Evaluation of re-endothelization extent at mid-term follow-up after drug eluting balloon plus bare metal stent implantation during primary coronary angioplasty: insight from OCT imaging

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One quarter of patients with STEMI submitted to primary percutaneous coronary intervention (PCI) need repeated target vessel revascularization (TVR) because of stent restenosis or thrombosis. Introduction of DES has effectively reduced the incidence of these complications but the safety of this type of stent in the setting of AMI is limited due to the unpredictable risk of stent malapposition and vessel remodelling in the long term follow-up. Recently, treatment with drug eluting balloon (DEB) in association with bare metal stenting (BMS) has been reported to have an excellent efficacy and safety profile. However, little is known regarding the extent of stent coverage in BMS after DEB utilization.

Key words: **Stents - Tomography, optical coherence - Myocardial revascularization.**

One quarter of patients with STEMI submitted to primary percutaneous coronary intervention (PCI) need repeated target vessel revascularization (TVR) because of stent restenosis or thrombosis.

Case report

We present the case of a 65-year-old man admitted to our Catheterization Laboratory for chest pain onset 1.5 hour before and basal ECG suggestive for inferior ST-elevation myocardial infarction (STEMI). He was on therapy for hypertension; no previous cardiac disease was known. At the admission the patient was in Killip class I but still symptomatic for chest pain. The coronary angiography showed a total occlusion of the proximal tract of the right coronary artery (Figure 1A).

Vascular access was obtained through right femoral artery puncture with 6F introducer followed by administration of 7000 units of heparin. Right coronary artery (RCA) occlusion was crossed with a BMW Universal 0.014 guide (Abbot Vascular, Santa Clara, CA, USA) through a JR 4 6F guiding catheter (Jr Cordis Corporation, Miami Lakes, FL, USA). The patient was enrolled in the DEB AMI study, a multicenter randomized study evaluating the safety and efficacy of drug eluting balloon (DEB) *vs.* other treatment strategies during primary angioplasty, and randomized to DEB+bare metal stents (BMS) implantation. Manual thromboaspiration was performed with Diver® clot extraction catheter (Invatec s.p.a., Rocadelle, BS, Italy) with minimal remove of thrombotic debris, followed by pre-dilatation with a standard balloon Sprinter Legend 2.5x15 mm (Medtronic, inc. Minneapolis, MN,USA) at 18 atm for 15 seconds. Successively a prolonged (60 seconds) inflation at 10 atm was done with a paclitaxel DEB Dior® 2.75/25 mm (Eurocor, Bonn, Germany). Subsequently, a chromo-cobalt stent Genius Magic 3.0/19 mm (Eurocor, Bonn, Germany) was implanted with a balloon inflation of 10 sec for 16 atm. The final angiographic result was extremely satisfactory

Received on October 4, 2010.
Accepted for publication on January 17, 2011.

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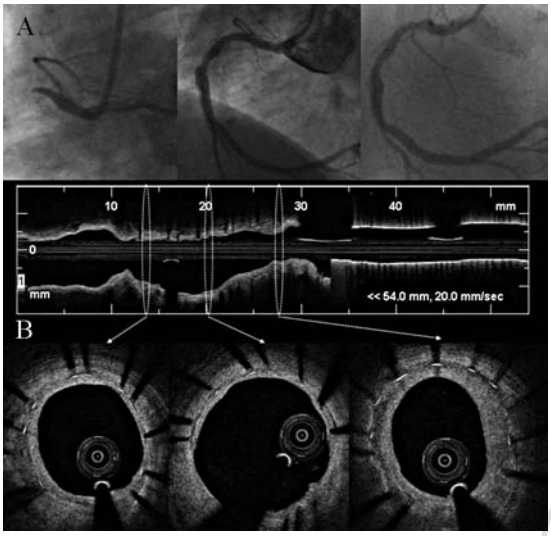

Figure 1.—A) Still frame angiographic images of the right coronary artery (pre procedure, final result and 6 months follow up), demonstrating complete occlusion of the proximal part of the coronary (left), final results after DEB and BMS implantation (central) and 6 mo FU angiography (rigth); B) OCT images at follow up evidence full coverage of stent struts without malapposition at different cross sections along the entire stented segment. The proximal part of the stent shows neointimal hyperplasia without significative reduction of lumen area.

with TIMI 3 flow and 0% residual stenosis (Figure 1A, central inset). Patient was discharged on dual antiplatelet therapy (Aspirin 100 mg and clopidogrel 75 mg daily) for twelve months.

During the following months the patient remained asymptomatic. At the angiographic control scheduled per protocol 6 months later the stent presented minimal focal hyperplasia (late loss 0.27, Figure 1A, right inset) with patent lumen. Optical coherence tomography (OCT) images evidenced completely full coverage of stent struts without stent malapposition at different cross sections along the entire. The proximal part of the stent showed neointimal hyperplasia without significant reduction of lumen area (Figure 1B).

Discussion

Introduction of DES has effectively reduced neointimal proliferation by addressing the biological mechanisms of neointimal proliferation and have become the mainstay of interventional treatment in clinical practice. However, the demonstrated efficacy of DES is balanced by the small but unpredictable risk of very late stent thrombosis thought to be due to delayed vascular healing resulting from either the antiproliferative effect or hypersensitivity reaction to drug, polymer coating or their combination. In addition, in contrast to stable patients, the effectiveness of drug eluting stents (DES) in STEMI is not clear [3, 4] because of limited and inconsistent data on clinical outcome of DES in this setting.[5, 6] Moreover, long-term clinical outcome of DES may be offset by the late acquired malapposition or delayed stent re-endothelialization.[7-14] In recent years, DEB have emerged as a therapeutic alternative in interventional cardiology.[15, 16] With this technology, short transfer of antiproliferative drug is achieved by the means of lipophilic diffusion without the requirement of a polymeric carrier and a sustained elution as in the one related to DES implantation. Therefore, such technology has the potential to reduce the untoward effects associated with polymer-stable-based technologies.[13, 14] Animal experiments have demonstrated that uncoated stents implantation following prolonged DEB inflation may normally re-endothelialize within two months without the risk of in-stent hyperplasia.[14] Albeit not proven yet in humans, such finding may suggest possible early discontinuation of dual antiplatelet therapy.

The present case demonstrates that in patients with STEMI, primary angioplasty with DEB/BMS could be a feasible and safe strategy and may represent a valid alternative strategy than BMS alone or DES implantation to reduce the need of target vessel revascularization and the risk of late acquired stent malapposition. This effect may be obtained without interfering with normal vascular healing and endothelial function. To evaluate these assumptions we have therefore started to use such strategy in STEMI patients in the ongoing Drug Eluting Balloon in Acute Myocardial Infarction (DEBAMI) randomized multicenter Trial.

According to the protocol, after successful thrombus aspiration, patients are randomized to one of the three treatment groups:

1) predilatation with a regular balloon and BMS (GeniusMagic, Eurocor, Bonn, Germany) implantation; 2) predilatation with a regular balloon followed by prolonged DEB (Dior™, Eurocor, Bonn, Germany) inflation and final BMS implantation; 3) predilatation with a regular balloon and DES (TaxusLibertè, BostonScientific, Natick, MA, USA) implantation.

The angiographic follow-up is planned at 6 months after the index treatment and clinical follow-up is done at 1, 6, 12 and 24 months after the index treatment. The DEB used is the 2nd generation Dior™ balloon, a paclitaxel-coated balloon surface, containing 3 mg paclitaxel/mm². The drug is maintained on the balloon surface by a covalent binding with a shellac acid carrier. The recommended balloon inflation time is 60 seconds at nominal balloon pressure, during which 45 to 60 % of paclitaxel is released to the vessel wall. The primary endpoint of the study is the in segment late lumen loss (LLL) at 6 months as determined by quantitative coronary analysis (QCA) while the secondary endpoints are the binary restenosis rate, stent struts coverage at 6 month using OCT performed at the site of the stented segment. The study is ongoing with 138 out of 150 patients currently enrolled.

Other technologies currently available on the market are represented by the hydrophilic-coating formulation Free Pac which is instead utilized in other DEB platforms such as the IN.PACT Falcon and Amphirion balloon and the Pacific or the Admiral DEB (Invatec-Medtronic, Brescia, Italy) for coronary and peripheral interventions; the Lutonix DEB (Lutonix Inc, Maple Grove, MN, USA), and the Pantera Lux paclitaxel-eluting balloon (Biotronik, Berlin Germany) with the addition of the excipient butyryltri-hexyl citrate, which keeps the paclitaxel in a micro-crystalline aggregate and leads to an even faster uptake of the drug by the vessel wall. Finally the Aachen Resonance DEB is characterized by a microspray nanotechnology that acts as carrier for drug transportation.

Conclusions

Drug-coated balloon catheters represent an alternative option for treatment of coronary and peripheral arteries. Local drug delivery of paclitaxel has been shown to be feasible in preclinical studies in inhibiting neointimal proliferation.

These results have been confirmed by clinical evidence in patients with coronary atherosclerotic disease (especially in small vessels), in-stent restenosis and peripheral artery disease. However, these encouraging results have to be clearly proven in larger studies and different spectrums of disease, like diabetes, diffuse disease, bifurcation and other cases where the benefit of stent implantation is still hampered by increased neointimal proliferation. The forthcoming availability of different PEB opens new possibilities for the future with the exciting possibility of an increase in efficacy maintaining at the same time a good long-term safety profile compared to current DES technology.

Riassunto

Un quarto dei pazienti con infarto miocardico acuto sottoposti ad angioplastica primaria necessitano di una rivascolarizzazione del vaso target a causa della re-stenosi o della trombosi intra-stent. L'introduzione degli stent medicati ha effettivamente ridotto la proliferazione neo-intimale risolvendo in parte questo problema e diventando quindi il trattamento di prima scelta nella pratica clinica; tuttavia, l'efficacia del loro utilizzo nel trattamento dell'infarto miocardico acuto è limitata dal rischio non prevedibile di malapposizione degli stent e di rimodellamento vascolare nel follow-up a lungo termine. Recentemente, sono stati riportati alcuni casi di angioplastica primaria eseguita utilizzando palloni medicati in associazione al posizionamento di stent metallici. In questi pazienti trattati per infarto miocardico acuto la metodica ha mostrato un eccellente profilo di efficacia e sicurezza. Nonostante ciò, si conosce ancora ben poco sull'estensione della ri-endotelizzazione degli stent metallici dopo l'utilizzo di palloni medicati. Noi riportiamo un caso clinico in cui l'estensione della ri-endotelizzazione successivamente all'utilizzo di questa strategia è stata valutata attraverso l'analisi con tomografia a coerenza ottica in un paziente precedentemente sottoposto ad angioplastica primaria. Sei mesi dopo il tratta-

mento con pallone medicato e stent metallico era visibile solamente una minima iperplasia focale e l'OCT mostrava una completa copertura delle maglie dello stent in assenza di malapposizione.

Parole chiave: Stents - Tomografia a coerenza ottica - Rivascolarizzazione miocardica.

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