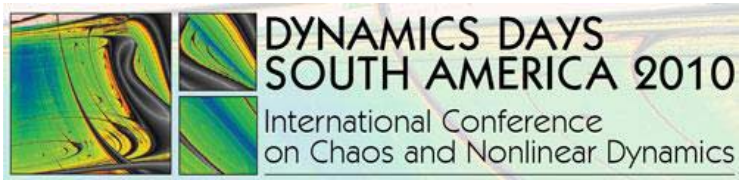

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Lacunarity as a Descriptor of Cellular Rejection in Myocardial Biopsies from Patients Submitted to Heart Transplantation

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Abstract: The present study describes an algorithm for quantifying patterns of cardiac cellular rejection in myocardial biopsies from patients submitted to heart transplantation. The model is based on Multiscale Lacunarity (ML). The algorithm also uses automatic multilevel thresholding with maximum entropy for image segmentation and confidence intervals in order to quantify cellular rejection groups. The results provide further information on cellular rejection and reveal the groups of patients that merit greater attention.

keywords: Lacunarity; Cellular Rejection; Myocardial Biopsies; Heart Transplantation.

1. INTRODUCTION

Many studies attempt to produce artificial visualization systems with the same efficiency as biological systems. This task remains highly complex, especially when implementing one of the more obvious problems – the quantification and qualification of information represented in a number of different fields. These difficulties are present in the evaluation of cardiac cellular rejection (CR), which has been standardized into four groups (R0 to R3) by the International Society for Heart and Lung Transplantation (ISHLT) [1]. For pathologists, there are features in each group, especially in R2, of tiny clusters of inflammation with one or two damaged cells or the presence of considerable infiltration with muscle cell lesions. As a result, a number of centers do not treat some patients and recommend monitoring with biopsies at intervals of one to two weeks. Therefore, CR remains a point of uncertainty, but offers data that can be studied with computational methods and models that are useful for minimizing the difficulties.

One possible solution is a computer program that can assist physicians in determining the diagnosis. The specificity and sensitivity required for a Computer Aided Diagnosis (CAD) applied in CR can be obtained if produced with methods that behave more like natural phenomena. One such method is the mathematics of fractals, particularly, lacunarity, which is a texture descriptor. The use of lacunarity is justified in [2], who found different patterns for different tissue conditions. The efficiency of lacunarity is enhanced when combined with one of the most interesting properties of objects in nature, which is the exhibition of different characteristics when observed on different spatial scales. This association is known as a multiscale fractal signature.

This paper presents an algorithm based on multiscale lacunarity to assess images of myocardial biopsies after heart transplantation in human patients and describe CR patterns. This method can provide more information and assist in supporting the diagnosis.

2. METHODS

The algorithm was developed with automatic multilevel thresholding and involves the methods of group histogram quantization, analysis of the percentage of histogram slope and the calculation of maximum entropy to define the threshold [3]. Thresholding based on maximum entropy is achieved from probabilistic calculations.

We consider an image as a result of a random process, where probability pi corresponds to the probability of a pixel in the image taking a value of intensity i (i = 1, .., n), as shown in (1); H is the entropy of the image; n is the total number of outputs; pi is the probability of gray level i being found in the image; n_i represents the number of pixels with intensity i; and N is the total number of pixels in the image. The gray level of the group indicated with the highest entropy is identified as a threshold.

$$H = -\sum_{i=1}^{n} p_i * \log p_i, \qquad p_i = \frac{n_i}{N} \tag{1}$$

Lacunarity was calculated with the Gliding-box method [4]. A cube of side r is placed on the top left corner of the image (S) and the number of points of the image is counted. This process is repeated for all rows and columns of the image, producing a frequency distribution of the mass of the image. This frequency distribution is then converted to a probability distribution Q (S,r), (2), determining the first (Z^1) and second (Z^2) moments of this distribution, (3). The lacunarity (Λ) is defined in (4).

$$Q(S,r) = n(S,r) / N(r) \tag{2}$$

$$Z^{(1)} = \sum SQ(S,r)$$
$$Z^{(2)} = \sum S^2 Q(S,r) \tag{3}$$

$$\Lambda(r) = Z^{(2)} / (Z^{(1)})^2 \tag{4}$$

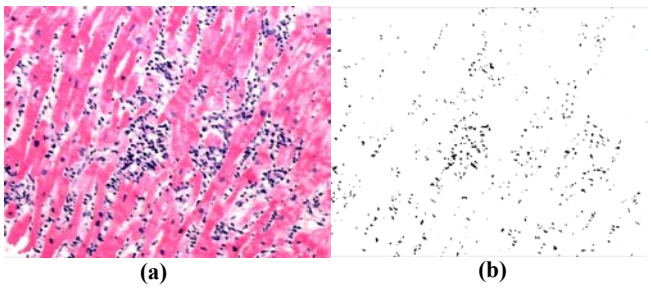
The algorithm was applied to 120 myocardial images from cardiac biopsies, separated into four groups: R0 (22 images); R1 (24 images); R2 (29 images) and R3 (43 images). The confidence interval (5) was used to ascertain the limits of each group. This approach can be an important descriptor of the behavior of each rejection class, from the perspective of the main parameters of the fractal geometry.

$$\overline{X} \pm Z \frac{S}{\sqrt{n}} \tag{5}$$

in which $\overline{X}$ is the sample mean; Z is the value obtained from the table of standard normal distribution (95%), S is the standard deviation; and n is the sample size.

3. RESULTS

The method was applied to myocardial biopsies from patients submitted to heart transplantation (Figure 1a). The cell core or tissue with rejection was segmented (Figure 1b) and analyzed using ML. Table 1 displays the data on the behavior of each group, along with the mean average and standard deviation (SD) for each degree and respective ranges. Figure 2 shown the behavior identified with the overlap found in each rejection group.



(a) (b)

Figure 1 - Example of R3 cardiac cellular rejection in myocardial biopsies from a patient submitted to heart transplantation (a); result of image processing (b), with cell core and tissue rejection separated.

Table 1 – Average Lacunarity for each CR group and respective 95% confidence intervals.

Parameters	R0	R1	R2	R3
Average	1.979	1.865	1.738	1.677
SD	0.14	0.088	0.14	0.17
Confidence Intervals				
Lower Value	1.903	1.819	1.670	1.611
Upper Value	2.056	1.911	1.806	1.743

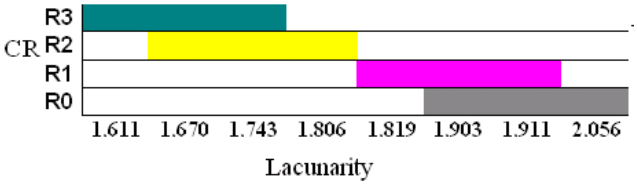


Figure 2 - Behavior of each CR group based on ML calculated on the basis of confidence intervals and their overlaps.

3. DISCUSSION AND CONCLUSIONS

Patients classified as R0 and R1, even with the overlap, did not demonstrate a progression toward more aggressive cellular rejection (R2 and R3) (Table 1 and Figure 2). This may indicate lower risk patients. Patients in groups R2 and R3 merit greater attention, as these cases have a higher probability of misclassification and there is the possibility of the development or reoccurrence of rejection. This quantification provides data that underscore the importance of greater attention at diagnostic centers that treat patients in the R2 group, as they may actually be in the R3 group or may progress to this group.

This paper presents a study on CR degrees from the perspective of lacunarity, which allowed identifying the groups that merit greater attention. Non-linear techniques, such as lacunarity, can provide important information for more effective treatment, thereby ensuring a greater survival rate among patients with heart transplants.

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