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Fractal and euclidean geometric generalization of normal and restenosed arteries

***Javier Rodríguez[1], Signed Prieto[2], Catalina Correa[3], Fernando Polo[4], Yolanda Soracipa[5], Vanessa Blanco[6] and Andrés Rodríguez[7]**

[1]MD, Insight Group Director. Fundación Universitaria Ciencias de la Salud. Research Center, Clínica del Country.
[2]Insight Group Researcher. Fundación Universitaria Ciencias de la Salud. Research Center, Clínica del Country.
[3]Insight Group Researcher. Fundación Universitaria Ciencias de la Salud. Research Center, Clínica del Country
[4]MD. Pathology Research Group Director. Fundación Universitaria de Ciencias de la Salud
[5]Insight Group Researcher. Fundación Universitaria Ciencias de la Salud. Research Center, Clínica del Country
[6]Student of IX Semester, Faculty of Medicine, Fundación Universitaria de Ciencias de la Salud
[7]Student of VIII Semester. Faculty of Medicine, Fundación Universitaria de Ciencias de la Salud

*Corresponding Author E-mail: grupoinsight2025@yahoo.es

Abstract

Euclidean geometry characterizes regular objects, while fractal geometry studies irregular objects. Building on previous work, it will be developed a generalization of all normal and diseased arterial prototypes in experimental models of restenosis in porcine based on fractal and euclidean measures. Fractal dimension and number of spaces occupied by parts and the whole in the generalized Box Counting space were evaluated in 10 normal and 10 restenosed arteries. Based on these spatial limits, it was developed a computer simulation of all the possibilities of spatial occupation of the layers (islands), determining all the possible arterial prototypes. The normality presented values below 100 on the surface of its three islands, while restenosis presents values equal to or greater than 100 in at least one of its three islands. The generalization makes possible to determine a total of 44267 arteries: 36770 restenosed and 7497 normal. The geometric self-organization of the parties with respect to the whole artery, assessed by fractal and euclidean simultaneous measures, allows to determine a finite number of fractal arterial prototypes. It makes possible to differentiate restenosis and normality, as well as quantifying their evolution; so its implementation could reduce costs in experimental models.

Keywords: Coronary arteries; stenosis; restenosis; fractal geometry; euclidean geometry.

INTRODUCTION

The World Health Organization reports that cardiovascular disease is the leading cause of death. Reports in 2008 show that about 17.3 million people have died from this disease, which represents 30% of all deaths in the world (WHO, 2013). It is estimated that by 2030 around 23.6 million people may die for the disease (PAHO, 2012). In the U.S. there are about a million heart attacks each year and coronary artery disease is responsible for one in six deaths (Liang et al., 2013). For this reason it is necessary to develop methodologies that provide a timely solution to this public health problem.

Coronary restenosis is a condition caused as a result of the implementation of techniques designed to restore the vessel wall in estenosis cases (Echeverri and Pineda, 2007). This term can describe variety of conditions, such as neointimal hyperplasia, arterial narrowing, or recurrence of signs and / or symptoms of ischemia after angioplasty (Echeverri and Pineda, 2007). For prevention there are designed multiple therapies, pharmacological, mechanical and biological, whose usefulness is evaluated in experimental models of restenosis (Echeverri, 2002), which are commonly assessed by euclidean measures, and analyzed using statistical procedures (Echeverri, 2002; Schwartz et al., 1992). The way to measure a physical quantity is diverse and is closely related to the purpose you have to make the measurement. Euclidean geometry is designed to measure straight lines and regular curves; fractal geometry instead originates from the impossibility of making a reliable euclidean measure in irregular objects (Mandelbrot, 2000; Mandelbrot, 1967) such as the human body (Luzi et al., 1999). There are three types of fractals: the abstract fractal (Peitgen et al., 1992a) whose fractal dimension is measured by the Hausdorff dimension, the statistical fractal, whose complexity is calculated by Zipf/Mandelbrot's law (Rodríguez, 2005), and the wild fractal whose fractal dimension is calculated from the box-counting method (Peitgen et al., 1992b).

Many works have been developed in medicine looking for differences between normality and disease, which could be useful as diagnostic support tools. For example, methodologies have been developed to differentiate neoplastic and non-neoplastic states of mammographic images, reducing the number of false positives (Pohlman et al., 1996; Lefebvre and Benali, 1995). However, many studies show that taking the fractal dimension as the only parameter of evaluation may be insufficient to establish diagnostic differences (Rodríguez et al., 2002, 2012a).

Applying fractal geometry and the concept of Intrinsic Mathematical Harmony, in an experimental model of restenosis (Rodríguez et al., 2002), it was developed a methodology that evaluates the fractal dimensions of the parts and the arterial whole of porcine, based on the concept of IMH, allowing to differentiate normality and restenosis. This methodology was subsequently taken to the context of a generalization, which set out all possible arterial prototypes for both states, based on a simulation of the arterial remodeling process (Rodríguez et al., 2010a). This simulation consisted of progressive spatial modifications of the islands of the arteries in the generalized Box Counting space, which is an abstract space consisting of two grids where the sides of the squares of a grid are twice that of the other. So, all possible arteries were obtained from normality until the total lumen occlusion, in the context of fractal geometry, achieving mathematical objective and reproducible results that make unnecessary to use large samples, decreasing costs and resources. Recently it was developed a methodology that differentiates normal and abnormal erythrocytes by the simultaneous use of euclidean and fractal geometry, obtaining measurements of the edge and the surface of the erythrocyte, useful for determining the viability of transfusion bags (Correa et al., 2012).

The purpose of this research is to determine the total arterial prototypes based on the simultaneous application of fractal and euclidean geometry, making a mathematical differentiation between all possible normal and restenosed arterial structures, useful for the evaluation of experimental models of restenosis.

Definitions

Fractal Dimension

Numerical measure which establishes the irregularity degree of a fractal object. In the case of wild fractals as the arteries, the Box Counting fractal dimension is used.

Fractal dimension of Box-Counting

It is defined by the equation 1 (Mandelbrot, 2000), Where the number of squares containing the outline of the object is represented by N; the grade of partition of the grid by K and the fractal dimension by D.

$$D = \frac{LogN(2^{-(K+1)}) - LogN(2^{-K})}{Log\,2^{K+1} - Log\,2^{K}}$$

$$= Log_2 \frac{N(2^{-(K+1)})}{N(2^{-K})} \quad \text{Equation 1}$$

Island

Mathematical object defined based on the limits of the arterial layers (Rodríguez et al., 2002, 2010a):

- Island 1 (I1): limited by the contours of the lumen and the external elastic lamina.
- Island 2 (I2): limited by the contours of the external elastic lamina and the adventitia.
- Total Island (TI): limited by the contours of the lumen and the adventitia.

Intrinsic Mathematical Harmony (IMH)

It measures the degree of similarity or difference between the units and the significant ciphers of the fractal dimensions of Islands 1, 2 and Total (Rodríguez et al., 2002, 2010a).

Surface of the Islands

Surface of the Islands is defined as the number of Interior pictures more than the outline of each of the measured objects (I1, I2, and TI), measured with the grid of 20 pixels in the generalized Box - Counting space.

MATERIALS AND METHODS

10 images of histological slides of normal arteries and 10 of arteries with restenosis were taken, along with the values of fractal dimension of their islands (see definitions), from previous studies made in the Fundación Cardio Infantil.

Additionally it was performed the measurement of the occupation spaces of each island surface in the Box Counting generalized space, formed by two grids with 20 and 40 pixels respectively, determining the spatial occupation limits of normal and restenosed arteries. When one of the layers is broken, the minimal connection between the two points of breaking is taken as a part of the edge, for performing mathematical calculations. So, arteries with any degree of injury were taken, regardless if the layers are broken or not.

A Software in C + + language was developed, which simulates the arterial deformation from normality to the total occlusion of lumen, by varying the spatial occupation of the islands. It was made based on the maximum and minimum values of spatial occupation found for surface of each island in both the normal arteries and the restenosed ones. It made possible to obtain all possible combinations of geometric space occupation of the island surfaces, where each combination was denominated as a prototype.

Since this methodology, each arterial prototype is described by a specific number of spaces occupied by each of its islands, restricted to the minimum and maximum limits of the islands of the arteries experimentally measured. Thus it is possible to determine all possible prototypes arterial, besides the difference in the assessment of restenosis is quantified by the increase in space occupation of the islands.

Mathematical analysis

For each prototype, it was calculated the fractal dimension of each one of its islands, mathematically determining the state of normality or restenosis based on the previously established concept of IMH (Rodríguez et al., 2002, 2010a), comparing the state established using the methodology based on spatial occupation of the islands, developed in this paper, regarding the results of the past work, based on the fractal dimension of the edges of these islands.

The measurements obtained from arteries evaluated in previous studies (Rodríguez et al., 2002, 2010a) were compared with the obtained prototypes, in order to determine the ability of the method to simulate any possible experimental artery. For this, it was established whether the measurements corresponding to these arteries were contained within the prototype set.

Since the developed software simulates the process of arterial remodeling to occlusion of lumen, it is unnecessary to make repetitions of the experiment or statistical analysis of the results obtained in order to check the ability of generalization to include any artery experimentally possible.

Being primarily a mathematical work, based on data-bases collected previously, this study does not affect animals or patients, because their results does not affect clinical decisions. For this reason it is cataloged under the category of research without risk, complying with the ethical, scientific and technical standards of Article 11, resolution 008 430 1993, from the Health Ministry of Colombia, for health research.

RESULTS

The surfaces of the islands of the arterial prototypes occupied between 27 and 167 spaces; the normal arteries ranged between 27 and 96, and the restenosed ones between 79 and 167. The results showed that normality is characterized by values less than 100 on the surface of its three islands at the same time, while the restenosis is characterized by values equal to or greater than 100 in at least one of its three islands (see tables 1 and 2).

Through the execution of the software based on the experimentally defined limits from the 20 measured arteries, it was found that the fractal dimension values for prototypes with restenosis varied between 0,3683 and 2 for the Island 1 (I1); between 0,1500 and 2 for the island 2 (I2); and between 0,1926 and 2 for the total Island (TI). For normal prototypes the fractal dimensions varies between 0,3683 and 2 for Island 1 (I1); between 0,3037 and 2 for the island 2 (I2); and between 0,3312 and 2 for the Total Island (TI) (see tables 1 and 2).

Analyzing the fractal IMH of the arterial prototypes obtained, it was found that normal arteries present similarities in the simultaneous comparison between I1-I2, I2-TI, and I1-TI at least in the second significant cipher, while restenosed arteries did not meet such feature, confirming the results of the preliminary investigation (Rodríguez et al., 2002, 2010a).

44267 arterial prototypes were found based on the

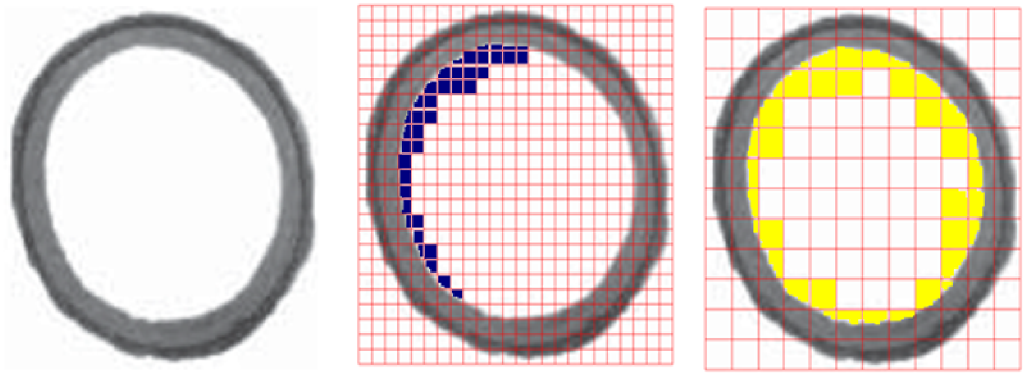

Figure 1. Simulation of the progressive spatial occupation of arterial lumen, based on increase of the spatial occupation of island 1. Left image corresponds to one of the original images taken to do the simulation; middle image is a simulation on the 20 pixel grill and right image corresponds to a simulation on the 40 pixel grill.

Table 1. Fractal dimension and surface of ten sick prototypes obtained from the sick arteries simulation based on IMH.

Prototype	IMH			Fractal Dimension			surface		
	I1	I2	TI	I1	I2	TI	I1	I2	TI
E1	1	2	1	0,8301	0,9551	0,8643	105	103	164
E2	1	1	2	0,9730	0,8745	0,8532	94	85	149
E3	0	2	0	1,0000	0,8769	1,0205	105	109	164
E4	0	1	0	1,1623	0,9798	1,0000	88	79	143
E5	0	2	0	1,0231	0,9275	1,0418	104	105	163
E6	1	1	1	0,7807	0,9014	0,8171	108	107	167
E7	1	1	2	0,8382	0,7901	0,7447	100	91	155
E8	1	1	2	0,9234	0,8443	0,8136	96	87	151
E9	1	0	0	0,5961	0,9048	1,0199	106	96	166
E10	0	0	1	1,0286	0,9069	0,8969	92	83	147

developed simulation, 36770 corresponding to disease prototypes including stenosis and restenosis, and 7497 corresponding to normal prototypes (see Figure 1).

Finally, it was found that the arteries previously evaluated by Rodríguez et al. (2002, 2010a), were included within the simulated prototypes. This confirms the competence of the developed methodology to simulate any artery (see Table 1 and 2).

DISCUSSION

This is the first work in which from the simultaneous application of fractal and euclidean geometry is achieved to generalize all possible arterial prototypes differentiating normal and disease states, useful in experimental models of restenosis in porcine. The evaluation of the spatial occupation of the islands surface in the generalized space of box counting allowed to mathematically differentiate between normal and restenosis and quantifying the evolution of restenosis. This is possible through the evaluation of the increase in the number of spaces occupied by the islands, which correspond to arterial layers, regardless of descriptive classifications of the stenosis or restenosis degree.

The 20 arteries on which this paper is based were chosen because they presented clear characteristics of both normality and different levels of restenosis, thereby such characteristics allow the development of this generalization. The variations in the spatial occupation of the simulated islands in the universal space of Box-counting allow to mathematically establishing a finite number of arterial prototypes, whereby the empiric limits used can be changed without affecting the underlying

Table 2. Fractal dimension and surface of ten normal prototypes obtained from the normal arteries simulation based on IMH.

Prototype	IMH			Fractal Dimension			surface		
	I1	I2	TI	I1	I2	TI	I1	I2	TI
N1	3	3	3	0,9313	0,9359	0,9344	61	66	82
N2	2	2	3	1,0614	1,0566	1,0589	27	30	46
N3	2	2	3	0,7447	0,7590	0,7521	41	44	60
N4	3	3	3	0,9005	0,9069	0,9048	63	68	84
N5	2	2	2	0,6374	0,6549	0,6464	49	52	68
N6	2	2	3	0,5406	0,5594	0,5502	59	62	78
N7	3	3	3	0,8717	0,8797	0,8771	65	70	86
N8	2	2	2	0,5575	0,5762	0,5670	57	60	76
N9	2	2	3	0,7521	0,7655	0,7612	75	80	96
N10	2	2	3	0,8447	0,8541	0,8511	67	72	88

order of the generalization.

This work is based in a previous one, in which a generalization of the totality of arterial prototypes was developed using the concept of Intrinsic Mathematical Harmony (Rodríguez et al., 2010a). Such work is based on the fractal measurements of the islands borders in the box-counting space; however it is limited in the fact that the IMH concept does not enable to differentiate states of major or minor severity in the restenosis process. This work confirms the capacity of the IMH concept to differentiate normality from restenosis, and builds a new generalization, based in the spatial occupation of the islands surface in the Box-counting space, thus overcoming the previous work. With this new generalization it is possible not only establish differentiation between normality and sickness, but also to show the restenosis advance based in the increase of the spatial occupation of the islands. Both works are based in searching simple mathematic relations among the parts and the totality of the objects, simplifying the complexity of the phenomena under study. This kind of methods, based in the search of generalizations and the use of fractal and euclidean simultaneous measures can be used to study diverse phenomena in medicine, decreasing the number of needed samples for the studies and making unnecessary the use of statistics methods. In this specific case, the establishing of the total of possible arterial prototypes can be useful to diminish the sacrifice of animals in experimental models of restenosis.

The conception with which restenosis is conventionally studied is based on euclidean rules or related to them. For instance, Lafont et al. (1997) found the index of vascular remodeling through an approach with euclidean figures such as the circle, with the aim of finding measures of barotrauma response. However, euclidean measures applied to irregular objects lead to paradoxical results (Schwartz et al., 1992). Instead, simultaneous application of fractal and euclidean measures leads to get objective and reproducible measures of arterial layers, just as it had been found diagnostic measures of red blood cell (Correa et al., 2012). This is evidence of the potential of the simultaneous applying of both types of measures in experimental and clinic fields.

The physical-mathematical approach to the analysis of medical phenomena has permitted to establish diagnostic and predictive methodologies in areas such as cardiology (Rodríguez, 2010b, 2011a; Rodríguez et al., 2010c, 2012b); the infectious diseases, where it was developed a prediction of CD4 count from leukocytes and lymphocytes (Rodríguez et al., 2012c, 2013a); immunology (Rodríguez, 2008); molecular biology (Rodríguez et al., 2010d) and predicting epidemics (Rodríguez, 2010e). Specifically looking for generalizations, works have been developed that establish all possibilities of phenomena in other fields of medicine. Such is the case of the setting of all possible cardiac dynamics, based on an exponential law, which differences normality, disease and evolution between them (Rodríguez, 2011b; Rodríguez et al., 2013b). Also a methodology was developed that allows to establish the total number of possible cells from normality to carcinoma, differentiating normality from disease, and mathematically clarifying the indeterminacy of ASCUS cells in cervical cytology, establishing if it has similar values to normal or disease (Rodríguez et al., 2010f). These works, just as the present investigation, show that the medical phenomena of can be simplified and understood being studied from a physical-mathematical perspective, providing solutions for clinical and experimental use, as well as in decision-making in public health.

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Competing Interests

The authors declare that they have no competing interests.

DEDICATION

To our children.

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