance, a surface or a volume. It can be inferred then that the area of a plane grows quadratically in relation to e and thus D = TD = 2. A similar situation is observed in curves and volumes, where the dimension acquires values corresponding to 1 and 3, respectively. This is the reason why the objects generated by means of Euclidian geometry acquire whole dimensional values. However, it is perfectly possible to conceive structures whose dimension differs from the established values so that they occupy greater or less

space than a traditional object [17]. The Euclidean geometric shapes go from one dimension to the other without generating detail in relation to its borders. However, there are natural and geometric processes which, through explicit rules, can generate structures that resemble each other when analysed at different scales of magnification. The development of 'self-similar processes' (among other qualities that will be analysed later) cannot be characterized under whole dimensional values, and thus the dimension becomes inevitably fractional. Therefore, objects occupying a metric space that fracture the TD value in which they are embedded are called fractals. As a result, the introduction of the concept of fractality leads to consider continuous dimension variations, unlike the Euclidian approach, which only admits discrete values. The fraction obtained describes the existence of a highly detailed structure whose representation is wholly ignored by the traditional perspective [19]. In mathematical terms, the measure of the dimension is found by means of the conceptualization proposed by Hausdorff (Hausdorff dimension, HD). Assuming that a disk is a set of points at a distance r of a centre, it can be inferred that for TD of value 1, the disks are segments; for TD of value 2, they are circles; and for TD of value 3, they are spheres [20]. Such disks having a radius *r*, whose dimension coincides with TD, are used to cover the object whose dimension needs to be known so that each point of the object is included at least in one of them, minimizing the number of elements used.

2.2. Fractality and time series behaviour

In general terms, fractal signals are those that show detail or structure when they are processed through all their timescales [21]. Formally, a fractal structure is an irregular geometric object that has self-similarity. It is composed of sub-units replicated iteratively so that under any scale of observation (considering ideal conditions), a structure similar to the whole set can be observed. Geometrically, it is possible to generate a fractal object from an initiating element, a morphogenesis rule (called generator) and a scaling interval. The latter determines the number of scales during which the above-mentioned rule must be applied. A traditional example is the Weierstrass curve [22] (**Figure 3**), whose iterative construction (defined as an infinite sum of cosine functions) gives rise to a fractal, continuous everywhere but differentiable nowhere time series.

Since this type of objects is characterized by a fractional dimension, it is called fractal dimension (FD). Conceptually, the FD can also be considered an irregularity measure. As the latter increases, the dimension increases its value as well, and thus it can be used a roughness or variation measure [23]. Natural structures are typically fractal. Their high irregularity can be observed in the contour of rock formations or in the structure of tree leaves. The intense manifestation of deformations and holes places such objects in non-integer intermediate dimensions. As a consequence, Euclidean geometry is unable to quantify the space occupied by a naturally generated object [17, 24]. Although it may be evident, clouds are not spheres, mountains are not cones and lightning bolts are not lines [25]. In physiological terms, fractal structures can be observed, for example, in arterial and venous branches, cardiopulmonary structures and bile ducts [26]. In the cardiovascular system, in particular, the recognition and quantification of this type of manifestations can only be performed through indexes such as

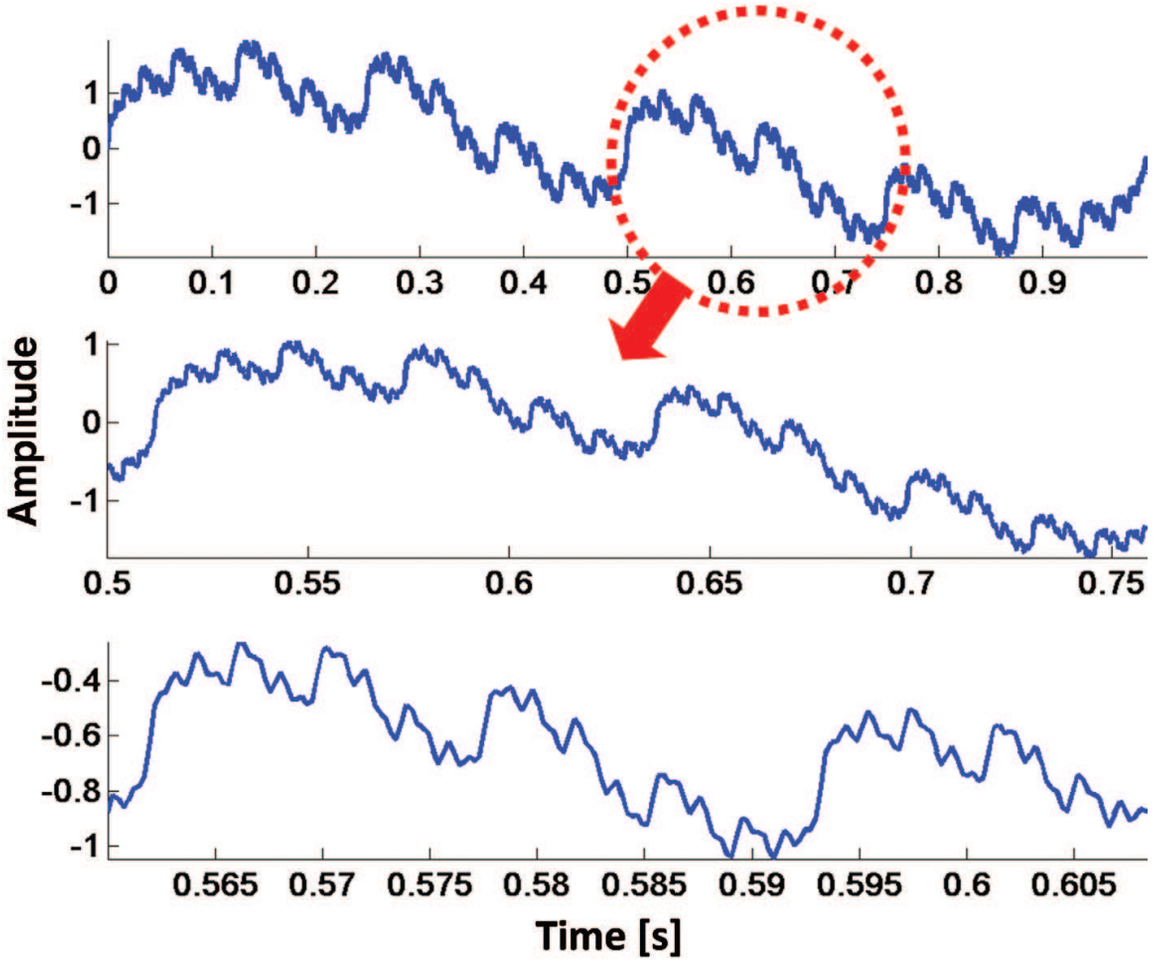

Figure 3. Self-similar Weierstrass time series, generated by a recursive procedure. Its fractal nature is revealed at different timescales.

FD [27]. In this regard, one of the excluding aspects that differentiate natural from geometric fractality is that, in natural fractals, the scale invariance is appreciated only within certain limits [28]. In addition, the presence of self-similarity does not convert a geometric object into a fractal. Although this is a necessary condition, it needs additional contributions for the consolidation of the concept. To such effect, a fractal object is characterized by the following conditions [17]: it has self-similarity; it has a fine structure (detail is observed irrespective of the scale); it is too irregular to be described by traditional geometry; usually, its Hausdorff dimension exceeds its topological dimension; and, in some cases, it can be defined through recursive procedures.

A classic example describing a non-fractal structure is the real line. Although it is self-similar (composed by reproductions of itself at different scales), the remaining imposed conditions cannot be attributed to it [17]. Therefore, finding the characteristics of fractal objects in time series does not necessarily mean that they may be considered fractal. However, having those characteristics would make them possible candidates for such behaviour and then a deeper

analysis would be required. To do this, it is necessary to have tools that can provide quantitative measures, such as FD [29].

Those fractals whose components are exact replicates of the initiator are called exact and present a self-similar dimension (SSD), which is exact as well. Alternatively, there are situations in which, when there are changes in the scale, similarity is not observed at structural levels but rather at statistical levels. A magnified vision of a shoreline may not reproduce the general vision with precision, but it shows the same qualitative appearance [18]. As a result, the fractal is considered statistical. Basically, the value acquired by HD is a real number, which characterizes the richness of geometric structures of limited sets. Since it is complex to calculate and although the information provided by HD is better than other types of measures, it is not used for practical purposes [24]. The approach closest to this concept is the capacity dimension (CD). The procedure required for its determination is similar to the one used for HD but the difference lies in the fact that minimal elements are counted, $N(r)$, required to cover the whole set. The operation is performed for diverse r values, so as to obtain the change in $N(r)$ as r decreases to 0 [20]. Consequently, DC is expressed as follows:

$$C_D = \lim_{r \to 0} \frac{\log N(r)}{\log\left(\frac{1}{r}\right)} \tag{2}$$

When disks do not overlap, and boxes are implemented in the form of grids, the procedure gives rise to the box counting dimension (BCD). In addition, and considering that natural fractals show self-similarity only in a limited number of scales, the SSD estimation is usually made using DC (and its simplest implementation, BCD), particularly in the presence of real, inaccurate and statistical fractal structures [30]. The methodologies proposed by [31–33] can be used to estimate BCD, among others in the existing literature. According to several authors [34–37], the Higuchi's method [32] can be highlighted as one of the most applied, owing to its well performance in FD estimation under different types of fractal time series. For this reason, any reference to the FD value in this chapter will be assumed to be the quantification of BCD. Finally, and unlike auto-similarity, the concept of self-affinity is applied to objects for which scaling is anisotropic. For these objects, the proportions between scales differ according to the direction of scaling. This situation is representative of the physiological time series, where amplitude has different units from those of time [30]. Therefore, it is more appropriate to use the auto-affinity concept (as will be done hereinafter) in relation to the morphological analysis of time variables related to cardiovascular mechanics.

3. Applications of fractal analysis to arterial pressure

Studies on the existence of hidden information in physiological time series have gained considerable popularity over the last few years. This has resulted in the application of techniques and concepts from statistical physics and chaos theory to biomedical issues [28]. Physiological parameters such breathing, heart rate (HR) and even AP itself do not show stationarity, and they are governed by non-periodic temporal fluctuations [30]. Thus, they should be characterized as non-stationary processes, whose analysis and processing require the application of mathematical

tools that can adapt to such behaviour. In this sense, the analysis provided by fractal geometry is among those which best describes the physiological phenomena observed [30].

3.1. Mapping the fractal dimension of the arterial tree

The fundamental goal of the systemic arterial network is to reach certain organs (or specific areas) in order to supply them with the correct amount of blood flow [38]. This network consists of a series of vascular conduits which recursively bifurcate in a dichotomic fashion (a parent branch, two child branches) until they reach the arteriole level. At this last level, the process no longer continues in a dichotomic fashion; the number of branches generated multiplies considerably [20]. Each bifurcation generated within the network implies the creation of a new scale or level. In particular, what makes the arterial tree different from other vascular structures (such as those observed in pulmonary cavities, the tracheobronchial tract, the His-Purkinje system or the kidneys) is the fact that the distribution of its branches and sub-branches is considerably uniform [38]. The presence of repetitive patterns at different scales can be observed, for example, in the relationship that exists between the length of the generating artery and the diameter of the generated one. This relation keeps constant if quantified using a double logarithmic scale, thus indicating the presence of a power law. As stated in other works, this mechanism is consistent with a fractal recursive rule [20]. As a result, the spatial fractal properties of the arterial tree can be assessed in terms of the FD. Together with the structural aspects of the relationship among its ramifications, the dimension has been also related to the flow rate value (or its velocity) in relation to the level of diversification reached [38]. There is previous evidence that the dimensional value acquired (between 1.2 and 1.4) results from the metabolic dependence of the tissue to be perfused and not from the tree structure itself [39]. The determination of the generation parameters, which defines the degree of symmetry of the branching angles and the value of the derived diameters, makes it possible to conceive differentiated structures which have either a blood supply function or a blood distribution function [38]. The structures mentioned are related to the heterogeneous distribution of flow, as established by the perfusion target site [20]. However, as branching progresses, instantaneous variations in symmetry rules are still not clear as a whole [38].

3.1.1. A conceptual model based on experimental measures

In [40, 41], continuous AP measurements were obtained in the following sites: left ventricle and descending thoracic aorta (five animals, instrumented with solid-state implantable pressure sensors) and carotid and femoral arteries (five male middle-aged subjects, without cardiovascular risks factors, evaluated by applanation tonometry). Due to experimental limitations, invasive (in animals) and non-invasive (in humans) measuring methodologies were performed. Assessment of FD in AP time series waveforms was developed by applying Higuchi's method where topological dimension was not considered in FD relative changes (ΔFD) calculation. Essentially, a significant increase in ΔFD was observed at the thoracic aorta (higher complexity) in respect to ventricular pressure FD values (+233.06 ± 75.34%). On the other hand, femoral artery AP manifested a decrease in ΔFD (lower complexity) in comparison to the carotid site (−56.51 ± 13.62%; **Figure 4A**).

http://dx.doi.org/10.5772/67784

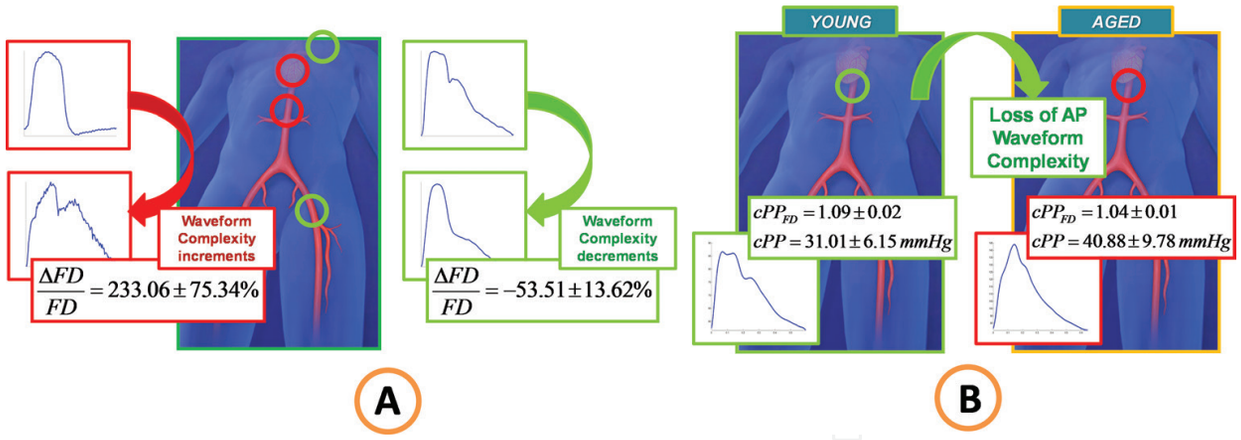

Figure 4. (A) Mapping the fractal dimension of arterial pressure along the arterial tree. (B) Changes of central pressure fractal dimension as a consequence of the ageing process.

From different experimental protocols that were carried out and assuming baseline states, a conceptual model of the morphological structure of AP waveform throughout the arterial network can be proposed. The ventricular pressure waveform, whose FD is minimal, is 'fractalized' during its path along the descending aorta, in addition to the effect caused by the arterial load. In particular, the latter is influenced by the general state of the vascular network, and it is affected by pathological states, which basically alter AS values (and thus PWV), in the same way as with wave reflection sites. As the mechanic wave propagates through the branches, the presence of a stiffness gradient and the vicinity of the periphery make its morphological structure less complex. For this reason, the loss of fractality in central pressure (as well as other CVR-related parameters) is relevant in terms of prevalence and development of CVDs.

3.2. Fractal dimension and ageing

Ageing is defined as the age-related decline in physiological function where arterial stiffening and hypertension constitute related disorders in the cardiovascular system [42]. Age can be considered one of the most powerful determinants of cardiovascular risk, usually regarded as a chronological, unmodifiable, and even untreatable factor [43]. Arterial mechanical properties of the small vessels are known to be altered with advancing age (dilating and stiffening), leading to a rise in PP [44, 45]. In this sense, central pulse pressure (cPP) has been more closely related to cardiovascular events than peripheral pulse pressure (pPP) where predictable changes occur in the arterial time series waveform whether recorded invasively or non-invasively [44, 46]. From the point of view of chaos theory, multiscale and non-linear complexity (structure and interactions of individual subsystems) appears to degrade with ageing and disease [47]. The structures and functions of the individual subsystems are not only affected by the process but also the interactions between them [48]. For this reason, the loss of complexity has even been hypothesized to be an indicator of the transition from normal ageing to frailty [49]. In [50], changes in the waveform complexity of cPP as a result of the ageing process were evaluated. A significant decrease in FD values was obtained in cPP waveform for aged subjects (−55.55%), concomitant to a cPP

increase (+31.87%). As a result, loss of waveform complexity was observed as a consequence of the ageing process in cPP (**Figure 4B**). Arterial structural changes were reflected in FD variations, independent of the AP calibration, due to the space filling property and the fine structure of the waveform were analysed. However, further studies are necessary in order to determine whether changes in waveform complexity can be utilized as a complementary factor of vascular ageing.

3.3. Fractal dimension, stiffness and wave reflection

The effect of arterial tree structure on arterial pressure fractal behaviour was assessed on laboratory animals in Refs. [51, 52]. Firstly, FD was applied, as a non-linear measure, in order to quantify waveform morphology complexity (or roughness) of aortic AP. Subsequently, aortic arterial wall stiffness was evaluated using the first derivative of the pressure-strain relationship, while the effect of wave reflection was estimated from AIX measurements. In order to eliminate peripheral wave reflections, a pneumatic cuff occluder made from silicon rubber was implanted around the descending thoracic aorta, proximally to the AP and AD transducers (piezo-resistive and ultrasonic, respectively). Aortic stiffness was studied by means of pressure-diameter loops both in basal and occlusion states (activation of the cuff and induction of total reflection). A biphasic model was adjusted, where the low pressure slope was related to the elastin elastic response, while the high pressure slope indicated the recruitment of collagen fibres.

As a result, a significant decrease in aortic pressure waveform complexity (pointed out by a FD diminution) was observed during the occlusion interval (−71.43%), concomitant to aortic stiffening (+155.71%) and an increase of AIX (+56.72%).This condition was also addressed in [53], during the evaluation the effect of arterial cross-clamping (a common strategy used in vascular surgery) on arterial stiffness, in humans. The Augmentation Index normalized to 75 beats-per-minute (AIx@75), and FD was calculated from radial arterial pressure tracings during surgery. In both aortic and iliofemoral interventions, after arterial clamping, median AIx@75 rose and FD dropped significantly; the opposite occurred after arterial unclamping.

4. Discussion

Along this chapter, a holistic evaluation of AP waveform complexity in the arterial network was performed, where its FD changes were related to the vascular site. While the ventricular pressure time series was observed to be 'fractalized' at the aortic level (due to the fact that the waveform is more exposed to the multiple wave reflections), AP showed a loss of complexity at distant sites from the cardiac muscle, as a consequence of AF. Concomitant changes in arterial stiffness (a rise of the elastic modulus towards periphery) jointly with the effects of wave reflection were particularly analysed.

4.1. The unwrinkling effect

The morphological changes observed in AP waveform during its propagation along the arterial tree can be summarized in an increase of amplitude combined with a loss of roughness.

This effect was first observed in the invasive experimental protocols implemented in the coronary network. The increase in vascular stiffness, induced by the smooth muscle activation of, was concomitant to an increase and loss of roughness in the time series structure [54]. A similar behaviour was observed in obstructive events of the descending aorta (absence of reflected peripheral waves) as well as in the pressure morphological variation analyses performed on the carotid and femoral arteries. The latter situation was associated with the effect produced by the arterial AF, whose activity has been described according to similar terms. Therefore, the scaling phenomenon with loss of complexity observed in mechanical waves in their path from the myocardium was conceptualized as a 'waveform unwrinkling', as shown in **Figure 5A**.

4.2. Structural fractality: the distributed model

The conception of the arterial system as a single, close-ended conduit, with constant or variable properties along its length, has generated acceptable results in relation to low-frequency perturbations [55]. However, in the case of high frequencies, the discrepancies are evident. The justification of this latter situation lies in the fact that although the arterial system is not a single conduit, it is made up of a set of tubular branches. In addition, the attenuation effect, produced by arterial wall viscosity, on the waves propagating through the network, must also be considered. One of the most relevant aspects is the inverse relationship that exists between frequency and wavelength since wavelengths corresponding to high frequencies will produce significant phase differences between the waves coming from different reflection sites. For this reason, the consideration of the stiffness gradient together with the distributed nature of the terminal branches significantly affects the overall behaviour of the arterial system [55].

In terms of non-linear processing, such behaviour may be expressed in multiple scales and thus evaluated through a fractal measure. The loss of high-frequency components is a typical feature of the loss of complexity, and it can be associated with the presence of diseases. In fact, this idea is part of the health/disease and FD conceptual framework, adopted in this chapter. In this sense, the transmission network models based on fractality have been consistently applied in the study of circulation [56]. In [57], arterial network simulations based on fractal

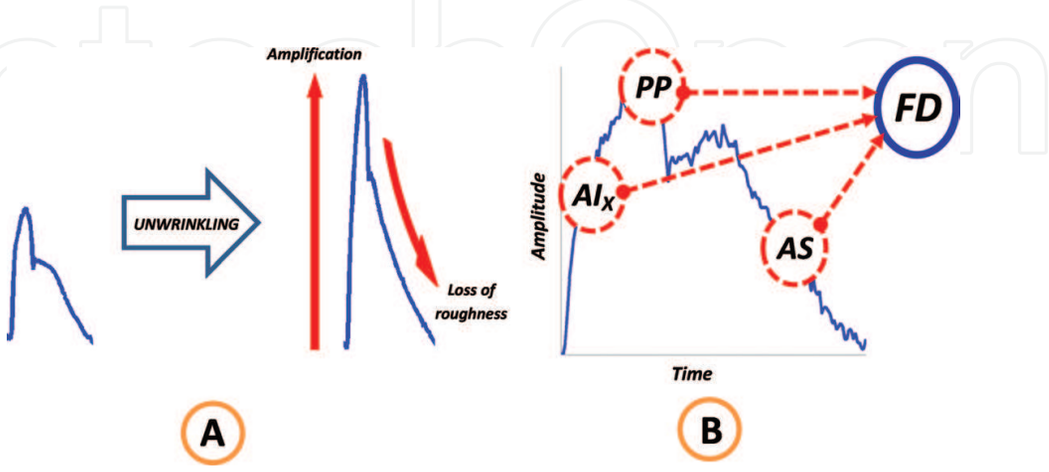

Figure 5. (A) Unwrinkling effect (stretching) evidenced by amplification and loss of roughness in the waveform. (B) Definition of the fractal dimension (FD) as a holistic indicator, which means that it may have variations in parameters related to wave pulsatility (pulse pressure, PP), arterial stiffness (AS) and wave reflection (augmentation index, AIX).

rules were developed, where Taylor's proposed premises were extended. One of the most relevant findings is that regardless of the dichotomic distribution of the branches and of the application of a power law to the relationship between their dimensions, the characteristic asymmetry of the bifurcations plays a fundamental role. This phenomenon is responsible for a marked reduction in the reflection coefficient and therefore affects the spectral oscillations in the input impedance.

Dispersion phenomena in physiological measurements are inevitable. The problem lies with the methodology used to quantify them, regardless of the size of the domain considered. Although a coincidence in the mean values is possible, this is not observed in the relative variance, since the latter depends on the measurement scale chosen to estimate the parameter. It is in these cases that the intervention of the concept of fractality cannot be disregarded [23]. This idea was first associated with physiological structures in [25]. In this work, explicit reference to the creation of vascular networks from fractal rules was made. As a result, an acceptably consistent hypothesis was posed: If the geometry of vascular beds has a fractal structure, isn't it expected that perfusion pressure and flow will be governed by such geometry? [23]. The impact of this structure on AP, its association with pathological states related to AS, and the presence of peripheral reflections constitute the great quest towards that direction.

The dichotomous branching of the arterial tree reflects its first fractal characteristic though in a more basic form. Indeed, the result is an open structure consisting of vascular segments and bifurcations, which constitute the universal block of the arterial network [58]. As stated above, the asymmetry present in each vascular division affects the magnitudes of the angles, lengths and diameters of the generated branches. Symmetrical bifurcations result in a rapidly progressing network, with a marked reduction in their diameters. This arterial structure has been observed at the coronary level in those vessels that enter the myocardium to reach the capillary bed, creating a blood supply pattern [39]. The opposite happens with highly asymmetric bifurcations. The parent branch maintains its structure since its reduction is minimal in each process. Again, in terms of coronary circulation, such structure corresponds to the major arteries surrounding the heart and has blood distribution patterns [39]. However, although the asymmetry factor is crucial in the formation of the structures mentioned, it shows variability in the vascular networks because it does not remain constant from one level to the other. Since there is no reason to consider this factor purely random, it may depend on the local anatomy or be the result of specific flow requirements [39].

In view of the foregoing, the fractal genesis of the arterial network is unquestionable. For this reason, the temporal behaviour of its hemodynamic variables was evaluated, using processing methodologies appropriate to such conception. However, although there are studies addressing the allocation of geometric parameters to each branch [58–60], no allocations related to intrinsic arterial wall features have been evaluated. As previously stated, the activity of the viscoelastic components of the arterial wall strongly determines arterial impedance. Therefore, the self-affine phenomenon observed in the AP time series can be modelled from the interaction of the reflected propagating components, whose distribution within the morphology is the result of local (or eventually systemic) biomechanical alterations of the arterial vascular structure.

4.3. Pressure waveform morphology: the influence of wave reflection

According to previous paragraphs, it may be inferred that exists an evident trend between the arterial network reflected waves and the morphology acquired by AP time series. Therefore, under total reflection (only carotid, subclavian and brachiocephalic branches remained without being occluded) aortic blood pressure unwrinkling (pulsatility increase in conjunction with a loss of roughness) is the consequence of the absence of the fractal nature, induced by the multiple branching of the arterial tree. It is noteworthy that FD analysis was performed over short-time intervals, no longer than two heartbeats. This consideration allowed the insolation of the intrinsic mechanical response, preventing the contribution of reflex regulation mechanisms (which take place around the fifth heartbeat after occlusion) whose intervention might contaminate the waveform structure. Additionally, the heart rate decrease, induced during the occlusion manoeuvre, constituted another intriguing result, which deserves further investigation. Fractal-based techniques have provided a nature-based approach, in order to identify the presence of multi-scale interactions, which are commonly generated by the characteristic of the physiological process [17]. In conclusion, arterial pressure fractality can be conceived as highly dependent on wave reflection.

In relation to this, a comparison of the structural complexity between a ventricular pressure wave and an aortic wave was presented above. Although the aortic wave is constrained in its frequency content (as a result of the buffer effect), it shows a marked irregularity in terms of morphology. The presence of wave reflections, coming from the multiple vascular branching sites, modifies its contour significantly. It was already stated that under pathological states, such as HBP, as represents a decrease in the system's global compliance. As a result, the elimination of high-frequency fluctuations is less efficient. In addition, the resulting increase in PWV generates an early return of the peripheral waves to the heart muscle, thus increasing the pressure in the abdominal aorta region [7]. In terms of fractal analysis, the processing of aortic pressure waveforms shows lower roughness values compared to normal states. Consequently, it may be inferred that the dispersion of reflections in relation to the structure plays a fundamental role. The early return of the reflected waves not only increases AP maximum values during its systolic excursion, but it also has an impact on the distribution of singularities that are part of heartbeat morphology. Such alterations are clearly differentiated by FD variation, which in fact presents the unwrinkling phenomenon.

4.4. Fractal dimension: a holistic index

The detection of a stretching in AP with a loss of complexity (unwrinkling) can be attributed to both an increase in AS (conductive factor) and to structural alterations typical of the arterial tree (obstructive factor). The loss of morphological roughness means that the AF has different impacts on pulsatility frequency components, making the waveform less complex and taking it to its pure oscillatory levels. This phenomenon may, in some aspects, be associated with the concept of oscillatory disease [26]. Consequently, proposing FD as a 'holistic index' is appropriate from more than one point of view. The holism concept entails the presence of non-linearity, where the whole is not the sum of the parts, thus not complying with the superposition principle. In addition, the FD has intrinsic behaviours based on multi-scale information, which are not specifically related to any particular magnitude or biological

system. Moreover, the calibration of the signal acquired in its determination is not required, and therefore, the measurement is independent of specific units. It should be stressed that the non-invasive determination of AP systo-diastolic variations (by means of the applanation tonometry technique) requires additional sphygmomanometric measurements, where the invariance of the mean and diastolic pressures throughout the vascular network are assumed. In this sense, the FD estimation may be affected by the values of such pressures.

The evolution of vascular diseases entails progressive changes, whose early stages are difficult to detect. Particularly in parietal alterations, they initially appear at a molecular level (e.g. excess of low density lipoproteins, nitric oxide deficiency), then at a cellular level (migration of smooth muscle cells, elastin fibre ruptures, leukocyte intervention), then at a local structural level (plaque formation, remodelling, vascular weakening) and finally at a global structural level (generalized disease with systemic consequences). In all these stages, the loss of complexity of the variables involved in the processes should become evident and, probably, a non-linear measure provided by the FD would be capable of identifying such abnormality. For this reason, the possible association between the multi-scale analysis of hemodynamic variables in the time domain and similar spatial behaviours, the latter representative of the different components present in the vascular structure has been proposed as a topic for future studies.

In conclusion, the various analyses performed indicated the presence of morphological variations in hemodynamic variables of the vascular mechanics, induced by the presence of pathological states. Such variations were quantified through non-linear processing based on fractal geometry. The main finding shows a decreased FD, concomitant to both the changes in AS and the absence of wave reflections. As a result, it may be inferred that the information provided by the measurement is systemic since it is influenced by both factors simultaneously. The FD observational analysis, associated with a potential marker, is significantly consistent in terms of health and disease. Through the adoption of this conceptual framework, it was possible to use the quantification of fractal complexity to detect underlying pathological states, associated with descriptive parameters of cardiovascular mechanics (**Figure 5B**).

Author details

Ricardo L. Armentano[1], Walter Legnani[2]* and Leandro J. Cymberknop[1]

*Address all correspondence to: walterlegnani@gmail.com

1 Group of Research and Development in Bioengineering, National Technological University, Buenos Aires, Argentina

2 Center of Signals and Images Processing, National Technological University, Buenos Aires, Argentina

References

[1] O'Rourke M. Mechanical principles in arterial disease. Hypertension. 1995; 26(1):2–9.

[2] Pessana F, Bia D, Pérez Campos H, Craiem D, Graf S, Zocalo Y, Risk M and Armentano R L. Dynamics of cryopreserved human carotid arteries. Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2004; 1:730–733.

[3] Armentano R L, Barra J G, Pessana F M, Craiem D, Graf S, Bia D, Sanchez R. Smart smooth muscle spring-dampers. IEEE Engineering in Medicine and Biology Magazine. 2007; 26: 62–70.

[4] Bia D, Zócalo Y, Pessana F, Armentano R L, Pérez H, Cabrera Fischer E I, Saldías M and Álvarez I. Acoplamiento viscoelástico y funcional entre arterias femorales nativas y homoinjertos arteriales y venosos, frescos y criopreservados. Revista Española de Cardiologia . 2006; 59(7): 679–687.

[5] Nichols W W. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. American Journal of Hypertension. 2005; 18(1): 3S–10S.

[6] Nichols W W, O'Rourke M F and Vlachopoulus C. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 6th ed. A Hodder Arnold Publication;London; UK; 2011.

[7] Westerhof N, Stergiopulos N and Noble M I M. Snapshots of Hemodynamics: An Aid for Clinical Research and Graduate Education. 2nd ed. Springer; US; 2010.

[8] Armentano R L, Cabrera Fischer E I, Barra J G, Levenson J A, Simon A C and Pichel R H. Single beat evaluation of circumferential aortic elastin elastic modulus in conscious dogs: Potential application in non-invasive measurements. Medical Progress Through Technology. 1994; 20(1–2): 91–99.

[9] Pannier B M, Avolio A, Hoeks A, Mancia G, Takazawa K. Methods and devices for measuring arterial compliance in humans. American Journal of Hypertension. 2002; 15:743–753.

[10] Greenwald S E. Pulse pressure and arterial elasticity. Quarterly Journal of Medicine. 2002; 95(2): 107–112.

[11] Safar M E. Pulse pressure, arterial stiffness, and cardiovascular risk. Current Opinion in Cardiology. 2000;15(4): 258–263.

[12] Mendis S. The contribution of the Framingham Heart Study to the prevention of cardiovascular disease: a global perspective. Progress in Cardiovascular Disease. 2010; 53:10–4.

[13] Hirai T, Sasayama S, Kawasaki T and Yagi S. Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. Circulation. 1989; 80(1): 78–86.

[14] Avolio A P, Van Bortel L M, Boutouyrie P, Cockcroft J R, McEniery C M, Protogerou A D, Roman M J, Safar M E, Segers P and Smulyan H. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. Hypertension. 2009; 54(2):375–383.

[15] Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I and Struijker-Boudier H. Expert consensus document on

arterial stiffness: methodological issues and clinical applications. European Heart Journal. 2006; 27(21): 2588–2605.

[16] Zamir M. The Physics of Coronary Blood Flow. 1st ed. Springer; US; 2010.

[17] Falconer K. Fractal Geometry: Mathematical Foundations and Applications. 2nd ed. Wiley; London; UK;2003.

[18] Theiler J. Estimating the fractal dimension of chaotic time series. The Lincoln Laboratory Journal. 1990; 3(1):63–86.

[19] Sharma V. Deterministic chaos and fractal complexity in the dynamics of cardiovascular behavior: Perspectives on a new frontier. Open Cardiovascular Medicine Journal. 2009; 3: 110–123.

[20] Bassingthwaighte J B, Liebovitch L S and West B J. Fractal physiology. Published for the American Physiological Society by Oxford University Press.; New York; US; 1994.

[21] Madisetti V. The Digital Signal Processing Handbook. 2nd ed. Boca Raton FL: CRC; 2009.

[22] Weierstrass K. On continuous functions of a real argument that do not have a well-defined differential quotient. Classics on Fractals, Edgar GA ed. Basic Books; New York; US; 1993.

[23] Bassingthwaighte J B. Physiological heterogeneity: fractals link determinism and randomness in structures and functions. News in Physiological Science. 1988; 3(1): 5–10.

[24] Barnsley M F. Fractals Everywhere. 2nd ed. Morgan Kaufmann; California; US; 2000.

[25] Mandelbrot B. The Fractal Geometry of Nature. New York: Freeman; 1983.

[26] Goldberger A L, West B J. Fractals in physiology and medicine. The Yale Journal of Biology and Medicine. 1987; 60(5): 421–435.

[27] Cerutti S, Signorini M G. Nonlinear advanced methods for biological signal analysis. In IEEE; 20022; 4(1):23.

[28] Goldberger A L, Peng C K and Lipsitz L A. What is physiologic complexity and how does it change with aging and disease? Neurobiology of Aging. 2002; 23: 23–26.

[29] Cymberknop L J, Legnani W, Pessana F, Bia D, Zócalo Y and Armentano R L. Stiffness indices and fractal dimension relationship in arterial pressure and diameter time series *in-vitro*. Journal of Physics: Conference Series. 2011; 332: 012024.

[30] Eke A, Herman P, Kocsis L and Kozak L R. Fractal characterization of complexity in temporal physiological signals. Physiological Measurement. 2002; 23: R1–R38.

[31] Katz M. Fractals and the analysis of waveforms. Computers in Biology and Medicine. 1988; 18: 145–156.

[32] Higuchi T. Approach to an irregular time series on the basis of the fractal theory. Physica D. 1988; 31: 277–283.

[33] Sevcik C. On fractal dimension of waveforms. Chaos Solitons & Fractals. 2006; 28: 579–580.

[34] Esteller R, Vachtsevanos G, Echauz J and Litt B. A comparison of waveform fractal dimension algorithms. IEEE Transactions on Circuits and Systems I: Fundamental Theory and Applications. 2001; 48: 177–183.

[35] Girault J M, Kouame D and Patat F. Mean fractal dimension» of blood ultrasonic Doppler signals. Engineering in Medicine and Biology Society, Proceedings of the 23rd Annual International Conference of the IEEE. 2001; 2:1577–1580.

[36] D'Addio G, Corbi G, Accardo A, Russo G, Ferrara N, Mazzoleni M C, Princi T. Fractal behaviour of heart rate variability reflects severity in stroke patients. Studies in Health Technology and Informatics. 2009; 150: 794–798.

[37] Khoa T Q D and Nakagawa M. Recognizing brain activities by functional near-infrared spectroscope signal analysis. Nonlinear Biomedical Physics. 2008; 2:3.

[38] Zamir M. Arterial branching within the confines of fractal L-system formalism. The Journal of General Physiology. 2001; 118(3): 267–276.

[39] Karch R, Neumann F, Podesser B K, Neumann M, Szawlowski P, and Schreiner W. Fractal properties of perfusion heterogeneity in optimized arterial trees. The Journal of General Physiology. 2003; 122(3): 307–322.

[40] Armentano R L, Cymberknop L J, Legnani W, Pessana F M, Barra J G and Simon A. Arterial blood pressure complexity provides insightful information about arterial system dynamics. 34nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2012.

[41] Cymberknop L J, Armentano R L, Legnani W, Alfonso M and Pessana F M. Mapping the fractal dimension of arterial pressure. world congress on medical physics and biomedical engineering (IUPESM'15). 2015.

[42] Sun, Z. Aging, arterial stiffness, and hypertension. Hypertension. 2015; 65(2), 252–256.

[43] Najjar S S, Scuteri A and Lakatta E G. Arterial aging: is it an immutable cardiovascular risk factor?. Hypertension. 2005; 46(3): 454–462.

[44] McVeigh G E. Bratteli C W, Morgan D J, Alinder C M, Glasser S P, Finkelstein S M and Cohn J N. Age-related abnormalities in arterial compliance identified by pressure pulse contour analysis: aging and arterial compliance. Hypertension. 1999; 33(6): 1392–1398.

[45] McEniery C M, Wallace S, Mackenzie I S, McDonnell B, Yasmin Newby D E, and Wilkinson, I B. Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. Hypertension. 2006. 48(4): 602–608.

[46] Cecelja M, Jiang B, Spector T D, and Chowienczyk P. Progression of central pulse pressure over 1 decade of aging and its reversal by nitroglycerin a twin study. Journal of the American College of Cardiology. 2012; 59(5): 475–483.

[47] Goldberger A L. Fractal dynamics in physiology: Alterations with disease and aging. Proceedings of the National Academy of Sciences. 2002; 99: 2466–2472.

[48] Sleimen-Malkoun R, Temprado J J and Hong S L. Aging induced loss of complexity and dedifferentiation: consequences for coordination dynamics within and between brain, muscular and behavioral levels. Frontiers in Aging Neuroscience. 2014; 6(140): 1–17

[49] Lipsitz L A. Physiological complexity, aging, and the path to frailty. Science of Aging Knowledge Environment: SAGE KE. 2004; (16): pe16.

[50] Armentano R L, Cymberknop L J, Legnani W, Alfonso M and Pessana F M. Aging process: central pressure waveform loss of complexity. World Congress on Medical Physics and Biomedical Engineering (IUPESM'15). 2015.

[51] Armentano R L, Cymberknop L J, Legnani W, Pessana F M, Craiem D, Graf S and Barra J G. Arterial pressure fractality is highly dependent on wave reflection. 35nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society; 2013.

[52] Cymberknop L J, Armentano R L, Legnani W, Pessana F M, Craiem D, Graf S and Barra J G. Contribution of arterial tree structure to the arterial pressure fractal behaviour. Journal of Physics: Conference Series. 2013; 477 012030. doi:10.1088/1742-6596/477/1/012030

[53] Politi M T, Wray S, Fernández J, Gaudric J, Ghigo A, Lagrée P-Y, Capurro C, Fullana J M and Armentano R. Impact of arterial cross-clamping during vascular surgery on arterial stiffness measured by the augmentation index and fractal dimension of arterial pressure. Health and technology. 2016; 6(3): 229–237.

[54] Cymberknop L J, Legnani W, Pessana F M, Crottogini A and Armentano R L. Coronary arterial stiffness is related with a loss of fractal complexity in the aortic pressure. 34nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society. 2012; 4200–03.

[55] Taylor M G. The input impedance of an assembly of randomly branching elastic tubes. Biophysical Journal. 1966; 6(1): 29–51.

[56] Milnor W R. Hemodynamics. 2nd ed. Williams & Wilkins; Philadelphia; US; 1989.

[57] Brown D J. Input impedance and reflection coefficient in fractal-like models of asymmetrically branching compliant tubes. IEEE Transactions on Biomedical Engineering. 1996; 43(7): 715–722.

[58] Zamir M. On fractal properties of arterial trees. Journal of Theoretical Biology. 1999;197: 517–526.

[59] Murray C D. The physiological principle of minimum work applied to the angle of branching of arteries. Journal of General Physiology. 1926; 9:835–841.

[60] Pollanen M S. Dimensional optimization at different levels of the arterial hierarchy. Journal of Theoretical Biology. 1992; 159:267–270.