Stiffness Indices and Fractal Dimension relationship in Arterial Pressure and Diameter Time Series in-Vitro

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Abstract. The advent of vascular diseases, such as hypertension and atherosclerosis, is associated to significant alterations in the physical properties of arterial vessels. Evaluation of arterial biomechanical behaviour is related to the assessment of three representative indices: arterial compliance, arterial distensibility and arterial stiffness index. Elasticity is the most important mechanical property of the arterial wall, whose natures is strictly non-linear. Intervention of elastin and collagen fibres, passive constituent elements of the arterial wall, is related to the applied wall stress level. Concerning this, appropriate tools are required to analyse the temporal dynamics of the signals involved, in order to characterize the whole phenomenon. Fractal geometry can be mentioned as one of those techniques. The aim of this study consisted on arterial pressure and diameter signals processing, by means of nonlinear techniques based on fractal geometry. Time series morphology was related to different arterial stiffness states, generated by means of blood flow variations, during experiences performed in vitro.

1. Introduction

During ventricular ejection, the cardiac muscle provides blood flow to the arterial system, exerting hemodynamic forces on the vessel walls. The main function of systemic circulation is to guarantee a continuous blood flow at capillary level. In this sense, mechanic behaviour of large arteries, denoted by its viscoelastic properties, plays a fundamental role [1]. The advent of vascular diseases, such as hypertension and atherosclerosis, is associated to significant alterations in the physical properties of arterial vessels [2].

Evaluation of arterial biomechanical behaviour is related to the assessment of three representative indices: arterial compliance (AC), Peterson's elastic modulus (E<sub>P</sub>) and arterial stiffness index (β). The latter are commonly used in clinical practice and can be easily obtained from systolic (maximal) and diastolic (minimal) values of blood pressure and arterial diameter measurements [3, 4]. During the last years, pulse wave analysis (PWA) has regained relevance, due to the development of

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new time-domain processing methods, which are capable of providing specific information related to the pathological/normal state of the arterial system. It should be emphasized that the study of arterial dynamics necessarily implies the analysis of the stress (applied pressure) – strain (diameter variation) relationship. Although pressure-diameter interactions have been addressed in previous studies [5], the implemented techniques were based on the assumption of a system’s linear behaviour. However, elasticity is the most important mechanical property of the arterial wall, whose nature is strictly nonlinear. Intervention of elastin and collagen fibres, passive constituent elements of the arterial wall, is related to the applied wall stress level [6]. 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. A fractal time series is characterized by self-similarity property. Specifically, it 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 [7].

The aim of this study consisted on arterial pressure and diameter signals processing, by means of nonlinear techniques based on fractal geometry [8]. Signals morphology evaluation (by applying a Fractal Dimension estimation algorithm) was related to different arterial stiffness states, during experiences performed in vitro. Several experiments were implemented, where the mean blood flow was varied, respecting the pulsatility regimes obtained from in vivo measurements. As a result, different arterial stiffness states were considered, as a consequence of the interaction of vessel’s elasticity components.

2. Materials and Method

2.1. Self-similarity in arterial pressure and diameter time series

Self-similarity presence in arterial pressure and diameter signals was verified by the application of the wavelet transform (WT) [9]. A wavelet based representation can be explained as the assessment of the resemblance index (wavelet coefficients) between the wavelet mother and the signal involved, at different wavelet dilations, during a specified time interval. A large index indicates high “similarity”. Consequently, application of WT generates a coefficient matrix, which provides signal information contained at different scales, or, in other terms, information contained at different “frequency bands”. The expression for the WT calculation is defined as follows:

\[
W(a,b) = \int_{-\infty}^{\infty} s(t) \psi^*(\frac{t-b}{a}) dt
\]  

(1)

where \(s(t)\) is the time series and \(W(a,b)\) corresponds to its WT coefficient. Parameters \(a\) and \(b\) indicate the scale and the time displacement of wavelet mother \(\psi\), respectively.

If a signal manifests similarities at different scales, its wavelet coefficients will indicate such particular behaviour. In a graph where the vertical axis corresponds to the selected scales whereas abscises axis is related to time, the presence of self-similarity will determine a vertical pattern, which is characteristic of sets with equal intensity [10]. In certain cases, the analysis of the properties of the wavelet transform modulus maxima (WTMM) is sufficient, due to its relation with the signal singularities [9-11]. A wavelet coefficient can be considered as a Modulus Maxima, if the following expressions are verified:

\[
\left| W(a,t_0) \right| \geq W(a,\tau), \quad \frac{\partial W(a,\tau)}{\partial \tau} = 0,
\]  

(2)

where \(a\) is the scale, \(t_0\) is the specified time and \(\tau\) belongs either to a left or right neighbourhood of \(t_0\). Since WTMM positions define geometrical arranges in the time-scale plane, existing self-similarities
may be observed throughout a geometric pattern with comparable intensity at all scales [9]. It should be emphasized that self-similarity is a necessary condition for a time series to be considered as a fractal but it is not sufficient. Pressure and diameter signals appear to be “potential fractal signals” due to the presence of self-similarity property. Consequently, fractal dimension estimation is applied in order to perform an irregularity measurement.

2.2. Fractal Dimension. Higuchi’s method

Fractal dimension (FD) quantifies how densely a metric space is occupied by the fractal set [12]. Moreover, FD determines the time series complexity measure defined by its geometrical representation [13]. 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 neighbourhood) is strictly larger than its topological dimension [14]. 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 [15]. The former has been selected for FD analysis, during the present study.

Assessment of FD was performed by applying the method proposed by Higuchi [16]. 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:

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

(3)

The term \( \left\lfloor \frac{N-m}{k} \right\rfloor \) in (3) 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:

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

(4)

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

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

(4)

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 analysed. 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) [13]. In the present study, Higuchi’s method was applied to time intervals of five cardiac cycles of length, which were acquired at a sampling rate of
400Hz. Established maximal value for $k$ ($k_{max}$) was of 32. FD error range was estimated by applying linear regression analysis to consecutive groups of 4, 5 and 6 points, belonging to the doubly logarithmic graph. The obtained error values (sensitivity of the method) did not exceed 5%.

2.3. Data analysis
Stiffness (or distensibility) indices assessment was performed based on the following expressions, in accordance with [17]:

$$\beta = \ln \left( \frac{SP}{SD} \right) \frac{DD}{SD-DD}, \quad AC = \frac{SD - DD}{SP - DP}, \quad E_p = \frac{(SP - DP)}{SD - DD} DD$$

(5)

where $SD$ y $DD$ are the arterial systolic and diastolic external diameters and $SD$ y $DP$ are the arterial systolic and diastolic pressures, respectively. Both Arterial compliance and Peterson’s modulus evaluate the vessel’s buffering capacity [18]. Nevertheless, the difference between AC and $E_p$ values lies in the fact that the latter provides information regardless of the variation in the vessel diameter. Consequently, $E_p$ allows the comparison between arterial segments of different sizes [4]. Stiffness index ($\beta$) evaluates elastic arterial condition with no dependence on arterial pressure changes or, similarly to $E_p$, the geometric properties of the vessel wall.

It may be appreciated then, that $E_p$ and AC considers a linear stress-strain relationship, whereas $\beta$ suggests a logarithmic adjustment. Considering the above, FD assessment, which is related to the existence of non-linear behaviours, prevents the a priori assumption of a linear stress-strain dynamic.

2.4. Surgical Procedure
Six healthy male Corredale sheep were selected for the present study, weighting 25 to 35 kg and aged between 30 to 48 months old. Animals were properly cared, feed and vaccinated and surgically operated under general anaesthesia induced by thiopental sodium (20 mg/kg, intravenous). Subsequently to the intubation, they were maintained with 2.5% of enflurane in pure oxygen (4 L/min) through a Bain tube connected to a Bird Mark VIII respirator. Each animal were positioned in left lateral decubitus and a sterile thoracotomy was performed at the left third intercostal space. Intra-arterial pressure measurement was performed by placing a high frequency response pressure microtransducer (1,200 Hz; Konigsberg, P7 model) into the aortic arterial lumen, through a collateral branch. Arterial external diameter measurement was obtained by using ultrasound technology. After a minimal dissection, a pair of ultrasound crystals (5 MHz, 4 mm diameter) was saturated at both sides of the aortic trunk’s adventitia. A sonometric device (Triton Technology Inc.) was used to convert the ultrasonic signal transit time (1580m/s) into distance. The resultant signal was observed in a digital oscilloscope (Tektronixs, TDS 210 model) in order to ensure optimal diameter signal quality. 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) [19].

After in vivo measurements, all aortic segments were extracted in order to perform in vitro experiments. Studies were developed on a specially manufactured closed loop device, constituted by a centrifuge pump (fluid drive, electronically controlled), a reservoir (compliant chamber), a perfusion line (polyethylene conducts) and a rectangular chamber with a support system, for the aortic segments placement. The chamber was filled with a Tyrode’s solution kept at a temperature of 37ºC, in order to maintain adequate physiological conditions of the specimen under study [20]. Once aortic segments were clamped, anticoagulated blood fluid (2-2.5 mPas viscosity) was putted into circulation, at different mean flow rates (70 to 340 ml/min). Fluid waveforms were pumped through the hydraulic circuit and controlled by the device system, according to in vivo measurements. The procedure was implemented in all extracted segments; in vitro pressure and diameter signals were digitalized using a data acquisition system (National Instruments CompactDAQ, USA), during at least five cardiac
cycles. Sampling frequency (400Hz) was in accordance to the level of detail required for FD estimation [14]. Storage of acquired data was performed by means of specially designed software, developed under MatLab® platform (Mathworks Inc, Massachusetts, USA).

2.5. 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 WT analysis was applied (denoising method, [21]) with the purpose of eliminating undesired fluctuations originated during the acquisition procedure.

2.6. Statistical Analysis
Data were expressed as mean values plus / minus the standard deviation. Functional relationships between the arterial parameters were calculated by means of linear regression analysis methods. Continuous variables were compared using a Student t test, unpaired, two tails. A Pearson correlation coefficient was applied for all studies, where p<0.05 was considered statistically significant.

3. Results
Arterial pressure and diameter measured signals may be observed in Figure I, for a typical case. Similar morphology was found in the rest of the processed cases, for different mean blood flow states.

WTMM was applied to arterial pressure and diameter time series. Both of signals revealed the presence of self-similarity, verified in the geometrical pattern described by its coefficients maximal values (Figure 2). Self-similarity condition was also observed for different aortic mean flow states.

FD obtained by applying Higuchi’s method, showed differences for different mean aortic values (Figure 3), for all processed time series. It can be observed that, throughout the whole procedure, pressure FD estimation remained higher than diameter FD, for the same aortic flow state.
Table I is constituted by stiffness indices assessments, related to the mean blood flow states performed during the in vitro experiments. Mean aortic flow values and hence, the increase of arterial pressure pulsatility, gave rise to a vascular response, expressed by changes in AC, E_p and β indices.

Estimated FD values evolution was in accordance with the variations experimented by the stiffness indices. Obtained calculations showed a decrease until mean aortic flow reached 120ml/min. At the time the mentioned threshold was exceeded, certain “stability” was observed.
Table 1. Assessed stiffness indices for mean blood flow variations. F is the mean flow, β is the stiffness index, AC is the arterial compliance, E_P is the Peterson’s modulus. Values are expressed as mean ± SD

| F (ml/min) | β | AC (10^{-3}mm.mmHg^{-1}) | E_P (10^{2}mmHg) |
|-----------|---|--------------------------|------------------|
| 70        | 10.52±2.23 | 16.91±3.88               | 6.50±3.41        |
| 100       | 10.84±2.41 | 14.48±3.81               | 7.94±4.23        |
| 140       | 11.17±2.30 | 13.45±3.53               | 8.61±4.36        |
| 200       | 12.12±3.45 | 11.48±3.07               | 10.48±5.73       |
| 250       | 12.48±3.06 | 10.59±2.18               | 11.16±5.16       |
| 340       | 14.06±2.80 | 9.16±2.00                | 12.77±4.88       |

Table 2 specifies the linear regression analysis results, performed between arterial pressure and diameter FD values and arterial stiffness indices, for each blood flow state. Even though all relationships exhibit a high correlation level, a slightly higher adjustment may be appreciated in the FD vs β stiffness index linear relationship.

| Parameters | Linear correlation index (r) | P         |
|------------|------------------------------|-----------|
| DF_P vs β  | 0.96                         | <0.01     |
| DF_P vs CA | 0.82                         | <0.05     |
| DF_P vs E_P| 0.83                         | <0.05     |
| DF_D vs β  | 0.96                         | <0.01     |
| DF_D vs CA | 0.84                         | <0.05     |
| DF_D vs E_P| 0.81                         | <0.05     |
| DF_P,D is the arterial pressure and diameter Fractal Dimension, respectively, AC is the arterial compliance, E_P is the Peterson’s Modulus, β is the stiffness index. |

4. Discussion

The purpose of this study was to process arterial aortic pressure and diameter time series, in order to evaluate the relationship between arterial stiffness and fractal dimension estimation. FD was applied, as a non-linear measure, due to the presence of self-similarity, revealed by the evaluation of the WTMM. 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 the calculation of arterial compliance, arterial distensibility and β stiffness indices.

As was previously referred, FD values appeared to be larger in arterial pressure than in diameter time series, for all performed experiences. Accordingly, the phenomenon may be explained based on stress-strain (pressure-diameter) relationship, that implies a filtering effect of high frequency vibrations, generating a loss of detail in morphology waveforms (elimination of an amount of self-
similar scales). In addition, both arterial pressure and diameter FD showed a decrease value in accordance to the rise of the mean blood flow. The foregoing might be justified by the fact that the loss of arterial vessel distensibility (or the stiffness increase) precludes fractal manifestations whereas its influence on the content (blood flow) denotes a similar behaviour when arterial pressure signals are analysed. It can be also observed, that the difference between FD values of pressure and diameter time series is higher at low mean blood flow values. An explanation could be that at higher flow rates, dumping function of arterial wall is affected mainly to the activation of smooth muscle cells. The low rate of change of FD values observed after mean blood flow exceeded 120ml/min, could be justified by the same reason.

Another observation to be highlighted is the high correlation index obtained between FD estimation and $\beta$ index regression analysis. An explanation might be found, based on the assumption of a linear stress-strain relationship, evidenced in the AC and $E_p$ assessments. $\beta$ index considers a non-linear (exponential) relationship, as the one observed in pressure and diameter curve, more in accordance with the known biological phenomena.

To conclude, numerical/mathematical cost of implementing FD estimation should be taken into account, in comparison with a linear clinical index assessment, widely used and validated. The revenue consists of information provided by the FD estimation, concerning waveform morphology, where significant manifestations associated to the vessel response might be obtained. Regarding the latter, a future study could quantify the degree of linkage between FD and elastic and viscous properties of the arterial wall as well as the individual contribution of each component to the self-similarity property. Such an approach might reduce the existing divergences between experimental data and linear models, essentially due to the non-linear presence in the stress-strain relationship.

5. Conclusion
Fractal characterization of arterial pressure and diameter time series and its linkage to the stress-strain relationship has not been previously documented in literature. As a result, FD references related to arterial stiffness have not been mentioned either. From the expressed results, the existence of a significant trend given by the wall arterial behaviour and morphology acquired by the time series could be inferred. The latter could be quantified by the application of non-linear analysis, as the one provided by fractal geometry. The relationship between estimated FD values of arterial pressure and diameter signals might be able to differentiate local/global arterial stiffness states, improving the information provided by linear-models based estimations.

One of the possible applications of the results of the present work in the near future is to include the calculus of the fractal dimension of the pressure signal acquired with Doppler velocities devices with the aim to estimate a measure of the systemic status of a particular circulatory system.

It is worth noting, that FD estimation requires a specific level of detail of the signal involved, in order to be able to quantify the complete self-similarity degree and to prevent certain fractal manifestations to be ignored. In this sense, sampling rate during data acquisition plays a major role and should not be underestimated. Even more, special consideration should be taken, if a similar analysis is to be implemented in non-invasive measurements obtained in vivo, which frequently do not have the appropriate resolution.

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