ORIGINAL RESEARCH

Characterization of aortic valve stenosis by mathematical modelling of the reflectance spectroscopy

Katia C. Rodrigues[1], Renato A. Zângaro[2], Adriano O. Andrade[3], Marcio Magini[4]

1. Universidade Federal de Pernambuco, Centro Acadêmico do Agreste, Caruaru, Brazil. 2. Universidade Camilo Castelo Branco, São Jose dos Campos, Brazil. 3. Universidade Federal de Uberlândia, Centro de Ciências Exatas e Tecnologia, Laboratório de Engenharia Biomédica. Campus Santa Mônica, Uberlândia, Brazil. 4. Universidade Federal Fluminense, Polo Universitário de Rio das Ostras, Departamento de Física e Matemática, Rio das Ostras, Brazil.

Correspondence: Marcio Magini. Address: Polo Universitário de Rio das Ostras, R. Recife s/n, Jardim Bela Vista, Rio das Ostras, Rio de Janeiro, 28890-000, Brazil. Telephone: 00-55-2764-9037. Email: marcio.magini@pq.cnpq.br.

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Abstract

Background: The stenosis of the aortic valve is a consequence of an increased thickness and disorganization of the collagen fibre network and extracellular matrix, plus the deposits of calcification in the layers of the valve. These characteristics are known to affect the diffuse spectral reflectance of the tissue.

Objective: The main focus of this work is to propose a model for the aortic valve reflectance whose parameters can be employed as features capable of discriminating distinct levels of tissue thickness and disorganization.

Methods: The data obtained from aortic valve reflectance show a S-type curve. Therefore, the modeling hypothesis is that the aortic valve stenosis generates a sigmoidal behavior at the reflectance spectroscopy. The mathematical modeling was obtained by a sigmoidal approaching and Euler methodology applied.

Results: The results show the successful application of the model in the investigation of heart valve tissues with distinct characteristics.

Conclusion: The solutions of this equation define parameters that can be interpreted quantitatively helping to discriminate the stenosis process in aortic valve predictable for different cases proposed in this study.

Key words

Reflectance modeling, Sigmoidal modelling, Aortic valve reflectance, Aortic valve Stenosis, Reflectance spectroscopy

1 Introduction

Diffuse reflectance spectroscopy is considered a simple technique to study and characterize biological tissues. The light focuses on the tissue through elastic scattering and absorption generate unique information regarding the subject before the study [1]. This technique can also give real time information with enough trust free of subjective interpretations, usually results from such techniques.

The normal aortic valve is composed of elastin-rich fibers that are aligned in a radial direction, perpendicular to the leaflet margin, fibroblasts and collagen fibers arranged circumferentially, parallel to the leaflet margin, and connective tissue at the base of the leaflet [2]. The extracellular matrix maintains the spatial relationship of the cells, which contribute to the physical properties of valve tissue, providing tensile strength and pliability for decades of repetitive motion [2, 3]. However, the stenosis of aortic valve is characterized by increased thickness, disorganization of the collagen fiber network and the extracellular matrix, and the deposits of calcification in the layers of valve [4]. These alterations on morphological structures are known to affect the diffuse spectral reflectance of the tissue and turn on the diffuse reflectance spectroscopy a powerful technique to study aortic valve stenosis [5]. The main consequence of aortic valve stenosis is the reduction of the orifice into a small opening due to calcium deposits which thicken the valve and cause cusp stiffness and decrease the aortic valve area [2]. Currently, the most effective treatment is the aortic valve replacement. The mechanical prosthesis is more durable but must be used simultaneously with drugs as anticoagulants to restrain thrombosis and the embolism. Therefore, the biological prostheses are preferred, but they are less durable and usually need to be replaced [6]. This makes necessary a successful tissue engineering that not only accommodates deformations but also has ongoing strength, flexibility, and durability, beginning at the instant of implantation and continuing indefinitely thereafter, possibly despite evolving tissue architecture [7].

More recently, pathologic processes of ectopic aortic valve calcification were reviewed and a working hypothesis is that calcific aortic valve stenosis involves active processes similar to those that occur in atherosclerotic arteries, including inflammation and lipid infiltration [2, 8]. Most studies rely on categorical scoring systems derived from echocardiographic valve morphology, including mathematical models [8-10]. The reflectance spectroscopy can contribute by verifying and quantifying fibrous thickening and calcification formation in supporting heart valve tissue engineering studies. However a quantitative interpretation of the calcification process can be useful to predict the essence of the cellular behavior in this situation and may contribute to understand in general way the parameters that influence positively or negatively this process.

The reflectance experiment provides an interesting behavior, it approaches to sigmoidal curves. It was not a surprise these results, many adjustments using curves sigmoid is already well used in many scientific fields, especially in artificial neural networks [11], biomathematics [12], economic and environment studies [13]. This type of curve has a crucial aspect that is related with the fact that biological systems respond as capacitance versus tension curves when submit to some radiation. This work developed a mathematical methodology to model experimental data obtained by reflectance spectroscopy using a differential equation as main measure the reflectance as wavelength function. The sigmoid curve parameters are adjusted by the different characteristics of the tissue given clues about how this process occurs quantitatively, generating, as consequence, the possibility to introduce this interpretation to understand how this biological process happens.

2 Material and methods

2.1 Diffuse reflectance spectroscopy data collection

The same aortic cusp can present areas of normal and abnormal tissue. Some specific points in an aortic cusp were chosen, by macroscopic presence of normal (thinner), fibrous (thicker), or calcified (nodule) tissue, as samples. A normal tissue presents mild severity of thickening, opaque and non-yellowed aspect, a fibrous tissue is characterized by a moderating thickening tissue and light yellowed aspect, the calcified tissue has severe thickening and strong yellowed aspect and presents calcified nodule. The samples were stretched over a black and opaque table to obstruct reflectance from sample holder. A total of 35 samples (specific points) of aortic valve were investigated, 8 normal, 16 fibrous and 11 calcified. These samples were analyzed using an appropriate fibre optic probe (FOP). The FOP has a diameter of 1.0 mm with a circular arrangement of six light collecting optical fibres of 200m diameter around one identical, central excitation fibre (see details of the 6 around 1 configuration FOP in Figure 1).

The reflectance system, showed in figure 1, is composed of a white light flash lamp (krypton lamp, flashtube Model FX 1160 Perkin Elmer, USA) with a power supply of 15 V and 50 mA. The flash lamp pulses were generated by a pulse generator (Philips, model PM5705) with pulse amplitude of 3 V and width of 50 ms. The reflectance intensity of any point was obtained by summing up the response of 30 pulses of the lamp over the point. The reflected light collected by the FOP was coupled into a ¼ m spectrometer (Oriel Instruments MS257). Appropriated lens were used to couple the flash lamp pulses into FOP and the collected signal into spectrometer. An intensified CCD (Charge Coupled Device) with 256×1024 pixels was connected at the monochromator detector port. The specified CCD gating capability was 5 ns. The CCD gating and time delay were controlled by a model DG535 delay generator, from Stanford Research. The wavelength calibration was performed by using a 632.8 nm He-Ne laser, and Hg-Cd-Zn spectral lamp, and the intensity calibration was performed by the reflectance of white Teflon.

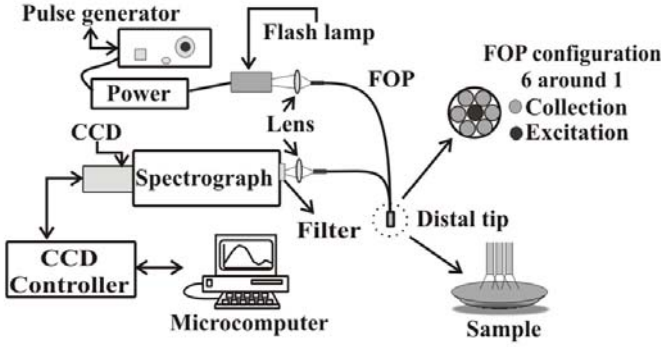

Figure 1. Block diagram of the reflectance system

Diffuse reflectance was measured by illuminating and collecting light at wavelengths ranging from 300 to 600 nm. The data were obtained on a 0 to 100% reflectance scale; all spectra were normalized for 30% at 425 nm and smoothing with adjacent averaging of 100 points with the Microcal(TM) Origin 6.0 (Microcal Software Inc., Northampton, MA) software package.

2.2 Strategy for data modelling

Firstly, the reflectance model proposed in this work was defined as in Eq. (1) applying Euler methodology [14] for solving ordinary differential equations (ODEs),

$$R(\lambda)_{n+1} = R(\lambda)_n + h \cdot \frac{dR(\lambda)_n}{d\lambda_n} \tag{1}$$

where, R is the reflectance of the sample as a function of the wavelength (λ), λ is the reflected wavelength by the sample, h is a step size and its value was the same as that for the wavelength interval between experimental data points ($h = \lambda_{n+1} - \lambda_n$), and n is the number of points of the modelling curve. Note that any point of this curve was estimated by the Euler method and the number of points of modelling curve is the same of the number of points of experimental curve, 680 points. The term $\frac{dR(\lambda)_n}{d\lambda_n}$ was defined as a sigmoidal function. This choice is supported by the fact that the data obtained from aortic valve reflectance show a curve having an S-type peculiar of a sigmoid function *f(x)* showed in (2).

$$f(x) = \frac{1}{1+e^{-\lambda x}} \tag{2}$$

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The sigmoidal function proposed for modelling the reflectance of aortic valve in this work is the composition of sigmoidal curves as in (3),

$$\frac{dR(\lambda)}{d\lambda} = \frac{f_r}{1+\exp[-k_1(\lambda-\lambda_a)]}\left[1+\exp\left(-\left(\frac{\lambda-\lambda_b}{d}\right)^2\right)\right]\left[\frac{1}{1+\exp[k_2(\lambda-\lambda_c)]}\right] \quad (3)$$

where f_r is the reflectance factor of the sample; k_1 and k_2 are adjust constants for curve inclination; λ_a is the wavelength that defines the initial inclination moment of the first sigmoid curve; λ_b is the wavelength at the centre of the curve, it defines the point where the two sigmoid are linked, at this point the curve shows a steepness factor d, where first sigmoid finishes and the second sigmoid starts, and λ_c is the wavelength that define the inclination of the second sigmoid function.

The values of these parameters were defined in order to fit the model to experimental data obtained from the aortic valve tissue. The λ_a, λ_b, λ_c are estimated by the inflections points observed on experimental curve. The steepness factor d and the adjust constants, k_1 and k_2 are calculate approximately in order to fit the experimental data. The f_r is the parameter who gives the best approach to inclination of the experimental curve.

As the Euler method is an initial-value-problem (IVP) type, this means that the new value $R(\lambda)_{n+1}$ is defined in terms of the $R(\lambda)_n$ value already known. So it was necessary to define the function value and the point value in the first interaction. The values of $R(\lambda)_0$ and λ_0 were taken from the experimental data. The h value was defined by the wavelength step of the experimental system, which was 0.33 nm.

3 Results

Table 1 shows the f_r, k_1, k_2, λ_a, λ_b, λ_c *e* d, values, from equation (2), defined by a */9-reflectance spectral curve approach, for normal, fibrous and calcified tissues. These parameters were obtained from the experimental data producing the starting point for the theoretical model.

Table 1. Parameters obtained by an approach of experimental curve

Parameter (unit)	Tissue Type		
	Normal	**Fibrous**	**Calcified**
f_r	0.022	0.26	0.44
k_1(nm^{-1})	0.025	0.05	0.09
k_2(nm^{-1})	0.5	0.045	0.09
λ_a (nm)	380	385	400
λ_b (nm)	505	505	505
λ_c (nm)	570	578	577
d (nm)	2	0.5	2

The sigmoidal data were obtained solving the equation numerically, assuming the step (h = 0.33) and $R(\lambda_0)$ as the first point of experimental data. Both, sigmoidal and experimental reflectance curves are presented in Figure 2 in three cases: normal tissue (i), fibrous tissue (ii) and calcified tissue (iii); for this, parameters from Table 1 were used.

The reflectance factor, f_r , is mainly responsible for the sigmoidal function fitting. Figure 3 show six curves of sigmoidal function with different f_r values. To construct these curves the follows values were assumed: k_1 = 0.07 nm^{-1}; k_2 = 0.07; λ_a = 390 nm; λ_b = 505 nm; λ_c = 575nm and d = 2 nm.

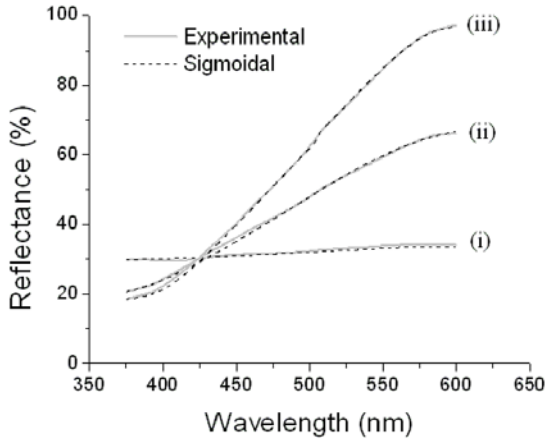

Figure 2. Reflectance experimental curve and sigmoidal model fitting for normal tissue (i), fibrous tissue (ii) and calcified tissue (iii).

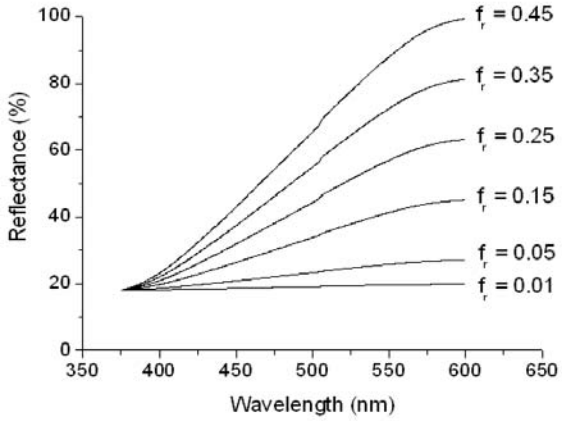

Figure 3. Sigmoidal fitting for different f_r values.

The results in figure 3 pointed this model for a predictable tissue behavior, by the f_r factor it is possible to know the reflectance spectrum produced by an specific stage of the progressive stenosis, the interpretation of these results will be discussed in the next section. The relation of the mathematical approach obtained from the fit of f_r values with the morphological aspects of different tissues as normal (i), fibrous (ii) and calcified (iii), is showed in Figure 4.

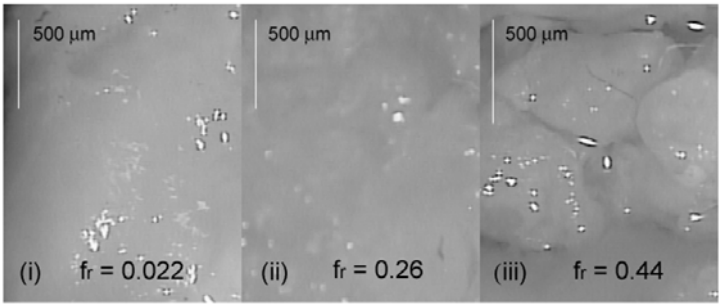

Figure 4. Correlation of f_r parameter and morphological aspects of normal tissue (i), fibrous tissue (ii) and calcified tissue (iii).

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4 Discussion

The results show how the behavior of parameters proposed in the mathematical model is well related with the experimental data, showing a predictive ability of the proposed model. The behavior of the reflectance is directly affected by a degenerative process that occurs on aortic valve tissue. Thus, the mathematical model proposed provides, essentially by the f_r parameter, the possibility for characterization of the different stages of aortic valve stenosis. The predictor character of a mathematical approach is a valuable instrument in complex systems. It may appear as different symmetries characteristics, or as distinct values of one specific variable [15, 16]. It can be seen in fibrous and calcified tissues a differentiated behavior, regarding the parameter reflectance at 425 nm, because the reflectance in green and blue regions is weakly affected by size of collagen fibres [5], one of the main components of aortic valve tissue. This behavior was predicted by the model, besides, through the model it can be observed small differences in the tissues to lower values of the wavelength. This result may help on the characterization of the degenerating process that occurs at the aortic valve tissue.

In accordance with the experimental spectra obtained, the reflectance spectra from tattoo phantom, under skin phantom or under typical pig skin [17] present the same S-type fit. From colon [5] and from bone [18] they include the characteristic absorption peaks of hemoglobin at 542 nm and 576 nm [19], despite that, they have the same S-type fit. However, when a simulation was applied in these studies, the Monte Carlo was the selected model. In our study the results show that the points calculated with the mathematical approach proposed from equation 2, follow the same general trend as the experimental data. The approach for different tissues may be considered the same initial condition, despite the reflectance factor, f_r, as show in Figure 3 that defines tissue characteristics.

From these results it is possible to reproduce all different stages of aortic valve stenosis, since the normal tissue passes by different stages of fibrous and calcified tissues. The reflectance spectroscopy defines the tissue behavior in different degeneration stages and the proposed model defines which parameter can be used to understand this process. Specifically we believe that the reflectance factor, f_r is closely involved in the process of deposition of calcium in the tissue or the tissue characteristics which may lead to the calcification process.

The equation proposes in model the reflectance spectra of aortic valve tissue showed consistency when compared with the experimental results. The main contribution of the present work is to provide a mathematical instrument to characterize by means of the reflectance spectra the progressive aortic valve stenosis.

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