34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Coronary Arterial Stiffness is Related With a Loss of Fractal Complexity in the Aortic Pressure

Leandro J. Cymberknop, Walter Legnani, Franco M. Pessana, Alberto Crottogini and Ricardo L. Armentano, *Senior Member IEEE*

Abstract— **Arterial stiffening is a common but highly variable disorder. Additionally, excessive arterial pulsatility is associated with various common diseases of aging and hypertension. Fractal dimension (FD) quantifies the time series complexity defined by its geometrical representation. Objective: Arterial pressure and diameter time series were evaluated in order to assess the relationship between arterial stiffness and FD. Methods: Three Corriedale male sheep were operated. Left anterior descending artery (LAD) was dissected and the external arterial diameter was measured trough sonomicrometry. Similarly, a pressure microtransducer was positioned in the upper third of the ascending aorta. Simultaneous pressure and diameter were measured in normal state and under smooth muscle activation. Each time series FD were assessed by the application of Higuchi's method while arterial wall elastic modulus was evaluated by means of the pressure-strain relationship. Results: Coronary stiffness was increased from normal state to phenylephrine state (47.32%, 21.12%, 10.87%) while aortic pressure FD was decreased (2.11%, 2.57%, 6.85%), respectively. Conclusion: Acute hypertension induced by phenylephrine produces an increase in the coronary wall elastic modulus with a concomitant decrease in the fractal nature of the aortic pressure, suggesting that coronary stiffening is associated with an unwrinkled aortic pressure.**

Key words—**coronary artery, fractal dimension, unwrinkling, coronary arterial stiffness.**

I. 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]. In this sense, mechanic behavior of large arteries, denoted by its viscoelastic properties, plays a fundamental role [2]. Concerning the above, the presence of changes in large arteries of coronary circulation (which is responsible for the blood supply to the heart muscle) can be directly related to the pathogenesis of myocardial ischemia in coronary heart disease (CHD).

Traditionally, the diagnosis of coronary stenosis severity was based only on angiography methods. However, the clinical significance of a coronary stenosis cannot be fully characterized based on its geometry alone [3]. Therefore, the analysis of the stress (applied pressure) - strain (diameter variation) relationship is required in order to perform an entire evaluation of the arterial biomechanical behavior [4, 5]. On the other hand, smooth muscle activation (SMA) also alters the viscosity as well as the elasticity of the vessel wall [6]. Recent studies have proposed that central (and not peripheral) aortic pressure (AP), by means of the evaluation of its "excess" component, results in the "best" indicator of cardiac events [7].

Arterial stress-strain relationship results highly nonlinear, as well as most of the interactions between parameters related to cardiovascular dynamics. However, linear approaches have been widely applied and nonlinear information has been frequently underestimated [8]. Even so, assessment of coronary stiffening remains difficult to obtain by traditional methods. Concerning this, appropriate tools are required to analyze the temporal dynamics of the signals involved, in order to characterize the whole phenomenon. Fractal geometry can be mentioned as one of these techniques, mainly due to the fractal nature of cardiac structure and its associated mechanical function [8]. In geometric terms, a fractal signal cannot be described or quantified by usual Euclidean measures, owing to its high irregularity [9].

The aim of this study consisted on AP processing by means of nonlinear techniques based on fractal geometry [10]. Additionally, obtained AP fractal complexity was related to different coronary wall stiffness states, during *in vivo* experiences. Coronary elastic modulus was obtained by means of the slope of the central pressure vs. coronary arterial diameter loop. Coronary arterial pressure (CP) and AP were measured simultaneously, in order to demonstrate that either of them can be used in coronary arterial stiffness assessment. Experiments were performed under acute hypertension states, induced by the activation of smooth muscle cells, by means of the administration of a sympatho-

Manuscript received March 15, 2012. This work was supported by National Technological University (NTU) – FONCyT – IP – PRH – 2007.

L. Cymberknop, F. M. Pessana, R. L. Armentano and W. Legnani are from Buenos Aires Regional Faculty, National Technological University, Medrano 951, (C1179AAQ), Ciudad Autónoma de Buenos Aires, Argentina (e-mail: lcymber@ieee.org).

F. M. Pessana, A. Crottogini and R. L. Armentano are from Faculty of Engineering and Exact and Natural Sciences, Favaloro University, Buenos Aires, Argentina (e-mail: armen@ieee.org)

mimetic drug.

II. Material and Method

A. Fractal Dimension. Higuchi's method

Fractal dimension (FD) quantifies how densely a metric space is occupied by the fractal set [11]. Moreover, FD determines the time series complexity measure defined by its geometrical representation [12]. 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 [13]. 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 [14]. The former has been selected for FD analysis, during the present study.

Assessment of FD was performed by applying the method proposed by Higuchi [15]. 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:

$$x_k^m = \left\{ x(m); x(m+k); x(m+2k), .., x\left(m + \left[\frac{N-m}{k} \right] k \right) \right\} \quad (1)$$

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:

$$L_m(k) = \frac{\sum_{i=1}^{\left[\frac{N-m}{k} \right]} \left| x(m+ik) - x(m+(i-1)k) \right| \frac{N-1}{\left(\frac{N-m}{k} \right) k}}{k} \quad (2)$$

Then, the time series length function for each time increment ($L(k)$) is assessed, according to the expression:

$$L(k) = \frac{\sum_{m=1}^{k} L_m(k)}{m} \quad (3)$$

Finally, if $L(k) \propto k^{-FD}$ 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_{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 lack 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) [14]. During the present study, arterial pressure time intervals acquired at a sampling rate of 400Hz, were processed by means of Higuchi's method, by applying a moving window to an obtained time series of a length of at least twenty five cardiac cycles. Established maximal value for k (k_{max}) was of 32, which 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.

B. Signal Processing algorithms development

Signal processing algorithms were developed on MatLab platform (MathWorks INC, Massachusetts, USA) through the design and implementation of a graphic user interface (GUI). Prior to the non-linear processing, existing trends were eliminated (by means of digital filtering) and a wavelet transform analysis was applied (de-noising method, [16]) with the purpose of eliminating undesired fluctuations originated during the acquisition procedure.

C. Surgical Procedure

Three Corriedale castrated male sheep weighing 28.4±3.2 kg were operated. After premedication with intramuscular acepromazine maleate (0.2 mg/kg), anesthesia was induced with intravenous sodium thiopental (20 mg/kg) and maintained with 2% halothane in pure oxygen under mechanical ventilation (Neumovent 910, Córdoba, Argentina). The electrocardiogram, heart rate and oxygen saturation (Novametrix 515A pulse oxymeter, Wallingford, CT) were monitored during surgery and recovery. After a sterile minithoracotomy at the 4th intercostal space, the left anterior descending artery (LAD) was dissected just proximal to the origin of the second diagonal branch. To measure the external diameter, a pair of ultrasonic crystals (5 MHz) was sutured to the upper third of the LAD. The ultrasonic signal transit time was converted into distance through a sonomicrometer (Triton Biosciences Inc., California, USA). A pressure microtransducer (Millar Micro-tip® catheter) was positioned in the upper third of the ascending aorta. In order to compare this pressure with coronary arterial pressure, one sheep was instrumented with a Konigsberg P2.5 microtransducer (1200Hz, Pasadena, USA) located in a lateral branch close to the upper third of the LAD. Simultaneous aortic pressure and diameter were measured in normal state and under SMA: PHE group (administration of phenylephrine 5 µg/kg/min). All experimental procedures were performed in agreement with ethics norms and international recommendations about research in laboratory animals, ratified in Helsinki and actualized by the Physiology American Society (1981) [17].

D. Coronary Stiffness Assessment

Changes in coronary wall stiffness were estimated assuming that the arterial wall is an isotropic homogeneous

elastic material. Consequently, a linear elastic theory was applied, as follows:

$$E = \frac{dP}{d\varepsilon} \tag{4}$$

where E is the pressure-strain elastic modulus [18], P corresponds to the aortic pressure and ε corresponds to the LAD strain. The latter was obtained by referring the dynamic diameter to its non-stressed value. The slope of the pressure-strain curve was evaluated at mean aortic pressure values (isobaric analysis).

III. Results

Arterial pressure and LAD diameter measured signals may be observed in Figure 1, for a typical case. Similar morphology was found in the rest of the processed cases, for different arterial stiffness states.

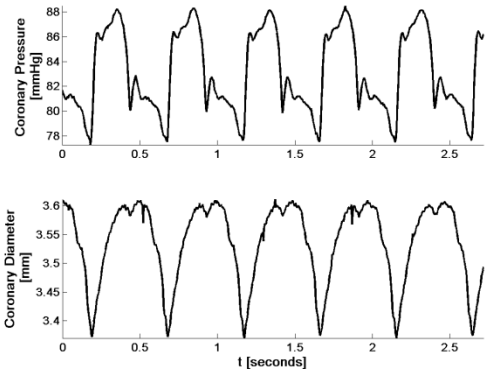

Fig. 1. Higher Panel: *In-vivo* measured coronary arterial pressure. **Lower Panel:** *In-vivo* measured coronary arterial diameter.

Comparison between aortic pressure and coronary arterial pressure can be appreciated in Figure 2. A strong linear dependence between both pressures was obtained (AP=1.046xCP-4.79, r^2=0.967; p<0.001), suggesting that both waveforms are indistinguishable.

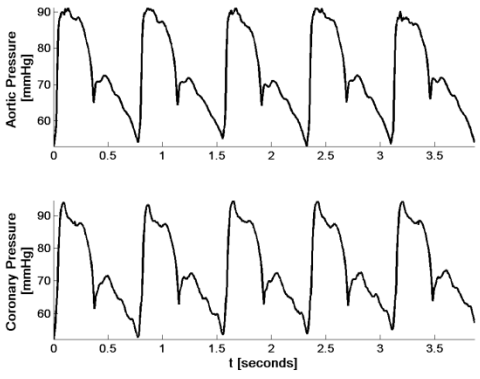

Fig. 2. Higher Panel: *In-vivo* measured aortic pressure. **Lower Panel:** *In-vivo* measured coronary arterial pressure.

FD obtained by applying Higuchi's method, showed differences during steady state phenylephrine administration (Figure 3), for all processed time series. An unwrinkled aortic pressure time series can be observed.

Table I shows FD and the elastic modulus variation, both referred to normal states, during *in vivo* experiments under drug administration. The increase of arterial pressure pulsatility, yield a vascular response, expressed by changes in the elastic modulus.

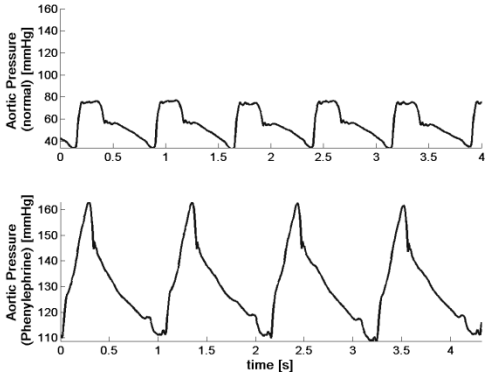

Fig. 3. Higher Panel: *In-vivo* measured aortic pressure, normal state. **Lower Panel:** *In-vivo* measured aortic pressure during steady state phenylephrine administration (unwrinkled time series).

IV. Discussion

The purpose of the present study was to process central pressure and coronary diameter time series, in order to evaluate the relationship between coronary arterial stiffness and aortic pressure fractal dimension estimation. FD was applied, as a non-linear measure, in order to quantify arterial pressure complexity (or roughness). Each time series FD assessment was performed by the application of Higuchi's method, which is widely utilized in non-linear signal processing literature. Arterial wall stiffness was evaluated by means of the first derivative of the pressure-strain relationship, at mean aortic pressure values since both measured pressures are equivalent (see Figure 2).

TABLE I
Aortic Pressure Fractal Dimension and Coronary Stiffness Variations Between Normal and Phenylephrine States.

Case #	Weight (kg)	Normal FD	ΔFD/FD	Normal E	ΔE/E
Sheep 1	31.25	1.2392	-2.1062	0.8296	47.3236
Sheep 2	28.95	1.0866	-2.5676	2.3952	21.1171
Sheep 3	24.88	1.5905	-6.8532	5.5164	10.8749

FD: Fractal Dimension. **E**: Elastic modulus (10^5 dyn/cm^2). **ΔFD/FD** (%): Aortic pressure FD variation. **ΔE/E** (%): Elastic Modulus variation. Percentage values were referred to its normal state.

Acute hypertension induced by SMA decreased FD concomitant to the coronary stiffening. This behavior suggests that arterial hyperpulsatility induced by a sympatho-mimetic drug administration is responsible for the "*unwrinkling*" of aortic blood pressure.

To our knowledge, fractal characterization of arterial pressure and its association to the coronary pressure-strain relationship has not been previously reported. The present results suggest an evident trend between arterial wall elasticity and the morphology of the acquired pressure time series. The latter could be quantified by the application of non-linear analysis, as provided by the fractal geometry. The relationship between estimated FD values of arterial pressure

might be able to differentiate local/global arterial stiffness states, improving the information provided by linear-models based estimations.

It is worth noting that pulse pressure, one of the most used indexes in cardiovascular disease risk prediction [19], is based on extreme values (difference between systolic and diastolic pressures) neglecting the richer morphological information of the pressure waveform. The present work proposes the use of fractal complexity to evaluate the whole information. A loss of fractal complexity (or AP unwrinkling), quantified by a decrease of its FD, could be useful as a marker of coronary stiffening to be used in the clinical practice. Furthermore, arterial stiffness assessment by means of time series fractal complexity could avoid problems related to the arterial pressure waveform calibration and to overcome the well-known statement that brachial pressure overestimates central pressure, especially in young people [19]. It has been stated that central aortic pressure is an indicator of generalized cardiac events. In reference to this, the loss of complexity of AP time series may be used as a complementary predictor of coronary disease development. One aspect to be considered is the variability observed in the elastic modulus variation, among the processed cases. The obtained differences could be the result of the myocardium influence over the coronary tree, beside other factors.

In conclusion, acute hypertension induced by phenylephrine produces an increase in the coronary wall elastic modulus with a concomitant decrease in the fractal nature of the aortic pressure, suggesting that coronary stiffening is associated with an unwrinkled aortic pressure. Further studies will be needed to demonstrate conclusively that arterial stiffness may be responsible for the loss of fractal complexity in arterial pressure.

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", *Circulation* (2003), 107(22): 2864–2869.

[2] Armentano RL, Graf S, Barra JG, Velikovsky G, Baglivo H., Sanchez R, Simon A, Pichel RH, Lenvenson J, "Carotid wall visosity increase is related to intima media thickening in hypertensive patients", in *Stroke* (2004), 35.

[3] Spaan J., Kolyva C., Van Den Wijngaard J., Ter Wee R., Van Horssen P., Piek J., y Siebes M., "Coronary Structure and Perfusion in Health and Disease", in *Phil. Trans. R. Soc. A* (2008), 366 (1878): 3137–3153.

[4] Bella J., Roman M., Pinni R., Schwartz J., Pickering T., Devereux R., "Assessment of Arterial Compliance by Carotid Midwall Stress-Strain Relation in Normotensive Adults" *in Hypertension* (1999), 33:787-792.

[5] Cabrera Fischer E, Bia D, Zócalo Y, Camus J, Forteza E, Armentano RL, "Effects of removing adventitia on the mechanical properties of ovine femoral arteries in vivo and in vitro", in *J. Circ.* (2010), 74.

[6] Barra JG, Levenson J, Armentano RL, Cabrera Fischer E, Piehel RH, Simón A, "Assessment of smooth muscle contribution to descending thoracic elastic mechanics on concious dogs", in *Circ. Res* (1993), 73: 1040-1050.

[7] Roman M. J., Devereux R. B., Kizer J. R., Lee E. T., Galloway J. M., Ali T., Umans J. G., y Howard B. V., "Central Pressure More Strongly Relates to Vascular Disease and Outcome Than Does Brachial Pressure The Strong Heart Study", in *Hypertension* (2007), 50(1):197–203.

[8] Goldberger A. L., "Fractal dynamics in physiology: Alterations with disease and aging", in *Proceedings of the National Academy of Sciences* (2002), 99: 2466–2472.

[9] Falconer K. (1990), *Fractal Geometry: Mathematical foundations and applications*, (Wiley, New York).

[10] Losa G. A., Merlini D., Nonnenmacher T. F., Weibel E. R (2005), *Fractals in Biology and Medicine*, (Birkhäuser Verlag)

[11] Barnsley M. F. (1983), *Fractals Everywhere, 2ed*, (New York. Academic Press Professional).

[12] Wlodzimierz K., "From conformons to human brains: an informal overview of nonlinear dynamics and its applications in biomedicine", in *Nonlin. Biomed. Phys*. (2007), 1(5).

[13] Mandelbrot B. (1983), *The fractal Geometry of nature*, (Freeman, New York).

[14] Raghavendra B. S., Narayana D., "Computing Fractal Dimension of signals using Multiresolution box counting method" (2010), in *Journal of Math. Sciences*, 6(1).

[15] Higuchi T., "Approach to an irregular time series on the basis of the fractal theory" (1988), in *Physica D.*, 31:277-283.

[16] Radunovic D. P. (2009), *Wavelets, from Math to Practice*, (Academic Mind, Belgrade, Serbia, Springer-Verlag, Berlin Heidelberg, Germany).

[17] Guide for the Care and Use of Laboratory Animals, National Institutes of Health (NIH Publication Nº 86-23, revisited 1985)

[18] 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", in *Med Prog Technol* (1994), 20(1–2):91–99.

[19] Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Panner B, Vlachopoulos V, Wilkinson I, Struijker-Boudier H, "Expert consensus on arterial stiffness: methodological issues and clinical applications" (2006), in *Eur. Heart. J*., 27:2588-2605.