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Imaging

Dual role of circulating endothelial progenitor cells in stent struts endothelialisation and neointimal regrowth: A substudy of the IN-PACT CORO trial ☆

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ABSTRACT

Background: Endothelialisation is a crucial event after percutaneous coronary intervention (PCI). Endothelial progenitor cells (EPCs) are bone marrow derived elements with reparative properties. We aimed to assess the relationship between circulating EPC levels and stent neointimal hyperplasia (NIH) using frequency domain optical coherence tomography (FD-OCT).

Methods: Patients undergoing elective PCI to native vessels and randomised to bare metal stent (BMS) alone versus BMS plus drug coated balloon (DCB) were included. At six months, angiographic follow-up and FD-OCT were performed to measure percentage neointimal hyperplasia volume obstruction (%NIHV), and percentage of uncovered stent struts (%US). Venous blood samples were obtained before the procedure and at six months to detect CD34+CD45dimKDR+ EPC levels.

Results: Twenty patients were enrolled. A significant relationship was observed between baseline EPC levels and %NIHV (R: 0.63, p: 0.03) and %US (R: −0.56, p: 0.01) at follow-up. Both EPC levels and DCB use were independently related to %NIHV (β: 0.55; $p < 0.001$ and β: −0.51; p: 0.001, respectively), while only EPC levels were independently associated to %US (β: −0.52; p: 0.01). Higher %NIHV (p: 0.004) and lower %US (p: 0.005) were observed in patients with stable or increasing EPC level.

Conclusion: Our study shows a relationship between EPC levels and stent strut coverage, supporting a dual role for these cells in favouring stent endothelialisation but also NIH growth.

1. Introduction

Stent endothelialisation is a crucial event after percutaneous coronary intervention (PCI), as a fully functional endothelium is essential to lower the risk of late stent thrombosis, but also important to avoid instent restenosis (ISR) [1], a progressive process due to a maladaptive response of the vessel wall to the stent-related injury resulting in uncontrolled neointimal hyperplasia (NIH) [2]. ISR, although reduced by the introduction of drug-eluting stents (DESs), remains a significant problem in some lesions subgroups [3].

Drug coated balloon (DCB) is a relatively new technology which has so far found an unchallenged indication in the field of ISR treatment [4], being capable of delivering antiproliferative drugs to the vessel wall without leaving behind further foreign bodies. The combination of DCB pre- or postdilatation plus a bare metal stent, additionally, has been extensively investigated due to the potential advantages of a more uniform drug distribution as compared to DES, although with mainly negative results [5–9]. Initial evidence from our group, however, support the potential application of at least one type of DCB to a subset of de novo lesions [10].

Endothelial progenitor cells (EPCs) are bone marrow derived elements with homeostatic and reparative properties [11], increased in the blood of patients with acute ST elevation myocardial infarction and linked to reduced left ventricular remodelling [12]. EPCs have also been controversially invoked to explain stent endothelialisation, as the regeneration of endothelium is considered to involve either EPC homing from blood flow at the site of injury, or endothelium regrowth from both sides of the stented part of the vessel [13].

Abbreviations: BMS, bare metal stent; CAD, coronary artery disease; DCB, drug coated balloon; DES, drug-eluting stent; EPC, endothelial progenitor cells; FD-OCT, frequency domain optical coherence tomography; ISR, instent restenosis; NIH, neointimal hyperplasia; NIHV, neointimal hyperplasia volume; PCI, percutaneous coronary intervention; %MS, percentage of malapposed struts; %NIHV, percentage of neointimal hyperplasia volume; %US, percentage of uncovered struts.

☆ Conflicts of interest: none.

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In the present study, we aimed to assess, by the application of frequency-domain optical coherence tomography (FD-OCT), the relationship between circulating EPC levels, stent struts coverage, and NIH in patients undergoing elective PCI to native vessels with bare metal stent (BMS), and enrolled in a randomised trial assessing the additional value of paclitaxel eluting balloon dilatation [14].

2. Materials and methods

This is a planned substudy of the INtimal hyPerplasia evAluated by oCT in de novo COROnary lesions treated by drug-eluting balloon and bare-metal stent (IN-PACT CORO trial, registration number in Clinicaltrials.gov: NCT01057563), a study conceived to test NIH reduction in simple, de novo lesion undergoing BMS implantation with or without DCB dilation. Rationale, design and methods of INPACT CORO trial were previously reported in a dedicated protocol paper [14] and main study results have recently been presented at EuroPCR conference [10].

Briefly, a homogeneous population of non-diabetic patients with stable angina, already on statin therapy at target dose and undergoing elective PCI with BMS for de novo, simple lesions (10–25 mm long, requiring a single stent with diameter of 3.0–3.5 mm) was enrolled [14]. Patients with left ventricular impairment (ejection fraction $\leq$30%), with a previous myocardial infarction within 48 h, or with severe comorbidities (infective, neoplastic, autoimmune diseases, clotting pathologies, creatinine >2.5 mg/dl, poor cardiac function, recent myocardial infarction) were not eligible for the study.

Recruited patients were randomised 1:2 to BMS implantation alone or BMS implantation with additional DCB use (IN.PACT™ Falcon™ balloon, Invatec Technology Center GmbH, Frauenfeld, Switzerland). Patients in the DCB group were further randomised to DCB predilatation and DCB postdilatation. However, since no differences in both primary and secondary endpoints were detected between DCB predilatation and postdilatation in the main study [10], only BMS + DCB and BMS groups will be considered in this substudy.

The angiographic results were assessed by Quantitative Coronary Angiography (QCA) using CASS 5.9.2 (Pie Medical Imaging B.V.). After PCI, aspirin (75–100 mg/day) life-long and clopidogrel (75 mg/day) for $\geq$3 months were prescribed and at six months, angiographic follow-up with FD-OCT assessment was performed to investigate the hallmarks of vascular wall healing after stenting (Fig. 1). Venous blood samples were collected at the time of enrolment and at six-month follow up to measure EPC levels. Cytofluorimetric detection of CD34+CD45dimKDR+ cells was performed as previously detailed [15]. The study protocol has been approved by the ethical committee of the Catholic University of the Sacred Heart and all enrolled patients signed a written informed consent.

2.1. FD-OCT evaluation

At 6 months, patients underwent repeat coronary angiography with FD-OCT study. FD-OCT scans were performed with the C7 XR Imaging system (LightLab Imaging Inc., Westford, Massachusetts), using a non-occlusive technique with automated intracoronary injection of iso-osmolar contrast [16]. Off-line, blinded analysis was independently performed in a validated core laboratory (Rome Heart Research, Italy). All cross sectional frames of the stented region were analysed.

Stent area and lumen area were measured for each cross-section, and mean stent area (mSA) and mean lumen area (mLA) were calculated. In-stent neointimal hyperplasia volume (NIHV) was expressed as (mSA − mLA)*stent length. Percentage of neointimal hyperplasia volume (%NIHV) was calculated as 100*NIHV/(mSA*stent length). For strut coverage analysis, struts were classified as covered if tissue was visible between the endoluminal surface and the vessel lumen, and labelled as uncovered if tissue layer on the endoluminal surface was not visible (Fig. 1) [17]. The percentage of uncovered struts (%US) was then calculated as number of uncovered struts/total struts number*100.

Incomplete strut apposition was considered present when the distance between endoluminal surface of at least one single strut and the vessel wall was higher than strut thickness. The maximum distance from the endoluminal surface to the vessel wall and the number of malapposed struts were measured in each frame and the percentage

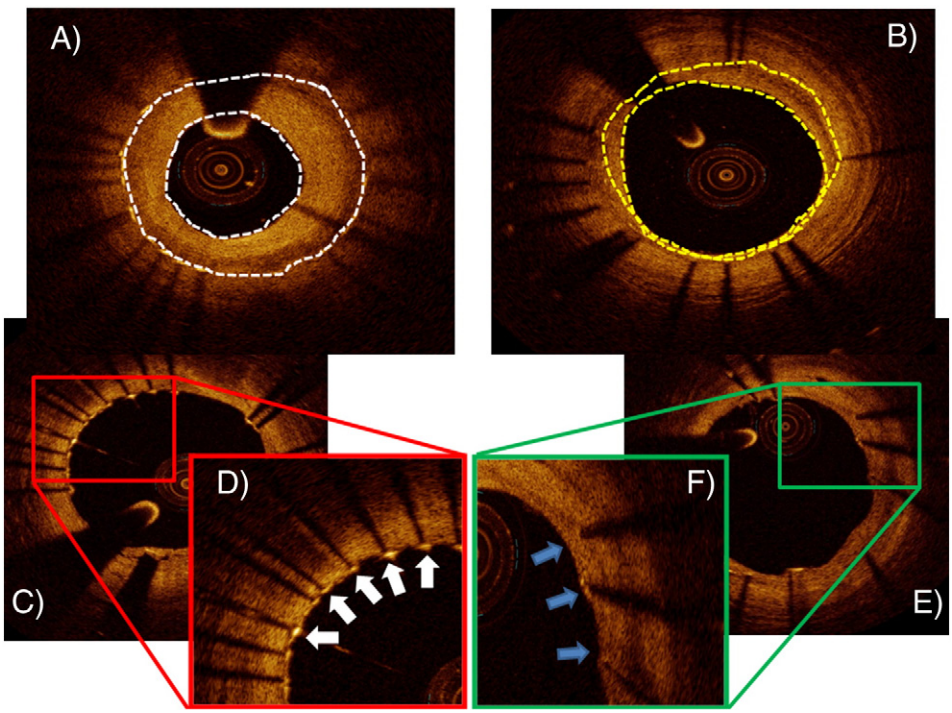

Fig. 1. FD-OCT cross-section of different degree of neointimal hyperplasia and stent strut coverage. Examples of neointimal hyperplasia, excessive (Panel A) and regular (Panel B) (the area comprised between the two dotted lines). Examples of uncovered stent struts (Panel C with magnification in Panel D, white arrows) and covered struts (Panel E with magnification in Panel F, blue arrows).