Contribution of arterial tree structure to the arterial pressure fractal behavior

Leandro J. Cymberknop\textsuperscript{1,3}, Ricardo L. Armentano\textsuperscript{1,2,3}, Walter Legnani\textsuperscript{1,3}, Franco M. Pessana\textsuperscript{1,2,3}, Damian Craiem\textsuperscript{2}, Sebastian Graf\textsuperscript{2} and Juan G. Barra\textsuperscript{2}

\textsuperscript{1}Buenos Aires Regional Faculty, National Technological University, Buenos Aires, Argentina
\textsuperscript{2}Favaloro University, Buenos Aires, Argentina
\textsuperscript{3}School of Advanced Studies in Engineering Sciences, National Technological University, Buenos Aires, Argentina

Email: ljcymber@ieee.org

Abstract Arterial vascular beds can be characterized considering the arterial segments in terms of their physical properties. These and other trees have an open structure based on repeated bifurcations, following fractal rules. Fractal dimension ($FD$) quantifies the time series complexity defined by its geometrical representation. Objective: To evaluate the arterial pressure and diameter time series in order to assess the influence of arterial tree structure in arterial pressure fractal dimension ($FD$). Methods: Simultaneous aortic pressure and diameter were measured in 14 conscious dogs. A pair of ultrasonic crystals, a pressure microtransducer and a pneumatic cuff occluder were positioned in the upper third of the descending aorta. Results: Total reflection induced by the occlusion maneuver decreased $FD$ concomitant to the aortic stiffening and early wave reflection. Conclusion: Arterial pressure fractality is highly dependent on the arterial tree structure.

1. Introduction
Arterial stiffening is a common but highly variable disorder that is associated with advancing age and exacerbated by many known cardiovascular disease risk factors, including genetic factors. The cardiac muscle provides blood flow to the arterial system, exerting hemodynamic forces on the vessel walls. About this, the main function of systemic circulation is to guarantee a continuous blood flow at capillary level. Previous works have stated that excessive arterial pulsatility is associated with various common diseases of aging and hypertension [1, 2]. In this sense, mechanic behavior of large arteries, denoted by its viscoelastic properties as well as the distributed nature of the terminations, play a fundamental role [3, 4]. Arterial vascular beds can be characterized either by determination of a global parameter or by considering the arterial segments in terms of their physical properties. One of the main features of arterial beds is the tree-like structure [4]. Accordingly, the term “arterial tree” refers to the branching structure from a main conduit artery up to the capillary beds, without including the latter. These and other trees in the arterial circulation have an open structure based on repeated bifurcations, following fractal rules [5]. A fractal time series behaves similarly at different degrees of magnification (observation scales), which may be deterministic or stochastic. In geometric terms, a fractal signal cannot be described or quantified by usual Euclidean measures, owing to its high irregularity [6]. Additionally, arterial wave reflection is recognized as an important phenomenon...
affecting pressure and flow contour from the ejecting ventricle [7]. Concerning the above, a time series complexity can be quantified in terms of its fractal characteristic. Part of the complexity arises from the basic structure of the cardiovascular system. The heart and the vasculature contain structures, which have a fractal-like appearance. The basic pattern of blood distribution is fractal, and this is imposed both by the anatomy of the vascular tree and by the local regulation of vascular tone [8]. In previous studies, a wavelet transform based technique was applied to arterial blood pressure and diameter time series, in order to reveal structures or patterns that cannot be observed by usual procedures. Self-similar presence was confirmed, which is a necessary condition (but not sufficient) for a signal to be considered as a fractal [9]. As a consequence of that behavior, fractal dimension (FD) estimation was adopted, in order to quantify the loss of waveform complexity in blood pressure time series under pathological conditions [10]. In addition, these previous works suggested that stiffening is associated with a decrease in the fractal nature of the aortic pressure, but the mechanism remains unrevealed. Even more, FD can be seen as a measure of irregularity, roughness and variation [11].

To our knowledge, the effect of the arterial tree structure on arterial pressure fractality has not been previously reported. The goal of the present work was to analyze the fractal complexity of the arterial pressure wave in basal state and during total occlusion, where multiple branching reflections are avoided.

2. Material And Method

2.1. Experiments
Data of previous protocols performed in 14 male mongrel dogs (4.9±1.9 years, 22.2±2.9 kg) were recompiled to this study [12, 13]. In all cases, anesthesia was induced with intravenous thiopental sodium (20 mg/kg) and, after intubation, maintained with 2% enflurane carried in pure oxygen (4 L/min) through a Bain tube connected to a Bird Mark VIII respirator. Under sterile conditions, a left thoracotomy was made at the fifth intercostal space. A pressure microtransducer (Konigsberg P7, 1200 Hz frequency response) and a fluid-filled polyvinyl chloride catheter (2.8 mm OD, for later calibration of the microtransducer) were implanted in the descending thoracic aorta through a little incision in the left brachial artery. A pair of ultrasonic crystals (5 MHz, 4-mm diameter) was sutured on the adventitia of the aorta, after minimal dissection, to measure external aortic diameter. The transit time of the ultrasonic signal (1580 m/s) was converted into distance using a sonomicrometer (Triton Technology Inc., 100 Hz frequency response) and observed on the screen of an oscilloscope (Tektronix 465B) to confirm optimal signal quality. A polyvinyl chloride catheter (2.3-mm OD) was advanced through the left mammary vein to lie in the superior vena cava or right atrium for drug administration. A pneumatic cuff occluder made from silicon rubber was implanted around the descending thoracic aorta, proximally to the pressure transducer and the ultrasonic crystals, at a distance of 150 mm from the left ventricle (Figure 1). Aortic arc bifurcations (carotid, subclavian and brachiocephalic trunk arteries) were not subjected to occlusive maneuvers. Before repairing the thoracotomy, all cables and catheters were tunneled subcutaneously to emerge at the intercapsular space. At least one week after surgery, the aortic pressure was registered using the pressure microtransducer, which had been calibrated against a Statham P23-D transducer connected to the aortic fluid-filled catheter. The zero reference point was set at the level of the right atrium. The Statham transducer had been previously calibrated using a mercury manometer. The external aortic diameter signal was calibrated in millimeters using the 1-mm step calibration facility of the sonomicrometer. Aortic pressure and diameter signals were digitized every 4 ms on a computer using an analog to digital converter (National Instruments Lab PC) and digitally stored for later analysis. Instantaneous pressure-diameter loops were displayed on-line on the computer monitor. The acquisition started with approximately 20 consecutive beats in basal state (baseline state) and then the pneumatic occluder was inflated in order to obtain a total wave reflection (total occlusion state) [12, 13]. The instantaneous pressure-diameter loops were monitored and registered until stabilization was
evidenced. After completion of the protocols, animals were euthanized with an intravenous overdose of thiopental sodium followed by potassium chloride; the correct position of the ultrasonic crystals was confirmed at necropsy in all cases.

**Figure 1.** Descending thoracic aorta instrumentation. Blood pressure was measured through the implantation of a high fidelity Konigsberg® transducer. Aortic pulsatility was determined by means of the sonomicrometry technique. Reflections from periphery were avoided using a pneumatic occluder.

All protocols were approved by the Research and Development Council of the Favaloro University, and the study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the United States National Research Council (National Academy Press, Washington, DC, 1996).

2.2. Fractal Dimension. Higuchi’s method
Fractal dimension quantifies how densely a metric space is occupied by the fractal set [14]. Moreover, *FD* determines the time series complexity measure defined by its geometrical representation [15].

From a theoretical point of view, a fractal can be defined as an affine self-similar set, whose Hausdorff dimension (a measure of the space “filled” by the set at its point’s neighborhood) is strictly larger than its topological dimension [16]. Considering a time series of one time dependent variable, its *FD* value is included in the interval [1, 2]. While the Hausdorff dimension is the most relevant measure, on a practical level, Box counting (*BCD*) or Correlation dimensions (*CD*) are implemented more frequently [17]. The former has been selected for *FD* analysis, during the present study. Assessment of *FD* in this study was performed by applying the method proposed by Higuchi [18]. A number of subsets based on the original temporal series (\(x(t)\), of length \(N\)) are generated, considering an initial time value (\(m\)) and a temporal increment (\(k\)) as parameters, as follows:

\[
x^m_k = \{x(m); x(m+k); x(m+2k),\ldots, x\left(m + \left\lfloor \frac{N-m}{k} \right\rfloor k \right)\}
\]

The term \((N-m)/k\) in (1) denotes the maximal time interval (Gauss notation) that can be considered for a selected \(m\) value. For each experimental time series, an averaged length is calculated (\(L_m(k)\)), as can be observed in the following expression:

\[
L_m(k) = \frac{\sum_{i=1}^{\left\lfloor \frac{N-m}{k} \right\rfloor} |x(m+ik) - x(m+(i-1)k)|}{k} = \frac{N-1}{\left\lfloor \frac{N-m}{k} \right\rfloor}
\]
Then, the time series length function for each time increment \( L(k) \) is assessed, according to the expression:

\[
L(k) = \frac{\sum_{m=1}^{m} L_m(k)}{m}
\]  

(3)

Finally, if \( L(k) \propto FD \) is found, the time series morphology may be quantified by its FD value. The latter can be obtained by applying a linear regression method to a doubly logarithmic scale representation of \( L(k) \) against \( 1/k \). In addition, maximal value of time interval \( k \) (\( k_{\text{max}} \)) should be emphasized, especially if adequate accuracy is required in the FD estimation process.

Higuchi proposed a method that may be applied to any kind of time series, stationary or not. However, the obtained value lacks of information related to the system involved (deterministic, chaotic or stochastic), which is responsible for the signal being analyzed. In consequence, the method should be applied in the evaluation of variations that have occurred in the same signal (before and after significant events or different physiological states, such as those considered for this procedure) [17]. During the present study, arterial pressure time intervals acquired at a sampling rate of 250 Hz were processed by means of Higuchi’s method. A value of 16 was adopted for \( k_{\text{max}} \), and was estimated by applying linear regression analysis to consecutive groups of 5 points, belonging to the doubly logarithmic graph, which remained within an error band of 5\% maximum variation.

2.3. Signal Processing algorithms development
Signal processing algorithms were developed on MatLab platform (MathWorks INC, Massachusetts, USA). Existing trends were eliminated (i.e. respiration induced fluctuations, electrical artifacts, etc.) by means of digital filtering (de-noising method) [19]. In order to characterize non-stationary events, Higuchi’s method was applied to short segments of the time series (2 beats interval). A maximal window length was selected in order to ensure, simultaneously, maximal number of samples as well as a stationary behavior of the time interval (moving window method) [17].

2.4. Statistical analysis
Data were expressed as mean values ± standard deviation (SD). The presence of significant differences between baseline state and total occlusion state was assessed using a paired Student’s t-test. For all statistical analyses, \( P<0.05 \) was adopted as statistically different.

2.5. Aortic mechanical behavior
Vascular mechanical properties were evaluated based on instantaneous recordings. In this sense, aortic stiffness was studied by means of pressure – diameter loops both in basal and occlusion states. The pure elastic relationship was obtained during diastolic phase. In terms of the contribution of the entire arterial tree (with the exception of the upper limb arterial conduits) to the pressure waveform morphology, augmentation index \((Al_a)\) was calculated, which is considered as a measure of central pressure wave reflection.

2.5.1 Aortic stiffness
Changes in aortic wall stiffness were estimated assuming that the arterial wall is an isotropic homogeneous elastic material. Consequently, a linear elastic theory was applied, as follows:

\[
E = \frac{dP}{dE}
\]  

(4)
where $E$ is the pressure-strain elastic modulus [20], $P$ corresponds to the measured aortic pressure and $\varepsilon$ constitutes the aortic strain. The variation of $\varepsilon$ was obtained by referring the dynamic diameter to its non-stressed value. A biphasic model was adjusted, assuming two linear regions with different elastic modulus. According to this, low pressure slope is related to the elastin elastic response while the high pressure slope indicates the recruitment of collagen fibers. Both behaviors were quantified by means of linear regression analysis.

![Figure 2.](a) Higher Panel: In-vivo measured aortic arterial pressure. Lower Panel: In-vivo measured aortic arterial diameter. Occlusion state is observed in the last two beats (b) Basal state (dashed line) and occlusion state (solid line) aortic pressure loops. $E_{PPB}$ and $E_{PDO}$ constitute the aortic elastic modulus for both physiological states, respectively.

2.5.2 Aortic Augmentation Index
Augmentation index is defined as the ratio of the peak above the shoulder of the pressure wave ($\Delta P$) to the pulse pressure ($PP$). In relation to this, assessment of $\Delta P$ was performed from the fourth time derivative of the aortic pressure, according to [21]:

$$AI_x = \frac{\Delta P}{PP} \%$$

3. Results
Aortic pressure and diameter measured signals may be observed in Figure 2 (a), both at basal state (first three beats) as well as at total occlusion state (last two beats). Pressure-diameter loops behavior and $E$ estimation for both states are shown in Figure 2 (b) for a representative dog.

| Table 1. Aortic pressure aortic stiffness, augmentation index and fractal dimension variation between normal and occlusion states. |
|-------------------------------------------------|-------------|--------------|
| Parameter                                      | Basal State | Occlusion State |
| Elastic Modulus [$10^6$ dyn/cm$^2$]             | 0.70±0.17   | 1.79±0.85*    |
| Augmentation Index [%]                          | 21.38±5.19  | 49.40±7.41*   |
| Fractal Dimension                               | 1.07±0.02   | 1.02±0.01*    |

*P<0.05 was considered as significant different. Values are expressed as mean ± standard deviation.
Concerning $FD$ values continuous variation, a significant decrease in aortic pressure waveform complexity (pointed out by a $FD$ diminution) is observed during the occlusion interval. Assessments obtained by applying Higuchi’s method, both under baseline and after the occlusion maneuver, are detailed in Table I. Corresponding values of aortic stiffness and augmentation index are also included.

4. Discussion

The purpose of the present study was to assess the effect of arterial tree structure on arterial pressure fractal behavior. $FD$ was applied, as a non-linear measure, in order to quantify the waveform morphology complexity (or roughness). To this end, Higuchi’s method was implemented, which is widely utilized in non-linear signal processing literature. Furthermore, arterial wall stiffness was evaluated using the first derivative of the pressure-strain relationship while the effect of wave reflection was estimated from $AI_X$ measurements. As a result, total reflection induced by pneumatic occluder decreased $FD$ concomitant to the aortic stiffening and increment of $AI_X$.

![Figure 3. Aortic blood pressure unwrinkling phenomenon (loss of waveform complexity) as a consequence of the occlusive maneuver.](image)

Regarding the above, it may be inferred that the higher $FD$ values assessed in basal state are the result of the manifestation of reflected waves, emerging from the presence of vascular bifurcations. Therefore, this behavior suggests that 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 (Figure 3).

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 maneuver, constituted another intriguing result. Considering that the development of the phenomenon occurred in less than a time constant of the system, the observation clearly deserves further investigation. Moreover, it is well known that physiological process originate complex, anisotropic fluctuations, which cannot be processed properly by usual measures. In this sense, fractal based techniques provide a nature based approach, in order to identify the presence of multi-scale interactions [8]. The present results suggest an evident trend between arterial wall reflection and the morphology of the acquired pressure time series. In previous studies [9, 10] it was demonstrated that loss of fractal complexity was related to an increase of arterial stiffness. In this study, the influence of wave reflection from the descending thoracic aorta and its posterior
successive bifurcations (the upper vascular bed was not interrupted) was also evaluated. What remains to be investigated, is if arterial stiffness can be considered as a factor in FD diminution or may be induced by the presence of reflected waves.

In conclusion, arterial pressure fractality is highly dependent on the arterial tree structure. Further studies will be needed in order to demonstrate the role of arterial stiffness itself and its relation to wave reflection in the loss of arterial pressure fractal complexity.

5. Acknowledgments
This work was supported by National Technological University (NTU) – FONCyT – IP – PRH – 2007.

6. References
[1] Safar M. E., Levy B. I. and Struijker-Boudier H. Current Perspectives on Arterial Stiffness and Pulse Pressure in Hypertension and Cardiovascular Diseases 2003 Circulation 107(22): 2864–69.
[2] Armentano RL, Graf S, Barra JG, Velikovsky G, Baglivo H., Sanchez R, Simon A, Pichel RH and Lenvenson J Carotid wall viscosity increase is related to intima media thickening in hypertensive patients 2004 Stroke 35.
[3] M. G. Taylor The input impedance of an assembly randomly branching elastic tubes 1966 Biophys. J. 6(1): 29-51.
[4] A. Avolio, Input impedance of distributed arterial structures as used in investigations of underlying concepts in arterial haemodynamics 2009 Med. Biol. Eng. Comput., 47(2): 143-151, 2009.
[5] M. Zamir, Arterial branching within the confines of fractal L-system formalism 2001 J. Gen. Physiol. 118(3) 267-276.
[6] K. Falconer 2003 Fractal Geometry: Mathematical Foundations and Applications (2nd. ed. Wiley).
[7] R. Burattini and K. B. Campbell Comparative analysis of aortic impedance and wave reflection in ferrets and dogs 2002 Am. J. Physiol. Heart Circ. Physiol. 282(1): H244-255.
[8] V. Sharma Deterministic chaos and fractal complexity in the dynamics of cardiovascular behavior: perspectives on a new frontier 2009 Open Cardiovasc. Med. J. 3: 110-123.
[9] L. J. Cymberknop, W. Legnani, F. Pessana, D. Bia, Y. Zócalo and R. L. Armentano Stiffness indices and fractal dimension relationship in arterial pressure and diameter time series in-vitro 2001 J. Phys.: Conference Series, 332: 012024.
[10] L. J. Cymberknop, W. Legnani, F. M. Pessana, A. Crottogini and R. L. Armentano Coronary arterial stiffness is related with a loss of fractal complexity in the aortic pressure 2012 Conf. Proc. IEEE Eng. Med. Biol. Soc. 4200-03.
[11] J. B. Bassingthwaighte Physiological Heterogeneity: Fractals Link Determinism and Randomness in Structures and Functions 1988 News Physiol. Sci. 3(1): 5-10.
[12] R. L. Armentano, J. G. Barra, J. Levenson, A. Simon and R. H. Pichel Arterial wall mechanics in conscious dogs. Assessment of viscous, inertial, and elastic moduli to characterize aortic wall behavior 1995 Circ. Res. 76(3): 468-478.
[13] J. G. Barra, J. Levenson, R. L. Armentano, E. I. Cabrera Fischer, R. H. Pichel and A. Simon In vivo angiotensin II receptor blockade and converting enzyme inhibition on canine aortic viscoelasticity 1997 Am. J. Physiol. 272(2): H859-68.
[14] M. F. Barnsley 1983 Fractals Everywhere (2nd. ed., New York. Academic Press Professional).
[15] W. Klonowski From conformons to human brains: an informal overview of nonlinear dynamics and its applications in biomedicine 2007 Nonlin. Biomed. Phys. 1(1): 5.
[16] B. Mandelbrot 1983 The Fractal Geometry of Nature (Freeman, New York).
[17] B. S. Raghavendra and Narayana D. Computing fractal dimension of signals using multiresolution box counting method 2010 Journal of Math. Sciences 6(1).
[18] T. Higuchi, Approach to an irregular time series on the basis of the fractal theory 1988 *Physica D.* 31: 277-283.

[19] D. L. Donoho De-noising by soft-thresholding 1995 *Information Theory IEEE Trans.* 41(3): 613-627.

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

[21] R. Kelly, C. Hayward, A. Avolio and M. O’Rourke Noninvasive determination of age-related changes in the human arterial pulse 1989 *Circulation* 80(6) 1652-59.