Evidences of Possible Necrotic-Core Artifact around Dense Calcium in Virtual Histology Images

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Abstract

Virtual Histology (VH) is a new medical imaging technique that allows the assessment of atherosclerotic plaque composition, a potential useful tool for the evaluation of individuals with coronary disease. Empirical observation has suggested that plaque areas adjacent to dense calcium (DC) are frequently coded as necrotic core (NC) in VH images. The main objective of the study was to evaluate whether the presence of DC induces an artifactual coding of NC in adjacent structures. To test this effect, a set of 89 coronary arteries segments have been analyzed in baseline and after stent implantation, which are coded as dense calcium into VH images. Necrotic tissue has risen significantly after stenting, especially in regions surrounding dense calcium structures, reinforcing the hypothesis of an artifactual relationship between those plaque components.

1. Introduction

Virtual Histology (VH) is a new medical imaging technique, based on intravascular ultrasound (IVUS) backscattered radiofrequency analysis, that allows the assessment of in-vivo atherosclerotic plaque composition [1]. For this, VH has been a potential useful tool for the evaluation of individuals with coronary disease. In its default output, VH provides a frame-by-frame assessment of the summed absolute and relative areas of all plaque components, which are divided into four classes – fibrous (FB), fibro-fatty (FF), necrotic core (NC) and dense calcium (DC) [2].

Some VH acquisition details have been useful to understand some procedures realized in this work. VH machine has an IVUS console inside and a PC, responsible for post-processing ultra-sonic data for plaque classification. IVUS data acquisition have been realized from a continuous pullback of the catheter at a velocity of 0.5mm/s, generating 10 frames per second which corresponds to a distance of 0.05 mm between two consecutives frames. However, VH images are ECG-gated resulting into an acquisition frequency of one frame per heart beat. As a result, the distance between two consecutive VH should not be extracted directly from their relative position from the pullback.

To solve this problem, temporal information from every VH image had been recovered for distance calculation as described in the next section.

Empirical observation has suggested that plaque areas adjacent to dense calcium are frequently coded as necrotic tissue in intravascular ultrasound Virtual Histology (IVUS-VH) images. The present study was conceived to evaluate if the co-localization of calcium and necrosis-coded pixels are due to artifact or not.

2. Methods

The main objective of the present study was to evaluate, in IVUS-VH images, whether the presence of calcium induces an artifactual coding of necrotic tissue in adjacent structures. We hypothesized that, in case the presence of dense calcium generates "false" necrotic tissue in its surroundings, any addition in calcium content would generate an artificial increment in the amount of necrotic tissue.

Since coronary stents are interpreted as dense calcium in IVUS and VH images, we use these implants to simulate the "addition" of calcium to the vessel wall in an attempt to check whether the increase in "calcium" content would be followed by an increase in necrotic-core area. After this, we have assessed the plaque composition at baseline (pre-PCI) and compared with the values obtained after stent implantation (post-PCI).

2.1. Study population

The present study prospectively included a group of 8 patients (9 lesions) who underwent successful single stent implantation (<30% residual stenosis with normal antegrade flow by angiography), for which high quality IVUS-VH examination was obtained at baseline and at the end of the procedure. All lesions were treated with the same stainless steel stent type (Apolo®, Cordynamic, Barcelona, Spain [strut thickness 0.0045"]). Patients with visible thrombus or intraluminal haziness at angiography, acute myocardial infarction < 48 hours or unstable angina with rest pain < 48 hours were excluded from analysis. The study protocol was approved by the local ethics committee and written informed consent was obtained from every patient.

2.2. Image processing tools

As our main goal is to evaluate a possibly artifactual relationship between the necrotic core and dense calcium components into VH images, we decided to compute the areas of connected pixels of both related plaque components. For this, mathematical morphologic operators have been used as described in the next paragraph. Algorithms have been developed in Java® using the ImageJ platform, an open-source image processing software which contains a set of classes implementing the major image processing techniques [3].

The first step was to identify all sets of confluent pixels, also named as *islands*, from each one of the four plaque components. For this, the VH images have been decomposed into four different binary images — red (necrotic core), white (dense calcium), light green (fibro-lipidic) and dark green (fibrous) — for further processing. A labeling plug-in — based on Suzuki's algorithm [4] — were implemented to identify the sets of islands into each VH frame and to extract their features for further analysis. As a result of this process, a RGB image has been created, where the pixels colors have the same value of the islands' labels, which is needed for future information retrieval.

The NC groups of pixels connected to DC were determined by means of morphologic operations over the binary masks. First of all, DC mask was dilated from one pixel and a logical AND operation was performed with the labeled NC mask and the dilated DC mask. After that, remaining colored pixels contains the label information of DC islands connected to DC and with these data; area of those related sets of pixels should be calculated, as shown in figure 1.

VH provides a results file which contains every component sectional area by frame and these informations have been used for measurements calibration process realized into VH images.

Temporal information from image acquisition has been available at the right top of every VH image. As the clock position has been known and its digits morphology also, a plug-in for automatically recovering and storing into VH results file has been developed.

The final stage consists on the division of stented region into subsegments of equal length. As previously described, the distance between two consecutives frames in VH depends of patient's heart rate. To avoid problems on segment division, acquisition time was read from each image and processed. For example, let's suppose that a segment had a total of 40 frames but time duration of 30 seconds. In this case, the segment was divided into 10 subparts of 3 seconds, which corresponds to 1,5mm of length. A loop read the clock of every image and includes it into a subsegment while its duration is smaller than 3 seconds. When a new image crosses this gap, the count restarted and a new subsegment created. After this division process, some average results are calculated for every subsegment which was submitted to statistical analysis.

3. Results

Baseline and post-stent implantation segments were analyzed resulting into 178 subsegments of 9 different arteries. Table 1 shows the differences between pre-PCI and post-PCI stages for average NC content and average DC content.

Table 1. Necrotic core and dense calcium findings for baseline stage (pre-PCI) and post-implantation stage (post-PCI) from all 178 subsegments in study.

Plaque Component	Average Area (mm^2) * Pre - PCI	Post- PCI	p **
Necrotic Core	$0,91 \pm 0,63$	$1,22 \pm 0,64$	<0,01
Dense Calcium	$0,40 \pm 0,53$	$1,06 \pm 0,59$	<0,01

* Notation: Mean ± Standard Deviation.
** Values from Paired Wilcoxon Rank Test

The differences described in table 1 were statistically significant according to the Paired Wilcoxon Rank Test. This test was used instead of Paired T-test by two major reasons: it's a non-parametric test and the analyzed data were not normally distributed. Both components have increased their areas but only DC increment was expected

as described previously in Methods section.

Stent implantation had never been described as a source of tissual necrosis or any similar process in the literature, especially in the first subsequent hours after the procedure. In face of this there was a potential indicator of an artifactual relationship between those related VH plaque components. Moreover, Spearman correlation coefficient (r) between variation of NC area and variation of DC area have been calculated — $r = 0.47$, $p < 0.01$ — and has shown a statistically significant association of these components.

Considering those results previously described, a depth investigation had been performed. Hypothetically, if there was an artifactual relationship between the NC (red pixels) and the DC (white pixels) in VH images, it would happen in the neighborhood of the white islands of pixels. Therefore the areas of NC islands connected to DC islands have been extracted from VH frames and computed for every segment, as shown in table 2.

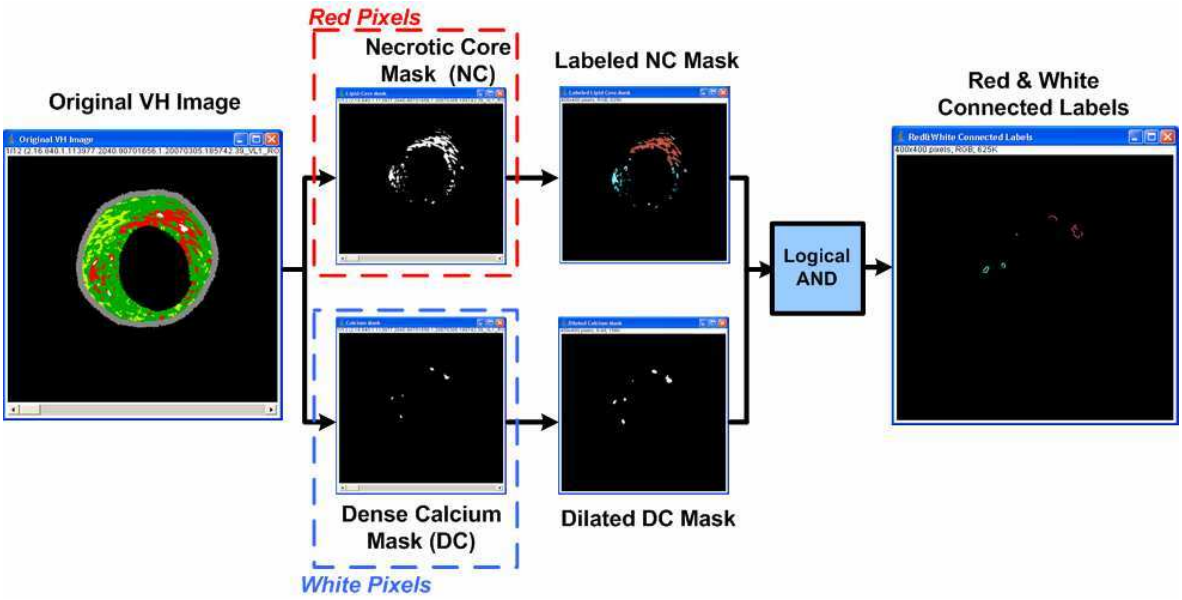

Figure 1: Block diagram describing the process of identification of NC islands connected to DC islands

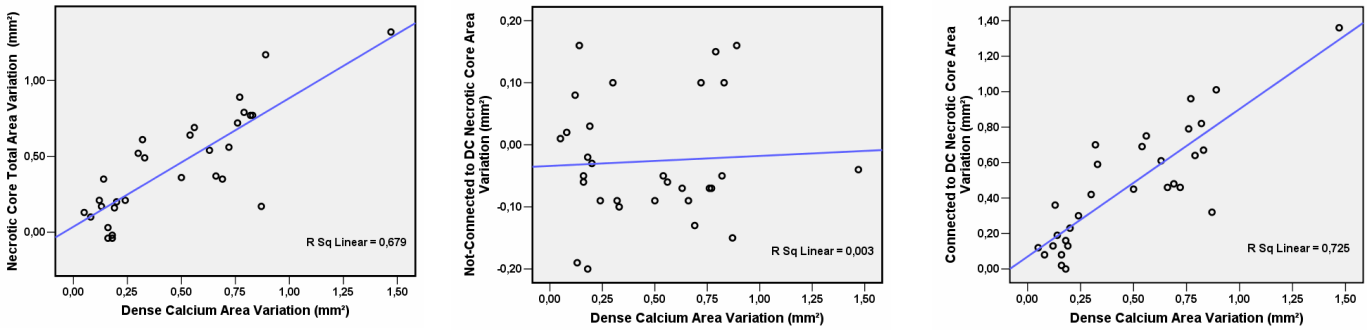

Figure 2: Graphs showing the variation of calcific component and the variation of necrotic component in every possible cases – total NC variation(left), connected to DC variation (middle) and not-connected to DC (right)

Results in table 2 have shown opposite effects suffered by necrotic core components after stent implantation. Differences between pre-PCI and post-PCI were statistically significant for both types of NC islands. Unlike not-connected to DC necrotic area has decreased, connected to DC area raised reinforcing the initial hypothesis of artifact. Conversely, not-connected NC reduction might be explained by a possibly tissual compression and/or longitudinal tissual dislocation caused by the high pressure in the stent deployment.

In order to reduce those effects cited in the last paragraph, a new analysis was performed, however, only subsegments containing low necrotic core area were considered. Frames with baseline higher than the

first tercile of necrotic core $(0.75mm^2)$ at baseline have been discarded, totalizing 30 segments. The graphs of figure 2 have shown a strong association between the NC variation and the DC variation after stent implantation, especially for the necrotic islands connected to calcific islands. However, not-connected NC variation has not correlated to DC variation, confirming the artifactual relationship between calcific component and necrotic component spatially connected.

Table 2. Pre-PCI and Post-PCI necrotic core average areas for connected and not connected to DC islands from all 178 subsegments in study.

Necrotic Core Islands	Average Area (mm^2) *		P**
	Pre - PCI	Post- PCI	
Connected to DC islands	0,65 ± 0,58	1,12 ± 0,64	<0,01
Not Connected to DC islands	0,26 ± 0,16	0,11 ± 0,09	<0,01

* Notation: Mean ± Standard Deviation
** Values from Paired Wilcoxon Rank Test

4. Discussion and conclusions

According to the displayed results, the main conclusions about the effects on the necrotic core content caused by the addition of dense calcium into VH images were:

1. Total NC average area has risen significantly and this variation was significantly correlated to DC variation caused by stent implantation;
2. Not-connected to DC necrotic core average area has decreased and was not significantly correlated to DC variation caused by stent implantation;
3. Connected to DC necrotic core average area has risen and was significantly correlated to DC variation caused by stent implantation;
4. An artifactual relationship between necrotic component and calcific component indeed exists, because there were not evidences in literature which describes tissual necrosis caused by stent implantation, especially on minutes after its deployment. In face of these arguments, the unique explication was a misclassification error or artefact on VH classification algorithm in regions with dense calcium.

Previous studies have already detected that the amount of necrotic tissue should be adjusted for the area of calcification in order to improve the association between IVUS-VH and clinical features [5]-[7]. Our findings are in line with these early studies, and, indeed, expand the understanding of the need for a correction factor, as well as a method to calculate it.

The present study has several limitations that should be highlighted. The sample size was small, thus our results should be viewed more as hypothesis-generating than as of conclusive nature. Moreover, the utilization of stent struts to imitate calcium restricted this simulation to small "artificial" calcific spots. Therefore, our findings cannot be extrapolated to larger calcification areas.

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