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Coronary calcification as a mechanism of plaque/media shrinkage in vessels treated with bioresorbable vascular scaffold: A multimodality intracoronary imaging study

Yaping Zeng [a, b, 1], Rafael Cavalcante [a, 1], Carlos Collet [c, g, 1], Erhan Tenekecioglu [a], Yohei Sotomi [c], Yosuke Miyazaki [a], Yuki Katagiri [c], Taku Asano [c], Mohammad Abdelghani [c], Shaoping Nie [b], Christos V. Bourantas [d], Nico Bruining [a], Yoshinobu Onuma [a, e], Patrick W. Serruys [f, *]

[a] ThoraxCentre, Erasmus Medical Center, Rotterdam, The Netherlands
[b] The Emergency & Critical Care Center of Beijing Anzhen Hospital, Capital Medical University, Beijing, People's Republic of China
[c] Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands
[d] Department of Cardiovascular Sciences, University College London, London, United Kingdom
[e] Cardialysis BV, Rotterdam, The Netherlands
[f] International Centre for Circulatory Health, Imperial College, London, United Kingdom
[g] Department of Cardiology, Universitair Ziekenhuis Brussel, Brussel, Belgium

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ABSTRACT

Background and aims: Whether coronary calcification is correlated with plaque/media shrinkage (PS) remains unclear. The aim of this study was to assess the relationship between the calcification process and PS, combining serial optical coherence tomography (OCT) and intravascular ultrasound (IVUS) in vessels treated with bioresorbable vascular scaffolds (BVS).

Methods: In 15 patients (16 vessels), OCT and IVUS images were matched using anatomic landmarks at post-procedure and five years. PS was defined as relative decrease in plaque/media area >5%. The association between the calcification process and PS was investigated. Mixed effect models were used to assess correlations and changes over time.

Results: Seventy-two OCT and IVUS paired cross sections in- and out-scaffolded segments were matched at baseline and follow-up (432 images). In total, 35 out of the 72 cross sections showed PS, and 37 cross sections showed no PS (non-PS) at 5-year follow-up. Delta (Δ) plaque/media area showed negative correlation with Δ OCT calcium area ($r = -0.29$, $p = 0.004$), Δ OCT calcium arc ($r = -0.42$, $p < 0.001$), Δ OCT calcium length ($r = -0.5$, $p < 0.001$), and Δ IVUS calcium arc ($r = -0.31$, $p = 0.024$), respectively. On echogenicity analysis, Δ plaque/media area was positively associated with Δ hypoechogenic area ($r = 0.47$, $p = 0.002$). An increase in calcium area was negatively correlated to Δ hypoechogenicity ($r = -0.29$, $p < 0.016$). The increase in calcium area was positively correlated with Δ lumen area ($r = 0.24$, $p = 0.044$).

Conclusions: In segments treated with BVS, the calcification process was associated with PS, decrease in the hypoechogenic tissue and late luminal enlargement. Combining IVUS and OCT provides a unique method to assess the correlation between the calcification process and plaque/media shrinkage.

1. Introduction

The regression of coronary atherosclerosis is one of the main goals of secondary preventive therapy [1,2]. Plaque shrinkage (PS) is sought to be one of the underlying mechanisms of the reduction of cardiac events observed with lipid-lowering drugs [2]. The

Abbreviations: NC, necrotic core; IVUS, intravascular ultrasound; OCT, optical coherence tomography; EEM, external elastic membrane; LA, lumen area; VA, vessel area; PA, plaque/media area; PS, plaque/media shrinkage; GS, grayscale-IVUS; EG, echogenicity.

* Corresponding author. Westblaak 98, 3012KM, Rotterdam, The Netherlands.
E-mail address: patrick.w.j.c.serruys@gmail.com (P.W. Serruys).

[1] These authors contributed equally to this manuscript.

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calcification of coronary plaques plays a pivotal role in the pathophysiology of atherosclerosis. Pathologic studies have showed that calcification co-localizes with large atheroma and is more extensive in lesions with a large necrotic core (NC) [3,4]. Furthermore, determination of radiocarbon (C-14) in coronary plaque has identified calcium as the oldest component in coronary plaques [5]. Interestingly, small (<3 mm) spotty calcification, which might have a different pathway of formation, was found to be an independent predictor of plaque rupture and acute coronary syndrome [6,7,8]. Coronary artery calcium progression has been correlated with HMG-CoA reductase inhibitors (i.e., statins) treatment [9]. In addition, statins have been shown to promote plaque shrinkage [10,11]. The paradox of calcification as a factor of both plaque vulnerability and stability raises the question of the filiation between lipidic degenerescence, the calcification process, and arterial remodeling.

Recently, bioresorbable vascular scaffolds (BVS) were introduced aiming at reducing very late adverse events related to the presence of permanent metallic stent. The polymeric (poly-L-lactide) scaffold resorbs within 3–4 years, restoring the vascular and physiological integrity of the treated region. However, the interaction between the polymeric device and the atherosclerotic process has not been investigated.

The objective of the present study was to assess the association among lipidic degenerescence, the calcification process, and changes in luminal dimensions, using serial invasive multimodality imaging after BVS implantation.

2. Materials and methods

2.1. Study design

The population included in the present study was derived from the first-in-man evaluation of bioresorbable vascular scaffold (Abbott Vascular, Santa Clara, USA). The design of the study was previously described [12]. In brief, it was a single-arm study including 101 patients with non-complex, not calcified lesions treated with second iteration of BVS [12]. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) were performed at baseline and 5-year follow-up. (Supplemental Fig. 1). We included all cases with adequate image quality with three modalities (OCT, Grey scale S-IVUS and echogenicity-IVUS).

2.2. IVUS image acquisition and analysis

After BVS implantation, the treated vessels were examined with 20 MHz, phased-array IVUS catheters (Eagle Eye, Volcano Corp., Rancho Cordova, California, USA), using an automated pullback at 0.5 mm/s, at the index procedure and follow-up. Semi-automatic detection of both lumen and external elastic membrane (EEM) was performed with the QCU-CMS-Research software v4.69 (Medis medical imaging systems, Leiden, the Netherlands). The following parameters were derived: lumen area (LA), vessel area (VA) and plaque/media area (PA). Based on boundaries of the reproducibility and using the standard deviation of intra and inter-observer variability of IVUS measurements, reported in the range of 2.9%–5% [13,14], we defined plaque/media shrinkage (PS) as a relative decrease in PA >5%. Calcified plaque on grayscale-IVUS (GS-IVUS) was defined as bright echoes with acoustic shadowing [15]. The arc of a calcification on IVUS image was determined automatically by the software by drawing two vectors from the center of the vessel to the corners of the acoustic shadowing [15].

2.3. Automatic quantitative echogenicity (EG) analysis on IVUS

Echogenicity aims to classify the vessel wall components located between the luminal boundary and the EEM into categories based on their grey-level intensity in IVUS images [16,17]. We quantified 5 types of tissue brightness: calcified, hyperechogenic, upper-echogenic, hypoechogenic, and unknown [16,17].

2.4. OCT image acquisition and analysis

OCT acquisition was performed using C7 and C8 frequency domain systems (Light Lab Imaging, Westford, Massachusetts, USA). Image acquisition was performed according to the recommended procedure for each OCT system [18]. OCT images acquired at baseline and follow-up were analyzed off-line, at 100 μm or 200 μm longitudinal intervals within the region of interest (ROI), using the QCU-CMS software. ROI was defined as scaffold segment and 5-mm proximal and distal. The following parameters were quantified: calcium area, arc, and length. Calcium length for a single calcium pool was measured as the maximal geometric length of calcification [19]. For the cross-sections with more than one calcified pool, the sum of the calcium measurements was used.

2.5. Matching cross sections of IVUS and OCT

OCT, IVUS (GS-IVUS and echogenicity-IVUS) images at end-diastolic phase were displayed simultaneously, and screened concomitantly frame by frame to match using the scaffolds' platinum radiopaque markers and anatomical landmarks such as side branch, vein and pericardium, position and configuration of calcified plaques, characteristic lumen shape and circumferential profile of plaque thickness, as well as the positional or directional relationship among all landmarks above (Fig. 1) [20]. The exclusion criteria of the cross sections are shown in Supplemental Materials. The matched cross-sections were then co-localized between the time points.

2.6. Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) or median (interquartile range), as appropriate. Binary variables are presented as counts and percentages (%). The correlation between plaque/media shrinkage and calcification process was assessed using Pearson's correlation coefficient. Mixed effects models with random intercept and slope was used to assess the significance of the correlation and changes over time accounting for the correlation of cross-section within the same lesion. A sensitivity analysis including only in-scaffold cross-section was performed. Levels were defined as patient and scaffold. A p-value <0.05 indicated statistical significance. All analyses were performed with the SPSS version 22 (IBM Corp, Armonk, NY, USA).

3. Results

3.1. Study population

Fifteen patients with 16 coronary lesions had OCT and IVUS images at post-procedure and 5-year follow-up. The clinical characteristics are shown in Table 1. Seventy-two cross sections (n = 52 in-scaffold and 20 out-scaffold) were acquired with three imaging modalities (OCT, GS-IVUS and echogenicity-IVUS) at post-procedure and 5-year follow-up, comprising 216 paired images matched to assess changes in plaque's components over time.